

Food Allergy and Anaphylaxis Guidelines

Supplementary materials



EAACI GUIDELINES

Food Allergy and Anaphylaxis

Supplementary materials

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The European Academy of Allergy and Clinical Immunology, EAACI, is a non-profit organisation active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. EAACI was founded in 1956 in Florence and has become the largest medical association in Europe in the field of allergy and clinical immunology. It includes over 7800 members from 121 countries, as well as 47 National Allergy Societies.

*To all the members of EAACI
and to our patients*

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SECTION

FOOD ALLERGY DIAGNOSIS AND MANAGEMENT

**Supplementary
materials**

1 . 1

THE EPIDEMIOLOGY OF FOOD ALLERGY IN EUROPE SYSTEMATIC REVIEW AND META-ANALYSIS

☞ Supplementary materials ☞

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METHODS

Search strategy

Articles were retrieved using a highly sensitive search strategy implemented in four electronic databases (OVID MEDLINE, OVID EMBASE, CINAHL, and ISI Web of Science). The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Box E1). Systematic reviews were retrieved by using the systematic review filter developed at McMaster University Health Information Research Unit (HIRU) (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). We also adapted the search filter from York University Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/intertasc/epidemiological_studies.html) to retrieve the characteristics describing the epidemiology of FA. The McMaster filter (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx#Prognosis) was applied for retrieving studies on prognostic factors. Additional references were located by hand search. Unpublished work and research in progress were searched through discussion with experts in the field. There were no language restrictions, and where possible the literature in languages other than English was translated. The literature we were unable to translate is shown in the PRISMA flow diagram (Figure 1).

Inclusion and exclusion criteria

As per the study design, we included systematic reviews and meta-analyses, cohort studies, case-control studies, cross-sectional studies, and routine healthcare studies. We excluded review and discussion papers, non-research letters and editorials, case studies and case series, animal studies, and all randomized controlled trials. Our initial inclusion criteria were broad by including studies published worldwide between January 1990 and September 2012. However, after assessing the large amount of articles, we made further restrictions to include studies published only in Europe (based on the United Nations definition (<http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe> accessed on December 28, 2012) between January 1, 2000 and September 30, 2012, with the exception of Greenland and Turkey, which were included in the review because we believe they are culturally and politically more European than North American and Asia, respectively.

Box E1 Ovid Medline search strategy

Term	Definition
1	exp Food Hypersensitivity/
2	food allerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal\$).ti.
7	exp animals/ not humans.sh.
8	6 or 7
9	*Incidence/
10	*Prevalence/
11	(incidence or prevalence or epidemiol\$).ti.
12	epidemiologic methods/
13	*cohort studies/
14	controlled clinical trial.pt.
15	*case-control studies/
16	exp Food Hypersensitivity/ep [Epidemiology]
17	exp Hospitalization/
18	exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
19	exp Mortality/sn, td [Statistics & Numerical Data, Trends]
20	exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
21	exp "Cause of Death"/
22	((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
23	or/9-22
24	or/1-5
25	23 and 24
26	25 not 8
27	limit 26 to yr="1990 - 2012"

Analysis, synthesis and reporting

We recalculated all the frequency estimates of FA occurrence if adequate data were provided by authors. If any discrepancies were observed between our recalculated estimates and those of the authors, we reported our recalculated estimates. Our recalculated estimates were based on the minimal measured events rather than extrapolated estimates. In studies where inadequate data were given to enable recalculation, we reported the estimates provided by the authors. Where needed and possible, we contacted authors of primary studies for clarifications. The 95% confidence intervals (95% CI) of our recalculations were computed by using the Wilson score method without continuity correction (15). Different reports from the same primary study were reported as one study. Although several specific food allergies were reported across the studies, the focus of the current report is to present the estimates for 'any FA'. The other specific foods will be presented in a future report. In studies reporting estimates of sensitization to food allergy alongside cross-reactivity to pollen (wheat and grass), we always used the true estimates without pollen cross-reactivity, where possible.

We performed a random-effects meta-analysis for clinically and methodologically comparable studies to estimate the frequency of FA. The following outcomes were considered: 1. point and life-time prevalence of self-reported FA; 2. point prevalence of specific IgE positivity; 3. point prevalence of SPT positivity; 4. point prevalence of symptoms plus IgE positivity; 5. point prevalence of symptoms plus SPT positivity; 6. point prevalence of clinical history or OFC/DBPCFC positivity; 7. point prevalence of positive response to food challenge (open food challenge [OFC] or DBPCFC). For outcomes 6 and 7 above, where a study reported estimates for both OFC and DBPCFC, the DBPCFC estimates were always used; otherwise OFC estimates were used if DBPCFC was not done in the study. We did not present pooled estimates for cumulative incidence of FA due to inconsistencies and very few data across studies.

We aimed to present stratified pooled estimates by different age groups (1 year and under, 2-5 years, 6-10 years, 11-17 years, 18-60 years, and older than 60 years). However, due to several overlapping ages of participants across the studies, the age-stratified pooled estimates were more feasibly computed for the age groups 0-17 years (children) and 18 years

and over (adults). A study with overlap between these two age groups was included in either age group if the age distribution was skewed to that age group. For studies that gave frequency estimates at different ages for the same individuals, we used the estimates for the highest age in computing the pooled estimates. We also present the pooled estimates stratified by geographical region in Europe (i.e., East, West, South, North, and 'Europe'; the last group being for studies that included several European countries and gave overall estimate for all the countries and in which it was not possible to calculate the frequency for each country studied) using the classification by the UN (<http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe> accessed December, 2012). Due to methodological differences across the studies investigating the risk and prognostic factors for FA (varied risk and prognostic factors studied, differences in study design, differences in statistical methods employed across studies, differences in factors considered for adjustment, and others), we did not perform meta-analysis for these studies.

RESULTS

Study characteristics

The characteristics, main results, and the overall risk of bias grading of the studies included for review are shown in Table E1. Of the 56 studies reviewed, 31 were cross-sectional, 19 cohort, three were systematic reviews, and three case-control studies. Over 50% of the studies were conducted in northern European countries. A majority of the studies (n=37) were undertaken only in children. Ten studies assessed FA only by self-report, 10 only by specific-IgE or SPT positivity, while the remainder was a combination of self-report, specific-IgE or SPT sensitization, and food challenge. Twenty-six of the studies undertook food challenges for verifying FA, and 22 of these employed DBPCFC. A majority of the studies (n=49) reported point prevalence as the occurrence measure for estimating the frequency of FA. The majority of studies had a moderate risk of bias (Table E2).

Frequency of FA

Self-reported FA: details of studies

Eighteen of the 27 studies on self-reported FA included children (i.e., < 18 years). Two studies

reported cumulative incidence in children: one study from Denmark reported the cumulative incidence of self-reported FA by the age of 6 years as 11.6% (27-29), whereas one study from the UK reported estimate of 25.8% by the age of 1 year and 28.1% by the age of 3 years (85-87). The lowest (1.6%) and highest (38.7%) point prevalence of FA were reported in Italy (20) and Norway (52), respectively (Figure E1). The lowest and highest life-time prevalence of FA was found in Turkey (5.7%) (59) and Poland (41.8%) (53), respectively (Table E3). The range of point prevalence of self-reported FA for all age groups was 1.6% to 38.7% and the highest point prevalence was found in the age group 2-5 years (Table 1). The range of life-time prevalence of self-reported FA for all age groups was 5.7% to 41.8% and the highest life-time prevalence was found in the age group 6-10 years (Table E3).

FA by positive SPT or IgE to specific food allergens: details of studies

Of the 18 studies (17-19,27-29,35-42,47,50-52,61-64,67-70,76,77,81,82,85-88) that defined FA by means of specific sensitization (positive SPT or IgE) to food allergens, 12 were undertaken among children (Table E4). The frequency of FA as defined by positive specific-IgE was generally higher than corresponding positive SPT, and often the correlation between the two types of tests was low. The cumulative incidence of positive SPT or specific-IgE to at least one food by the age of 4 years was reported to be 5.5% in Finland (69). The cumulative incidence of positive specific-IgE by 6 years was 47.3% in Denmark (27-29), while that of positive SPT was 5.3% by the age of 3 years in the UK (Table E4) (85-87). The point prevalence of positive SPT to at least one food was lowest in France (1.8%) (67) and highest in the UK (7.7%) (88). In general, the point prevalence of SPT positivity was highest in Northern Europe than other regions (Figure E3), with only one study each being undertaken in Western and Southern Europe. No study was found from Eastern Europe on FA by SPT positivity to any specific food allergen. Studies on specific-IgE positivity to food allergens were from only Northern and Western Europe. The point prevalence of positive specific-IgE was lowest in Finland (2.0%) (41) and highest in Germany, Italy, Norway, and Denmark (each country having approximately 22%) (Table E4) (18). In general, the point prevalence was higher in Western than in Northern Europe (Figure E2), although only

one study was undertaken in Western Europe. The range of the prevalence of positive SPT positivity for all age groups was 1.8% to 6.1%, with the highest prevalence in the age group the 6-10 years; that of positive specific-IgE ranged from 2.0% to 52.0%, the age group 6-17 also having the highest prevalence (Table 1).

FA defined by symptoms plus allergic sensitization and by clinical history or food challenge

Nine studies (23,48,53,60,67,68,78-80,85-88) defined FA based on symptoms plus sensitization (SPT and IgE) to specific food allergens (n=5) or based on convincing clinical history or positivity to food challenge (OFC or DBPCFC) (n=4) (Table E5). All of these studies were among children and a majority from Northern Europe (n=6) (23,48,53,68,85-88). FA based on symptoms plus sensitization involved subjects who were symptomatic for FA (usually by self-report) and subsequently had positive results when they underwent SPT or IgE tests. On the other hand, FA based on clinical history or food challenge was defined as either having a convincing clinical history (without any food challenge) or being positive with food challenge.

The pooled point prevalence of symptoms plus positive IgE to at least one food was similar in Northern and Western Europe (Figure 3). The lowest (2.2%) and highest (4.6%) point prevalence of symptoms plus positive specific-IgE to at least one food were both found in Germany (78-80). The range of the point prevalence of symptoms plus positive specific-IgE by age group was 1.3% to 4.6%, those 1 year and less having the lowest frequency (Table 1).

The point prevalence of symptoms plus SPT positivity was just highest in Southern Europe compared to other regions (Figure 4). The lowest point prevalence was found in France (0.1%) (66) and the highest in Germany (13.1%) (77-79). The range of the point prevalence of symptoms plus positive SPT by age group was 0.1% to 13.1%, the age groups 6-10 and 11-17 years having the lowest estimates.

The overall pooled point prevalence of clinical history or food challenge positivity was lowest in the UK (1.1%) (87) and highest in Norway (6.8%) (53) (Table E5). The range of the point prevalence of clinical history or food challenge by age group was 1.1% to 6.8%, the age group 2-5 years having the highest frequency (Table 1). Differences may be explained by the use of

OFC versus DBPCFC.

There was significant heterogeneity between the studies ($P < 0.05$ for I^2) despite stratification by age and region.

Challenge-verified FA: details of studies

Of the 12 primary studies (23,27-29,34,48,60,65,66,68-70,78-80,85-88) that assessed FA by performing food challenge (OFC or DBPCFC), eight only included children (23,27-29,48,60,68-70,85-88) and nine came from Northern Europe (23,27-29,48,65,66,68-70,85-88), two from Southern Europe (34,60), and one from Western Europe (78-80) (Table E6). Three of the studies reported cumulative incidence of challenge positive FA by 1 year (1.5% [95% CI 0.9-2.5]) (27-29), by 4 years (3.3% [95% CI 2.8-3.9]) (69,70), and by 6 years (3.6% [95% CI 2.3-5.4]) (85-87). The lowest point prevalence of challenge-verified FA was found in the UK (almost zero per cent) (85-87) while the highest was found in Germany (5.7%) (78-80) (Table E6). The range of the point prevalence of challenge-verified FA was from 0% to 5.7%, with the age group 11-17 having the highest frequency (Table 1). There was significant heterogeneity between the

studies ($P < 0.05$ for I^2) even after stratification by age and region.

Cumulative incidence

Only one of the nine studies in these categories reported estimates for cumulative incidence (84-86), showing that the cumulative incidence of FA by the age of 3 years was 6.0% (95% CI 4.6-6.7) based on clinical history or OFC positivity and 5.0% (95% CI 3.8-6.5) based on clinical history or DBPCFC positivity.

Risk and prognostic factors for FA

Although a number of the reviewed studies examined the risk and prognostic factors for self-reported FA and sensitization to specific food allergen, *a priori*, we were interested in studying the risk and prognostic factors for clinician-diagnosed or objectively-verified FA, which is expected to give stronger evidence for causality and would be more meaningful for clinical intervention. Thirteen studies (22,24-26,32,34,40,46,53,58,68-70,73,84-87) were found of which 11 were among children (Table 3). Due to several methodological differences between the studies, they were not combined in a meta-analysis.

Table E1 The main features, main results of frequency of FA, and overall risk of bias assessment of the studies included in the systematic review on the epidemiology of FA in Europe: studies published 1 January 2000 - 30 September 2012

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number participated						
Bant <i>et al.</i> 2008, Poland	Cross-sectional study	Not indicated	156	18-27 years old	Any food allergen	SPT, sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA: 1.1%	Moderate
Burney <i>et al.</i> 2010; Woods <i>et al.</i> 2001; Europe, United States of America, Australia, New Zealand	Cross-sectional study	Not indicated	17280	20-44 yrs old	Any FA, fish, egg, cow's milk, mustard, melon, poppy seed, soya, sunflower, walnut, banana, peanut, buckwheat, rice, tomato, corn, celery, kiwifruit, carrot, sesame, apple, wheat, shrimp, peach, hazelnut	Self-reported, sIgE	Point and life-time prevalence	Point prevalence of sIgE positivity to at least one FA for all countries 12.3%	Moderate
Caffarelli <i>et al.</i> 2011, Italy	Cross-sectional study	900	625	5-14 years old	Any FA, cow's milk, egg, tomato, peanut, wheat, chocolate, kiwi, strawberry, melon, orange, hazelnut, sesame	Self-reported	Point and life-time prevalence	Point prevalence of self-reported FA: 1.6% (0.9-2.9)	Moderate
Chafen <i>et al.</i> 2010, Worldwide	Systematic review	12378 studies identified	72 studies included	All age groups	Cow's milk, egg, peanut, fish, shellfish	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, life-time prevalence; cumulative incidence, incidence rate	The same frequency estimates as given in Rona <i>et al.</i> 2007	Strong
Colver <i>et al.</i> 2005, UK and Ireland	Cross-sectional study	13028933	13028933	Children < 16 years	Any food allergic reaction	Physician diagnosis	Point prevalence	Frequency estimates not obtainable from the study	Moderate
Du Toit <i>et al.</i> 2008, UK and Israel	Cross-sectional study	10786	8826	4-18 years old	Peanut, sesame, tree nuts, egg, milk	Self-reported, clinical history, OFC	Point prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 0.4% (0.3-0.6) in UK and Israel	Moderate
Dubakiene <i>et al.</i> 2012, Lithuania	Cohort study	1558	1558	6-12 months old	Any FA, milk, egg, wheat, peanut, potato, and fish	Self-reported, SPT, sIgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed FA: 0.3% (0.1-0.7)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Eggeløs <i>et al.</i> 2003, 2001a and 2001b, Norway	Cohort study	4973	3754	2.5 years old	Any FA, cow's milk, hen's egg, fish, nuts, cereals, chocolate, fruits, vegetables	Self-reported, physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence, cumulative incidence	Point prevalence of OFC/DBPCFC-confirmed egg allergy 0.3% (0.2-0.6) and milk allergy 0.4% (0.2-0.7)	Moderate
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Johnke <i>et al.</i> 2006, Denmark	Cohort study	1095	562	6 years old	Any FA, cow's milk, hen's egg, peanut, wheat, codfish, soy, shrimp, hazelnut, Brazil nut, celery	Self-reported, SPT, sIgE, OFC, DBPCFC	Point prevalence, cumulative incidence	Point prevalence of OFC/DBPCFC-confirmed FA at 6 years: 1.2% (0.5-2.9)	Moderate
Falcão <i>et al.</i> 2004, Portugal	Cross-sectional study	1565	659	>39 years old	Any FA, fresh fruits, meat, fish, eggs, octopus and squid, chocolate, milk, spices, legumes	Self-reported	Point prevalence	Point prevalence of self-reported FA: 5.2% (3.7-7.1)	Moderate
Flokstra-de Blok <i>et al.</i> 2011, The Netherlands	Cross-sectional study	No information	2284	11-20 years old	Any FA	Self-reported	Point prevalence	Point prevalence of self-reported FA: 2.1% (1.6-2.8)	Weak
Fox <i>et al.</i> 2009, UK	Case-control study	133 cases, 310 controls	133 cases, 310 controls	< 4 years	Peanut allergy	SPT, sIgE, DBPCFC	Point prevalence	Case-control study: frequency estimates not given	Moderate
Frongia <i>et al.</i> 2005, Italy	Cross-sectional study	5040	4602	1-2 years old	Any FA, peanut, egg, milk, tomato	Self-reported	Lifetime prevalence of FA: 7.8% (7.0-8.6)	Lifetime prevalence of FA: 7.8% (7.0-8.6)	Moderate
Gelincik <i>et al.</i> 2008, Turkey	Cross-sectional study	17064	11816	≥ 18 years old	Any FA, any non-allergenic food hypersensitivity, tomatoes, hen's egg, cacao, orange, eggplant, peanut, strawberry, carrot, banana, hazelnut, pear, spinach, red chili, black pepper, food additives, chocolate, walnut, potato, fish	Self-reported, SPT, sIgE, DBPCFC	Point and life-time prevalence	Point prevalence of DBPCFC-confirmed FA: 0.1% (0.1-0.2)	Moderate
Grundy <i>et al.</i> 2002, UK	Cohort study	2858	1273	3-4 years old	Peanut allergy	Self-report, SPT, OFC	Point prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.6% (0.3-1.2)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Gupta <i>et al.</i> 2007, 2004, 2003, UK	Cross-sectional study	Not indicated	Not indicated	All age groups	Any FA	Physician diagnosis	Cumulative incidence	Please see results in Table 7 (time trends)	Moderate
Høst <i>et al.</i> 2002, Denmark	Cohort study	1758	1749	15 years old	Any FA, cow's milk allergy	SPT, sIgE, OFC, DBPCFC	Point prevalence	Point prevalence of history or OFC/DBP-CFC-confirmed milk allergy 2.2% (1.6-3.0)	Moderate
Hourihane <i>et al.</i> 2007, UK	Cross-sectional study	5072	1125	4-5 years old	Peanut allergy	SPT, sIgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 1.4% (0.8-2.3)	Moderate
Isolauri <i>et al.</i> 2004, Finland	Cross-sectional study	400	400	7, 27, 47, 67 years	Any FA, milk	Self-reported, sIgE	Lifetime prevalence and point prevalence	Point prevalence of sIgE positivity to at least one FA at 67 years: 9% (5-18)	Moderate
Johansson <i>et al.</i> 2005, Sweden and Norway	Cross-sectional study	Not indicated	Sweden 1002; Norway 500	Adults	Any FA, peanut, soybean, egg white, cow's milk, cod fish, wheat flour, penicilloyl G, suxamethonium, latex, hazel nut	sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA for both Norway and Sweden 3.6% (2.8-4.7)	Moderate
Julge <i>et al.</i> 2001, Västar <i>et al.</i> 2000, Estonia	Cohort study	455	298	5 years	Egg white, cow's milk	SPT, sIgE	Point prevalence	Point prevalence of SPT positivity to egg at 5 years 0% and sIgE positivity to egg at 5 years 2.4%	Moderate
Kanny <i>et al.</i> 2001, France	Cross-sectional study	44000	31110	≤ 60 years	Any FA	Self-reported	Point prevalence	Point prevalence of self-reported FA 3.5% (3.3-3.7)	Moderate
Kotz <i>et al.</i> 2011, UK	Cohort study	2958366	2958366	All age groups	Peanut allergy	Physician diagnosis	Lifetime incidence rate	Please see results in Table 7 (time trends)	Moderate
Krause <i>et al.</i> 2002, Greenland	Cross-sectional study	1213	1068	5-18 years old	Any FA, egg, milk, fish, peanut, wheat, soy	sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA; 4.1% (3.0-5.5)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Kristinsdottir <i>et al.</i> 2011, Iceland	Cohort study	No information	1341	1 year old	Any FA, hen's egg, cow's milk, peanut, fish, wheat, soy, shrimp, cranberry, potato, pineapple, almond, nutramigen, green peas	Self-reported, SPT, specific IgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed FA: 1.9% (1.3-2.7)	Moderate
Kucukosmanoglu <i>et al.</i> 2008, Turkey	Cross-sectional study	1415	1015	8-18 months	Egg allergy	SPT	Point prevalence	Point prevalence of SPT positivity to egg 1.9% (1.2-2.9)	Moderate
Kurulaaratchy <i>et al.</i> 2005, Arshad <i>et al.</i> 2001, Tariq <i>et al.</i> 2000, UK	Cohort study	1536	1456	4 years old	Any FA, milk, egg, peanut, cod, wheat, soy	SPT	Point prevalence, cumulative incidence	Point prevalence of SPT positivity to at least one FA: 3.5%	Moderate
Kvenshagen <i>et al.</i> 2009, Norway	Cohort study	Not indicated	609	2 years old	Any FA, egg, milk, peanut, hazelnut	Self-reported, SPT, IgE, OFC, DBPCFC	Point prevalence	Point prevalence of Clinical history or OFC/DBPCFC FA 6.8% (5.0-9.4)	Moderate
Majkowska-Wojciechowska <i>et al.</i> 2009, Poland	Cross-sectional study	3260	2148	7-10 years old	Any FA, milk, chocolate, dairy, strawberries, eggs, tomatoes, cocoa, nuts, fruits, oranges	Self-reported	Life-time prevalence of FA 41.6% (39.5-43.7)	Life-time prevalence of FA 41.6% (39.5-43.7)	Moderate
Marklund <i>et al.</i> 2004, Sweden	Cross-sectional study	2064	1488	13-21 years old	Any food hypersensitivity	Self-reported	Point prevalence	Point prevalence of self-reported FA: 18.7% (16.8-20.8)	Moderate
Matricardi <i>et al.</i> 2007, Germany	Cohort study	7609	1314	2-10 years old	Cow's milk, hen's egg, soy, and wheat	IgE	Point prevalence	Point prevalence of IgE positivity to at least one FA at 10 years: milk 1.0% (0.5-2.3), egg 0.9% (0.4-2.0), soy 6.1% (4.4-8.3), wheat 8.8% (6.8-11.4)	Moderate
Mossakowska <i>et al.</i> 2008, Poland	Cross-sectional study	Not indicated	301	>100 years old	Strawberries, bananas, oranges, eggs, pepper, garlic, chamomile, ice cream	Self-reported	Point prevalence	Point prevalence of FA: 3.3% (1.8-6.0)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Nicolaou <i>et al.</i> 2010, UK	Cohort study	1499	1085	8 years old	Peanut, milk, egg, fish, tree nut	Self-reported, SPT, IgE, OFC, DBPCFC	Point and lifetime prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.7% (0.3-1.4)	Moderate
Niggemann <i>et al.</i> 2011, Germany	Cross-sectional study	26787	17641	0-17 years old	Peanut allergy	IgE	Point prevalence	Point prevalence of IgE positivity to peanut allergen 10.9%	Moderate
Orhan <i>et al.</i> 2009, Turkey	Cross-sectional study	3500	2739	6-9 years old	Any FA, cocoa, hen's egg, beef, cow's milk, fish, tomato, hazelnut, kiwi, black pepper, chickpea, peanut, walnut, corn, banana, strawberry, potato	Self-reported, SPT, OFC, DBPCFC	Life-time and point prevalence	Point prevalence of DBPCFC-confirmed FA 0.7% (0.5-1.1)	Moderate
Östblom <i>et al.</i> 2008a, 2008b, 2008c and Almqvist <i>et al.</i> 2005, Sweden	Cohort study	7221	4089	4-8 years old	Any FA, cow's milk, citrus, peanut, tree nuts/almond, hen's egg, stone fruit, chocolate, fish, pea, soy bean, wheat, banana, cod fish	Self-reported, IgE	Point and period prevalence	Point prevalence of IgE positivity to at least one FA at 8 years: 13.8% (12.5-15.4)	Moderate
Osterballe <i>et al.</i> 2009, Denmark	Cross-sectional study	1094	843	Mean age 22 years	Any FA, additives, codfish, cow's milk, hen's egg, octopus, peanut, shrimp, soy, wheat, beer, cheese, red wine (other secondary food allergies also reported in the paper)	Self-reported, SPT, OFC, DBPCFC	Point prevalence	Point prevalence of OFC/DBPCFC-confirmed FHS: 1.8% (1.1-2.9)	Moderate
Penard-Morand <i>et al.</i> 2005, France	Cohort study	Not indicated	1834	Children and adults	Any FA, additives, codfish, cow's milk, hen's egg, peanut, shrimp, soy, wheat, fruit/vegetables	Self-reported, physician diagnosis, SPT, IgE, OFC, DBPCFC	Point prevalence	Point prevalence of OFC/DBPCFC-confirmed FHS: at 3 years 2.3% (1.3-4.0); adults 3.2% (2.3-4.5)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome(s) studied	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Pereira <i>et al.</i> 2005, UK	Cross-sectional study	3144	1532	11 and 15 year old	Any FA, milk, egg, wheat, fish, peanut, sesame, tree nuts, additives, shellfish	Self-reported, physician diagnosis, SPT, OFC, DBPCFC	Point prevalence	Point prevalence for all children: OFC-confirmed FA 2.3% (1.6-3.2) DBPCFC-confimed 1.8% (1.2-2.6)	Moderate
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	Cohort study	5973	3899	0-4 years old	Any FA, milk, egg, wheat, barley or rye, nut, fish, citrus fruit	Self-reported, physician-diagnosis, SPT, IgE, OFC	Life-time prevalence, cumulative incidence	Lifetime prevalence of self-reported physician-diagnosed FA 30.3% (28.7-31.9) Cumulative incidence of OFC-confirmed FA by 4 years: 3.3% (2.8-3.9)	Moderate
Pyziak and Kamer 2011, Poland	Cross-sectional study	115	83	6-17 years old	Any FA, cow's milk, hen's egg, soy, pork, beef	Self-reported, IgE, SPT, OFC	Point prevalence	Frequency estimates not given in the study	Moderate
Rance <i>et al.</i> 2005, France	Cross-sectional study	3500	2716	Mean age 8.9 years	Any FA, cow's milk, egg, kiwi, peanut, fish, tree nut, shrimp	Self-reported	Point and life-time prevalence	Point prevalence of self-reported FA: 4.7 (3.9-5.5)	Moderate
Roberts <i>et al.</i> 2005 and Lack <i>et al.</i> 2003, UK	Cohort study	13971	12090	0-7 years	Egg, milk, cod fish, soya, sesame, peanut, tree nut, cashew, almond, walnut, hazelnut, brazil nut, pecan nut	Self-reported, SPT, DBPCFC	Point Prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 0.2% (0.1-0.3)	Moderate
Rona <i>et al.</i> 2007, World-wide	Systematic review	934 studies identified	Number of studies included in review not indicated	All age groups	Any FA, cow's milk, hen's egg, peanut, fish, shellfish	Self-reported, physician-diagnosis, SPT, IgE, OFC, DBPCFC	Point, period, life-time prevalence	Range of prevalence of SPT or IgE to at least one FA: 2%-5% SPT only: 7%-17% IgE only: 4%-6%	Moderate
Ronchetti <i>et al.</i> 2008, Italy	Cross-sectional study	Not indicated	380	9 and 13 years old	Any FA, cow's milk, hen's egg, tomato, wheat flour	SPT	Point prevalence	Point prevalence of SPT positivity to at least one FA for all children 4.2% (2.6-6.7)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Sandin <i>et al.</i> 2005, Sweden and Estonia	Case-control study	All 985 Sweden 645 Estonia 340	All 770 Sweden 483 Estonia 287	10-11 years old	Any FA; apple, peach, kiwi, or carrot; nut or peanut; orange, mandarin or tomato; milk, egg, fish or wheat	Self-report, sIgE	Point prevalence	Point prevalence to at least one FA for Estonia and Sweden 13.9% (11.3-16.9)	Moderate
Schäfer <i>et al.</i> 2001, Germany	Nested case-control study	2539	1537	25-74	Any FA	Self-reported, SPT	Point prevalence, lifetime prevalence	Point prevalence to at least one FA in the population of the allergy MONICA study: 16.8%	Moderate
Schnabel <i>et al.</i> 2010, Germany	Cohort study	3097	1082	6 years old	Any FA	Self-reported, sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA at 6 years: 11.7% (10.0-13.8)	Moderate
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004, Reehr <i>et al.</i> 2004, Germany	Cross-sectional study	All: 4093 Age 0-17 years: 739 Age 18-79 years: 3227	All: 40426 Not indicated	0-79 years old	Any FA, vegetables, legumes, soy, spices, fish, cereals, meat and fat, stonefruit, chocolate/sweets, cow's milk, hen's egg, pippfruit, nuts, vegetable oil, carrot, celery, sesame, apple, apple, hazelnut, potato, wheat, peanut, walnut, shrimp	Self-reported, physician diagnosis, SPT, sIgE, OFC, SBPCFC, DBPCFC	Point and life-time prevalence	Point prevalence of OFC/DBPCFC-confirmed FA: All: 2.8% (2.4-3.4) Children: 4.2% (3.0-5.9) Adults: 2.9% (2.3-3.5)	Moderate
Steinke <i>et al.</i> 2007, Europe	Cross-sectional study	Not indicated	40426	< 18 years	Any FA, fish, seafood, wheat, meat, eggs, milk, fruits, legumes, vegetables, nuts	Self-reported	Point prevalence	Point prevalence of self-reported FA: All countries: 5.0% (4.5-5.4)	Moderate
Venter <i>et al.</i> 2010, UK	Cohort study	5283	3382	3-4 years old	Peanut allergy	Physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.3% (0.1-1.0)	Moderate

Table E1 (continued)

Reference, country	Study design	Study population		Age of subjects	Outcome studied and assessment method	Method of outcome assessment ¹	Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		N (children/adults; source of study population)	Number approached						
Venter <i>et al.</i> 2008; Dean <i>et al.</i> 2007; Venter <i>et al.</i> 2006, UK	Cohort study	1063	969	3 years old	Any FA, milk, egg, fish, peanut, sesame, wheat	Self-report, SPT, OFC, DBPCFC	Point and period prevalence, cumulative incidence	Point prevalence of OFC-confirmed FA at 3 years: 0.8% (0.4-1.6)	Moderate
Venter <i>et al.</i> 2006, UK	Cross-sectional study	1440	798	6 years old	Any FA, milk, peanut, egg, additives & colourings, tree nuts, wheat, strawberry, sesame, fish, chocolate, banana	Self-report, SPT, OFC, DBPCFC	Point prevalence	Point prevalence of OFC-confirmed FA 1.3% (0.7-2.3) and DBPCFC-confirmed FA 0.4% (0.1-1.1)	Moderate
von Hertzen <i>et al.</i> 2006, Finland and Russia	Cross-sectional study	Finland: 546 child-mother pairs	Finland: 413 children, 409 mothers	7-16 years children	Fish, egg, wheat, cow's milk, peanut, hazelnut	SPT	Point prevalence	Point prevalence of SPT positively to peanut allergen: children: 8.2%; (5.8-1.5), mothers: 10.1% (7.4-13.6)	Moderate
Zuidmeer <i>et al.</i> 2008, Worldwide	Systematic review	396 studies identified	33 studies included	All age groups	Fruits, vegetables, tree nuts, soy, wheat	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, and life-time prevalence	Point prevalence of DBPCFC-confirmed allergy to vegetables: 1.4%	Moderate

DBPCFC: double-blind, placebo-controlled food challenge; OFC: oral food challenge; sIgE: specific immunoglobulin E test; SPT: skin prick test for sensitization to specific food allergens

Table E2 Quality assessment of studies included in the systematic review: included studies 1 January 2000 - 30 September 2012

Reference, country	Overall risk of bias assessment	Components of risk of bias assessment			
		Study design	Selection bias	Exposure assessment	Outcome assessment
Bant <i>et al.</i> 2008, Poland	Moderate	Strong	Weak	Not applicable	Moderate
Burney <i>et al.</i> 2010; Woods <i>et al.</i> 2001, Europe, USA, Australia, New Zealand	Moderate	Moderate	Moderate	Moderate	Moderate
Caffarelli <i>et al.</i> 2011, Italy	Moderate	Strong	Moderate	Moderate	Weak
Chafen <i>et al.</i> 2010, World-wide	Strong	Moderate	Moderate	Not applicable	Strong
Colver <i>et al.</i> 2005, UK and Ireland	Moderate	Moderate	Weak	Moderate	Moderate
Du Toit <i>et al.</i> 2008, UK and Israel	Moderate	Moderate	Moderate	Moderate	Strong
Dubakiene <i>et al.</i> 2012, Lithuania	Moderate	Strong	Moderate	Moderate	Strong
Egesbø <i>et al.</i> 2003, 2001a, 2001b, Norway	Moderate	Strong	Moderate	Moderate	Strong
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Johnke <i>et al.</i> 2006, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Falcaõ <i>et al.</i> 2004, Portugal	Moderate	Strong	Moderate	Not applicable	Weak
Flokstra-de Blok <i>et al.</i> 2011, The Netherlands	Weak	Strong	Weak	Not applicable	Weak
Fox <i>et al.</i> 2009, UK	Moderate	Strong	Moderate	Moderate	Strong
Frongia <i>et al.</i> 2005, Italy	Moderate	Strong	Moderate	Not applicable	Weak
Gelincik <i>et al.</i> 2008, Turkey	Moderate	Moderate	Weak	Moderate	Strong
Grundy <i>et al.</i> 2002, UK	Moderate	Strong	Moderate	Not applicable	Strong
Gupta <i>et al.</i> 2007, 2004, 2003, UK	Moderate	Strong	Weak	Not applicable	Moderate
Høst <i>et al.</i> 2002, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
HouriHane <i>et al.</i> 2007, UK	Moderate	Moderate	Weak	Moderate	Strong
Isolauri <i>et al.</i> 2004, Finland	Moderate	Strong	Moderate	Moderate	Moderate
Johansson <i>et al.</i> 2005, Sweden and Norway	Moderate	Moderate	Weak	Not applicable	Moderate
Julge <i>et al.</i> 2001, Vassar <i>et al.</i> 2000, Estonia	Moderate	Strong	Moderate	Moderate	Moderate
Kanny <i>et al.</i> 2001, France	Moderate	Strong	Moderate	Moderate	Weak

Table E2 (continued)

Reference, country	Overall risk of bias assessment	Study design	Components of risk of bias assessment		Outcome assessment
			Selection bias	Exposure assessment	
Kotz <i>et al.</i> 2011, UK	Moderate	Moderate	Moderate	Moderate	Moderate
Krause <i>et al.</i> 2002, Greenland	Moderate	Strong	Moderate	Not applicable	Moderate
Kristinsdottir <i>et al.</i> 2011, Iceland	Moderate	Strong	Moderate	Not applicable	Strong
Kucukosmanoglu <i>et al.</i> 2008, Turkey	Moderate	Strong	Moderate	Not applicable	Moderate
Kurulaaratchy <i>et al.</i> 2005, Arshad <i>et al.</i> 2001, Tariq <i>et al.</i> 2000, UK	Moderate	Strong	Moderate	Not applicable	Moderate
Kvenshagen <i>et al.</i> 2009, Norway	Moderate	Strong	Moderate	Moderate	Strong
Majkowska-Wojciechowska <i>et al.</i> 2009, Poland	Moderate	Strong	Moderate	Not applicable	Weak
Marklund <i>et al.</i> 2004, Sweden	Moderate	Strong	Moderate	Not applicable	Weak
Matricardi <i>et al.</i> 2007, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Mossakowska <i>et al.</i> 2008, Poland	Moderate	Strong	Moderate	Not applicable	Weak
Nicolaou <i>et al.</i> 2010, UK	Moderate	Strong	Moderate	Moderate	Strong
Niggemann <i>et al.</i> 2011, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Orhan <i>et al.</i> 2009, Turkey	Moderate	Strong	Moderate	Not applicable	Strong
Östblom <i>et al.</i> 2008a, 2008b, 2008c; Almqvist <i>et al.</i> 2005, Sweden	Moderate	Strong	Moderate	Not applicable	Moderate
Osterballe <i>et al.</i> 2009, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Osterballe <i>et al.</i> 2005, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Penard-Morand <i>et al.</i> 2005, France	Moderate	Moderate	Moderate	Moderate	Moderate
Pereira <i>et al.</i> 2005, UK	Moderate	Strong	Moderate	Not applicable	Strong
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	Moderate	Moderate	Moderate	Moderate	Strong
Pyziak and Kamer 2011, Poland	Moderate	Moderate	Weak	Moderate	Strong
Rance <i>et al.</i> 2005, France	Moderate	Strong	Moderate	Not applicable	Weak

Table E2 (continued)

Reference, country	Overall risk of bias assessment	Components of risk of bias assessment			Outcome assessment
		Study design	Selection bias	Exposure assessment	
Roberts <i>et al.</i> 2005 and Lack <i>et al.</i> 2003, UK	Moderate	Strong	Moderate	Moderate	Strong
Rona <i>et al.</i> 2007, World-wide	Moderate	Strong	Moderate	Not applicable	Strong
Ronchetti <i>et al.</i> 2008, Italy	Moderate	Moderate	Moderate	Not applicable	Moderate
Sandin <i>et al.</i> 2005, Sweden and Estonia	Moderate	Moderate	Moderate	Not applicable	Moderate
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004, Roehr <i>et al.</i> 2004, Germany	Moderate	Moderate	Moderate	Moderate	Strong
Schnabel <i>et al.</i> 2010, Germany	Moderate	Strong	Moderate	Moderate	Moderate
Schäfer <i>et al.</i> 2001, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Steinke <i>et al.</i> 2007, Europe	Moderate	Strong	Moderate	Not applicable	Weak
Venter <i>et al.</i> 2010, UK	Moderate	Strong	Moderate	Moderate	Strong
Venter <i>et al.</i> 2008; Dean <i>et al.</i> 2007; Venter <i>et al.</i> 2006, UK	Moderate	Strong	Moderate	Moderate	Strong
Venter <i>et al.</i> 2006, UK	Moderate	Strong	Moderate	Not applicable	Strong
von Hertzen <i>et al.</i> 2006, Finland and Russia	Moderate	Moderate	Moderate	Moderate	Moderate
Zuidmeer <i>et al.</i> 2008, World-wide	Moderate	Strong	Weak	Not applicable	Strong

The overall risk assessment was based on the component risk assessments (i.e., on the suitability of the study design for the research question, potential for selection bias, methods of exposure assessment, and methods of outcome assessment).

For the study design, all cross-sectional and cohort studies that studied only the prevalence of food allergy received a “strong” grading.

Only case-control and cohort studies (and not cross-sectional studies) received a “strong” grading when the research question was on the risk/prognostic factors for food allergy.

Table E3 Frequency of self-reported food allergy in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence food allergy			Lifetime Prevalence Percentage (95% CI)	Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)			
Burney <i>et al.</i> 2010 and Woods <i>et al.</i> 2001 Europe, USA, Australia	Adults 20-44 years			all countries 19.2% (18.6-19.8)		USA, Australia and New Zealand are included in the overall figure. Our own calculation with the given data is 19.2% (18.6-19.8); authors' calculation 12.2% (12-13).
Caffarelli <i>et al.</i> 2011, Italy	Children 5-14 years		1.6% (0.9-2.9)		10.6% (8.4-13.2)	Data also reported for milk, egg, wheat, peanut, sesame, hazelnut, tomato, chocolate and different fruits in the paper
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Johnke <i>et al.</i> 2006, Denmark	Children 6 years	By age 6 years 11.6% (9.2-14.5)				
Falcaõ <i>et al.</i> 2004, Portugal	Adults >39		5.2% (3.7-7.1)			Data also reported for fruits, meat, fish, egg, octopus and squid, chocolate, milk, spices, and legumes
Flokstra-de Blok <i>et al.</i> 2011, Netherlands	Adolescents 11-20 years		2.1% (1.6-2.8)			These are minimal reported estimates. Extrapolated estimates are reported in the paper.
Frongia <i>et al.</i> 2005, Italy	Children 1-2 years				7.8% (7.0-8.6)	Data also reported for peanut, egg, milk, and tomato in the paper
Gelincik <i>et al.</i> 2008, Turkey	Adults >18				9.5% (8.9-10.0)	Estimates for different age bands reported in the paper
Kanny <i>et al.</i> 2001, France	Population < 61 years		3.5% (3.3-3.7)			
Kristinsdottir <i>et al.</i> 2011, Iceland	Children at 1 year		5.5% (4.4-6.9)			Data also reported for milk, egg, fish, wheat, peanut, and soya in the paper
Kvenshagen <i>et al.</i> 2009, Norway	Children at 2 years		38.7% (34.6-43.0)			
Majkowska-Wojciechowska <i>et al.</i> 2009, Poland	Children 7-10 years					Parental reported adverse reactions to any food: 41.6% (39.5-43.7) Parental reported DD of food allergy 27.4% (25.6-29.4) Insufficient data given in the paper to understand authors' calculations and to enable the calculation of the confidence intervals around the point estimates and

Table E3 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence food allergy			Lifetime Prevalence Percentage (95% CI)	Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)			
Marklund <i>et al.</i> 2004, Sweden	Adolescents 14-21 years		18.7% (16.8-20.8)			
Mossakowska <i>et al.</i> 2008, Poland	Adults >100		3.3% (1.8-6.0)			
Orhan <i>et al.</i> 2009, Turkey	Children 0-6 years			5.7% (4.8-6.6)	Data also reported for egg, milk, fish, tomato, hazelnut, kiwi, black pepper, chickpea, peanut, walnut, corn, banana, strawberry, potato, beef, cocoa	
Östblom <i>et al.</i> 2008a, 2008b, 2008c; Almqvist <i>et al.</i> 2005, Sweden	Children 1-8 years				Parental report of FHS • At 1 year: 9.8 (8.7-10.8) • At 2 years: 9.5% (8.4-10.5) • At 4 years: 10.9% (9.5-12.4) • At 8 years: 13.8% (12.5-15.4)	
Osterballe <i>et al.</i> 2009, Denmark	Young adults Mean 22				Parental report of DD of FHS • At 1 year: 3.1% (2.5-3.7) • At 2 years: 4.4% (3.7-5.1) • At 4 years: 4.9% (3.9-5.9) • At 8 years 7.6% (6.4-8.9)	
Osterballe <i>et al.</i> 2005, Denmark	Children at 3 years and adults				Data also reported for additives, codfish, milk, egg, octopus, peanut, shrimp, soy, wheat Primary FHS was defined as being independent of pollen sensitization, whereas secondary FHS was defined as reactions to pollen related fruits and vegetables in pollen allergic patients.	
Penard-Morand <i>et al.</i> 2005, France	Children 9-11 years			All: 13.0% (11.6-14.7) Adults: 14.1% (12.0-16.5) Children: 11.9% (10.0-14.1)	Siblings (younger and older) and adults of the children from the DARC birth cohort were examined	
Pereira <i>et al.</i> 2005, UK	Children at 11 and 15 years			2.1% (1.8-2.5)	Data also reported for milk, egg, fish, seafood, fruits and vegetables, peanuts, nuts,	
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	0-4 years old			All: 12.0% (10.5-13.7) Age 11 years: 11.6% (9.5-14.1) Age 15 years: 12.4% (10.3-15.0)	Data also reported for milk, egg, fish, wheat, peanut, sesame. Tree nut, Shellfish, Additives	
				30.3% (28.7-31.9)	Prevalence of parental-perceived and parental report of physician-diagnosed FA	

Table E3 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence food allergy				Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	Lifetime Prevalence Percentage (95% CI)		
Rance <i>et al.</i> 2005, France	Children Mean age 8.9 years	4.7 (3.9-5.5)		6.7% (5.8-7.7)	Data also reported for milk, egg, fish, shrimp, peanut and tree nut	
Rona <i>et al.</i> 2007, World-wide	All ages		Range of prevalence of self-reported FHS to any food: 3%-35%		Include also non-European studies. There was significant heterogeneity among the studies. Data is also reported for milk, egg, fish, shellfish and peanut	
Sandin <i>et al.</i> 2005, Sweden and Estonia	Children 10-11 years	All: 22.9% (20.0-26.0) Estonia: 20.2% (16.0-25.2) Sweden: 24.4% (20.8-28.5)			Data also reported for peach, kiwi, or carrot; nut or peanut; orange mandarin or tomato; milk, egg, fish, or wheat	
Schäfer <i>et al.</i> 2001, Germany	Adults 25-74 years				MONICA is the base population for the nested case-control study population. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates. Data also reported for other foods, such as milk, egg, flour, fish, meat, tomatoes, etc.	
Schnabel <i>et al.</i> 2010, Germany	Children 2-6 years		Self-report of doctor diagnoses of FA • At 2 years 6.6% • At 5 years 3.9% • At 6 years 3.9%		Population of the allergy MONICA study: 15.5% Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates.	
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004 and Roehr <i>et al.</i> 2004, Germany					Suspected adverse reactions to any food Population 0-79: 53.9% (52.4-55.5) Adults 18-79: 55.7% (54.0-57.4) Children 0-17 years: 6.1.6% (58.0-65.0) Still suspected after second contact 0-79 years: 35.0% (33.6-36.5) 18-79 years: 34.9% (33.2-36.5) Children 0-17 years: 38.4% (35.0-42.0)	

Table E3 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence food allergy			Lifetime Prevalence Percentage (95% CI)	Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	Lifetime Prevalence Percentage (95% CI)		
Steinke <i>et al.</i> 2007, Europe	Children < 18 years		Overall in all countries: 5.0% (4.5- 5.4)			Our own calculation for all countries is 4.96%, different from authors' calculation of 4.7%.
Venter <i>et al.</i> 2008 and 2006, Dean <i>et al.</i> 2007, UK	Children 1-6 years	By age 1 year Any food: 25.8% (23.1-28.6)	At 1 year: 7.2% (5.7-9.1) At 2 years: 8.4% (6.7-10.4) At 3 years: 8.3% (6.7-10.3)			
Venter <i>et al.</i> 2006, UK	Children at 6 years	28.1% (25.3-31.0)	11.8% (9.6-14.2)		Data is also reported for milk, egg, fish, peanut, tree nut, wheat and sesame	

Table E4 Frequency of sensitization (positive skin prick test [SPT], immunoglobulin E [IgE]) to at least one food allergen in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of SPT and IgE positivity to at least one food allergen		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Bant <i>et al.</i> 2008, Poland	Adults 18-27 years		IgE positivity 11%	Food allergens measured: milk, egg, wheat, soya, fish, and peanuts. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates.
Burney <i>et al.</i> 2010 and Woods <i>et al.</i> 2001 Europe, USA, Australia	Adults 20-39 years			Country-specific estimates include birch positivity which is excluded in the all countries estimate. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates.
				Data incomplete for Switzerland and Iceland
				Food allergens measured: milk, egg white, fish, soya bean, peanut and wheat, sesame, buckwheat, corn and rice, hazelnut, walnut, celery, tomato and carrot, mustard, shrimp, sunflower seed, poppy seed and lentil, banana, kiwi, apple, peach and melon.
				Data also reported for fish, egg, milk, soya, walnut, sesame, wheat, shrimp hazelnut.
				SPT positivity At 6 month: 3.1%
				• At 12 month: 4.3%
				• At 18 month: 3.2%
				• At 6 years: 3.7% (2.2-6.0)
				IgE positivity At 6 month: 19.4%
				• At 12 month: 20.3%
				• At 18 month: 21.5%
				• At 6 years 15.1% (11.7-19.2)
				SPT positivity to at least one food allergen
				• 7 years: 52.0% (41.0-62.0)
				• 27 years: 9.0% (5.0-18.0)
				• 47 years: 2.0% (0.1-7.0)
				• 67 years: 9.0% (5.0-18.0)
				IgE positivity
				• All 3.6% (2.8-4.7)
				• Sweden: 3.9% (2.9-5.3)
				• Norway: 3.0% (1.8-4.9)
Johansson <i>et al.</i> 2005, Sweden	Adults			Food allergens measured: milk, egg white, cod fish, soya bean, peanut, wheat flour. Data also reported for milk, egg, fish, peanut wheat and sesame.
Krause <i>et al.</i> 2002, Greenland	Children 5-18 years		IgE positivity: 4.1% (3.0-5.5)	Food allergens measured: egg, milk, fish, wheat, peanut and soy. Data also reported for different age bands, both sexes, origin and for egg, milk, fish, peanut, wheat, and soy

Table E4 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence of SPT and IgE positivity to at least one food allergen		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Kurukulaaratchy <i>et al.</i> 2005, Arshad <i>et al.</i> 2001, Tariq <i>et al.</i> 2000, UK	Children 2-4 years	SPT positivity at 4 years: 3.5%	The estimates were presented in a figure, so actual numbers were not shown to enable the calculation of confidence limits around the estimates. Data is also reported for the single allergens. Food allergens measured: milk, egg, soya, cod fish, wheat, and peanut	
Östblom <i>et al.</i> 2008a, 2008b, 2008c; Almqvist <i>et al.</i> 2005, Sweden	Children 4-8 years	sIgE positivity At 4 years: 1.3% to 1.6% At 8 years: 13.8% (12.5-15.4)	In their reports the authors present different prevalence estimates for the same study at the age of 4 years because of different denominators used for calculations. Food allergens measured: milk, egg white, codfish, peanut, soybean and wheat.	
Penard-Morand <i>et al.</i> 2005, France	Children 9-11 years	SPT positivity: 1.8% (1.5-2.1)	Food allergens measured: egg, cod fish, peanut Data also reported for egg, cod fish, and peanut	
Pereira <i>et al.</i> 2005, UK	Children at 11 and 15 years	SPT positivity All 5.0% (4.0-6.3) Age 11 years: 5.2% (3.7-7.0) Age 15 years: 4.9% (3.5-6.9)	The estimates here are SPT sensitization without cross-reactivity to pollen Food allergens measured: milk, egg, wheat, fish, peanut and sesame	
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	Children by 4 years	sIgE or SPT positively 5.5% (4.8-6.3)	Food allergens measured not stated in the paper Data also reported for milk, egg and food essentials	
Rona <i>et al.</i> 2007, UK	All ages	Range of prevalence of SPT and IgE positivity SPT or sIgE: 2%-5% SPT only: 7%-17% IgE only: 4%-6%	Results include non-European populations There was significant heterogeneity among the studies. Food allergens measured: depends on the different studies included Data is also reported for milk, egg, fish, shellfish and peanut	
Ronchetti <i>et al.</i> 2008, Italy	Children 9 and 13 years	SPT positivity for all 4.2% (2.6-6.7) SPT positivity At 9 years: 2.2% (0.8-5.5) At 13 years: 6.1% (3.5-10.4)	Food allergens measured: fresh food allergens (whole milk, whisked egg, tomato and wheat flour Data also reported for milk, egg, tomato, wheat	
Sandin <i>et al.</i> 2005, Sweden and Estonia	Children 10-11 years	sIgE positivity: All 13.9% (11.3-16.9) Estonia 8.0% (4.7-13.2) Sweden 16.1% (12.9-19.9)	Food allergens measured: egg white, milk, soya bean, fish, wheat and peanut.	

Table E4 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence of SPT and IgE positivity to at least one food allergen		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Schäfer <i>et al.</i> 2001, Germany	Adults 25-74 years	IgE positivity: from the population of the allergy MONICA study 16.8%		MONICA is the base population for the nested case-control study population. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates. Food allergens measured: milk, egg, peanut, pork, mackerel, celery, hazelnut, wheat, soy, and crab.
Schnabel <i>et al.</i> 2010, Germany	Children 2-6 years	IgE positivity: At 2 years: 9.4% (7.8-11.3) At 6 years: 11.7% (10.0-13.8)		Food allergens measured: egg, milk, peanut, soybean, wheat flour and codfish. Data also reported for milk, egg and peanut, soya, wheat, codfish
Venter <i>et al.</i> 2008 and 2006, UK Dean <i>et al.</i> 2007, UK	Children 1-3 years	SPT positivity by 3 years of age: 5.3% (3.9-7.1)	SPT positivity At 1 year: 2.2% (1.4-3.5) At 2 years: 3.8% (2.6-5.5) At 3 years: 4.5% (3.2-6.4)	The authors reported different prevalence estimates from the same study because of different denominators used for calculations. Dean <i>et al.</i> 2007 calculated the estimates based on children who underwent SPT on all 3 occasions. Food allergens measured: milk, egg, wheat, peanut, sesame and fish Data also reported for milk, egg, wheat, fish, peanut, sesame
Venter <i>et al.</i> 2006, UK	Children at 6 years		SPT positivity 3.6% (2.3-5.2)	Food allergens measured: milk, egg, wheat, codfish, peanut and sesame

Table E5 Frequency of clinician diagnosed food allergy (based on symptoms and sensitization and convincing clinical history or food challenge in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of any food allergy (FA)		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Dubakiene <i>et al.</i> 2012, Lithuania	Children 0-1 years	Symptoms + SPT or sIgE positivity: • At 6 months: 1.3 (0.8-2.0) • At 1 year: 2.8 (2.1-3.7)	Food allergens measured not stated in the paper Data also reported for milk, egg, fish, peanut, potato and wheat	
Kristinsdottir <i>et al.</i> 2011, Iceland	Children at 1 year	Symptoms + SPT positivity: 1.6% (1.0-2.4) Symptoms + sIgE positivity: 3.0% (2.2-4.0) Symptoms + SPT or sIgE: 3.3% (2.5-4.4)	Food allergens measured not stated in the paper Data also reported for milk, egg, fish, wheat, peanut, soy available	
Kvenshagen <i>et al.</i> 2009, Norway	Children at 2 years	Clinical history or OFC/DBPCFC Any food: 6.8% (5.0-9.4) IgE-mediated any food 1.8% (0.9-3.3) Non-IgE-mediated any food 5.3% (3.7-7.6)	Food allergens measured: milk, egg, cod fish, hazelnut, peanut, wheat and soya. Children with a history of an immediate reaction to a food allergen, a positive SPT and an elevated IgE to that food allergen were not challenged	
Orhan <i>et al.</i> 2009, Turkey	Children 6-9 years	Symptoms + SPT positivity 1.8% (1.3-2.3)	Food allergens measured: milk, egg, soy, wheat, peanut, fish, and hazelnut Data also reported for egg, milk, fish, hazelnut, peanut, walnut, beef, cocoa, etc.	
Penard-Morand <i>et al.</i> 2005, France	Children 9-11 years	Symptoms + SPT positivity: 0.1% (0.1-0.3)	Food allergens measured: egg, cod fish, peanut Data also reported for egg, cod fish, and peanut	
Pereira <i>et al.</i> 2005, UK	Children at 11 and 15 years	All: • Clinical history or OFC: 2.3 (1.6-3.2) • Clinical history or DBPCFC: 1.8 (1.2-2.6) At 11 years: • Clinical history or OFC: 2.3% (1.5-3.6) • Clinical history or DBPCFC: 1.4% (0.8-2.5) At 15 years: • Clinical history or OFC: 2.2% (1.4-3.6) • Clinical history or DBPCFC: 2.1% (1.3-3.4)	Unchallenged children with a clear history of adverse reactions in the presence of a positive SPT or sIgE responses or with a physician diagnosis of FA were included as having FA.	
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004 and Roehl <i>et al.</i> 2004, Germany	Children (0-17 years) and adults	Children • Symptoms + SPT positivity: 13.1% (10.9-15.8) • Symptoms + sIgE positivity: 4.6% (3.3-6.4) Total population: • Symptoms + sIgE positivity: 2.2% (1.8-2.7)	Food allergens measured: milk, egg, wheat, soy, carrot and peanut	

Table E5 (continued)

Reference, country	Age(s) of subjects	Frequency of occurrence of any food allergy (FA)			Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)		
Venter <i>et al.</i> 2008 and 2006, Dean <i>et al.</i> 2007, UK	Children 1-6 years	<p>Clinical history or OFC-confirmed any FA by 3 years: 6.0% (4.6-6.7)</p> <p>Clinical history or DBPCFC-confirmed any FA by 3 years: 5.0% (3.8-6.5)</p>	<ul style="list-style-type: none"> At age 1 year: <ul style="list-style-type: none"> Clinical history or OFC: 3.0% (2.1-4.3) Clinical history or DBPCFC: 2.7% (1.8-3.9) At age 2 years: <ul style="list-style-type: none"> Clinical history or OFC: 2.4% (1.6-3.7) Clinical history or DBPCFC: 2.1% (1.3-3.3) At age 3 years: <ul style="list-style-type: none"> Clinical history or OFC: 3.0% (2.1-4.4) Clinical history or DBPCFC: 2.9% (2.0-4.2) 	<p>Cumulative incidence also given for age 1 and 2 years in the paper.</p> <p>Not clear what the authors used as a convincing clinical history.</p>	
Venter <i>et al.</i> 2006, UK	Children at 6 years		<p>Clinical history or OFC 2.1% (1.3-3.4)</p> <p>Clinical history or DBPCFC 1.1% (0.6-2.1)</p>		Unchallenged children with prior hospital diagnosis of food allergy or a history of inadvertent reaction with positive skin test were included as having FA.

Table E6 Frequency of objectively verified food allergy in Europe by food challenge: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Cumulative incidence Percentage (95% CI)	Frequency of occurrence of any food allergy (FA) Point prevalence Percentage (95% CI)	Comment
Dubakiene <i>et al.</i> 2012, Lithuania	Children at 6 month		DBPFCF-confirmed FA: 0.3% (0.1-0.7)	Data also reported for milk, egg and wheat
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Children 0-6 years Johnke <i>et al.</i> 2006, Denmark		OFC/DBPFCF-confirmed any FA by 6 years: 3.6% (2.3-5.4)	OFC/ DBPFCF-confirmed FA: • Age 6 months: 0.4% (0.1-1.5) • Age 1 year: 1.3% (0.6-2.8) • Age 3 years: 3.0% (1.7-5.0); • Age 6 years: 1.2% (0.5-2.9)	Data also reported for peanut, egg, and milk confirmed challenges. At 3 years authors reported an estimate of 3.4% while our own calculation shows 3.0%.
Gelincik <i>et al.</i> 2008, Turkey	Adults >18		DBPFCF-confirmed FA/NAFA: 0.11% (0.1-0.2) DBPFCF-confirmed FA: 0.1% (0.1-0.2) DBPFCF-confirmed NAFA: 0.1% (0.1-0.2)	Data also reported for tomato, egg, orange, eggplant, peanut, strawberry, carrot, banana, hazelnut, pear, spinach, red chili, black pepper, food additives, chocolate, walnut, potato, fish
Kristinsdottir <i>et al.</i> 2011, Iceland	Children at 1 year		DBPFCF-confirmed FA: 1.9% (1.3-2.7)	Data also reported for milk, egg, fish, wheat, peanut, soya
Orhan <i>et al.</i> 2009, Turkey	Children 6-9 years		DBPFCF-confirmed FA 0.7% (0.5-1.1)	Data also reported for egg, milk, fish, hazelnut, peanut, walnut, beef, cocoa. Authors used number of positive challenges (2/2) instead of number of children (20) as the numerator. Our estimates are based on number of positive children.
Osterballe <i>et al.</i> 2009, Denmark	Young adults mean 22		OFC/DBPFCF-confirmed FHS: 1.8% (1.1-2.9)	Data also reported for fish, milk, peanut, shrimp, soy
Osterballe <i>et al.</i> 2005, Denmark	Children and adults		OFC/DBPFCF-confirmed primary food hypersensitivity All: 2.4% (1.8-3.2) Children: 1.6% (0.9-2.6) • Age 3 years: 2.3% (1.3-4.0) • Age <3 years: 0.0% (0.0-3.3) • Age >3 years: 1.0% (0.3-2.9) Adults: 3.2% (2.3-4.5)	Children from the DARC birth cohort and their siblings (younger and older) and adults were examined

Table E6 (continued)

Reference, country	Age(s) of subjects	Cumulative incidence Percentage (95% CI)	Frequency of occurrence of any food allergy (FA) Point prevalence Percentage (95% CI)	Comment
Pereira <i>et al.</i> 2005, UK	Children at 11 and 15 years	All: <ul style="list-style-type: none"> OFC-confirmed FA 1.0% (0.6- 1.7) DBPFCF-confirmed 0.3% (0.1-0.8) At 11 years: <ul style="list-style-type: none"> OFC-confirmed FA: 1.0% (0.5-2.0) DBPFCF-confirmed FA: 0.1% (0-0.7) At 15 years <ul style="list-style-type: none"> OFC-confirmed FA: 1.1% (0.5-2.1) DBPFCF-confirmed FA: 0.5% (0.2-1.4) 	Results include also non-European studies Estimates presented if at least 4 studies of the food item were available There was significant heterogeneity among the studies. Data is reported available for milk, egg, fish, shellfish and peanut	
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	Children by 4 years	OFC-confirmed any FA by 4 years: 3.3% (2.8-3.9)	Range of prevalence of allergy to any food based on food challenge: 1%- 10.8%	OFC/DBPFCF-confirmed FA: Total population (0-79 years): <ul style="list-style-type: none"> 2.8% (2.4-3.4) 2.6% (2.1-3.2) (weighted for Germany) Adults 18-79 years: <ul style="list-style-type: none"> All 2.9 (2.3-3.5) IgE mediated 1.9% (1.4-2.4) Non IgE mediated 1.0% (0.7-1.4) Children: <ul style="list-style-type: none"> 0-17 years: 4.2% (3.0-5.9) 0-14 years: 3.8% (2.6-5.7) 15-17 years: 5.7% (2.9-10.8) IgE-mediated (0-17 years): 3.5% (2.4-5.1) Non-IgE-mediated (0-17 years): 0.7% (0.3-1.6)
Rona <i>et al.</i> 2007, UK	All ages			

Table E6 (continued)

Reference, country	Age(s) of subjects	Cumulative incidence Percentage (95% CI)	Frequency of occurrence of any food allergy (FA) Point prevalence Percentage (95% CI)	Comment
Venter <i>et al.</i> 2008 and 2006, Children Dean <i>et al.</i> 2007, UK	1-6 years	OFC-confirmed any FA by 1 year: 3.6% (2.5-5.0) DBPFCF-confirmed any FA by 1 year: 1.5% (0.9-2.5)	At age 1 year: • OFC-confirmed FA: 2.8% (1.9-4.1) • DBPFCF-confirmed FA: 1.3% (0.8-2.3) At age 2 years: • OFC-confirmed FA: 1.0% (0.6-2.0) • DBPFCF-confirmed FA : 0.1% (0.0-0.7) At age 3 years: • OFC-confirmed FA: 0.8% (0.4-1.6) • DBPFCF-confirmed FA: 0.0%	Cumulative incidence also given for age 1 and 2 years in the paper.
Venter <i>et al.</i> 2006, UK	Children at 6 years		OFC and DBPFCF-confirmed food allergy OFC-confirmed FA: 1.3% (0.7-2.3) DBPFCF-confirmed FA : 0.4% (0.1-1.1)	

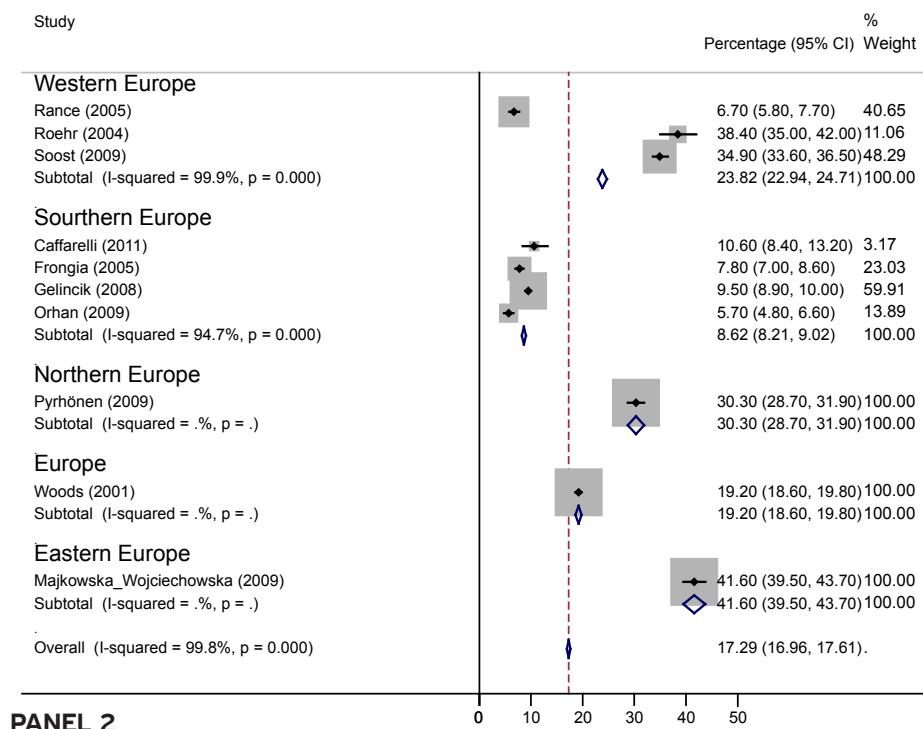
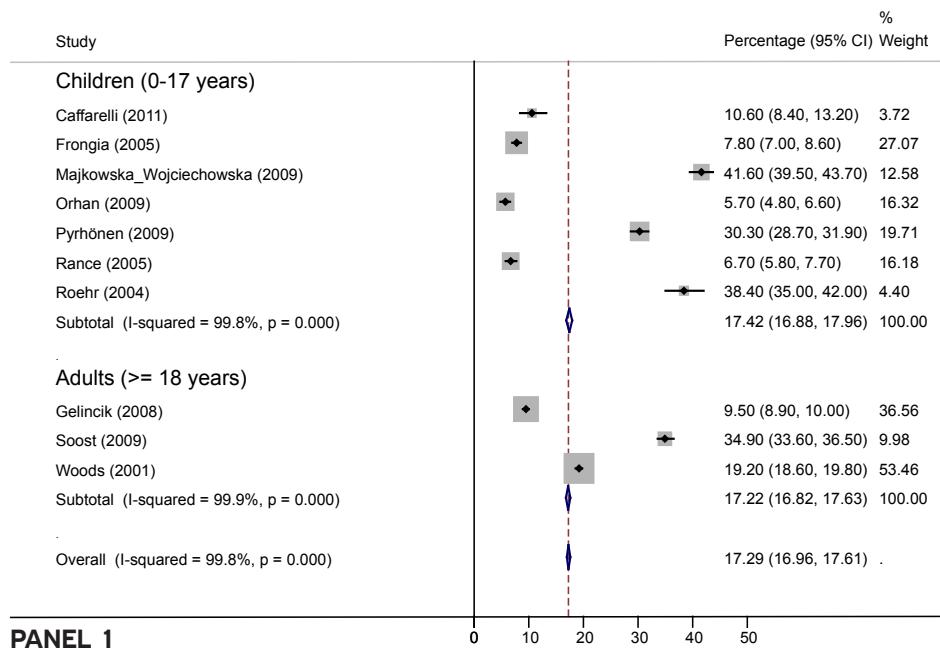


Figure E1 Pooled life-time prevalence of self-reported food allergy stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

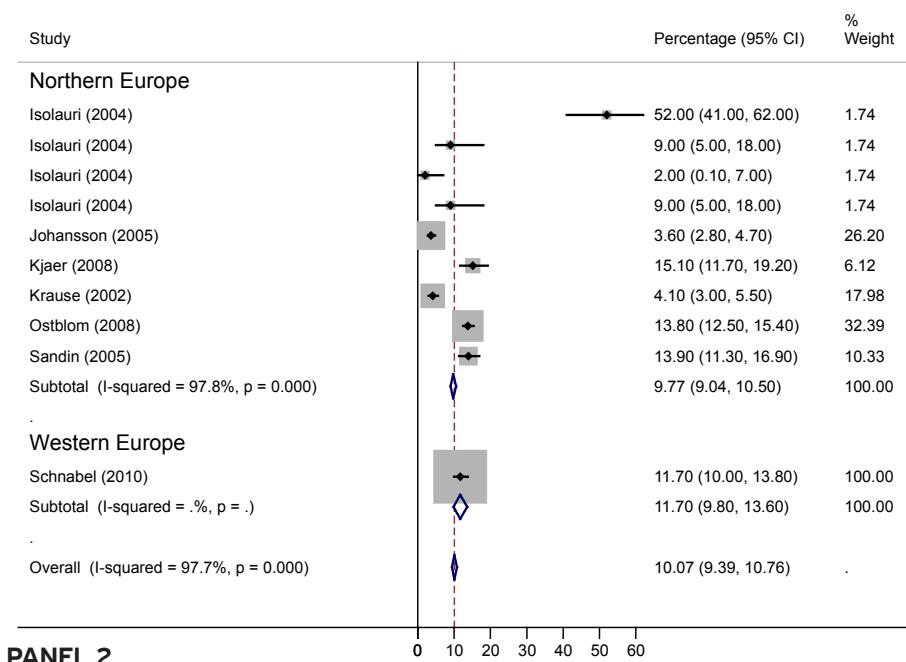
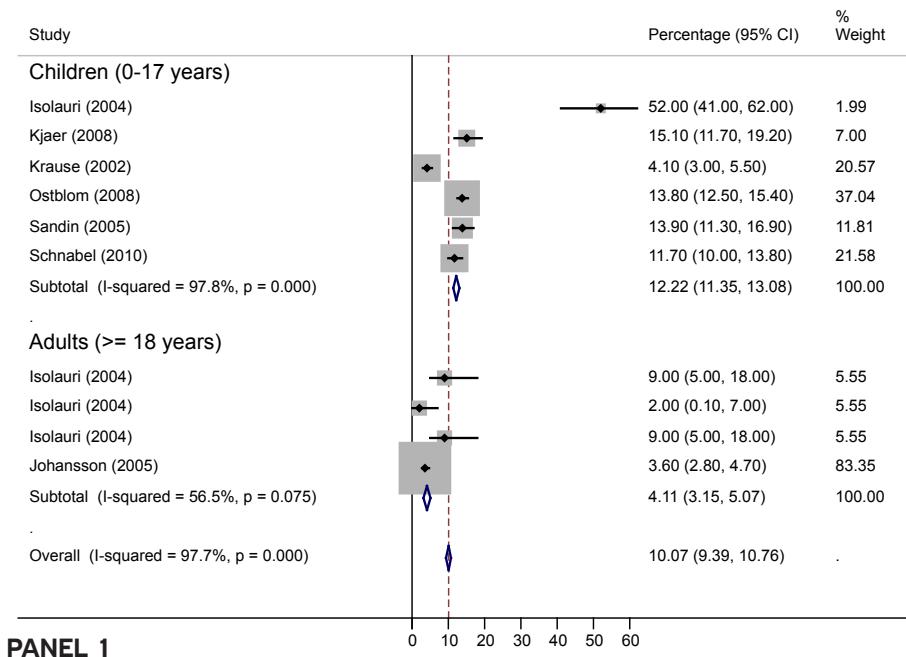


Figure E2 Pooled point prevalence of specific immunoglobulin E (IgE) positivity to at least one food allergen stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

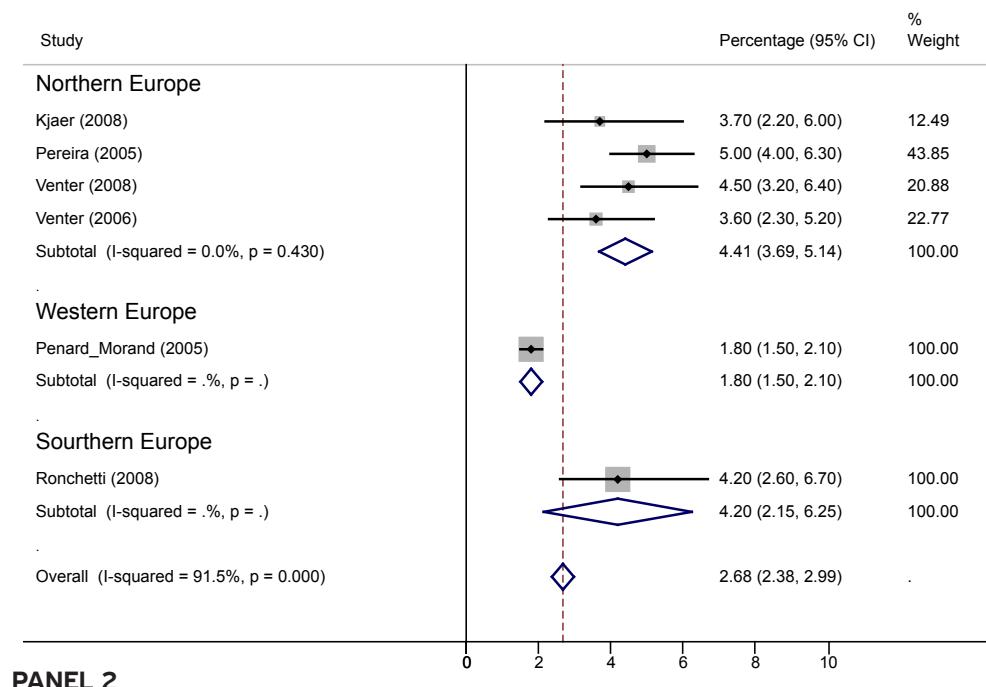
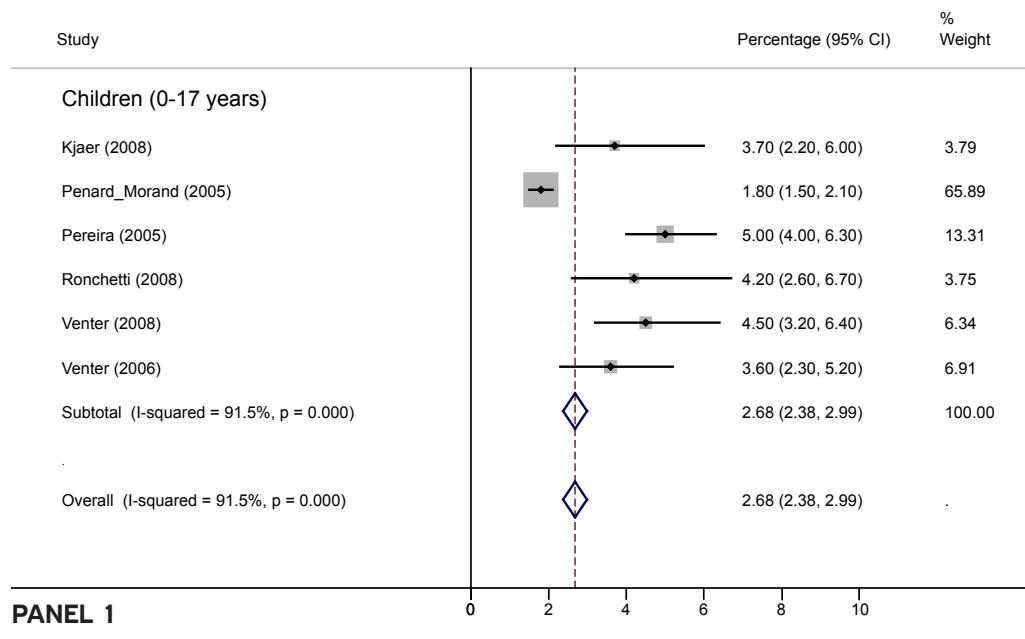


Figure E3 Pooled point prevalence of skin prick test (SPT) positivity to at least one food allergen stratified by age (only studies among children were available) (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

1.2

PREVALENCE OF COMMON FOOD ALLERGIES IN EUROPE SYSTEMATIC REVIEW AND META-ANALYSIS

☞ Supplementary materials ☞

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Table E1 Summary of evidence on the frequency of allergy to cow's milk, hen's egg, wheat, and soy in Europe: studies published 1 January 2000 - 30 September 2012

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Burney <i>et al.</i> 2010; Woods <i>et al.</i> 2001, Europe, United States of America, Australia, New Zealand	slgE point prevalence for all countries 0.7%	slgE point prevalence for all countries 0.2%	slgE point prevalence for all countries 3.4%	slgE point prevalence for all countries 1.4%	Estimate of sensitization is a weighted average over all countries in the study excluding birth positivity. No weighting factor or baseline data given, so we were unable to recalculate the estimate
Caffarelli <i>et al.</i> 2011, Italy	SR lifetime prevalence 3.5% (2.3-5.3)	SR lifetime prevalence: 2.4% (1.5-3.9)	SR lifetime prevalence: 1.0% (0.4-2.1)		The same frequency estimates as given in Rona <i>et al.</i> 2007
Chafen <i>et al.</i> 2010, World-wide					
Du Toit <i>et al.</i> 2008, UK and Israel	SR point prevalence 2.2% (1.8-2.7) in UK	SR point prevalence 1.5% (1.1-1.9) in UK	Point prevalence at 6 mo: • History + sensitization 1.0% (0.6-1.6); DBPCFC 0.1% (0.0-0.5); Point prevalence at 12 mo: History + sensitization 1.7% (1.1-2.4)	Point prevalence at 6 mo: • History + sensitization 0.8% (0.4-1.3); DBPCFC 0.1% (0.0-0.04); Point prevalence at 12 mo: History + sensitization 1.7% (1.1-2.5)	Point prevalence at 6 mo: • History + sensitization 0.1% (0.0-0.5); DBPCFC 0.1% (0.0-0.04); Point prevalence at 12 mo: History + sensitization 0.5% (0.3-1.0)
Dubakiene <i>et al.</i> 2012, Lithuania			Point prevalence SR 3.6% (3.0-4.4); • By history and slgE: 0.1% (0.0-0.3)	Point prevalence • SR 2.4% (1.9-3.0); • By history and slgE: 0.5% (0.3-0.8)	Study involved UK and Israel.
Eggesbø <i>et al.</i> 2003, 2001a and 2001b, Norway			• History or OFC/DBPCFC 0.59% (0.3-0.8); History or DBPCFC 0.4% (0.2-0.7); OFC/DBPCFC 0.4% (0.2-0.7); DBPCFC 0.3% (0.2-0.6); DBPCFC 0.2% (0.1-0.4)	• History or OFC/DBPCFC 0.8% (0.5-1.2); History or DBPCFC 0.7% (0.4-1.0); OFC/DBPCFC 0.3% (0.2-0.6); DBPCFC 0.2% (0.1-0.4)	

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Johnke <i>et al.</i> 2006, Denmark	<p>Point prevalence:</p> <ul style="list-style-type: none"> • At 3 mo: sIgE 0.7% (0.2-2.0); SPT 0.4% (0.1-1.4) • At 6 mo: sIgE 1.6% (0.7-3.4); SPT , 0.8% (0.3-2.1) • At 12 mo: sIgE 1.3% (0.6-3.0); SPT 1.3% (0.6-2.8) • At 18 mo: sIgE, 0.9% (0.3-2.6); SPT 0.7% (0.2-2.0) <p>• At 6 years by OFC/DBPCFC: 0.0% (0.0-0.9)</p> <p>• Cumulative incidence by 18 mo: sIgE 3.4% (2.1-5.4); SPT 2.0% (1.1-3.5)</p>	<p>Point prevalence:</p> <ul style="list-style-type: none"> • At 3 mo: sIgE 1.1% (0.5-2.6); SPT 0.4% (0.1-1.4) • At 6 mo: sIgE 3.4% (2.0-5.7); SPT , 1.9% (1.0-3.5) • At 12 mo: sIgE 3.6% (2.2-5.9); SPT 3.6% (2.3-5.8) • At 18 mo: sIgE 6.0% (3.9-9.1); SPT 2.6% (1.4-4.5) <p>• At 6 years by OFC/DBPCFC: 0.7% (0.3-2.2)</p> <p>• Cumulative incidence by 18 mo: sIgE 6.6% (4.7-9.1); SPT 4.5% (3.1-6.6)</p>			
Falcaõ <i>et al.</i> 2004, Portugal	SR point prevalence 0.3% (0.1-1.1)	SR point prevalence 0.6% (0.2-1.6)	SR lifetime prevalence 2.0%		Estimates for SR lifetime prevalence for other foods given in a figure in the paper.
Frongia <i>et al.</i> 2005, Italy	SR lifetime prevalence 5.4% (4.8-6.1)	Estimates not given in the paper			
Gelincik <i>et al.</i> 2008, Turkey					
Grundy <i>et al.</i> 2002, UK	SPT point prevalence 0.7% (0.4-1.4)	SPT point prevalence 1.4% (0.9-2.2)			
Høst <i>et al.</i> 2002, Denmark	Clinician diagnosed point prevalence 2.2% (1.6-3.0)				

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
<i>Iisolauri et al. 2004, Finland</i>	<p>SR lifetime prevalence:</p> <ul style="list-style-type: none"> • 7-year olds 14% (7.9-22.4) • 27-year olds 10% (4.9-17.6) • 47-year olds 14% (8.0-22.6) • 67 year olds 13% (7.1-21.2) <p>slgE point prevalence</p> <ul style="list-style-type: none"> • 7-year olds 9% (4.2-16.4) • 27-year olds 4.4% (1.2-10.8) • 47-year olds 1.0% (0.03-5.5) • 67-year olds 7.1% (2.9-14.0) 				No absolute data where presented to recalculate the estimates
<i>Johansson et al. 2005, Sweden and Norway</i>	<p>slgE point prevalence:</p> <ul style="list-style-type: none"> • Sweden 0.7% (0.3-1.4) • Norway 0% • Sweden + Norway 0.5% (0.2-1.0) 	<p>slgE point prevalence:</p> <ul style="list-style-type: none"> • Sweden 0.5% (0.2-1.2) • Norway 0.6% (0.2-1.8) • Sweden + Norway 0.5% (0.3-1.1) 	<p>slgE point prevalence:</p> <ul style="list-style-type: none"> • Sweden 2.0% (1.3-3.1) • Norway 0.4% (0.1-1.5) • Sweden + Norway 1.5% (1.0-2.2) 	<p>slgE point prevalence:</p> <ul style="list-style-type: none"> • Sweden 2.0% (1.3-3.1) • Norway 0% • Sweden + Norway 1.3% (0.9-2.1) 	slgE estimates are available but these are selective because they included only children who took part in all 3 study assessments.
<i>Julge et al. 2001, Väsar et al. 2000, Estonia</i>	<p>SPT point prevalence:</p> <ul style="list-style-type: none"> • At 6 mo 1.7% (0.6-5.0) • At 12 mo 0.9% (0.2-3.3) • At 24 mo 0.0% (0.0-0.0) 	<p>SPT point prevalence:</p> <ul style="list-style-type: none"> • At 6 mo 5.2% (2.8-9.6) • At 12 mo 4.1% (2.2-7.6) • At 24 mo 1.8% 80.7-4.5) 			
<i>Krause et al. 2002, Greenland</i>	slgE point prevalence 0.5% (0.2-1.1)	slgE point prevalence 0.4% (0.2-1.0)	slgE point prevalence 0.4% (0.3-1.4)	slgE point prevalence 0.7% (0.3-1.4)	slgE point prevalence 1.2% (0.7-2.0)
<i>Kristinsdottir et al. 2011, Iceland</i>	<p>Point prevalence:</p> <ul style="list-style-type: none"> • SR 4.2% (3.2-5.4) • History + SPT 0.7% (0.4-1.4) • History + slgE 1.7% (1.2-2.6) 	<p>Point prevalence:</p> <ul style="list-style-type: none"> • SR 0.5% (0.3-1.1) • History + SPT 1.3% (0.8-2.0) • History + slgE 2.2% (1.5-3.1) • History + SPT or slgE 2.4% (1.7-3.3) • DBPCFC 1.4% (0.9-2.2) 	<p>Point prevalence:</p> <ul style="list-style-type: none"> • SR 0.5% (0.3-1.1) • History + SPT 0% • History + slgE 0.6% (0.3-1.2) • History + SPT or slgE 0.6% (0.3-1.2) • DBPCFC 0.1% (0.0-0.5) 	<p>Point prevalence</p> <ul style="list-style-type: none"> • SR 0.1% (0.0-0.5) • History + SPT 0% • History + slgE 0.3% (0.1-0.8) • History + SPT or slgE 0.6% (0.3-1.2) • DBPCFC 0.1% (0.0-0.4) 	
<i>Kucosmanoglu et al. 2008, Turkey</i>	SPT point prevalence 1.9% (1.2-2.9)				

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Kurulaaratchy et al., 2005, Arshad et al., 2001, Tariq et al., 2000, UK		• SPT point prevalence at 4 yrs 0.8% (0.4-1.6) • SPT cumulative incidence by 2 yrs 1.9% (1.3-2.7)			Estimates for other foods given in a figure in the paper.
Kvenshagen et al., 2009, Norway	Point prevalence by Clinician history or OFC 5.5% (3.8-7.9)	Clinician history or OFC: point prevalence 1.0% (0.4-2.3)	Estimates not given in the paper.	Estimates not given in the paper.	Authors' report of results difficult to follow, hence we were unable to recalculate the estimates based on numbers given in the paper.
Majkowska-Wojciechowska et al., 2009, Poland	SR lifetime prevalence 15.0% (13.6-16.6)	SR lifetime prevalence 2.9% (2.3-3.7)			These are indirect-recalculated estimates as the authors provided only the percentage estimates.
Marklund et al., 2004, Sweden	SR point prevalence 1.3% (0.8-2.0)	SR point prevalence 1.0% (0.6-1.6)		SR point prevalence 1.3% (0.8-2.0)	
Matricardi et al., 2007, Germany	slgE point prevalence at age 10 1.0% (0.5-2.3)	slgE point prevalence at age 10: 0.9% (0.4-2.0)	slgE point prevalence 8.8% (6.8-11.4)	slgE point prevalence 6.1% (4.4-8.3)	
Mossakowska et al., 2008, Poland	SR lifetime prevalence 1.5% (0.9-2.4)	SR point prevalence 0.3% (0.1-1.9)			
Nicolaou et al., 2010, UK	SR lifetime prevalence 2.3% (1.6-3.4)				
Orhan et al., 2009, Turkey	SR lifetime prevalence 0.9% (0.6-1.4) Point prevalence: • History and SPT 0.4% (0.2-0.7) • DBPCFC 0.1% (0.0-0.3)	SR lifetime prevalence 1.9% (1.5-2.5) Point prevalence: • History and SPT 0.9% (0.6-1.3) • DBPCFC 0.1% (0.0-0.3)			Estimates at 4 years: • SR point prevalence 0.5% (0.3-0.8)
Östblom et al., 2008a, 2008b, 2008c and Almqvist et al., 2005, Sweden	Estimates at 4 years: • SR point prevalence 3.5% (3.0-4.1) • slgE point prevalence 8.4% (7.4-9.6)	Estimates at 4 years: • SR point prevalence 2.5% (2.1-3.1) • slgE point prevalence 4.8% (4.0-5.7)	Estimates at 4 years: • SR point prevalence 0.5% (0.3-0.8) • slgE point prevalence 3.8% (3.1-4.6)	Estimates at 4 years: • SR point prevalence 0.8% (0.6-1.2) • slgE point prevalence 3.0% (2.4-3.8)	Estimates also available at 8 years but these were only presented in figures.

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Osterballe <i>et al.</i> , 2009, Denmark	• SR point prevalence 3.3% (2.3-4.8) • DBPCFC point prevalence 0.1% (0.02-0.7)	• SR point prevalence 0.9% (0.5-1.9) • DBPCFC point prevalence 0%	SR point prevalence 0.9% (0.4-1.7)	SR point prevalence 0.8% (0.4-1.7)	• SR point prevalence 0.6% (0.3-1.4) • DBPCFC point prevalence 0.1% (0.02-0.7)
Osterballe <i>et al.</i> , 2005, Denmark	• History or SPT point prevalence: at < 3 yrs 0.9% (0.2-4.9); at 3 yrs 1.6% (0.8-3.2); at > 3 yrs 1.0% (0.3-2.9); All children 1.3% (0.8-2.3); Adults 0.9% (0.4-1.7) • DBPCFC point prevalence: at < 3 yrs 0%; at 3 yrs 0.6% (0.2-1.8); at > 3 yrs 0.3% (0.1-1.9); All children 0.4% (0.2-1.1); Adults 0.3% (0.1-0.9)	• History or SPT point prevalence: at < 3 yrs 1.8% (0.5-6.3); at 3 yrs , 2.9% (1.7-4.8); at > 3 yrs 0%; All children 1.8% (1.1-2.9); Adults 0.2% (0.1-0.8)	• History or SPT point prevalence: at < 3 yrs 0%; at 3 yrs 0%; All children 0%; Adults 0.1% (0.0-0.6)	• History or SPT point prevalence: at < 3 yrs 0%; at 3 yrs 0%; All children 0%; Adults 0.1% (0.0-0.6)	• History or SPT point prevalence: at < 3 yrs 0.4% (0.1-1.5); at > 3 yrs 0.3% (0.1-1.9); All children 0.3% (0.1-1.0); Adults 0.3%
Penard-Morand <i>et al.</i> 2005, France	SR point prevalence 0.3% (0.2-0.4)	SR point prevalence 0.2% (0.1-0.4) SPT point prevalence 0.3% (0.2-0.5)	SR point prevalence: 0.2% (0.1-0.4) SPT point prevalence 0.3% (0.2-0.5)	SR point prevalence: 0.2% (0.1-0.4) SPT point prevalence 0.3% (0.2-0.5)	SR point prevalence: 0.2% (0.1-0.4) SPT point prevalence 0.3% (0.2-0.5)
Pereira <i>et al.</i> , 2005, UK	SR point prevalence: • 11-yr-olds 2.8% (1.9-4.3) • 15-yr-olds 3.4% (2.4-5.0) • Both 3.1% (2.4-4.1)	SPT point prevalence: • 11-yr-olds 0.3% (0.1-1.0) • 15-yr-olds 0.3% (0.1-1.1) • Both 2.3% (1.6-3.2)	SR point prevalence: • 11-yr-olds 1.5% (0.9-2.7) • 15-yr-olds 3.0% (2.0-4.5) • Both 2.3% (1.6-3.2)	SR point prevalence: • 11-yr-olds 0.3% (0.1-1.0) • 15-yr-olds 0.2% (0.0-0.9) • Both 0.2% (0.1-0.7)	SR point prevalence: • 11-yr-olds 1.3% (0.7-2.4) • 15-yr-olds 1.2% (0.6-2.2) • Both 1.2% (0.8-1.9)

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	<p>Lifetime prevalence:</p> <ul style="list-style-type: none"> • SR parent-perceived 6.4% (5.7-7.3) • SR physician diagnosed 6.4% (5.7-7.3) • SR parent-perceived or physician diagnosed 12.8% (11.8-14.0) <p>Cumulative up to age 4</p> <ul style="list-style-type: none"> • By SPT or sIgE: 3.1% (2.6-3.6) • By OFC: 2.7% (2.2-3.3) 	<p>Lifetime prevalence:</p> <ul style="list-style-type: none"> • SR parent-perceived 3.4% (2.9-4.1) • SR physician diagnosed 2.8% (2.3-3.5) • SR parent-perceived or physician diagnosed 6.3% (5.5-7.1) <p>Cumulative incidence:</p> <ul style="list-style-type: none"> • sIgE or SPT or OFC 3.1% (2.6-3.7) • sIgE or SPT 3.1% (2.6-3.7) • OFC 0.1% (0.01-0.2) 	<p>Lifetime prevalence:</p> <ul style="list-style-type: none"> • SR parent-perceived 1.5% (1.2-2.0) • SR physician diagnosed 2.6% (2.1-3.2) • SR parent-perceived or physician diagnosed 4.1% (3.5-4.9) 	<p>Lifetime prevalence estimates also given for age groups 2-5, 6-10, and 11-14 yrs, but only the point prevalence were given, no CI and the number of endpoints</p>	
Pyziak and Kamer 2011, Poland		<p>Frequency estimates not given in the study</p>		<p>Frequency estimates not given in the study</p>	
Rance <i>et al.</i> 2005, France	SR lifetime prevalence for all children 1.1% (0.7-1.5)	SR lifetime prevalence for all children 0.8% (0.6-1.3)			
Roberts <i>et al.</i> 2005 and Lack <i>et al.</i> 2003, UK	SPT point prevalence 0.2% (0.1-0.5)	SPT point prevalence 0.4% (0.3-0.6)	SPT point prevalence 0.4% (0.3-0.6)	SPT point prevalence 0.2% (0.1-0.6)	
Rona <i>et al.</i> 2007, Worldwide	<ul style="list-style-type: none"> • Pooled estimate for SR point prevalence: 3.5% (2.9-4.1) • Ranges of estimates: SR 1.2% to 17%; sIgE 2% to 9%; SPT 0.2% to 2.5%; History + SPT or IgE 0% to 0.2%; OFC or DBPCFC 0% to 3% 	<ul style="list-style-type: none"> • Pooled estimate for SR point prevalence: 1.3% (1.0-1.6) • Range of estimates: SR 0.2% to 7%; sIgE < 1% to 9%; SPT 0.5% to 5%; History + SPT or IgE 0.5% to 2.5%; OFC or DBPCFC 0% to 1.7% 			

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Ronchetti <i>et al.</i> 2008, Italy	<p>APT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 11.4% (7.6-16.8) • 13-yr-olds 4.1% (2.1-7.9) • All children 7.6% (5.4-10.7) <p>SPT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 0.5% (0.1-3.0) • 13-yr-olds 2.0% (0.8-5.1) • All children 1.3% (0.6-3.0) 	<p>APT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 8.2% (5.0-13.0) • 13-yr-olds 10.2% (6.7-15.2) • All children 9.2% (6.7-12.5) <p>SPT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 0% • 13-yr-olds 1.0% (0.3-3.6) • All children 0.5% (0.1-1.9) 	<p>APT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 6.0% (3.4-10.4) • 13-yr-olds 5.6% (3.3-10.8) • All children 5.8% (3.9-8.6) <p>SPT point prevalence:</p> <ul style="list-style-type: none"> • 9-yr-olds 0.5% (0.1-3.0) • 13-yr-olds 1.5% (0.5-4.4) • All children 1.1% (0.4-2.7) 		Specific foods studied in the paper but estimates for each food not given by the authors rather several foods were studied together
Sandin <i>et al.</i> 2005, Sweden and Estonia	Estimates for each specific not given in the paper	Estimates for each specific not given in the paper	Estimates for each specific not given in the paper	Estimates for each specific not given in the paper	
Schnabel <i>et al.</i> 2010, Germany	<p>SR point prevalence at 6 yrs:</p> <ul style="list-style-type: none"> • Doctor diagnosis 4.7% (3.6-6.1) • New onset 3.1% (2.3-4.4) <p>slgE point prevalence:</p> <ul style="list-style-type: none"> • At 2 yrs 5.0% (3.8-6.5) • At 6 yrs 4.3% (3.3-5.7) 	<p>SR point prevalence at 6 yrs:</p> <ul style="list-style-type: none"> • Doctor diagnosis 4.7% (3.6-6.1) • New onset 3.1% (2.3-4.4) <p>slgE point prevalence:</p> <ul style="list-style-type: none"> • At 2 yrs 5.7% (4.5-7.3) • At 6 yrs 2.7% (1.9-4.0) 	<p>slgE point prevalence at 6 yrs 4.6% (3.5-6.0)</p>	<p>slgE point prevalence at 6 yrs 3.8% (2.8-5.1)</p>	Estimates are weighted for the general population. Authors did not provide numbers used for weighting, hence we were unable to recalculate the estimates.
Schäfer <i>et al.</i> 2001, Germany	SR lifetime prevalence 1.8% SPT point prevalence 2.3%	SR lifetime prevalence 0.4% SPT point prevalence 1.9%	SPT point prevalence 2.8%	SR lifetime prevalence 0.3% SPT point prevalence 1.7%	SR lifetime prevalence 0.3% (0.1-1.0) History and SPT point prevalence
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004, Roehr <i>et al.</i> 2004, Germany	<p>SR lifetime prevalence 1.5% (0.8-2.6)</p> <p>History and SPT point prevalence</p> <ul style="list-style-type: none"> • 0-17 yrs 0.5% (0.2-1.4) • Children and adults 0.8% (0.3-1.6) • Children and adults 0.6% (0.3-1.4) 	<p>SR lifetime prevalence 1.6% (0.9-2.8)</p> <p>History and SPT point prevalence</p> <ul style="list-style-type: none"> • 0-17 yrs 1.1% (0.5-2.1) • Children and adults 4.7% (3.5-6.4) <p>DBPCFC point prevalence:</p> <ul style="list-style-type: none"> • 0-14 yrs 0.5% (0.2-1.5) • 15-17 yrs 0% • All children 0.4% (0.1-1.2) • All children 0.1% (0.0-0.8) 	<p>History and SPT point prevalence</p> <ul style="list-style-type: none"> • 0-17 yrs 1.4% (0.7-2.5) • Children and adults 3.4% (2.3-4.8) <p>DBPCFC point prevalence:</p> <ul style="list-style-type: none"> • 0-14 yrs 0.7% (0.3-1.7) • 15-17 yrs 0% • All children 0.5% (0.2-1.4) • All children 0.5% (0.2-1.4) 	<p>SR lifetime prevalence 0.3% (0.1-1.0) History and SPT point prevalence</p>	

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Steinke <i>et al.</i> 2007; Europe	SR point prevalence Austria 28.6%; Belgium 55.8%; Finland 22.7%; Germany 41.7%; Greece 16.7%; Italy 33.3%; Poland 55.7%; Slovenia 27.9%; Switzerland 34.8%; All countries 38.5%	SR point prevalence Austria 7.1%; Belgium 14.0%; Denmark 0%; Finland 14.6%; Germany 9.5%; Greece 27.1%; Italy 15.2%; Poland 27.3%; Slovenia 27.9%; Switzerland 21.7%; All countries 19.0%	SR point prevalence Austria 28.6%; Belgium 9.3%; Denmark 4.5%; Finland 12.5%; Germany 19.0%; Greece 0%; Poland 6.8%; Slovenia 23.3%; Switzerland 13.0%; All countries 11.4%	SR point prevalence Austria 28.6%; Belgium 9.3%; Denmark 4.5%; Finland 12.5%; Germany 19.0%; Greece 0%; Poland 6.8%; Slovenia 23.3%; Switzerland 13.0%; All countries 11.4%	The numbers the authors used in making the calculation for the estimates were not given in the paper. Therefore it was not possible to recalculate the estimates.
Venter <i>et al.</i> 2010, UK	SPT point prevalence 0.5% (0.2-1.4)	SPT point prevalence 1.4% (0.7-2.6)	SPT point prevalence 1.2% (0.6-2.4)	SPT point prevalence 1.2% (0.6-2.4)	Estimates based on the latest cohort in the study, i.e. Cohort C, which is first reported in Venter <i>et al.</i> 2008; Dean <i>et al.</i> 2007; Venter <i>et al.</i> 2006, UK (see below).

Table E1 (continued)

Reference, country	Estimates of the frequency of cow's milk allergy Percentage (95% CI)	Estimates of the frequency of hen's egg allergy Percentage (95% CI)	Estimates of the frequency of wheat allergy Percentage (95% CI)	Estimates of the frequency of soy allergy Percentage (95% CI)	Comment
Venter <i>et al.</i> 2006, UK	<ul style="list-style-type: none"> SR point prevalence 3.6% (2.5-5.2) SPT point prevalence 0.4% (0.1-1.3) OFC point prevalence 0.6% (0.2-1.5) DBPCFC point prevalence 0.3% (0.1-1.0) 	<ul style="list-style-type: none"> SR point prevalence 1.9% (1.1-3.1) SPT point prevalence 0.9% (0.4-1.9) OFC point prevalence 0% 	<ul style="list-style-type: none"> SR point prevalence 1.3% (0.7-2.3) SPT point prevalence 0.4% (0.1-1.3) OFC point prevalence 0.3% (0.1-1.0) DBPCFC point prevalence 0.1% (0.0-0.8) 		
von Hertzen <i>et al.</i> 2006, Finland and Russia	<p>SPT point prevalence in Finland</p> <ul style="list-style-type: none"> Children 0.3% (0.0-1.5) Mothers 2.8% (1.5-5.1) 	<p>SPT point prevalence in Finland</p> <ul style="list-style-type: none"> Children 1.9% (0.9-3.9) Mothers 3.1% (1.7-5.4) 	<p>SPT point prevalence in Finland</p> <ul style="list-style-type: none"> Children 11.8% (8.9-15.5) Mothers 8.7% (6.2-12.1) 	<ul style="list-style-type: none"> SR pooled point prevalence for adults 0.40% (0.21-0.59) SPT pooled point prevalence for children 0.43% (0.16-0.70) slgE pooled point prevalence for adults 2.08% (0.87-3.29) 	Zuidmeer <i>et al.</i> 2008, Worldwide

CI = confidence interval; DBPCFC = double blind placebo-controlled food challenge; OFC = oral food challenge; slgE = specific immunoglobulin E; SPT = skin prick test; SR = self-reported

Table E2 Summary of evidence on the frequency of allergy to peanut, tree nut, fish, shellfish in Europe: studies published 1 January 2000 - 30 September 2012

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Burney <i>et al.</i> 2010; Woods <i>et al.</i> 2001, Europe, USA, Australia, New Zealand	slgE point prevalence for all countries 1.4%	slgE point prevalence for all countries • Hazelnut 3.1% • Walnut 1.8%	slgE point prevalence for all countries 0.1%	slgE point prevalence for all countries (shrimp) 5.2%	Estimate of sensitization is a weighted average over all countries in the study excluding birth positivity. No weighting factor or baseline data given, so we were unable to recalculate the estimate.
Caffarelli <i>et al.</i> 2011, Italy	SR lifetime prevalence: 1.1% (0.5-2.3)	SR lifetime prevalence of hazelnut 0.3% (0.1-1.2)			
Du Toit <i>et al.</i> 2008, UK and Israel	• SR point prevalence 1.9% (1.5-2.3) in UK • History or OFC: 0.4% (0.3-0.6) in UK	SR point prevalence 2.0% (1.6-2.5)			
Dubakiene <i>et al.</i> 2012, Lithuania	Point prevalence at 6 mo: History + sensitization 0.1% (0.00-0.4); Point prevalence at 12 mo: History + sensitization 0.1% (0.0-0.5)		Point prevalence at 12 mo: History + sensitization 0.1% (0.00-0.04)		Point prevalence at 12 mo: History + sensitization 0.1% (0.00-0.04)
Eller <i>et al.</i> 2009, Kjaer <i>et al.</i> 2008, Johnke <i>et al.</i> 2006, Denmark	Point prevalence: • At 3 mo: slgE 0.2% (0.0-1.3) • At 6 mo: slgE 1.6% (0.7-3.3) • At 12 mo: slgE 1.6% (0.7-3.3) • At 18 mo: slgE 1.2% (0.5-3.1) • At 6 years by OFC/DBPCFC: 0.5% (0.1-1.8) • Cumulative incidence by 18 mo: slgE 1.8% (1.0-3.4)			At age 6 by OFC/DBPCFC: 0.0% (0.0-0.9)	Types of shellfish studied were octopus and squid.
Falcaõ <i>et al.</i> 2004, Portugal			SR point prevalence 0.9% (0.4-2.0)	SR point prevalence 0.5% (0.2-1.3)	
Fox <i>et al.</i> 2009, UK	Case-control study: frequency estimates not given				
Frongia <i>et al.</i> 2005, Italy	Estimates not given in the paper				

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Gelincik <i>et al.</i> 2008, Turkey	Point prevalence: • History + SPT (hazelnut) 0.0% (0.0-0.0) • History + slgE (hazelnut) 0.0% (0.0-0.0) • DBPCFC (hazelnut) 0.0% (0.0-0.0) • DBPCFC (walnut) 0.0% (0.0-0.0)	Point prevalence: • History + SPT (hazelnut) 0.0% (0.0-0.0) • History + slgE (hazelnut) 0.0% (0.0-0.0) • DBPCFC (hazelnut) 0.0% (0.0-0.0) • DBPCFC (walnut) 0.0% (0.0-0.0)	Point prevalence: • SR: 1.0% (0.6-1.7) • SPT 3.3% (2.4-4.4) • OFC + history 1.4% (0.9-2.9) • OFC 0.6% (0.3-1.3)	Point prevalence: • SPT 2.7% (1.9-3.9) • DBPCFC or history 1.9% (1.2-2.9) • DBPCFC 1.4% (0.8-2.3)	Type of fish studied was cod fish.
Hourihane <i>et al.</i> 2007, UK	slgE point prevalence: • Sweden 2.3% (1.5-3.4) • Norway 0.6% (0.2-1.8) • Sweden + Norway 1.7% (1.2-2.5)	slgE point prevalence: • Sweden 3.5% (2.5-4.8) • Norway 0.6% (0.2-1.8) • Sweden + Norway 2.5% (1.9-3.5)	slgE point prevalence: • Sweden 0.1% (0.0-0.6) • Norway 0% • Sweden + Norway 0.1% (0.0-0.4)	slgE point prevalence: 0.7% (0.3-1.4)	Point prevalence: • SR 0.4% (0.2-0.9) • History + SPT 0.1% (0.0-0.4)
Krause <i>et al.</i> 2002, Greenland	slgE point prevalence 1.2% (0.7-2.0)				• History + slgE 0.1% (0.0-0.4) • History + SPT or slgE 0.1% (0.4-1.3) • DBPCFC 0.1% (0.0-0.5)
Kristinsdottir <i>et al.</i> 2011, Iceland	Point prevalence: • History + SPT 0.2% (0.1-0.7) • History + slgE 0.7% (0.4-1.3) • History + SPT or slgE 0.7% (0.4-1.3) • DBPCFC 0.1% (0.0-0.5)	Point prevalence: • SR 0.1% (0.0-0.4) • History + SPT 0.1% (0.0-0.4) • History + slgE 0.1% (0.0-0.5) • History + SPT or slgE 0.1% (0.0-0.5) • DBPCFC 0.2% (0.1-0.7)	SR point prevalence 0.1% (0.0-0.4)	SR point prevalence 0.1% (0.0-0.4)	Type of shell fish studied was shrimp.

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Kurulaaratchy et al. 2005, Arshad et al. 2001, Tariq et al. 2000, UK	SPT point prevalence at 4 yrs 1.1% (0.6-2.0)				Estimates given in a figure in the paper.
Kvenshagen et al. 2009, Norway	Point prevalence by Clinician history or OFC 1.0% (0.4-2.0)	Estimates not given in the paper.			
Majkowska-Wojciechowska et al. 2009, Poland		SR lifetime prevalence 1.6% (1.2-2.3)			The type of tree nuts studied not specified in the paper
Marklund et al. 2004, Sweden	SR point prevalence 6.0% (4.9-7.3)	SR point prevalence • Nuts 7.3% (6.1-8.8) • Almond 4.1% (3.2-5.3)	SR point prevalence 1.0% (0.6-1.6)	SR point prevalence 1.7% (1.1-2.4)	These are indirect-recalculated estimates as the authors provided only the percentage estimates.
Nicolaou et al. 2010, UK		• SR lifetime prevalence 1.7% (1.0-2.6) • Point prevalence: sIgE 9.3% (7.2-11.9); SPT 5.1% (3.9-6.7); SPT or sIgE 11.8% (9.9-14.0); History + sIgE 8.6% (6.6-11.2); History + SPT 0.9% (0.4-2.0); History + SPT + sIgE 3.4% (2.2-5.2); History or DBPCFC 2.0% (1.3-3.2); DBPCFC 0.8% (0.4-1.5)	SR lifetime prevalence 1.0% (0.5-1.8)	SR lifetime prevalence 0.5% (0.2-1.1)	
Niggemann et al. 2011, Germany		sIgE point prevalence 10.9% (10.4-11.4)			These are indirect-recalculated estimates as the authors provided only the percentage estimates.

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Orhan <i>et al.</i> 2009, Turkey	SR lifetime prevalence 0.1% (0.0-0.3) Point prevalence: • History and SPT 0.1% (0.0-0.3) • DBPCFC 0%	SR lifetime prevalence: • Hazelnut 0.3% (0.1-0.6) • Walnut 0.1% (0.0-0.3) History and SPT point prevalence: • Hazelnut 0.1% (0.0-0.3) • Walnut 0.1% (0.0-0.3) DBPCFC point prevalence: • Hazelnut 0% • Walnut 0%	SR lifetime prevalence: • Hazelnut 0.3% (0.1-0.6) • Walnut 0.1% (0.0-0.3) History and SPT point prevalence: • Hazelnut 0.1% (0.0-0.3) • Walnut 0.1% (0.0-0.3) DBPCFC 0.0% (0.0-0.2)	SR lifetime prevalence 0.3% (0.2-0.6) Point prevalence: • History and SPT 0.2% (0.1-0.4) • DBPCFC 0.0% (0.0-0.2)	Estimates also available at 8 years but these were only presented in figures. Tree nut studied was almond.
Östblom <i>et al.</i> 2008a, 2008b, 2008c and Almqvist <i>et al.</i> 2005, Sweden	Estimates at 4 years: • SR point prevalence 2.8% (2.3-3.3) • sIgE point prevalence 5.4% (4.5-6.3)	Estimates at 4 years: • SR point prevalence 2.7% (2.2-3.2)	Estimates at 4 years: • SR point prevalence 1.1% (0.8-1.5) • sIgE point prevalence 0.7% (0.5-1.2)	Estimates at 4 years: • SR point prevalence 0.2% (0.1-0.9) • DBPCFC point prevalence 0.1% (0.02-0.7)	Estimates also available at 8 years but these were only presented in figures.
Osterballe <i>et al.</i> 2009, Denmark	• SR point prevalence 5.3% (4.0-7.1) • DBPCFC point prevalence 0.6% (0.3-1.4)	SR point prevalence: • Almond 0.2% (0.1-0.9) • Brazil nut 2.7% (1.8-4.1) • Hazelnut 6.6% (5.2-8.5) • Walnut 0.5% (0.2-1.2)	SR point prevalence: • SR point prevalence 0.2% (0.1-0.9) • DBPCFC point prevalence 0.1% (0.0-0.7)	SR point prevalence: • Octopus 0.4% (0.1-1.0) • Shrimp 2.0% (1.3-3.2) OFC point prevalence: • Octopus 0.1% (0.0-0.7) • Shrimp 0.2% (0.1-0.9)	Type of wish studied was cod fish.
Osterballe <i>et al.</i> 2005, Denmark	History or SPT point prevalence: st < 3 yrs 0%; at 3 yrs 1.6% (0.8-3.2; at > 3 yrs 1.0% (0.3-2.9); All children 1.2% (0.7-2.2); Adults 1.2% (0.7-2.1) • DBPCFC point prevalence: at < 3 yrs 0%; at 3 yrs 0.2% (0.0-1.2); at > 3 yrs 0%; All children 0.1% (0.0-0.6); Adults 0.4% (0.2-1.1)	History or SPT point prevalence: st < 3 yrs 0%; at 3 yrs 0.8% (0.3-2.1); at > 3 yrs 0.3% (0.1-1.9); All children 0.1% (0.0-0.6); Adults 1.1% (0.6-1.9) • DBPCFC point prevalence: at < 3 yrs 0%; at 3 yrs 0%; at > 3 yrs 0%; All children 0%; Adults 0.2% (0.1-0.8)	History or SPT point prevalence: st < 3 yrs 0%; at 3 yrs 0%; at > 3 yrs 0%; All children 0%; Adults 0.3% (0.1-0.9)	History or SPT point prevalence: at < 3 yrs 0%; at 3 yrs 0%; at > 3 yrs 0%; All children 0%; Adults 0.3% (0.1-0.9)	Type of shellfish studied was shrimp. Type of wish studied was cod fish.

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Penard-Morand <i>et al.</i> 2005, France	<ul style="list-style-type: none"> SR point prevalence 0.3% (0.2-0.5) SPT point prevalence 1.0% (0.8-1.3) 	SR point prevalence 0.1% (0.1-0.3)	<ul style="list-style-type: none"> SR point prevalence 0.1% (0.1-0.3) SPT point prevalence 0.7% (0.5-0.9) 	<ul style="list-style-type: none"> SR point prevalence 0.1% (0.1-0.3) SPT point prevalence 0.7% (0.4-0.7) 	SR point prevalence 0.5% (0.4-0.7)
Pereira <i>et al.</i> 2005, UK	<p>SR point prevalence:</p> <ul style="list-style-type: none"> 11-yr-olds 1.8% (1.1-3.0) 15-yr-olds 2.5% (1.6-3.9) <p>Both 2.2% (1.5-3.0)</p> <p>SPT point prevalence:</p> <ul style="list-style-type: none"> 11-yr-olds 3.7% (2.6-5.4) 15-yr-olds 2.6% (1.6-4.2) Both 3.2% (2.4-4.3) 	SR point prevalence:	<p>SR point prevalence:</p> <ul style="list-style-type: none"> 11-yr-olds 0.9% (0.4-1.9) 15-yr-olds 1.8% (1.1-3.1) <p>Both 1.4% (0.9-2.1)</p> <p>SPT point prevalence:</p> <ul style="list-style-type: none"> 15-yr-olds 2.1% (1.3-3.4) Both 1.6% (1.1-2.4) 	<p>SR point prevalence:</p> <ul style="list-style-type: none"> 11-yr-olds 0.9% (0.4-1.9) 15-yr-olds 1.8% (1.1-3.1) Both 1.4% (0.9-2.1) <p>SPT point prevalence:</p> <ul style="list-style-type: none"> 15-yr-olds 2.1% (1.3-3.4) Both 1.6% (1.1-2.4) 	The type of shellfish studied with DBPCFC was shrimp.
Pyrhönen <i>et al.</i> 2011 and 2009, Finland	Lifetime prevalence:	Lifetime prevalence:	Lifetime prevalence:	Lifetime prevalence:	Lifetime prevalence
Rance <i>et al.</i> 2005, France	SR lifetime prevalence for all children 0.7% (0.5-1.1)	SR lifetime prevalence for all children 0.7% (0.4-1.1)	SR lifetime prevalence for all children 0.7% (0.4-1.1)	SR lifetime prevalence for all children 0.7% (0.4-1.1)	SR lifetime prevalence for all children 1.4% (1.0-1.9)
Roberts <i>et al.</i> 2005 and Lack <i>et al.</i> 2003, UK	<p>Point prevalence:</p> <ul style="list-style-type: none"> SR 0.4% (0.3-0.5) SPT 1.4% (1.2-1.7) History + SPT, 0.2% (0.2-0.3) DBPCFC, 0.2% (0.1-0.3) 	Mixed tree nuts 1.0% (0.8-1.3)	<p>Almond 0.5% (0.2-0.9)</p> <p>Brazil nut 0.5% (0.3-0.9)</p> <p>Cashew nut 0.4% (0.2-0.8)</p> <p>Hazel nut 0.1% (0.0-0.4)</p> <p>Pecan nut 0.2% (0.1-0.4)</p> <p>Walnut 0.5% (0.3-0.9)</p>	<p>Almond 0.5% (0.2-0.9)</p> <p>Brazil nut 0.5% (0.3-0.9)</p> <p>Cashew nut 0.4% (0.2-0.8)</p> <p>Hazel nut 0.1% (0.0-0.4)</p> <p>Pecan nut 0.2% (0.1-0.4)</p> <p>Walnut 0.5% (0.3-0.9)</p>	Type of fish studied was cod fish.

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Rona <i>et al.</i> , 2007, Worldwide	<ul style="list-style-type: none"> Pooled estimates for SR point prevalence: 0.75% (0.6-0.9) Range of estimates: SR 0% to 2%; sIgE <1% to 6%; SPT 1% to 6%; History + SPT or IgE 0.5% to 2.5% 		<ul style="list-style-type: none"> Pooled estimates for SR: 0.6% (0.5-0.7) Range of estimates: SR 0% to 2%; sIgE ~0%; SPT ~0% to 2%; History + SPT or IgE ≤0.5%; OFC or DBPCFC ~0% 	<ul style="list-style-type: none"> Pooled estimate for SR: 0.6% (0.5-0.7) Range of estimates: SR 0% to 10%; SPT 2.5%; History + SPT or IgE 0% to 1.4%; OFC or DBPCFC ~0% 	Specific foods studied in the paper but estimates for each food not given by the authors rather several foods were studied together
Sandin <i>et al.</i> 2005, Sweden and Estonia	Estimates for each specific not given in the paper	Estimates for each specific not given in the paper		Estimates for each specific not given in the paper	Type of fish studied for SPT was cod.
Schnabel <i>et al.</i> 2010, Germany	<p>SR point prevalence at 6 yrs:</p> <ul style="list-style-type: none"> Doctor diagnosis 4.7% (3.6-6.1) New onset 3.1% (2.3-4.4) <p>sIgE point prevalence:</p> <ul style="list-style-type: none"> At 2 yrs 2.1% (1.4-3.2) At 6 yrs 5.2% (4.0-6.7) 		<p>slgE point prevalence at 6 yrs 0.6% (0.3-1.3)</p>	<ul style="list-style-type: none"> SR lifetime prevalence 1.3% SPT point prevalence (hazelnut) 11.3% 	<p>Estimates are weighted for the general population.</p> <p>Authors did not provide numbers used for weighting, hence we were unable to recalculate the estimates.</p>
Schäfer <i>et al.</i> 2001, Germany	<ul style="list-style-type: none"> SR lifetime prevalence 1.3% SPT point prevalence 6.8% 		<ul style="list-style-type: none"> SR lifetime prevalence 5.3% SPT point prevalence (mackerel) 1.8% 	<ul style="list-style-type: none"> SR lifetime prevalence 1.0% (fish and shellfish) SPT point prevalence (crab) 1.9% 	<ul style="list-style-type: none"> SR lifetime prevalence SPT point prevalence

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Soost <i>et al.</i> 2009 and Zuberbier <i>et al.</i> 2004, Roehr <i>et al.</i> 2004, Germany	History and SPT point prevalence: • 0-17 yrs 1.1% (0.5-2.1) • Children and adults 2.4% (1.5-3.7)	SR lifetime prevalence 2.7% (1.8-4.1) History and SPT point prevalence: • Hazelnut: 0-17 yrs 2.0% (1.2-3.3); Children and adults 23.0% (20.2-26.0) • Walnut: 0-17 yrs 0.7% (0.3-1.6); Children and adults 7.1% (5.5-9.1) DBPCFC point prevalence of Hazelnut: 0-14 yrs 0.7% (0.3-1.7); 15-17 yrs 4.3% (2.0-9.0); All children 1.4% (0.7-2.5)	SR lifetime prevalence 0.5% (0.2-1.4) History and SPT point prevalence: • 0-17 yrs: Mackerel 0.1% (0.0-0.8) • Children and adults: Herring 0.5% (0.2-1.3); Mackerel 0.4% (0.1-1.1)	SR lifetime prevalence 0.5% (0.2-1.4) History and SPT point prevalence: • 0-17 yrs 0% (shrimp) • Children and adults: Crab 1.2% (0.7-2.3); Mussels 0.1% (0.0-0.7)	The type of tree nuts studied for lifetime prevalence not specified in the paper
Steinke <i>et al.</i> 2007, Europe		SR point prevalence Austria 7.1%; Belgium 9.3%; Denmark 13.6%; Finland 13.5%; Germany 19.0%; Greece 2.1%; Italy 9.1%; Poland 6.8%; Slovenia 9.3%; Switzerland 13.0%; All countries 9.7%	SR point prevalence Austria 0%; Belgium 4.7%; Denmark 0%; Finland 19.8%; Germany 4.8%; Greece 8.3%; Italy 6.1%; Poland 1.1%; Slovenia 7.0%; Switzerland 17.4%; All countries 8.4%	SR point prevalence Austria 0%; Belgium 2.3%; Denmark 4.5%; Finland 2.1%; Germany 4.8%; Greece 0%; Italy 3.0%; Poland 2.3%; Slovenia 4.7%; Switzerland 13.0%; All countries 3.0%	The numbers the authors used in making the calculation for the estimates were not given in the paper. Therefore it was not possible to recalculate the estimates.
Venter <i>et al.</i> 2010, UK	SPT point prevalence 2.0% (1.2-3.4) History or OFC 1.2% (0.7-2.2) OFC point prevalence 0.3% (0.1-1.0)	SPT point prevalence 0.5% (0.2-1.4)			Estimates based on the latest cohort in the study. i.e. Cohort C.

Table E2 (continued)

Reference, country	Estimates of the frequency of peanut allergy Percentage (95% CI)	Estimates of the frequency of tree nut allergy Percentage (95% CI)	Estimates of the frequency of fish allergy Percentage (95% CI)	Estimates of the frequency of shellfish allergy Percentage (95% CI)	Comment
Venter <i>et al.</i> 2008; Dean <i>et al.</i> 2007; Venter <i>et al.</i> 2006, UK	SPT point prevalence: • At 1 yr 0.4% (0.1-1.1) • At 2 yrs 2.0% (1.1-3.4) • At 3 yrs 2.0% (1.2-3.4) History or OFC point prevalence: • At 1 yr: Cashew nut 0.0% (0.0-0.4); Hazelnut 0.0% (0.0-0.4) • At 2 yrs: Cashew nut 0.0% (0.0-0.4); Hazelnut 0.0% (0.0-0.4) • At 3 yrs: Cashew nut 0.1% (0.0-0.6); Hazelnut 0.1% (0.0-0.6) History or OFC cumulative prevalence at 3 yrs 1.1% (0.6-2.0) OFC point prevalence: • At 3 yrs 0.3% (0.1-1.0)	History or OFC point prevalence: • At 1 yr: Cashew nut 0.0% (0.0-0.4); Hazelnut 0.0% (0.0-0.4) • At 2 yrs: Cashew nut 0.0% (0.0-0.4); Hazelnut 0.0% (0.0-0.4) • At 3 yrs: Cashew nut 0.1% (0.0-0.6); Hazelnut 0.1% (0.0-0.6) History or OFC cumulative prevalence at 3 yrs 0.1% (0.0-0.6) OFC point prevalence: • Cashew nut 0.1% (0.0-0.6) • Hazelnut 0.1% (0.0-0.6)	SPT point prevalence: • At 1 yr 0.3% (0.1-1.0) • At 2 yrs 0.5% (0.2-1.3) • At 3 yrs 0.5% (0.2-1.4) History or OFC point prevalence: • At 1 yr 0.1% (0.0-0.6) • At 2 yrs 0.0% (0.0-0.4) • At 3 yrs 0.0% (0.0-0.4) History or OFC cumulative prevalence at 3 yrs 0.1% (0.0-0.6) OFC point prevalence: • At 3 yrs 0% • SR point prevalence 1.9% (1.1-3.1)	SPT point prevalence: • At 1 yr 0.3% (0.1-0.9) • SPT point prevalence 1.4% (0.8-2.5) SR point prevalence 1.4% (0.8-2.5)	
Venter <i>et al.</i> 2006, UK	• SPT point prevalence 2.6% (1.6-4.0) • OFC point prevalence 0.3% (0.1-1.0)	• Children 6.3% (4.0-9.8) • Mothers 11.3% (8.1-15.6)	• Children 0.3% (0.0-1.5) • Mothers 2.8% (1.5-2.1)	SPT point prevalence in Finland • SR pooled point prevalence for children 0.52% (0.20-0.85)	Type of tree nut studied was hazelnut
von Hertzen <i>et al.</i> 2006, Finland and Russia	SPT point prevalence in Finland • Children 8.2% (5.8-11.5) • Mothers 10.1% (7.4-13.6)			• Ranges for SR point prevalence: 0-6 yrs 0.03% to 0.2%; 6-18 yrs 0.2% to 2.3%; Adults 0.4% to 1.4% • Range for SPT point prevalence for children 0.02% to 0.7%	
Zuidmeer <i>et al.</i> 2008, World-wide					= self-reported

CI = confidence interval; DBPCFC = double blind placebo-controlled food challenge; OFC = oral food challenge; sIgE = specific immunoglobulin E; SPT = skin prick test; SR = self-reported

Table E3 Summary of range of estimates of lifetime and point prevalence of each specific food allergy in Europe by different methods of assessment: estimates from studies published between 1 January 2000 and 30 September 2012

	Age bands (years) for each food allergy	Number of studies	SR lifetime prevalence %	Self - report	Point prevalence, %			
					IgE positivity	SPT positivity	Clinical history or FC (OFC or DBPCFC)	OFC or DBPCFC)
Cow's milk	≤ 1	9	1.5 - 12.8	1.5 - 55.7	0.7 - 9.0	0.1 - 2.5	1.6 - 3.7	0.0 - 3.0
	2 - 5	20	1.5 - 12.8	2.2 - 55.7	0.5 - 10.1	0.0 - 2.5	0.2 - 2.1	0.0 - 3.0
	6 - 17	28	0.9 - 15.0	1.3 - 55.7	0.5 - 10.1	0.2 - 2.5	—	0.0 - 3.0
	≥ 18	12	1.5 - 14.0	0.3 - 3.5	0.0 - 7.1	0.2 - 2.8	—	0.0 - 3.0
Hen's egg	≤ 1	11	1.6 - 6.3	0.2 - 27.9	<1.0 - 9.0	0.4 - 5.2	0.0 - 1.4	0.0 - 1.7
	2 - 5	21	1.6 - 6.3	0.2 - 27.9	0.4 - 9.0	0.4 - 5.0	0.7 - 1.3	0.0 - 1.7
	6 - 17	25	0.8 - 2.9	0.2 - 27.9	0.4 - 9.0	0.0 - 5.0	—	0.0 - 1.7
	≥ 18	10	1.6 - 2.0	0.2 - 2.0	0.2 - 9.0	0.5 - 5.0	—	0.0 - 1.7
Wheat	≤ 1	7	1.5 - 4.1	0.5 - 28.6	—	0.0 - 0.4	0.1 - 0.4	0.0 - 0.4
	2 - 5	13	1.0 - 4.1	0.4 - 28.6	0.7 - 8.8	0.2 - 1.2	0.1 - 0.3	0.0 - 0.5
	6 - 17	11	~1.0	0.4 - 28.6	0.7 - 8.8	0.4 - 11.8	—	0.0 - 0.3
	≥ 18	6	—	0.4 - 0.8	0.7 - 3.4	0.4 - 8.7	—	~0.0
Soy	≤ 1	5	~0.3	0.1 - 0.3	—	~0.2	—	0.0 - 0.7
	2 - 5	9	~0.3	0.3 - 0.8	1.2 - 6.1	~0.2	—	0.0 - 0.7
	6 - 17	9	~0.3	0.3 - 1.3	1.2 - 6.1	~0.2	—	0.0 - 0.7
	≥ 18	8	~0.3	0.3 - 1.3	0.0 - 1.4	~1.7	—	0.0 - 0.1
Peanut	≤ 1	10	—	0.0 - 2.0	0.2 - 10.9	0.4 - 6.0	—	0.0 - 0.2
	2 - 5	18	~1.1	0.0 - 2.8	<1.0 - 10.9	1.0 - 3.3	0.4 - 1.9	0.0 - 1.4
	6 - 17	21	0.1 - 1.7	0.0 - 6.0	<1.0 - 10.9	1.0 - 8.2	0.4 - 2.0	0.0 - 0.8
	≥ 18	8	~1.3	0.0 - 6.0	1.2 - 1.8	1.0 - 10.1	—	0.0 - 0.6
Tree nut	≤ 1	6	1.7 - 2.7	0.03 - 19.0	—	0.02 - 1.0	~0.0	0.7 - 1.4
	2 - 5	9	0.3 - 2.7	0.03 - 19.0	—	0.02 - 1.0	0.0 - 0.1	0.7 - 1.4
	6 - 17	16	0.1 - 2.7	0.2 - 19.0	—	0.02 - 6.3	—	0.0 - 4.3
	≥ 18	7	2.7 - 5.3	0.4 - 7.3	0.6 - 3.5	11.3	—	~0.0
Fish	≤ 1	9	0.5 - 4.6	0.0 - 17.4	~0.0	0.0 - 2.0	~0.1	0.0 - 0.2
	2 - 5	13	0.5 - 4.6	0.0 - 17.4	0.0 - 0.7	0.0 - 2.0	~0.0	~0.0
	6 - 17	18	0.3 - 0.7	0.0 - 17.4	0.0 - 0.7	0.0 - 2.0	—	~0.0
	≥ 18	11	0.5 - 1.0	0.0 - 2.0	0.0 - 0.7	0.0 - 2.8	—	0.0 - 0.2
Shell fish	≤ 1	3	—	0.0 - 13.0	—	~2.5	—	~0.0
	2 - 5	2	—	0.0 - 13.0	—	~2.5	—	~0.0
	6 - 17	4	~1.4	0.0 - 13.0	—	~2.5	—	0.0 - 0.1
	≥ 18	5	~1.0	0.0 - 10.0	~5.2	1.9 - 2.5	—	0.0 - 0.5

DBPCFC = double blind placebo - controlled food challenge; OFC = oral food challenge; sIgE = specific immunoglobulin E; SPT = skin prick test; SR = self - reported

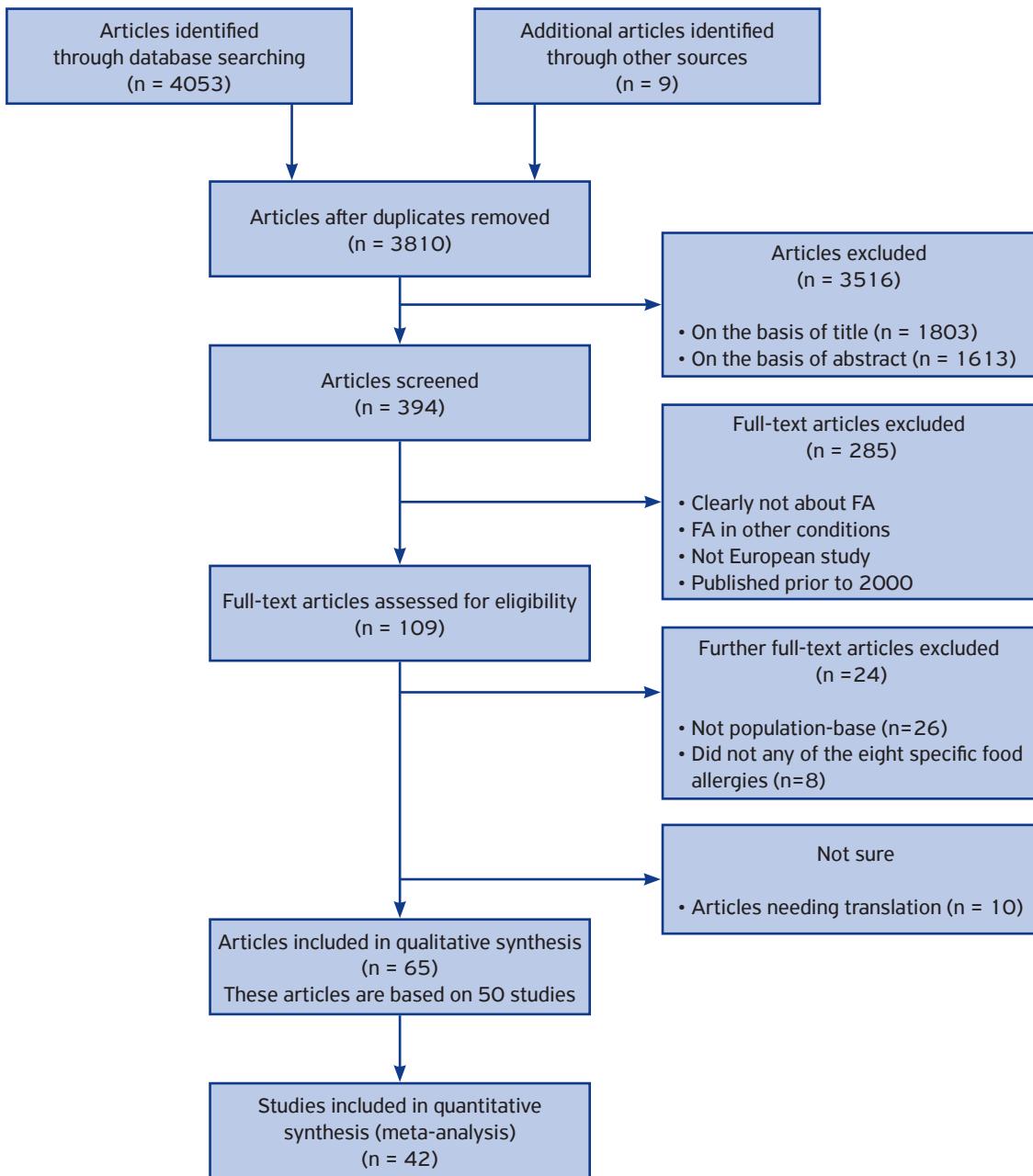
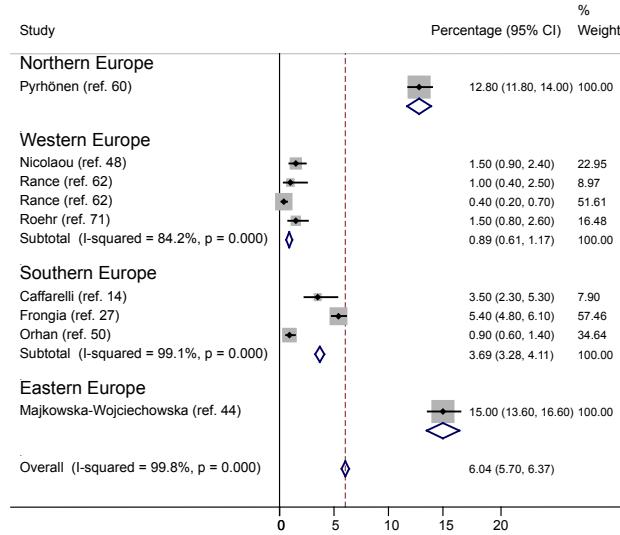
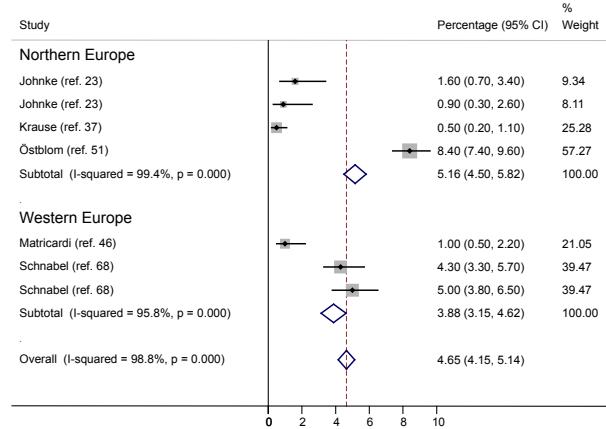


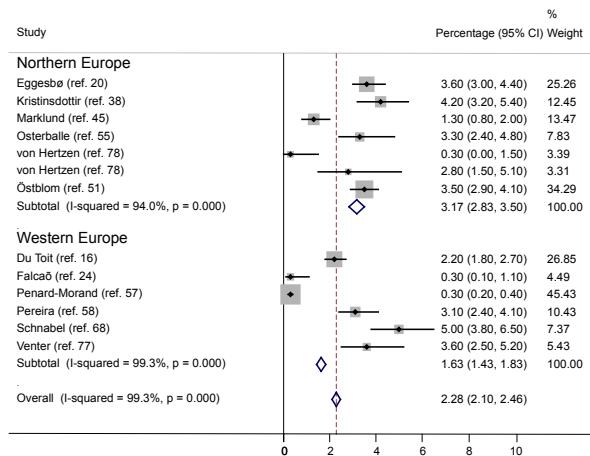
Figure E1 PRISMA flow diagram for studies on the epidemiology of food allergy in Europe, 2000-2012



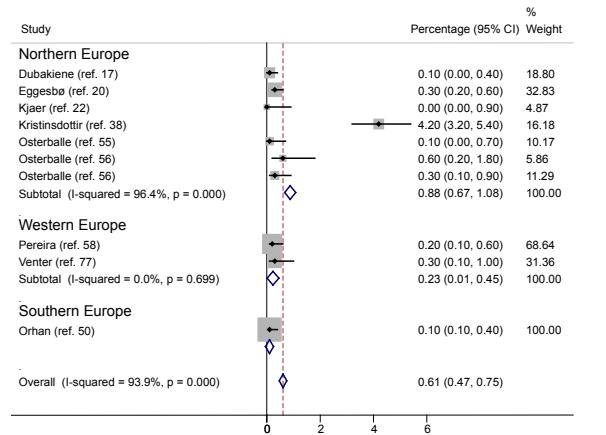
PANEL I: Lifetime prevalence of self-reported CMA



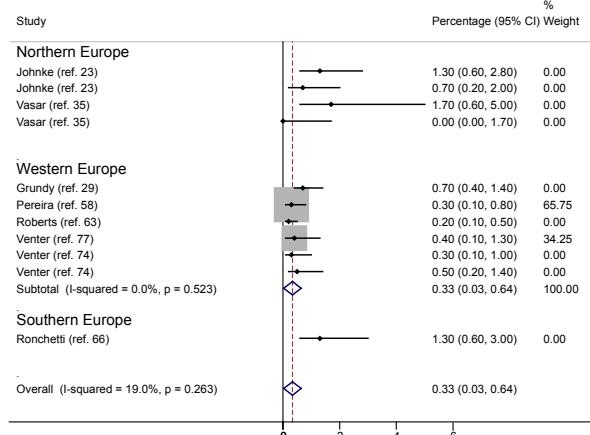
PANEL IV: Point prevalence of IgE positive CMA



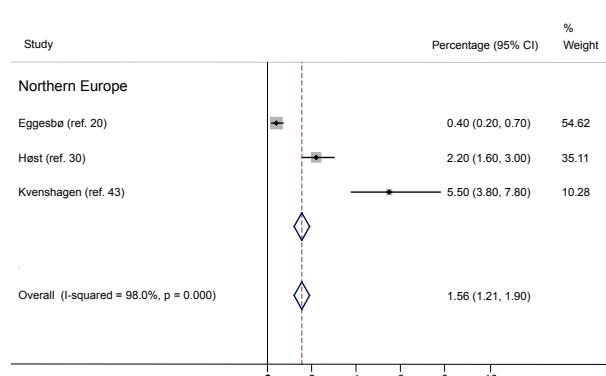
PANEL II: Point prevalence of self-reported CMA



PANEL V: Point prevalence of FC positive CMA



PANEL III: Point prevalence of SPT positive CMA



PANEL VI: Point prevalence of FC or history of CMA

Figure E2 Region-stratified pooled prevalence of cow's milk allergy (CMA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

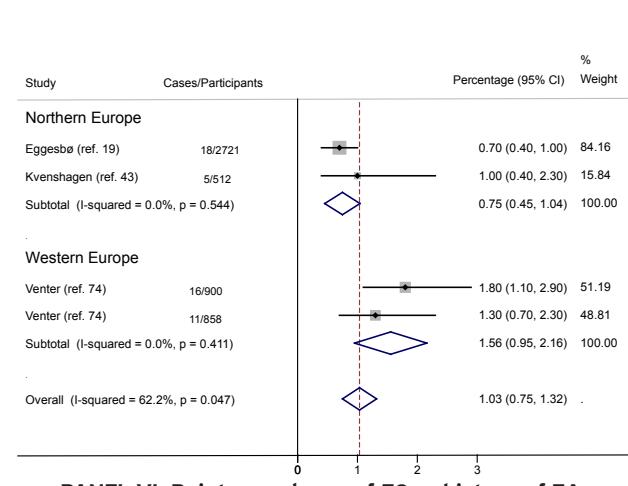
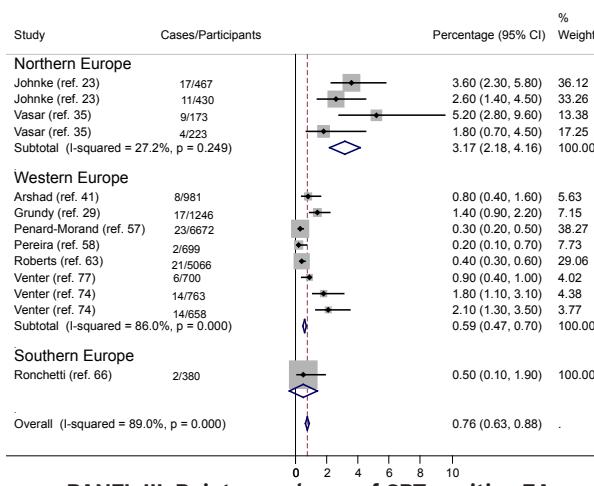
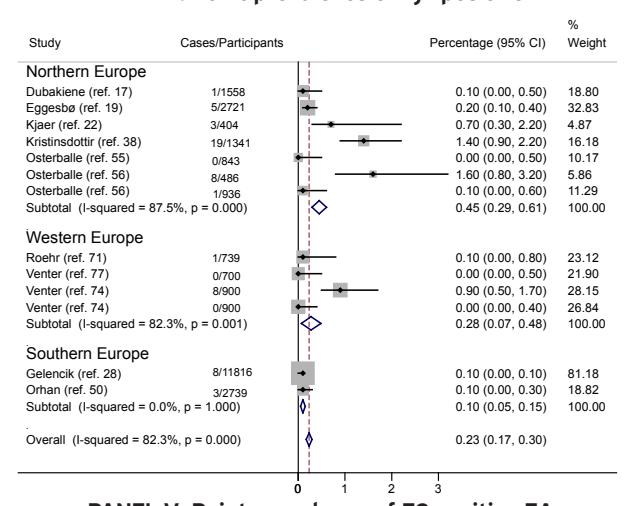
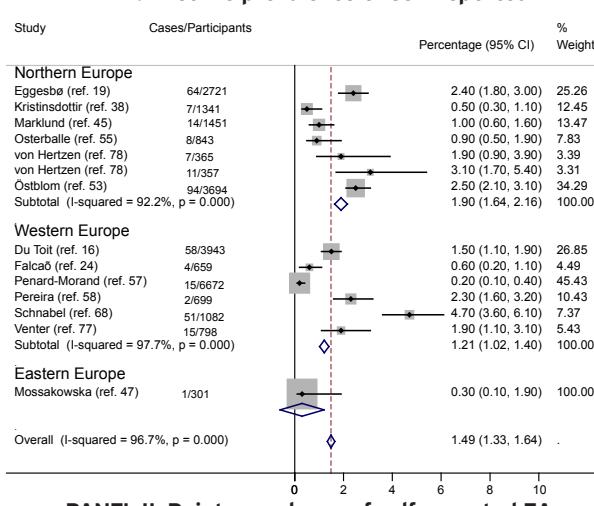
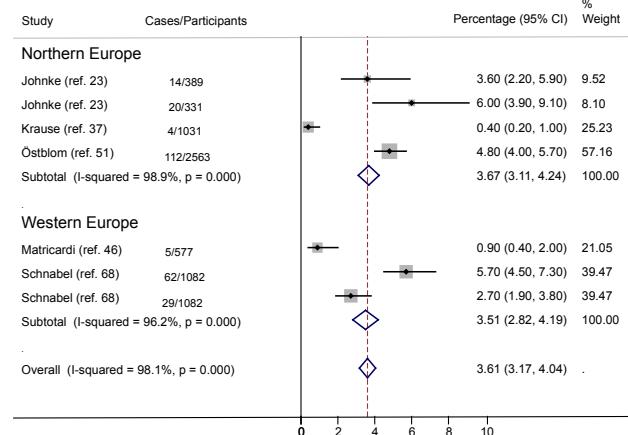
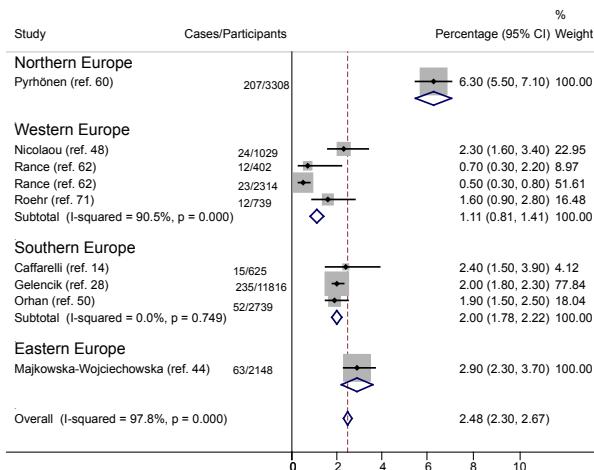
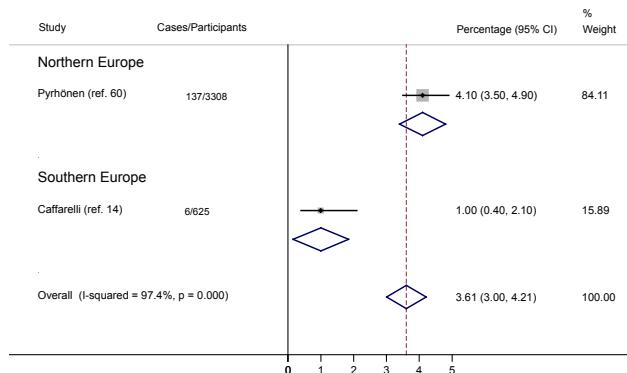
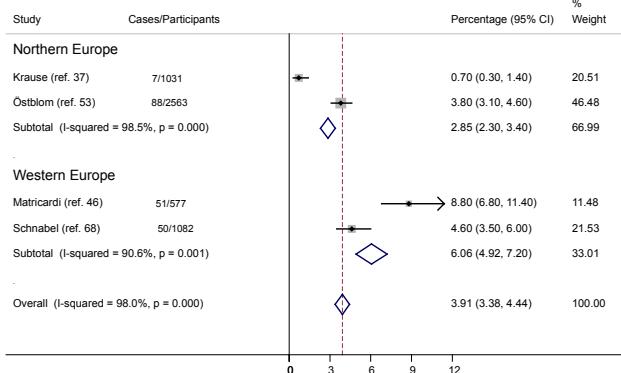


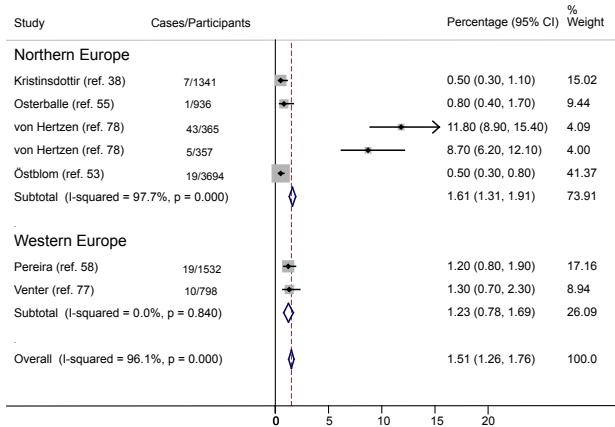
Figure E3 Region-stratified pooled prevalence of egg allergy (EA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size



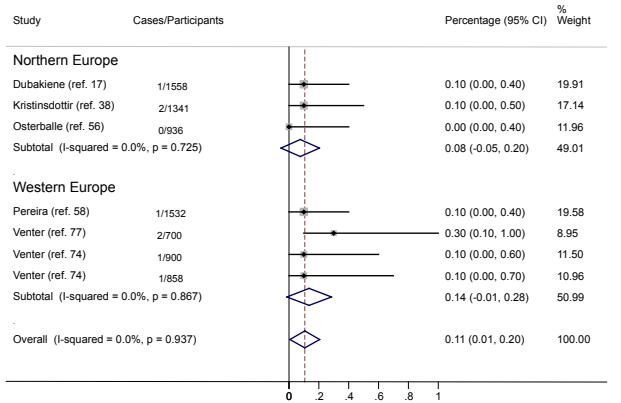
PANEL I: Lifetime prevalence of self-reported WA



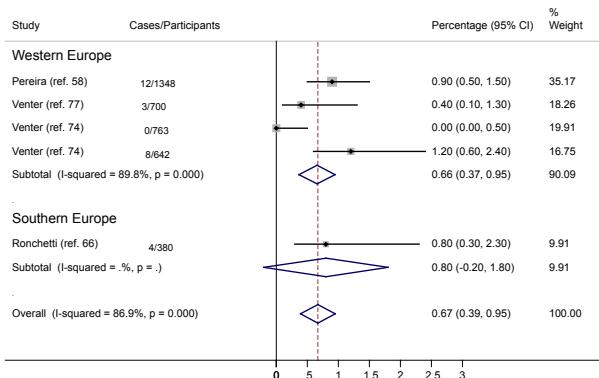
PANEL IV: Point prevalence of IgE positive WA



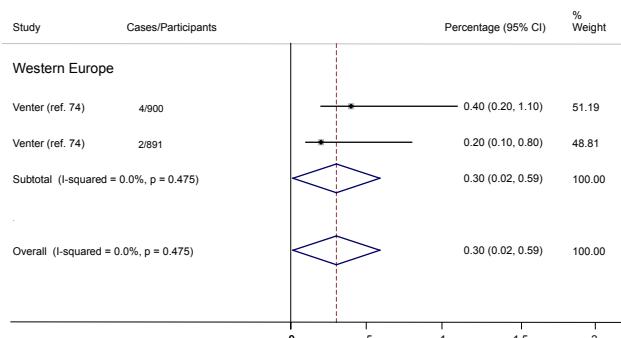
PANEL II: Point prevalence of self-reported WA



PANEL V: Point prevalence of FC positive WA

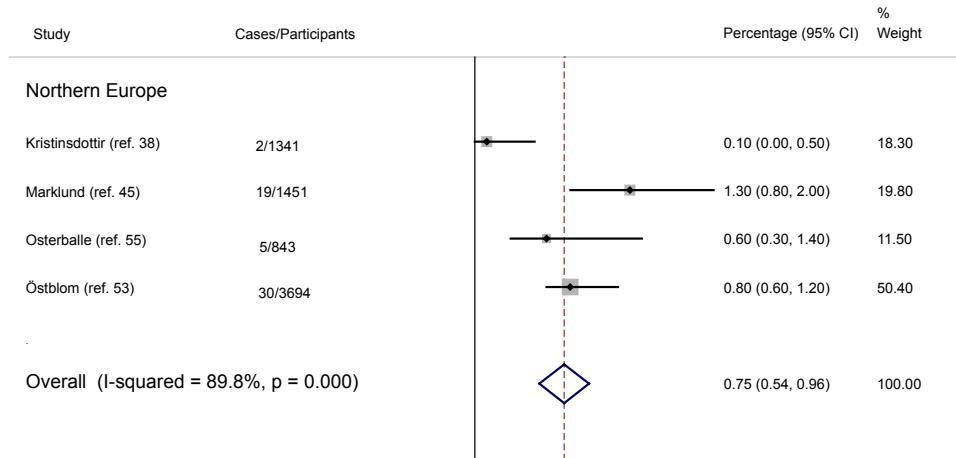


PANEL III: Point prevalence of SPT positive WA

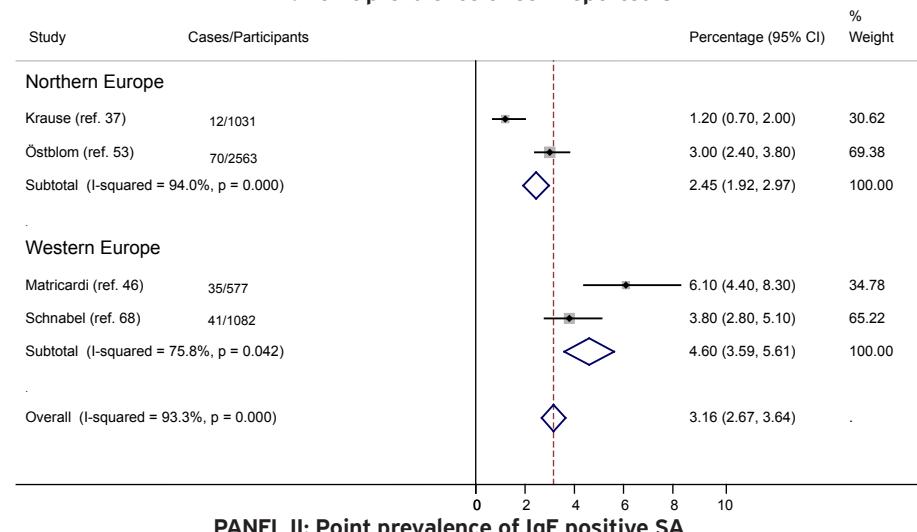


PANEL VI: Point prevalence of FC or history of WA

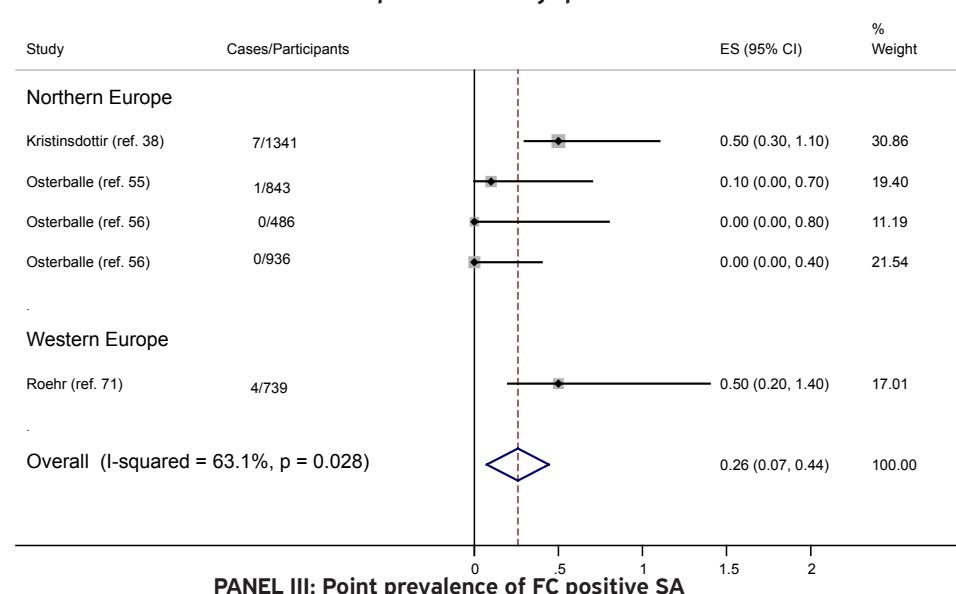
Figure E4 Region-stratified pooled prevalence of wheat allergy (WA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size



PANEL I: Point prevalence of self-reported SA

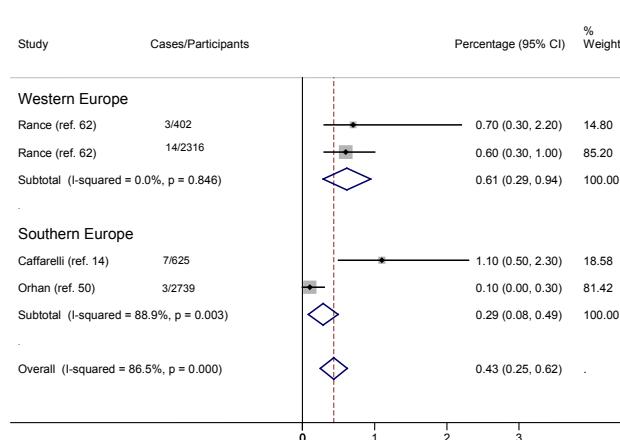


PANEL II: Point prevalence of IgE positive SA

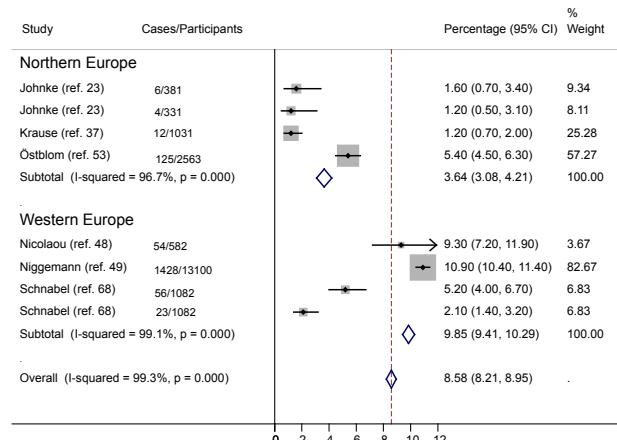


PANEL III: Point prevalence of FC positive SA

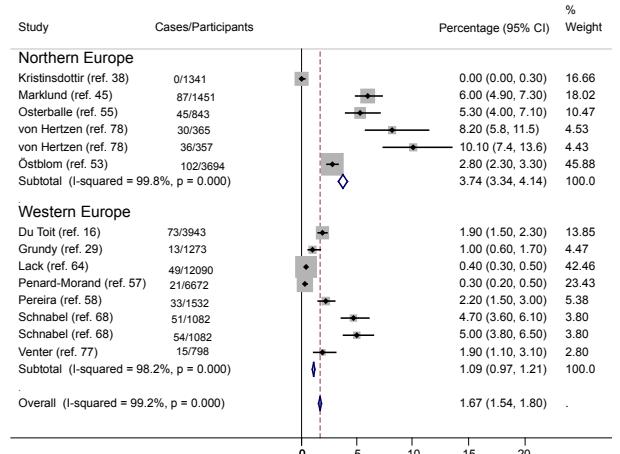
Figure E5 Region-stratified pooled prevalence of soy allergy (SA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size



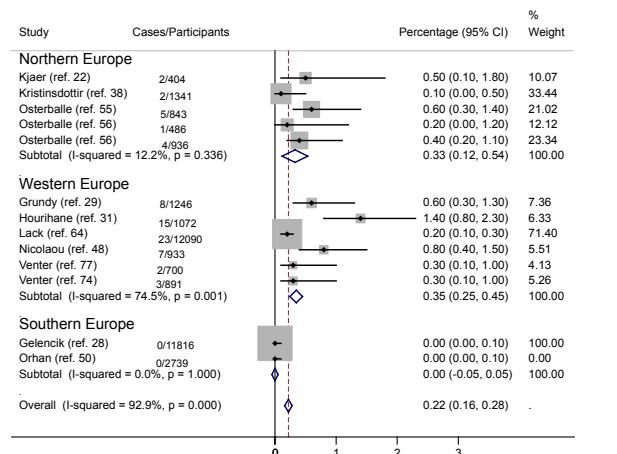
PANEL I: Lifetime prevalence of self-reported PA



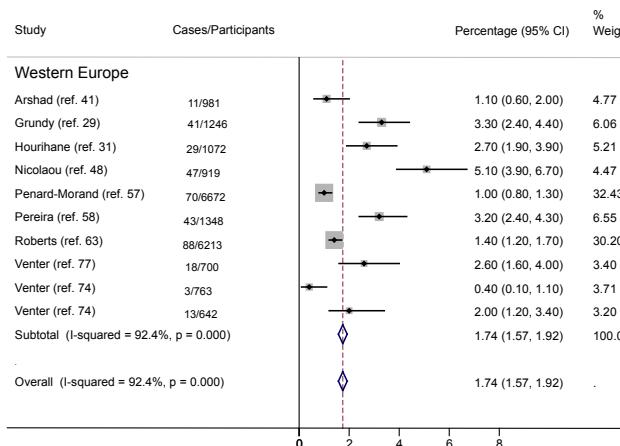
PANEL IV: Point prevalence of IgE positive PA



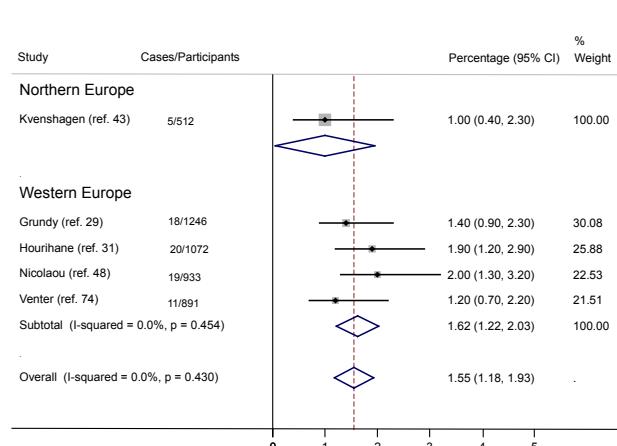
PANEL II: Point prevalence of self-reported PA



PANEL V: Point prevalence of FC positive PA



PANEL III: Point prevalence of SPT positive PA



PANEL VI: Point prevalence of FC or history of PA

Figure E6 Region-stratified pooled prevalence of peanut allergy (PA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

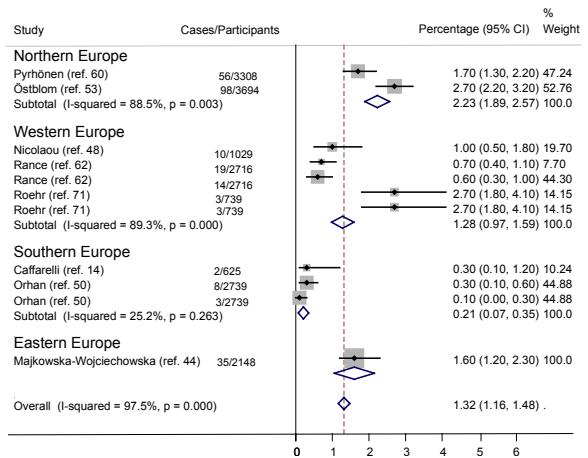
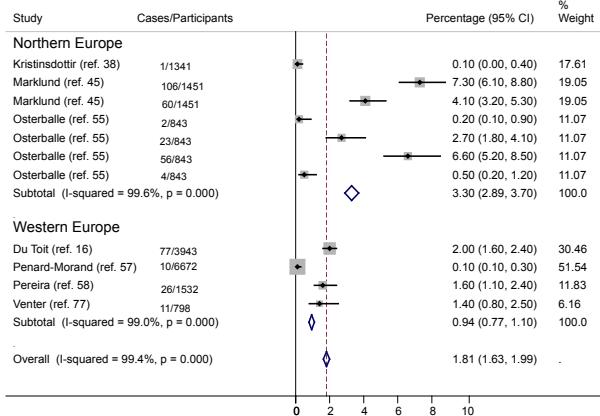
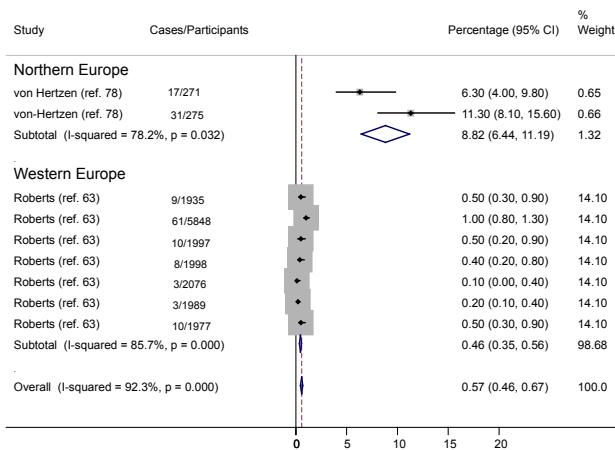
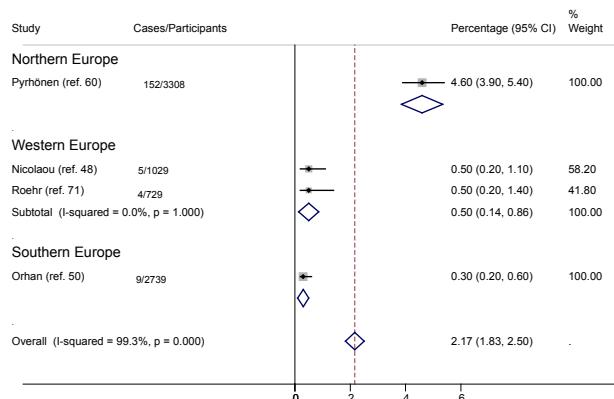
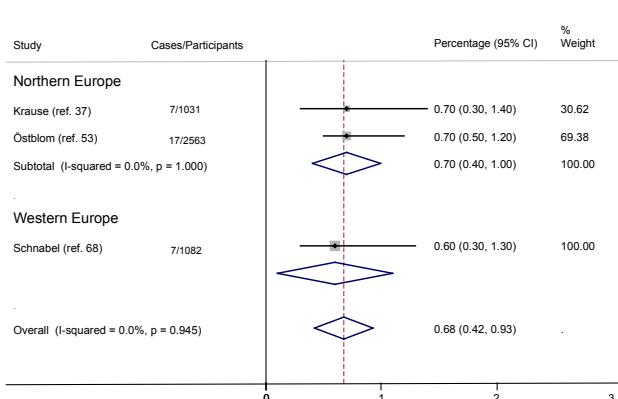
**PANEL I: Lifetime prevalence of self-reported TNA****PANEL II: Point prevalence of self-reported TNA****PANEL III: Point prevalence of SPT positive TNA**

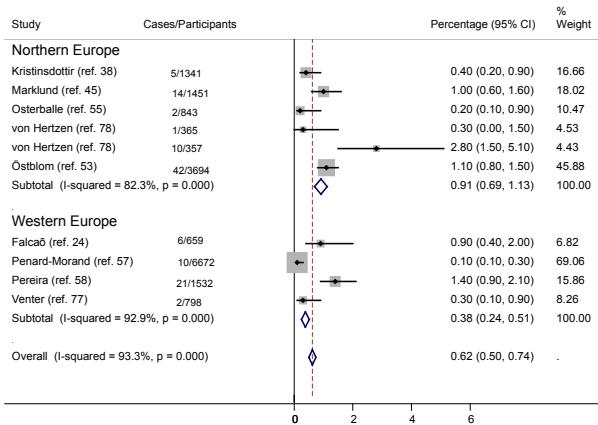
Figure E7 Region-stratified pooled prevalence of tree nut allergy (TNA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size



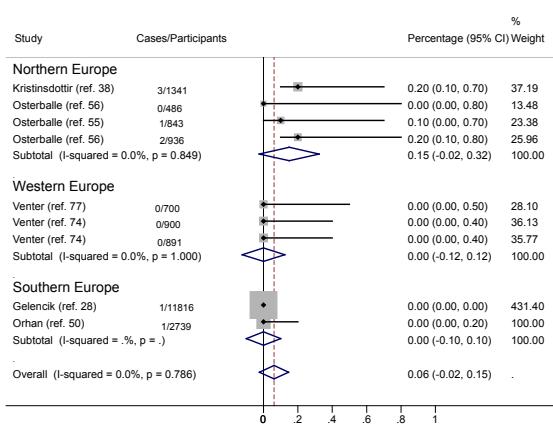
PANEL I: Lifetime prevalence of self-reported FA



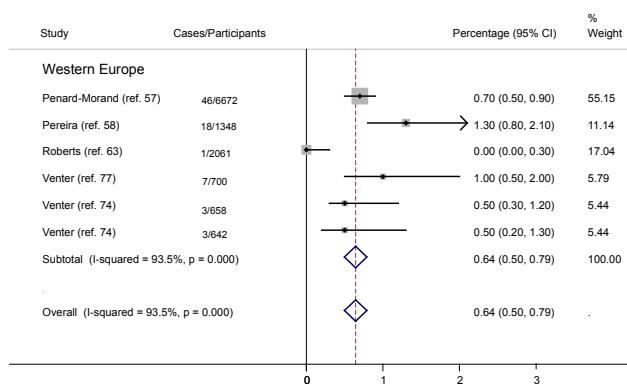
PANEL IV: Point prevalence of IgE positive FA



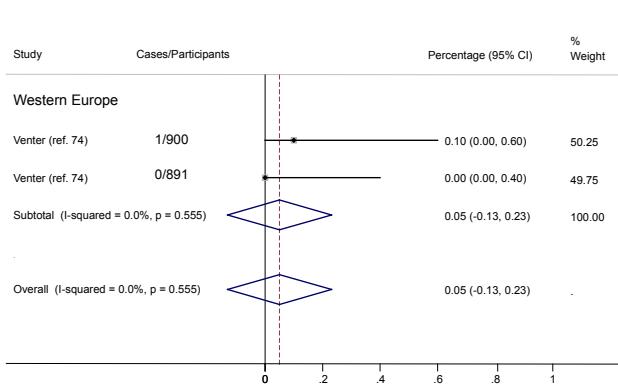
PANEL II: Point prevalence of self-reported FA



PANEL V: Point prevalence of FC positive FA



PANEL III: Point prevalence of SPT positive FA



PANEL VI: Point prevalence of FC or history of FA

Figure E8 Region-stratified pooled prevalence of fish allergy (FA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the study size

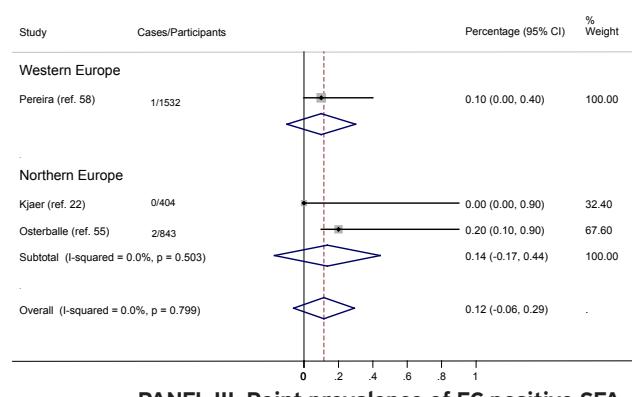
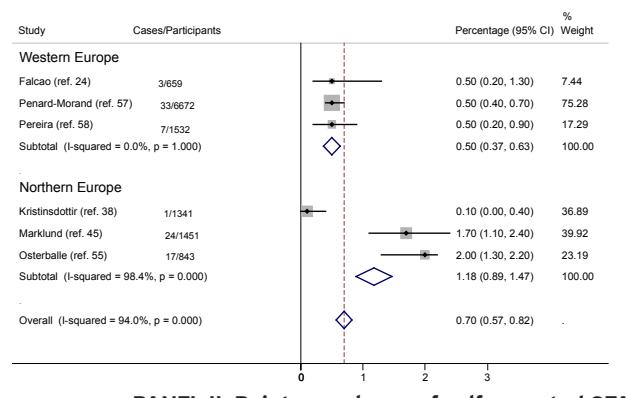
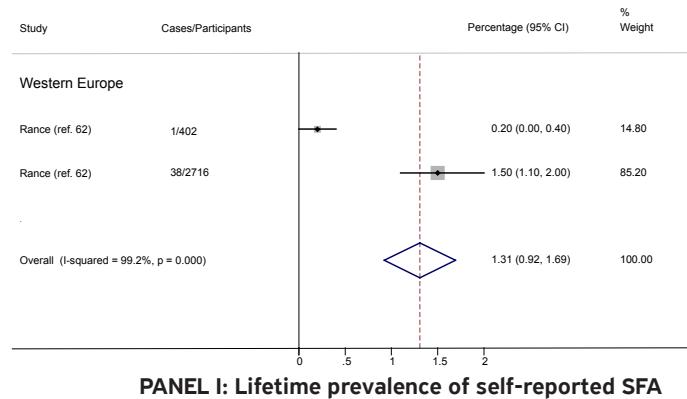


Figure E9 Region-stratified pooled prevalence of shellfish allergy (SFA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the size of the study

1.3

THE DIAGNOSIS OF FOOD ALLERGY SYSTEMATIC REVIEW AND META-ANALYSIS

☞ Supplementary materials ☞

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On behalf of the EAACI Food Allergy and Anaphylaxis Group: CA Akdis, R Alvarez, K Beyer, C Bindslev-Jensen, V Cardona, P Demoly, A Dubois, P Eigenmann, M Fernandez Rivas, A Høst, G Lack, MJ Marchisotto, B Niggemann, C Nilsson, N Papadopoulos, I Skypala, M Worm



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RESULTS

Study characteristics

Figure E1 shows the PRISMA flowchart for our study selection and screening. The tests assessed in the studies were atopy patch testing (APT) ($n=5$), skin prick testing (SPT) ($n=18$), serum food-specific-IgE (specific-IgE) ($n=22$), and component specific-IgE ($n=4$); the target foods were: cow's milk allergy ($n=10$), hen's egg allergy ($n=12$), wheat ($n=8$), soy ($n=7$), peanut ($n=9$), hazelnut ($n=4$), fish ($n=2$), and shrimp ($n=2$).

Risk of bias of included studies

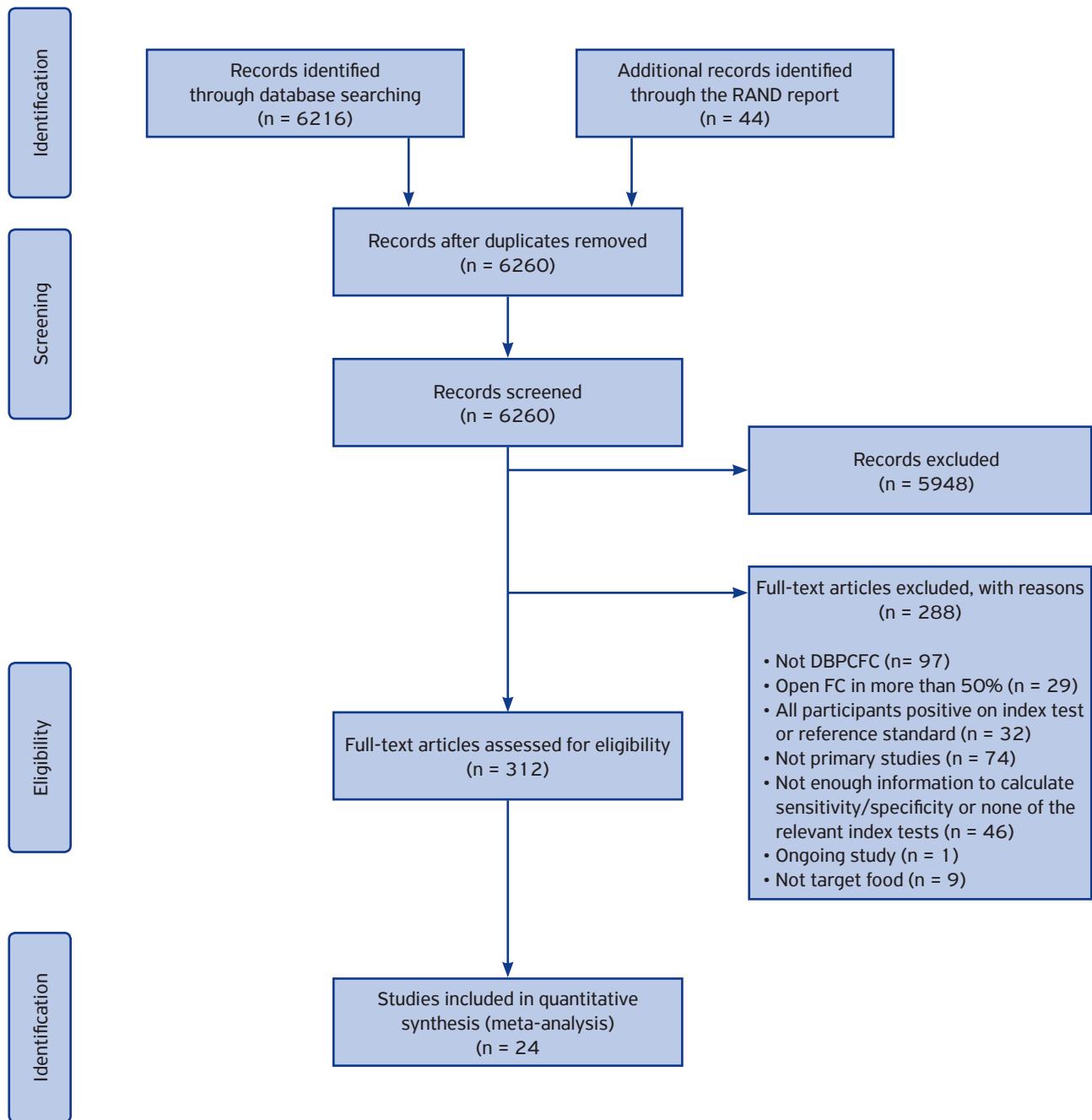
In the patient selection domain, 10 (42%) studies did not randomly select or consecutively enrol participants, two studies (8%) used a case-control design, and 23 (96%) studies had inappropriate exclusions or the study did not report how they managed exclusions. Twelve (50%) studies were considered to be at high risk of bias and 6 (25%) studies were judged as unclear risk of bias. In terms of applicability concerns regarding patient characteristics and setting, we judged 19 (79%) studies to be of low concern; this was mostly because the inclusion criteria for participating in these studies were similar to our review criteria.

For the index test domain, in 12 (50%) studies the results of the index test were interpreted with knowledge of the results of the reference standard, or

they did not report whether this was the case. Twenty-two (92%) studies reported using a threshold of $\geq 3\text{mm}$ for SPT and/or $>0.35 \text{ kU/L}$ for specific-IgEs. Eleven (46%) studies were considered to be a high or unclear risk of bias. In terms of applicability concerns, 18 studies (75%) were judged as high concern because in these studies the index tests (SPT and/or specific-IgE) had been previously used when a diagnosis of food allergy was suspected.

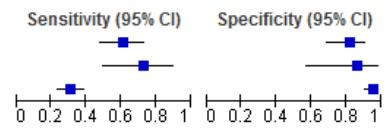
For the reference standard domain, 17 (71%) studies clearly reported that they had only used double-blind, placebo-controlled food challenge (DBPCFC), and another 7 (29%) studies used an open food challenge in up to 50% of the population. In addition, 13 (54%) interpreted the results of the reference standard with knowledge of the index test, or did not report whether the interpreter was blind to the results of the index test. Fifteen (62%) studies were considered to be a high or unclear risk of bias. In terms of applicability concerns, 21 studies (87%) were judged as low concern because most of these papers looked specifically at diagnosing food allergies as defined by the reference standard.

For the flow and timing domain, we considered only four (17%) studies to be of low risk of bias because in these studies all participants received the same reference standard within six months of having received the index test, even though it was unclear whether all participants were accounted for in the analysis. Five (21%) studies were considered as high risk and 15 (62%) as unclear risk of bias in this domain.

**Figure E1** Flow chart

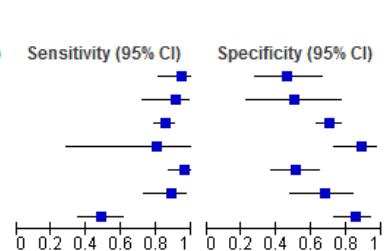
Target food: Cow's milk. Index test: APT

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Isolauri 1996	39	10	25	44		0.61 [0.48, 0.73]	0.81 [0.69, 0.91]
Keskin 2005	16	2	6	12		0.73 [0.50, 0.89]	0.86 [0.57, 0.98]
Mehl 2006	52	9	116	164		0.31 [0.24, 0.39]	0.95 [0.90, 0.98]



Target food: Cow's milk. Index test: SPT (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998 (A)	33	15	2	13	$\geq 3\text{mm}$	0.94 [0.81, 0.99]	0.46 [0.28, 0.66]		
Keskin 2005	21	7	2	7	$\geq 3\text{mm}$	0.91 [0.72, 0.99]	0.50 [0.23, 0.77]		
Mehl 2006	143	52	25	121	$\geq 3\text{mm}$	0.85 [0.79, 0.90]	0.70 [0.63, 0.77]		
Sampson 1984	4	4	1	31	$\geq 3\text{mm}$	0.80 [0.28, 0.99]	0.89 [0.73, 0.97]		
Sampson 1997	51	26	2	27	$\geq 3\text{mm}$	0.96 [0.87, 1.00]	0.51 [0.37, 0.65]		
Eigenmann 1998 (B)	31	9	4	19	$\geq 5\text{mm}$	0.89 [0.73, 0.97]	0.68 [0.48, 0.84]		
Isolauri 1996	31	8	33	46	1/2 histamine reaction	0.48 [0.36, 0.61]	0.85 [0.73, 0.93]		



Target food: Cow's milk. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Breuer 2004	11	9	4	8	$>0.35 \text{ kU/L}$	0.73 [0.45, 0.92]	0.47 [0.23, 0.72]		
Mehl 2006	146	88	22	85	$>0.35 \text{ kU/L}$	0.87 [0.81, 0.92]	0.49 [0.41, 0.57]		
Sampson 1997 (A)	95	71	0	30	$>0.35 \text{ kU/L}$	1.00 [0.96, 1.00]	0.30 [0.21, 0.40]		
van den 2012	69	56	15	45	$>0.35 \text{ kU/L}$	0.82 [0.72, 0.90]	0.45 [0.35, 0.55]		
Keskin 2005 (A)	18	4	5	10	$>0.59 \text{ kU/L}$	0.78 [0.56, 0.93]	0.71 [0.42, 0.92]		
Keskin 2005 (B)	17	3	6	11	$>0.70 \text{ kU/L}$	0.74 [0.52, 0.90]	0.79 [0.49, 0.95]		
Keskin 2005 (C)	17	2	6	12	$\geq 0.84 \text{ kU/L}$	0.74 [0.52, 0.90]	0.86 [0.57, 0.98]		
Keskin 2005 (D)	14	0	9	14	$\geq 4.18 \text{ kU/L}$	0.61 [0.39, 0.80]	1.00 [0.77, 1.00]		
Sampson 1997 (B)	76	19	19	82	$\geq 4.18 \text{ kU/L}$	0.80 [0.71, 0.88]	0.81 [0.72, 0.88]		
Sampson 1984	3	8	2	27	NR	0.60 [0.15, 0.95]	0.77 [0.60, 0.90]		

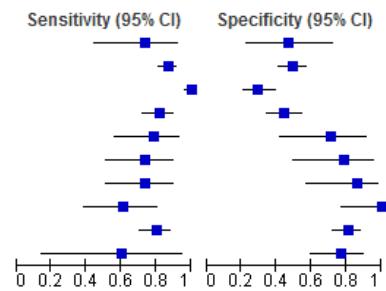


Figure E2a Individual study estimates of sensitivity and specificity for atopy patch test, skin prick test, and specific-IgE for diagnosis of cow's milk allergy (APT = atopy patch test; FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. Eigenmann 1998 and Sampson 1997 (suffixes A and B) reported test accuracy at 2 cutoffs for SPT and specific IgE, respectively. Keskin 2005 (suffixes A to D) reported 4 cutoffs for specific IgE.)

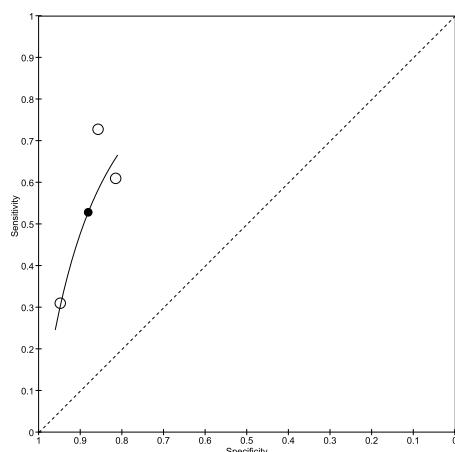


Figure E2b Summary ROC plot for atopy patch test (APT) for diagnosis of cow's milk allergy. Each hollow circle represents a pair of sensitivity and specificity from each study. (The point on the SROC curve corresponds to the summary sensitivity and specificity. A 95% confidence region around the point could not be computed because there were fewer than 4 studies)

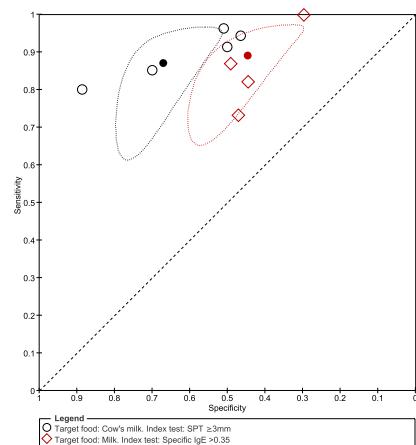
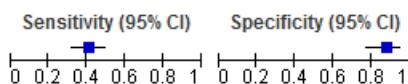


Figure E2c Summary ROC plot comparing skin prick test (SPT) and specific-IgE for diagnosis of cow's milk allergy. (The black point corresponds to the summary sensitivity and specificity of SPT. The red point corresponds to the summary estimates for specific-IgE. 95% confidence regions are drawn around each point)

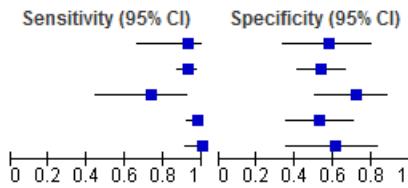
Target food: Hen's egg. Index test: APT

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	52	8	76	57	NR	0.41 [0.32, 0.50]	0.88 [0.77, 0.95]



Target food: Hen's egg. Index test: SPT (mixed cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Caffarelli 1995	13	8	1	11	$\geq 3\text{mm}$	0.93 [0.66, 1.00]	0.58 [0.33, 0.80]
Mehl 2006	119	30	9	35	$\geq 3\text{mm}$	0.93 [0.87, 0.97]	0.54 [0.41, 0.66]
Sampson 1984	11	7	4	18	$\geq 3\text{mm}$	0.73 [0.45, 0.92]	0.72 [0.51, 0.88]
Sampson 1997	88	16	2	18	$\geq 3\text{mm}$	0.98 [0.92, 1.00]	0.53 [0.35, 0.70]
Eigenmann 1998	40	7	0	11	$\geq 4\text{mm}$	1.00 [0.91, 1.00]	0.61 [0.36, 0.83]



Target food: Hen's egg. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	123	34	5	31	$>0.35\text{ kU/L}$	0.96 [0.91, 0.99]	0.48 [0.35, 0.60]	0.96 [0.91, 0.99]	0.48 [0.35, 0.60]
Sampson 1997 (A)	142	28	3	23	$>0.35\text{ kU/L}$	0.98 [0.94, 1.00]	0.45 [0.31, 0.60]	0.98 [0.94, 1.00]	0.45 [0.31, 0.60]
van den 2012	33	40	11	26	$>0.35\text{ kU/L}$	0.75 [0.60, 0.87]	0.39 [0.28, 0.52]	0.75 [0.60, 0.87]	0.39 [0.28, 0.52]
Sampson 1997 (B)	119	8	26	43	$\geq 3.4\text{ kU/L}$	0.82 [0.75, 0.88]	0.84 [0.71, 0.93]	0.82 [0.75, 0.88]	0.84 [0.71, 0.93]
Caffarelli 1995	12	6	2	13	NR	0.86 [0.57, 0.98]	0.68 [0.43, 0.87]	0.86 [0.57, 0.98]	0.68 [0.43, 0.87]
Sampson 1984	12	9	3	16	NR	0.80 [0.52, 0.96]	0.64 [0.43, 0.82]	0.80 [0.52, 0.96]	0.64 [0.43, 0.82]

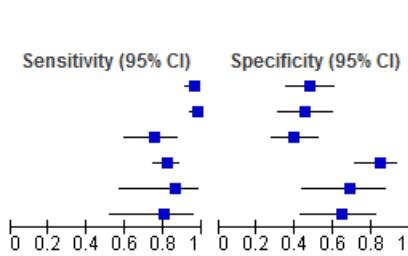


Figure E3a Individual study estimates of sensitivity and specificity for atopy patch test, skin prick test, and specific-IgE for diagnosis of hen's egg allergy (FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. The study Sampson 1997 (suffixes A and B) reported the accuracy of specific-IgE at two cut-offs. If a study reported multiple cut-offs, only data at one cut-off was chosen for the meta-analysis.)

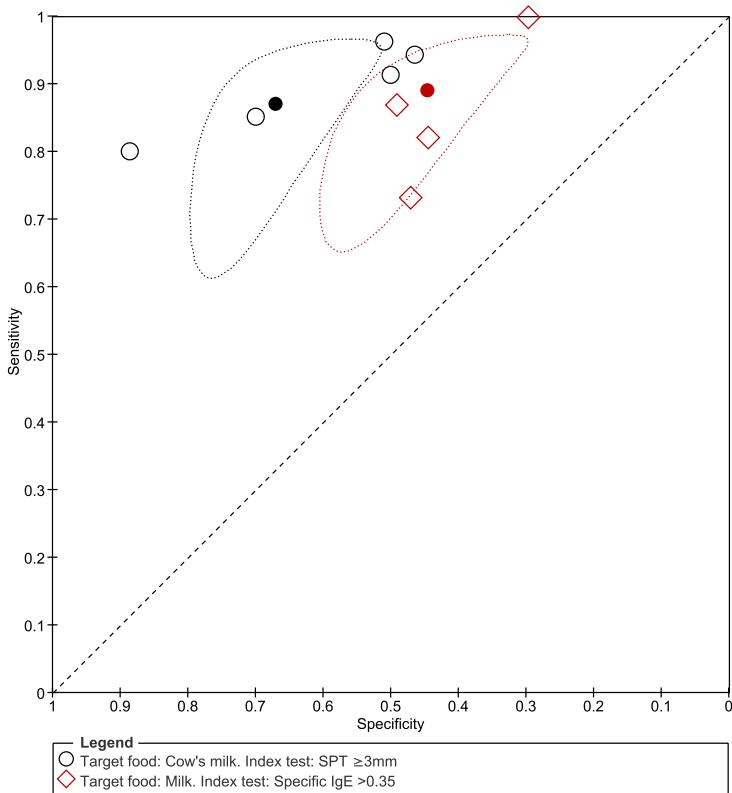
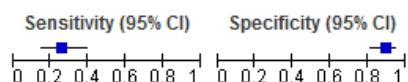


Figure E3b Summary ROC plot comparing skin prick test (SPT) and specific-IgE for diagnosis of hen's egg allergy. (The black point corresponds to the summary sensitivity and specificity of SPT. The red point corresponds to the summary estimates for specific-IgE. 95% confidence regions are drawn around each point).

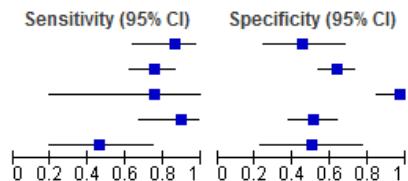
Target food: Wheat. Index test: APT

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	15	11	42	91		0.26 [0.16, 0.40]	0.89 [0.82, 0.94]



Target food: Wheat. Index test: SPT ($\geq 3\text{mm}$)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998	18	12	3	10	$\geq 3\text{mm}$	0.86 [0.64, 0.97]	0.45 [0.24, 0.68]
Mehl 2006	43	37	14	65	$\geq 3\text{mm}$	0.75 [0.62, 0.86]	0.64 [0.54, 0.73]
Sampson 1984	3	1	1	32	$\geq 3\text{mm}$	0.75 [0.19, 0.99]	0.97 [0.84, 1.00]
Sampson 1997	17	32	2	33	$\geq 3\text{mm}$	0.89 [0.67, 0.99]	0.51 [0.38, 0.63]
Scibilia 2006	6	7	7	7	$\geq 3\text{mm}$	0.46 [0.19, 0.75]	0.50 [0.23, 0.77]



Target food: Wheat. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Breuer 2004	6	3	3	14	$>0.35 \text{ kU/L}$	0.67 [0.30, 0.93]	0.82 [0.57, 0.96]
Mehl 2006	47	67	10	35	$>0.35 \text{ kU/L}$	0.82 [0.70, 0.91]	0.34 [0.25, 0.44]
Sampson 1997 (A)	22	138	1	35	$>0.35 \text{ kU/L}$	0.96 [0.78, 1.00]	0.20 [0.15, 0.27]
Scibilia 2006	11	11	2	3	$>0.35 \text{ kU/L}$	0.85 [0.55, 0.98]	0.21 [0.05, 0.51]
Sampson 1997 (B)	17	46	7	126	$\geq 8.1 \text{ kU/L}$	0.71 [0.49, 0.87]	0.73 [0.66, 0.80]
Sampson 1984	3	12	1	21	Score system	0.75 [0.19, 0.99]	0.64 [0.45, 0.80]

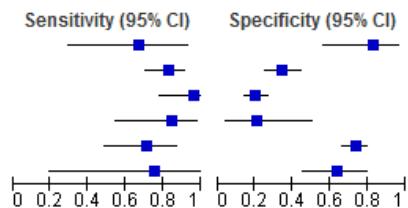


Figure E4a Individual study estimates of sensitivity and specificity for atopy patch test, skin prick test, and specific-IgE for diagnosis of wheat allergy (APT = atopy patch test; FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. Sampson 1997 (suffixes A and B) reported the accuracy of specific-IgE at 2 cut-offs. If a study reported multiple cut-offs, only data at one cut-off was chosen for the meta-analysis)

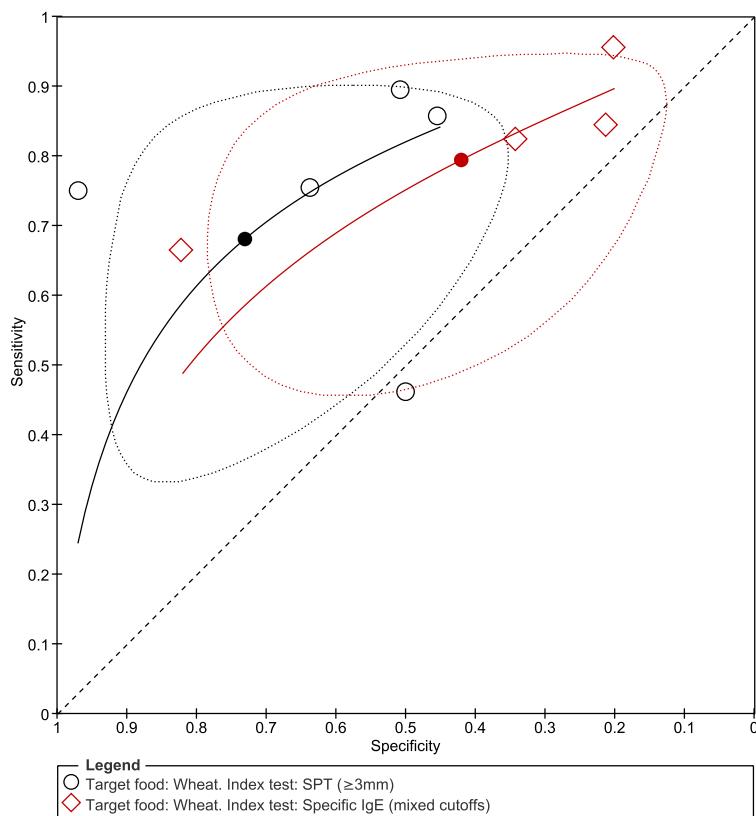
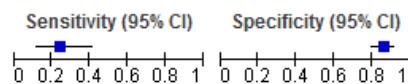


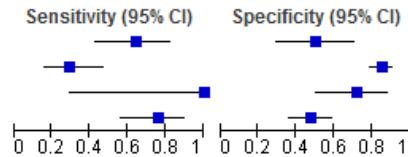
Figure E4b Summary ROC plot comparing skin prick test (SPT) and specific-IgE for diagnosis of wheat allergy (The point on the SROC curve for each test corresponds to the summary sensitivity and specificity for the test. 95% confidence regions are drawn around each point)

Target food: Soy. Index test: APT

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	9	20	28	123		0.24 [0.12, 0.41]	0.86 [0.79, 0.91]

Target food: Soy. Index test: SPT ($\geq 3\text{mm}$)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998	16	13	9	13	$\geq 3\text{mm}$	0.64 [0.43, 0.82]	0.50 [0.30, 0.70]
Mehl 2006	11	21	26	122	$\geq 3\text{mm}$	0.30 [0.16, 0.47]	0.85 [0.78, 0.91]
Sampson 1984	3	7	0	18	$\geq 3\text{mm}$	1.00 [0.29, 1.00]	0.72 [0.51, 0.88]
Sampson 1997	22	41	7	37	$\geq 3\text{mm}$	0.76 [0.56, 0.90]	0.47 [0.36, 0.59]



Target food: Soy. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Mehl 2006	24	71	13	72	$>0.35 \text{ kU/L}$	0.65 [0.47, 0.80]	0.50 [0.42, 0.59]
Sampson 1997 (A)	32	121	2	41	$>0.35 \text{ kU/L}$	0.94 [0.80, 0.99]	0.25 [0.19, 0.33]
Sampson 1997 (B)	23	60	11	102	$\geq 5 \text{ kU/L}$	0.68 [0.49, 0.83]	0.63 [0.55, 0.70]
Sampson 1984	2	9	1	16	NR	0.67 [0.09, 0.99]	0.64 [0.43, 0.82]

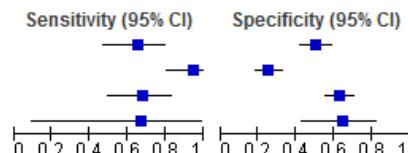


Figure E5a Individual study estimates of sensitivity and specificity for atopy patch test, skin prick test, and specific-IgE for diagnosis of soy allergy (APT = atopy patch test; FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. Sampson 1997 (suffixes A and B) reported the accuracy of specific-IgE at 2 cut-offs. If a study reported multiple cut-offs, only data at one cut-off was chosen for the meta-analysis)

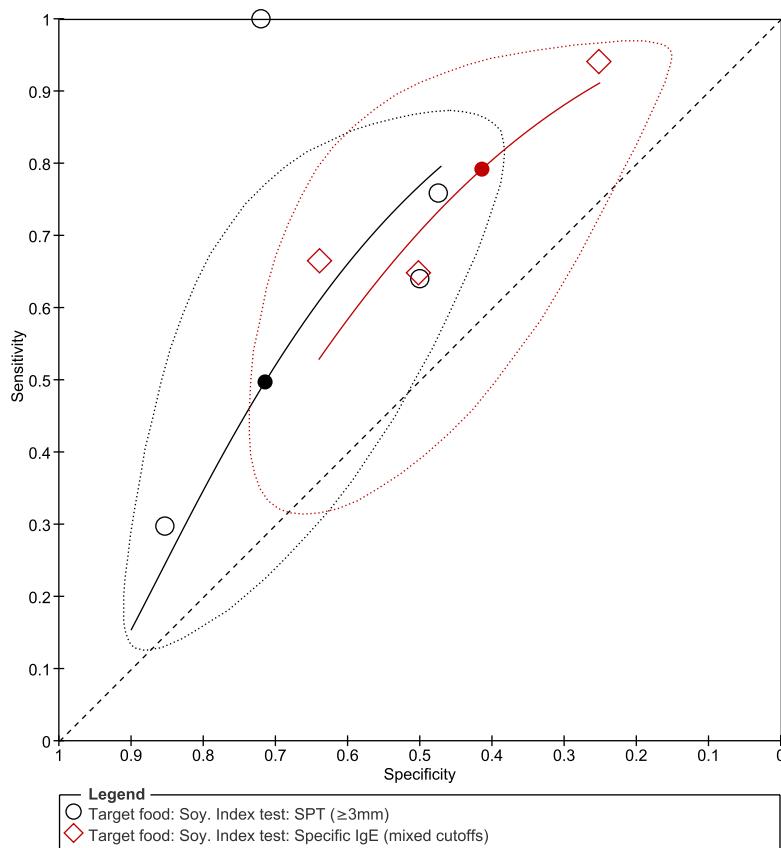
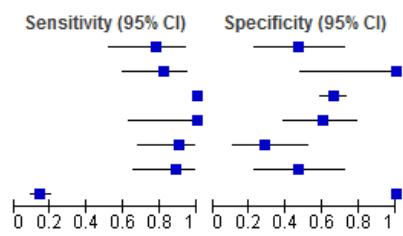


Figure E5b Summary ROC plot comparing skin prick test (SPT) and specific-IgE for diagnosis of soy allergy (The point on the SROC curve for each test corresponds to the summary sensitivity and specificity for the test. 95% confidence regions are drawn around each point)

Target food: Peanut. Index test: SPT (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Eigenmann 1998 (A)	14	9	4	8	$\geq 3\text{mm}$	0.78 [0.52, 0.94]	0.47 [0.23, 0.72]
Flinterman 2006	18	0	4	5	$\geq 3\text{mm}$	0.82 [0.60, 0.95]	1.00 [0.48, 1.00]
Rance 2002 (A)	177	63	0	123	$\geq 3\text{mm}$	1.00 [0.98, 1.00]	0.66 [0.59, 0.73]
Sampson 1984	8	10	0	15	$\geq 3\text{mm}$	1.00 [0.63, 1.00]	0.60 [0.39, 0.79]
Sampson 1997	18	15	2	6	$\geq 3\text{mm}$	0.90 [0.68, 0.99]	0.29 [0.11, 0.52]
Eigenmann 1998 (B)	16	9	2	8	$\geq 6\text{mm}$	0.89 [0.65, 0.99]	0.47 [0.23, 0.72]
Rance 2002 (B)	26	0	151	186	$\geq 16\text{mm}$	0.15 [0.10, 0.21]	1.00 [0.98, 1.00]



Target food: Peanut. Index test: Specific IgE (all cutoffs)

Study	TP	FP	FN	TN	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
Flinterman 2006	22	1	0	4	$>0.35 \text{ kU/L}$	1.00 [0.85, 1.00]	0.80 [0.28, 0.99]
Rance 2002 (A)	171	70	6	116	$>0.35 \text{ kU/L}$	0.97 [0.93, 0.99]	0.62 [0.55, 0.69]
Sampson 1997 (A)	132	37	4	23	$>0.35 \text{ kU/L}$	0.97 [0.93, 0.99]	0.38 [0.26, 0.52]
van den 2012	105	25	4	64	$>0.35 \text{ kU/L}$	0.96 [0.91, 0.99]	0.72 [0.61, 0.81]
Sampson 1997 (B)	103	7	33	53	$\geq 10.7 \text{ kU/L}$	0.76 [0.68, 0.83]	0.88 [0.77, 0.95]
Rance 2002 (B)	27	0	150	186	$\geq 57 \text{ kU/L}$	0.15 [0.10, 0.21]	1.00 [0.98, 1.00]
van Nieuwaal 2010 (A)	37	4	19	43	10.4 kU/L	0.66 [0.52, 0.78]	0.91 [0.80, 0.98]
van Nieuwaal 2010 (B)	27	1	29	46	24.1 kU/L	0.48 [0.35, 0.62]	0.98 [0.89, 1.00]
van Nieuwaal 2010 (C)	27	0	29	47	26.5 kU/L	0.48 [0.35, 0.62]	1.00 [0.92, 1.00]
Sampson 1984	8	10	0	15	NR	1.00 [0.63, 1.00]	0.60 [0.39, 0.79]

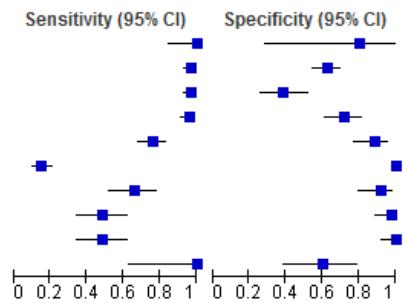


Figure E6a Individual study estimates of sensitivity and specificity for skin prick test and specific-IgE for diagnosis of peanut allergy (FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. Eigenmann 1998, Rance 2002, and Sampson 1997 (suffixes A and B) reported the accuracy of a test at 2 cut-offs. Van Nieuwaal 2010 (suffixes A to C) reported 3 cut-offs for specific IgE. If a study reported multiple cut-offs, only data at one cut-off was chosen for the meta-analysis)

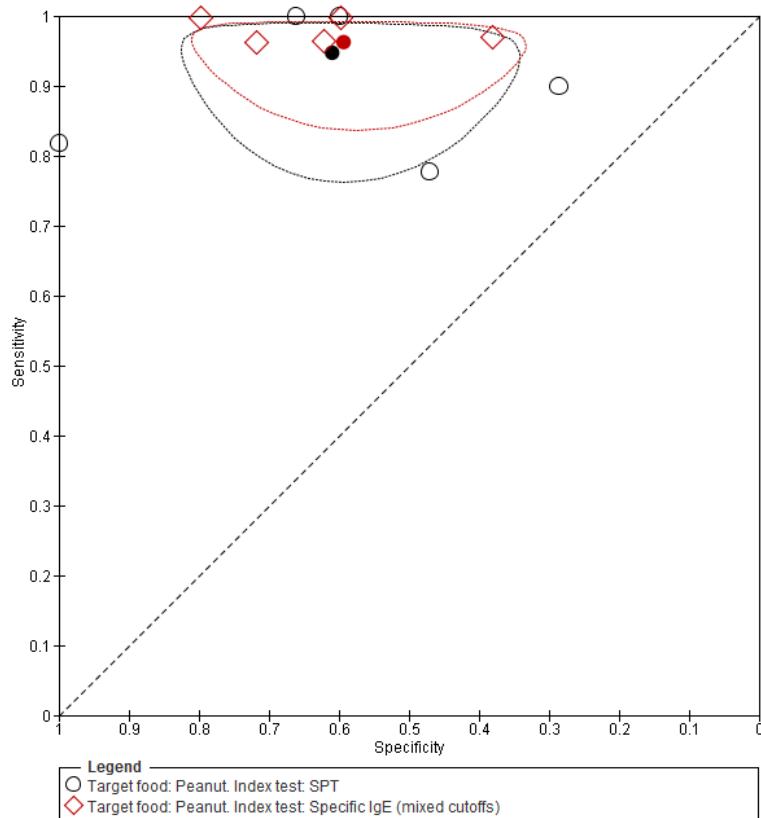
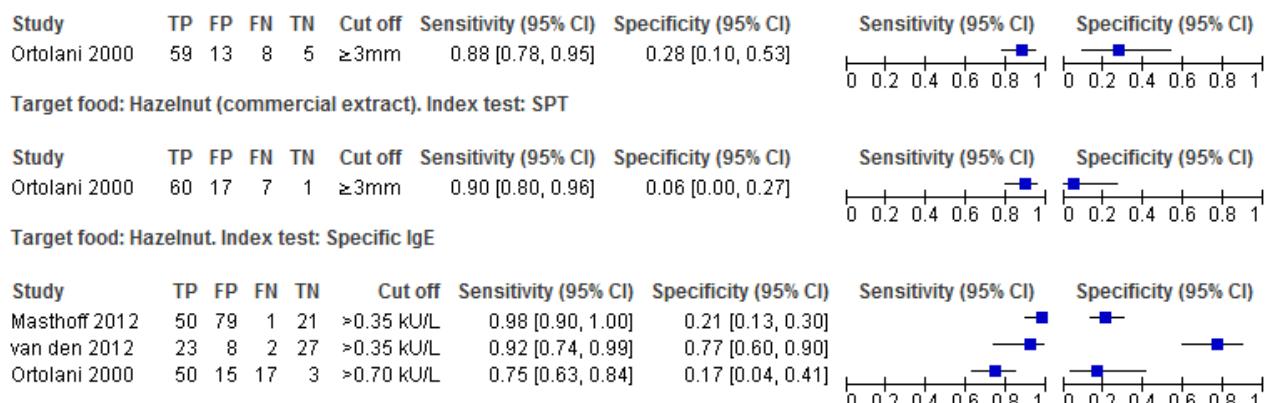
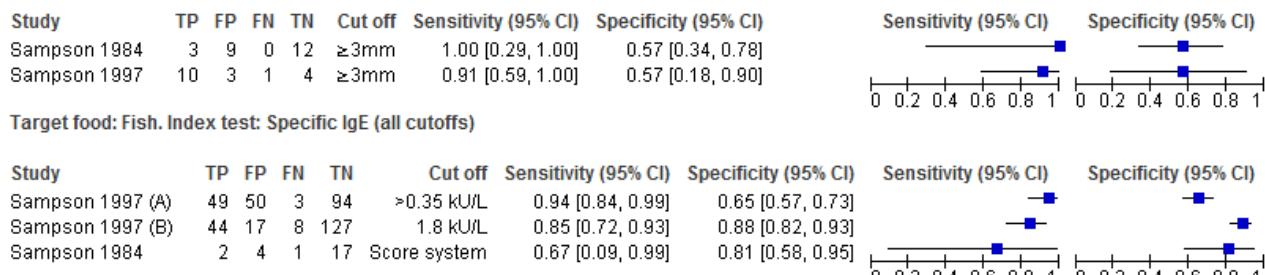


Figure E6b Summary ROC plot comparing skin prick test (SPT) and specific-IgE for diagnosis of peanut allergy (The black point corresponds to the summary sensitivity and specificity of SPT. The red point corresponds to the summary estimates for specific-IgE. 95% confidence regions are drawn around each point)

Target food: Hazelnut (natural extract). Index test: SPT

**Figure E7** Individual study estimates of sensitivity and specificity for skin prick test and specific-IgE for diagnosis of allergy to hazelnuts

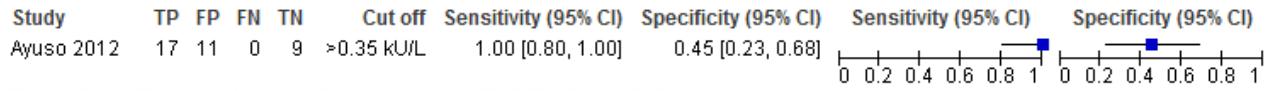
Target food: Fish. Index test: SPT

**Figure E8** Individual study estimates of sensitivity and specificity for skin prick test and specific-IgE for diagnosis of fish allergy (FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive. Sampson 1997 (suffixes A and B) reported the accuracy of specific-IgE at 2 cut-offs)

Target food: Shrimp. Index test: SPT



Target food: Shrimp. Index test: Specific IgE



Target food: Shrimp. Index test: Component specific IgE (rPen a1 IgE)

**Figure E9** Individual study estimates of sensitivity and specificity for skin prick test, specific-IgE and component specific-IgE for diagnosis of shrimp allergy (FN = false negative; FP = false positive; NR = not reported; SPT = skin prick test; TN = true negative; TP = true positive)

1.4

ACUTE AND LONG-TERM MANAGEMENT OF FOOD ALLERGY SYSTEMATIC REVIEW

❖ Supplementary materials ❖

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Table E1 Studies included in the systematic review

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
STRATEGIES TARGETING ACUTE NON-LIFE THREATENING SYMPTOMS: PHARMACOLOGICAL TREATMENT							
Bindsvell-Jensen 1991	Denmark	Randomized controlled trial (RCT), double blind	30 people with allergy to hazelnuts and silver birch	Astemizole 10 mg versus placebo for 2 weeks	Symptoms	People with oral allergy syndrome are advised to avoid problematic foods. This may not always be possible. This study suggested that treatment with antihistamines might be suitable if symptoms following ingestion of hazelnuts are not life-threatening. Astemizole significantly reduced symptoms compared with placebo but did not completely eliminate them ($p = 0.004$). In the treatment group, 73% had a reduction in symptom severity exceeding two points compared with 6% of controls ($p < 0.05$).	Low
Ciprandi 1987	Italy	Non-random comparison	39 adults with food allergy and 41 adults with pseudo-allergic reactions	Terfenadine 60 mg twice daily versus oral cromolyn 200 mg to 400 mg four times per day versus ketotifen 2 mg daily versus ranitidine 150 mg plus terfenadine 60 mg twice daily versus placebo	Symptoms	Terfenadine had no benefit over placebo for food allergy symptoms. Oral cromolyn and ketotifen both had benefits. The most benefits came from combining the antihistamine drugs ranitidine and terfenadine.	Low
Ciprandi 1987	Italy	Non-random comparison	105 adults with cutaneous symptoms due to food allergy	Placebo versus terfenadine alone versus terfenadine plus pirenzepine versus terfenadine plus rosaprostol versus terfenadine plus ranitidine versus terfenadine plus famotidine for 4 weeks	Symptoms	Terfenadine alone had no benefits over placebo. Terfenadine plus other drugs was more beneficial, particularly combining with cytoprotective drugs. No significant side effects were observed in any of the groups.	Low
Lin 2000	US	RCT	91 adults with acute allergic syndromes, half of which tested positive for food allergy	50 mg of diphenhydramine and saline solution (H1 antagonist control group) versus with 50 mg of diphenhydramine and 50 mg ranitidine (H1 + H2)	Symptoms	Two hours after treatment, the H1 + H2 antagonist group was less likely to have urticaria or bothuricaria and angioedema. There were no differences between Moderate groups in absence of erythema or angioedema, blood pressure and other symptoms.	Moderate
Pacor 1992	Italy	RCT	20 adults with chronic urticaria or atopic eczema / dermatitis due to food allergy or intolerance	Oxatomide 60 mg daily versus disodium cromoglycate 2000 mg daily for 6 weeks then crossed over after 3 week washout	Symptoms	Both drugs reduced symptoms and were well tolerated. Wheals disappeared totally from 75% of the oxatomide group versus 33% disodium cromoglycate. Eczema lesions disappeared in 64% of the oxatomide group versus 50% disodium cromoglycate. Itching disappeared in 70% of the oxatomide group versus 50% disodium cromoglycate.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
STRATEGIES TARGETING LONG-TERM MANAGEMENT: PHARMACOLOGICAL TREATMENT							
Boner 1986	Italy	RCT, double blind	26 children and adults with food allergy	Ketotifen 1 mg twice daily versus placebo for 1 month	Symptoms	Ketotifen protected patients significantly more than placebo (54% of the treatment group had no reaction to oral food challenge versus 15% placebo, $p < 0.05$).	Low
Cavagni 1989	Italy	RCT, double blind	19 children with food allergy manifesting as atopie dermatitis	Thymomodulin 120 mg versus placebo for 90 days. All participants used an elimination diet throughout	Symptoms	Thymomodulin reduced skin lesions ($p < 0.01$).	Low
Burks 1988	US	RCT, double blind	8 children aged 3 to 15 years with atopie dermatitis and documented food hypersensitivity	Oral cromolyn sodium up to 40 mg per kg per day versus placebo for 1 week, then crossed over following 3 to 5 week washout period	Symptoms	There was no difference between groups in the amount of egg needed to induce a response ($p = 0.5$), in the time to onset of first subjective symptoms ($p = 0.2$) or in the duration of symptoms ($p = 0.6$).	Low
Businco 1986	Italy	RCT, double blind	31 children aged 6 months to 10 years with atopie dermatitis due to food allergy	Oral sodium cromoglycate versus placebo for 8 weeks, then crossed over. Dose was based on weight. For the first 4 weeks, patients were on an exclusion diet. For the final 4 weeks, foods were reintroduced.	Symptoms	Oral sodium cromoglycate was associated with improved atopie eczema / dermatitis symptoms (mean clinical symptom assessment 9.5 versus 13.3 placebo, $p < 0.05$). Treatment was also better than placebo in preventing symptom exacerbation caused by food reintroduction (mean clinical symptom assessment 7.7 versus 22.5 placebo, $p < 0.01$).	Low
Dannaeus 1977	Sweden	RCT, double blind	20 children aged 1 to 15 years with food allergy	Oral sodium cromoglycate, 400 mg daily versus placebo for three weeks	Symptoms	There was a trend towards reduced symptoms but this was not statistically significant (mean challenge score 1.2 treatment versus 1.9 controls, $p = 0.05$).	Low
Daugbjerg 1984	Denmark	RCT, double blind	35 children and adults with chronic atopie eczema / dermatitis related to food allergy	Oral sodium cromoglycate 200 mg to 1 600 mg daily versus placebo for six weeks, then crossing over. The first 4 weeks of each segment included an elimination diet	Symptoms	There was no difference in symptoms of atopie eczema / dermatitis and itch between groups. Treatment resulted in side effects for 51% of participants. One person withdrew due to side effects.	Low
Ellul-Micallef 1983	Kuwait	RCT, double blind	20 adults with fish induced bronchial asthma	Oral sodium cromoglycate 400 mg 4 times daily versus ketotifen 1 mg twice daily versus placebo for 3 days	Symptoms	Before treatment, eating fish was associated with a fall in forced expiratory volume. Sodium cromoglycate blocked this fall in 80%. Ketotifen had no effect.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Gerrard 1979	Canada	RCT, double blind	32 children and adults with food allergy	Oral sodium cromoglycate, 50 mg or 100 mg four times daily for 7 days versus placebo, then crossed over following 1 week washout period	Tolerability	There was a significant benefit from oral sodium cromoglycate (81% versus 13% placebo). 29% suffered adverse reactions from treatment, including headaches, hives and abdominal pain.	Low
Ortolani 1983	Italy	RCT, double blind	24 adults with adverse reactions to foods	Oral sodium cromoglycate, 1600 mg daily versus placebo for 8 weeks	Symptoms	Oral sodium cromoglycate was associated with reduced self-reported symptom severity compared with placebo ($p < 0.01$). Side effects were minimal.	Low
Spira 1988	France	Non-random comparison	38 children and adults with food allergy	Nalcron in various doses combined with a food elimination diet	Symptoms	Nalcron can help to reduce symptoms if food is eliminated from the diet at first and gradually reintroduced.	Low
Wang 2010	US	RCT, double blind	19 children and adults with food allergy	Three times daily 2.2g of food allergy herbal formula versus 3.3g herbal formula versus 6.6g herbal formula versus placebo for 7 days	Symptoms	There were no significant differences between groups in vital signs, physical examination results or functional tests. However treatment groups had decreased interleukin 5 levels after 7 days.	Low
Zur 2002	Poland	Non-random comparison	150 children aged 0.5 to 15 years with food allergy or hypersensitivity	Oral sodium cromoglycate in two different doses versus placebo	Symptoms	Oral sodium cromoglycate was associated with reduced symptoms. Adverse effects were noted in 10% of children, but were not severe.	Low
STRATEGIES TARGETING LONG-TERM MANAGEMENT: ALTERNATIVES TO COWS' MILK FORMULA							
Cantani 2006	Italy	Non-random comparison	51 infants with food allergy and food induced atopic dermatitis	Homemade meat-based formula versus usual feeding for 2 months	Symptoms of atopic dermatitis	The meat-based formula was associated with a significant improvement in symptoms. After two months, compared to controls, the treatment group had a significant increase in weight gain ($p = 0.0001$) and a significant reduction in the severity score of skin lesions ($p = 0.0001$). There were no differences between groups in diagnoses of cows' milk, wheat or egg allergies after treatment.	Low
Galil 1996	Italy	Non-random comparison	55 children aged 2 to 48 months with cows' milk allergy	Replacement formula based on soy versus hydrolysate of soy and bovine collagen versus hydrolysate of casein. Follow-up occurred at 2 years	Tolerability, sensitivity	22% of the soy formula group, 8% of the soy hydrolysate and bovine group and 3.8% of the casein hydrolysate group experienced sensitivity reactions. Weight and growth was equal in all groups. Seven out of ten children achieved tolerance within two years. There was no significant difference between groups in tolerance acquisition.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Halken 1993	Denmark	Non-random comparison	31 children younger than one year with cows' milk allergy (plus other children included in non-eligible parts of the study)	15 children were fed an ultrafiltrated whey hydrolysate infant formula. Results were compared with 16 children fed an extensively hydrolysed casein hydrolysate.	Tolerability	Both the whey and casein formulas were well tolerated and no side effects were registered.	Low
Hill 2007	Australia	Systematic review	20 studies in children and adults with cows' milk allergy	Amino acid-based formula versus extensively hydrolysed formula / soy-based formula / cows' milk / cows' milk-based formula	Symptoms	Amino acid-based formula was safe and effective. Randomized trials found that amino acid-based formula was as effective for reducing symptoms as extensively hydrolysed formula, and may be more effective for some subgroups. Meta-analysis was not undertaken due to heterogeneity.	High
Isolauri 1995	Finland	RCT	45 infants aged 4 to 7 months with cows' milk allergy	Extensively hydrolysed whey formula versus amino acid-based formula	Symptoms	Extensively hydrolysed formulas and amino acid-based formulas both appear safe and effective for children with cows' milk allergy. Symptoms improved equally in both groups. Growth was initially better with amino acid-based formula, but this evened out. In both groups, atopic eczema / dermatitis improved significantly. Progressive improvement of the skin condition was reflected in significant reduction in the SCORAD scores in both groups. There were improvements in the extent, the intensity and the subjective scores and there was a trend towards reduced serum total and milk-specific IgE concentrations.	Low
Jirapinyo 2007	Thailand	RCT	38 infants aged 2 to 24 months with cows' milk allergy	Chicken-based formula versus soy-based formula for 14 days	Tolerability	The number of infants who were intolerant to chicken formula was significantly lower than the number of those fed soy-based formula ($p = 0.009$). 66% of those fed soy milk had intolerance and could not continue. 20% of those receiving chicken-based formula had evidence of intolerance. Chicken-based formula may be better than soy formula for infants with cows' milk allergy.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Klemola 2002	Finland	RCT	170 infants allergic to cows' milk	Formula with soy versus extensively hydrolysed whey formula. Follow-up occurred after two years	Tolerability	Soy formula was tolerated in most infants, but perhaps less so than extensively hydrolysed whey formula. Those younger than 6 months were more likely to have reactions to soy. Adverse reactions to formula were confirmed by challenge in 10% of the soy group and 2% of the extensively hydrolysed whey formula group. Parents suspected adverse reactions to the formula in 28% of the soy group and 11% of the extensively hydrolysed whey formula group. RR 2.48, $p = 0.006$.	High
McLeish 1995	England	RCT	29 infants allergic to cows' milk	Formula with hydrolysed whey versus formula with amino acids for 24 weeks	Tolerability	There were few differences between groups. The formulas were both well tolerated. Amino acid formula may have a role for infants who react to whey formula.	Low
Muraro 2002	Italy	Systematic review	Unlisted number of studies focused on children in the first year of life allergic to cows' milk	Milk derived from vegetable proteins or goat or donkey milk or elemental formula	Tolerability	Soy milk is nutritionally adequate and well tolerated in children allergic to cows' milk. Donkey or mare's Moderate milk is as allergenic as cows' milk.	Moderate
Niggemann 2001	Germany	RCT	73 1 to 10 month old infants allergic to or intolerant of cows' milk with atopic dermatitis	Extensively hydrolysed cows' milk whey formula versus amino acid-based formula for 6 months	Symptoms, growth	Both formulas were well tolerated and resulted in improved symptoms (symptom score reduced from mean 24.6 at baseline to 10.7, $p < 0.0001$). Amino acid-based formula resulted in better growth.	Moderate
Niggemann 2008	Germany	RCT	66 infants with cows' milk allergy	Extensively hydrolysed formula containing lactose versus amino acid-based formula for 180 days	Gastro-intestinal and respiratory tract allergy symptoms were similar between groups. Amino acid-based formula was more likely to reduce SCORAD scores for atopic dermatitis. There were no significant differences between groups in growth. Those fed extensively hydrolysed formula containing lactose had fewer vomiting incidents. The authors concluded that extensively hydrolysed formula containing lactose is safe and well tolerated in infants with cows' milk allergy.	Moderate	
Reche 2010	Spain	RCT	81 1-10 month old infants allergic to cows' milk	Hydrolysed rice protein formula versus extensively hydrolysed cows' milk protein formula	Tolerability	Hydrolysed rice protein formula was as effective and well tolerated as extensively hydrolysed cows' milk protein formula among infants with moderate to severe symptoms.	Moderate

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Salpietro 2005	Italy	RCT	52 children aged 5 to 9 months allergic to cows' milk	Almond-based milk versus soy-based formula versus protein hydrolysate-based formula	Symptoms	When coupled with elimination of the food that children were allergic to, formula free of milk protein reduced symptoms within 5 to 12 days. Almond milk did not negatively impact on growth compared to soy milk or protein hydrolysate-based formula. 23% of the soy group, 15% of the protein hydrolysate-based formula group and 0% of those receiving almond milk developed secondary sensitization.	Low
Savino 2005	Italy	RCT	58 infants with cows' milk allergy and atopic dermatitis and 30 infants with atopics dermatitis but no cows' milk allergy	Rice-based hydrolysate formula versus soy-based formula versus extensively hydrolysed casein formula for those with cows' milk allergy. Usual diet for those without allergy	Weight	There were no differences between groups, but there was a trend towards lower weight in the rice hydrolysate formula group which raises doubts about nutritional adequacy.	Low
STRATEGIES TARGETING LONG-TERM MANAGEMENT: DIETARY ELIMINATION							
Agata 1993	Japan	Non-random comparison	54 children aged 3 months to 10 years with atopics dermatitis and allergies to egg or milk	Elimination diet versus no diet	Symptoms	Symptoms were in remission during the elimination diet and reactions to allergens improved.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Alonso 1994	Argentina	Non-random comparison	41 children aged 8 to 12 years suffering symptoms when drinking orange juice and 20 non atopic children	Citrus fruit exclusion diet for 180 days	Symptoms	There was no improvement in skin reactivity or sensitization before and after the diet.	Low
Chen 2011	US	Systematic review	Unlisted number of studies about adults and children with spice allergy	Dietary avoidance	Symptoms	It is difficult to avoid spices due to unclear food labelling. No trials of immunotherapy were identified.	Low
STRATEGIES TARGETING LONG-TERM MANAGEMENT: PROBIOTICS							
Brouwer 2006	The Netherlands	RCT	55 children with atopic eczema / dermatitis and sensitivity to eggs	Mother's were given general advice about care of eczema and advice from a dietitian about egg-exclusion diet versus general advice for 4 weeks (controls)	Symptoms	Symptoms and severity reduced more in the diet group. The average reduction in surface area affected by atopic eczema / dermatitis was significantly greater in the group receiving dietary advice (from 19.6% to 10.9% area affected) than in the control group (from 21.9% to 18.9%, $p = 0.02$). There was also a significant improvement in severity score: from 33.9 to 24.0 units for the diet group compared with a decrease from 36.7 to 33.5 in the control group ($p = 0.04$).	Low
BerniCanani 2012	Italy	RCT	50 infants less than 5 months old with atopic dermatitis and suspected cows' milk allergy	Hydrolysed whey-based formula alone (placebo) or supplemented with Lactococcushamnosus or Lactobacillus GG for 3 months	Symptoms	There were no significant differences between groups in terms of sensitization, inflammatory parameters or symptoms. Probiotic bacteria did not appear to have an effect in unselected infants.	Moderate
				Extensively hydrolysed casein formula alone or supplemented with Lactobacillus GG. Follow-up occurred at 6 and 12 months	Tolerability	Probiotic supplementation was associated with accelerated development of tolerance to cows' milk protein. All infants were able to consume regular doses of cows' milk daily without showing any signs or symptoms related to cows' milk allergy for six months after achieving tolerance, which suggests persistence of tolerance.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Cukrowska 2010	Poland	RCT, double blind	60 children aged up to 2 years with atopic eczema / dermatitis and cows' milk allergy	Probiotic mixture of 3 strains versus placebo daily for 3 months. Follow-up occurred at 5 months and 2 years	Symptoms, tolerance	At three months, symptoms improved in 93% of children taking probiotics compared with 54% of controls. Symptoms improved mainly for those with IgE dependent allergy. Five month follow-up suggested differences did not persist once treatment was stopped. However follow-up at two years found those who received probiotics had better tolerance of cows' milk (81% versus 68% controls).	Moderate
Flinterman 2007	The Netherlands	RCT, double blind	13 children aged 6 months to 3 years with food allergy	Mixture of probiotics or placebo orally daily for 3 months	Tolerability, clinical markers	Sensitization towards peanut, egg and cows' milk remained unchanged after three months but markers of immune response altered.	Low
Helin 2002	Finland	RCT, double blind	36 young adults with apple allergy, birch pollen allergy and atopic allergy or mild asthma	Lactobacillus rhamnosus versus placebo for 5.5 months	Symptoms	Lactobacillus rhamnosus had no effect on respiratory or eye symptoms or use of medication.	Low
Hol 2008	The Netherlands	RCT, double blind	119 infants younger than 6 months with cows' milk allergy	Usual extensively hydrolysed formula (control) or combined with the probiotics Lactobacillus casei and Bifidobacterium lactis for 1 year	Tolerability	Probiotics did not accelerate cows' milk tolerance. Tolerability to cows' milk at 6 and 12 months was similar in both groups (77% probiotics versus 81% controls, $p > 0.5$).	High
Kirjavainen 2003	Finland	RCT, double blind	35 infants with atopic eczema / dermatitis and cows' milk allergy	Symptoms	Treatment with heat-inactivated Lactobacillus GG was associated with adverse gastrointestinal symptoms and diarrhea. Treatment with active probiotic tended to reduce symptoms compared to placebo. Atopic eczema / dermatitis and subjective symptoms were reduced in all groups. SCORAD scores decreased from 13 (interquartile range, 4-29) to 8 (interquartile range, 0-29) units in the placebo group, from 19 (interquartile range, 4-47) to 5 (interquartile range, 0-18) units in the viable LGG group, and from 15 (range, 0-29) to 7 (range, 0-26) units in the heat-inactivated LGG group. The decrease in SCORAD scores within the viable LGG group tended to be greater than within the placebo group ($p = 0.02$).	Low	

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Majamaa 1997	Finland	Non-random comparison	37 infants with atopic eczema / dermatitis and cows' milk allergy	Lactobacillus GG given to breastfeeding mothers versus cows' milk elimination for those formula fed versus cows' milk elimination plus Lactobacillus GG in extensively hydrolysed whey formula for 1 month	Symptoms of atopic eczema / dermatitis	Probiotic supplemented formula was associated with reduced symptoms compared to other groups. There was a significant improvement of SCORAD score for eczema after one month's intervention in those receiving Lactobacillus GG ($p = 0.008$) but not in those receiving extensively hydrolysed formula without LactobacillusGG ($p = 0.89$).	Low
Sistek 2006	NZ	RCT, double blind	59 children aged 1-10 years with atopic eczema / dermatitis and sensitization to common food or environmental allergens	Two probiotics versus placebo daily for 12 weeks	Symptoms	There was no difference between groups in dermatitis severity (symptom score mean ratio 0.8, 95% CI 0.62-1.04, $p = 0.10$). Lactobacillushamnosus and <i>bifidobacterialactis</i> only improved outcomes in food sensitized children (symptom score mean ratio 0.73, 95% CI 0.54-1, $p = 0.047$).	Moderate
Szajewska 2002	Poland	Systematic review of RCTs	2 Randomized trials in 64 infants with food allergy	Probiotics versus placebo or no intervention	Symptoms	Probiotics reduced the intensity of atopc dermatitis symptoms in infants with food allergy.	High
STRATEGIES TARGETING LONG-TERM MANAGEMENT: IMMUNOTHERAPY							
Asero 1998	Italy	Non-random comparison	75 adults with apple allergy	Injection immunotherapy with birch pollen for 12, 24 or 36 months versus no treatment	Tolerability, symptoms	Immunotherapy improved tolerance. 84% of those treated versus 0% of controls reported reduction or disappearance of symptoms. All treatment durations were equally effective.	Low
Bolhaar 2004	The Netherlands	RCT	23 adults with apple allergy and birch pollen allergy	Birch pollen immunotherapy by injection versus control (drugs for symptoms only) for 1 year	Tolerability	Immunotherapy reduced clinical markers for allergy. Visual analogue scale scores decreased more than ten-fold in 69% of the treatment group versus 0% of controls.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Bucher 2004	Switzerland	Non-random comparison	27 adults allergic to apple or hazelnut and birch pollen	Birch pollen immunotherapy by injection versus usual care for 1 year	Tolerability	Immunotherapy reduced clinical markers for allergy and increased food tolerance. 87% of the treatment group and 8% of controls could eat significantly more apple or hazelnut without any symptoms. However the effect was small as the amount of food tolerated was minimal. The average tolerated quantity increased from 12.6g to 32.6g apple after one year.	Low
Burks 2012	US	RCT, double blind	55 children aged 5 to 11 years with egg allergy	Oral immunotherapy for 24 months, after which time egg consumption was avoided for 4 to 6 weeks. At 24 months children who were fully desensitized were placed on a diet with egg consumption as desired and evaluated up to 36 months	Tolerability	Oral immunotherapy may desensitize a high proportion of children and support sustained desensitization in a smaller subsample. After 10 months of therapy, 55% of the treatment group and 0% of controls were desensitized. After 22 months, Moderate 75% of those treated were desensitized (versus 0% of controls) but at 24 months only 28% were considered to have sustained unresponsiveness. At 36 months all of this subgroup were consuming egg without incident.	High
Calvani 2010	Italy	Systematic review of RCTs	6 trials of children and adults with food allergy	Oral desensitization or sublingual immunotherapy versus placebo	Tolerability	Four trials found that specific oral tolerance induction improved tolerance in children with food allergies. Two trials found sublingual immunotherapy improved tolerance. Adverse effects ranged from 35% to 100% of those in the treatment groups, but were usually not severe.	High
Caminiti 2009	Italy	Non-random comparison	13 children with IgE-mediated food allergy to milk	Oral desensitization with milk versus oral desensitization with soy (control). Desensitization began with one drop diluted 1:25. The dose was doubled weekly until the 18th week to achieve an intake of 200 mL in approximately 4 months	Tolerability	Tolerability to 200mL milk was achieved in 70% of the intervention group and 0% of controls, but the sample size was too small for significance.	Low
Dretzke 2004	England	Systematic review of RCTs	5 trials of provocation-neutralization and children with food allergy	Symptoms	Three studies found that neutralization therapy reduced symptoms, one found no benefit and one found mixed outcomes, depending on the measures used.	High	

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Enrique 2005	Spain	RCT, double blind	23 adults with hazelnut allergy	Sublingual hazelnut immunotherapy versus placebo for 8 to 12 weeks	Tolerability	Immunotherapy improved clinical markers and tolerance to hazelnut. Mean hazelnut quantity provoking a reaction increased from 2.29g to 11.56g in the treatment group ($p = 0.02$) and 3.49g to 4.14g in controls (not significant). The treatment was well tolerated, with reactions observed in only 0.2% of total doses.	Low
Fernandez-Rivas 2009	Spain	RCT, double blind	49 adults with peach allergy	Sublingual immunotherapy with peach extract versus placebo for 6 months	Tolerability	Those receiving immunotherapy could tolerate three to nine times more peach than controls. There were no serious adverse effects but local reactions were more likely in the treatment group.	Moderate
Fisher 2011	England	Systematic review of RCTs	3 trials with children aged 0-18 years with IgE mediated food allergy	Specific oral tolerance induction versus allergen avoidance	Tolerability	Specific oral tolerance induction cannot be recommended as routine practice. Two out of three studies found a reduction in allergy as measured by oral food challenges but meta-analysis found the reduction did not meet statistical significance (RR 0.61, 95% CI 0.31-1.16).	High
Garcia 2010	Spain	RCT, double blind	56 adults with peach allergy	Sublingual immunotherapy with peach abstract versus placebo for 6 months	Tolerability	Immunotherapy was associated with reduced reactions ($p < 0.05$).	Moderate
Hansen 2004	Denmark	RCT, double blind	40 people with birch pollen allergy, most of whom had apple allergy	Sublingual swallow immunotherapy versus subcutaneous immunotherapy with birch pollen extract versus placebo	Symptoms	Immunotherapy was not associated with improvements. Symptom scores to apple during challenges decreased in all groups, but only significantly in the placebo group ($p = 0.03$). The self-reported severity of food allergy did not change and there were no differences in self-reported changes between groups.	Moderate
Keet 2012	US	RCT	30 children aged 6 to 17 years with cows' milk allergy	Sublingual immunotherapy alone or followed by oral immunotherapy at 1000 mg or 2000 mg milk protein per day	Tolerability	Adding oral immunotherapy to sublingual immunotherapy increased tolerance, but had side effects. After therapy 10% of the sublingual therapy alone group and 60% of the added oral immunotherapy group passed a challenge ($p=0.002$). Symptoms returned after therapy stopped. Systemic reactions were more common during oral immunotherapy.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Kim 2011	US	RCT, double blind	18 children aged 1 to 11 years with peanut allergy	Sublingual immunotherapy versus placebo for 6 months of biweekly dose escalation and 6 months of maintenance dosing at 2000mcg	Tolerability	The group receiving treatment were able to ingest 20 times more peanut than the placebo group (median, 1710 versus 85 mg; $p = 0.01$). Peanut sublingual immunotherapy safely induced clinical desensitization and there was evidence of immunologic changes. There was a decrease in skin prick test wheal size ($p = 0.02$). Peanut-specific IgE levels increased over the initial 4 months ($p = 0.002$) and then decreased over the remaining 8 months ($p = 0.003$), whereas peanut-specific IgG4 levels increased during the 12 months ($p = 0.04$).	Low
Kim 2011	US	Non-random comparison	88 children allergic to cows' milk	Children were evaluated for tolerance to baked milk (muffin). The reactive group were asked to avoid all forms of milk. The tolerant group were instructed to incorporate baked-milk products daily into their diets. After more than 6 months, those who tested as tolerant to baked-cheese products were asked to incorporate unheated milk into their diet. Follow-up occurred over a median of 37 months	Tolerability	Adding baked milk to the diet of children who can tolerate this appears to accelerate the development of unheated milk tolerance compared with strict avoidance. Children who incorporated dietary baked milk were 16 times more likely than the comparison group to become tolerant to unheated milk ($p < 0.001$).	Low
King 1988	US	Controlled crossover	33 people with food hypersensitivity	Three 2-week injection sessions, with 1 week off in between. The injection was a placebo for one session and an active allergen for the other two. Most patients were treated for 3-5 food allergens.	Symptoms	Neutralization subcutaneous treatment was more effective than placebo 65% of the time, the same as placebo 12% of the time and aggravated symptoms more than placebo in 23% of cases. The authors suggested that treatment is four times more likely to lead to improvements than placebo ($p < 0.001$).	Low
Kopac 2012	Switzerland	RCT	40 people with birch pollen rhinoconjunctivitis and associated allergy to apple	Daily consumption of apple (1-128 g, doubling the amount every two to three weeks) versus no intervention.	Tolerability	At the end of the intervention, 63% of the treatment group and 0% of controls could tolerate a whole apple ($p = 0.0001$). The small sample size meant differences in endpoints reflecting systemic immune reactivity did not reach statistical significance. There was relapse after discontinuing apple consumption suggesting that any induced tolerance is likely to be transient.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Lee 2010	Korea	RCT	148 children with IgE, non IgE mediated or other food allergy	Immunotherapy using subcutaneously administered interferon gamma specific for IgE or non IgE versus control.	Tolerability	Immunotherapy with interferon gamma improved tolerance. Interferon gamma at low dose was most effective for IgE mediated food allergy and high dose was effective for non IgE mediated allergy.	Moderate
Leung 2003	US	RCT, double blind	82 children and adults with peanut allergy and history of immediate hypersensitivity to peanut.	Anti IgE therapy with TNX-901, 150 mg, 300 mg or 450 mg or placebo subcutaneously every 4 weeks for 4 doses.	Tolerability	450 mg TNX-901 improved tolerance compared with placebo ($p < 0.001$) and did not cause significant side effects. Tolerability was improved from half a peanut to almost nine peanuts, which may guard against accidental consumption.	High
Martorell 2011	Spain	RCT	60 children aged 24-36 months with IgE-mediated allergy to cows' milk	Oral desensitization versus milk-free diet. Follow-up occurred at 1 year.	Tolerability	90% of the treatment group were completely tolerant at follow-up compared with 23% of controls. Eight out of ten of the treatment group developed some Moderate reaction during the treatment period: 47% developed a moderate reaction and 33% a mild reaction.	Moderate
Mauro 2011	Italy	RCT	10 adults with birch-apple syndrome	Subcutaneous immunotherapy versus sublingual immunotherapy with birch extract for 1 year.	Tolerability	25% of those undergoing subcutaneous therapy and 14% undergoing sublingual therapy developed complete tolerance to apple (significance not reported). Around one third had an increase in the amount of apple required to produce a response. Different doses of birch extract may be needed in different patients to improve associated apple allergy.	Low
Miller 1977	US	Crossover, double blind	8 children and adults with food allergy	Injection with food extract specific to each patient and maintenance diet versus placebo. 4 crossover cycles were used, each of 20 days.	Symptoms	There was a significantly better response to food injection therapy than to placebo. Symptoms sometimes reduced three to four days after beginning therapy and returned three to four days after stopping and beginning placebo.	Low
Morisset 2007	France	RCT	57 children with cows' milk allergy and 84 children with egg allergy. Children were aged 1 to 8 years.	After 6 to 12 months of an avoidance diet, continued avoidance diet (control) versus oral desensitization for 6 months.	Tolerability	Avoiding foods may increase sensitization and lower the threshold of reactivity so more active treatment may be required. Oral desensitization was associated with improved tolerance to cows' milk. Skin prick test was positive for milk in 11% of the desensitization group versus 40% of the avoidance group ($p < 0.025$). There was a non-significant trend towards improved tolerance of egg. Skin prick test was positive for egg in 31% of the desensitization group and 49% of the avoidance group ($p < 0.1$).	Moderate

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Nurmatov 2012	Scotland	Systematic review	1 trial of 25 children with peanut allergy	Allergen specific oral immunotherapy versus placebo.	Tolerability	One small trial found that peanut immunotherapy reduced sensitization. Those receiving immunotherapy were able to ingest a dose equivalent to 20 peanuts without developing symptoms. However during treatment about half of the intervention group experienced adverse effects requiring treatment with histamines.	High
Oppenheimer 1992	US	RCT, double blind	4 people with peanut allergy	Peanut rush immunotherapy versus placebo.	Tolerability, symptoms	The treatment group displayed a 67% to 100% decrease in symptoms whereas there was no change for controls. The treatment group were more likely to be able to tolerate peanuts at the maintenance dose. However, the rate of systemic reactions with rush immunotherapy was 13.3%.	Low
Pajno 2010	Italy	RCT	30 children aged 4 to 10 years with IgE-mediated cows' milk allergy	Desensitization with cows' milk versus soy milk (control) using weekly up-dosing for 14 weeks. Desensitization stopped if severe reactions occurred.	Tolerability	Weekly up-dosing desensitization performed under medical supervision worked well. Full tolerance to 200ml cows' milk was achieved in 66% of the treatment group versus 0% controls. Two treatment patients discontinued due to severe reactions (versus 0 controls).	Low
Patriarca 1998	Italy	Non-random comparison	22 children with food allergy	Oral desensitization versus elimination diet.	Tolerability	100% of children that completed oral sensitization were able to tolerate foods compared to no change in controls.	Low
Patriarca 2003	Italy	Non-random comparison	75 adults and children with food allergy	Oral desensitization versus elimination diet (control). Follow-up occurred over 18 months.	Tolerability	Desensitization was more effective than elimination diets. Desensitization was successful for 80%. However 51% of participants experienced side effects such as hives or abdominal pain. In 17% treatment was stopped due to skin reactions or gastrointestinal symptoms. There was no difference in outcomes between children and adults.	Low
Skripak 2008	US	RCT, double blind	19 children aged 6 to 17 years with cows' milk allergy	Milk oral immunotherapy versus placebo. Dosing increased in three phases to a maximum of 500 mg, equivalent to 15ml of milk. This continued in daily maintenance doses for 3 to 4 months.	Tolerability	Oral immunotherapy increased tolerance. After immunotherapy, the median cumulative dose eliciting a reaction was 5 140 mg whereas all controls reacted at 40 mg ($p = 0.0003$). There were some side effects (45% treatment versus 11% control doses). Local reactions were most common but one child dropped out due to persistent atopic eczema / dermatitis.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Outcomes	Key findings	Quality
Staden 2007	Germany	RCT	45 children with cows' milk or egg allergy	Specific oral tolerance induction at home daily versus elimination diet (control).	Tolerability	There were few significant differences between groups. In the treatment group, 36% had permanent tolerance, 12% were tolerant with regular intake and 16% were partial responders. In the control group, 35% were tolerant; allergen-specific immunoglobulin E decreased significantly both in children who developed natural tolerance during the elimination diet ($p < 0.05$) and in those treated ($p < 0.001$).	Low
van Hoffen 2011	The Netherlands	RCT	19 adults with birch pollen and hazelnut allergy	10 birch pollen specific immunotherapy injections versus placebo injections. Follow-up occurred at one year.	Tolerability, symptoms	There was no significant difference between groups in tolerance or symptoms.	Low
Varshney 2011	US	RCT, double blind	25 children aged 1 to 16 years with peanut allergy	Oral immunotherapy with peanut flour (dose 20 peanuts) versus placebo.	Tolerability	At about one year, peanut immunotherapy was associated with desensitization and immune modulation.	Low
MIXED INTERVENTIONS							
Chaudhry 2012	US	Systematic review of studies published 2010-2012	About 25 studies of management of adults with food allergy	Avoidance, epinephrine, immunotherapy	Symptoms, tolerance	Avoiding foods is not sufficient to reduce allergic reactions. Research about immunotherapy is in the early stages but may be useful for increasing tolerance.	Moderate
Schneider Chafen 2010	US	Systematic review of RCTs and reviews	25 studies of management of adults and children with food allergy	Dietary modification, probiotics, formula, immunotherapy, medication and education	Symptoms	There are insufficient data to recommend one form of treatment over another. Elimination diets are commonly used, but have not been studied fully. Moderate immunotherapy shows promise, but there are insufficient data.	Moderate
Schneider Chafen 2010	US	Systematic review	13 studies of management of children and adults with food allergy	Dietary modification, probiotics, formula, immunotherapy, medication and education	Symptoms	Allergen-specific immunotherapy and specific-immunotherapy with cross reactive allergens improve clinical symptoms of food allergy. Diets avoiding allergens may improve atopic dermatitis, but there is moderate insufficient evidence about other conditions. There is insufficient evidence to evaluate the extent to which pharmacologic therapy is useful.	Moderate
Thong 2004	England	Systematic review	Unlisted number of studies of children with IgE mediated food allergy	Multidisciplinary teams, dietary restriction, education.	Symptoms	A multidisciplinary team, including a dietitian, allergy specialist and primary care, is useful for managing children with food allergies. Educating children about what to avoid and how to manage their condition is useful.	Moderate

Table E2 Quality assessment of systematic reviews

First author	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of synthesis studies	Appropriateness of synthesis of review	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits versus harms / overall quality costs
Calvani 2010	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chaudhry 2012	✗	✓	✓	✗	✓	✓	✓	✓	✓
Chen 2011	✗	✗	✗	✗	✓	✓	✓	✗	Low
Dretzke 2004	✓	✓	✓	✓	✓	✓	✓	✓	Moderate
Fisher 2011	✓	✓	✓	✓	✓	✓	✓	✓	High
Hill 2007	✓	✓	✓	✓	✓	✓	✓	✓	High
Muraro 2002	✓	✗	✗	✗	✓	✓	✓	✓	Moderate
Nurmatov 2012	✓	✓	✓	✓	✓	✓	✓	✓	High
Schneider Chafen 2010 (report)	✗	✓	✓	✓	✓	✓	✓	✓	Moderate
Schneider Chafen 2010 (article)	✗	✓	✓	✓	✓	✓	✓	✗	Moderate
Szajewska 2002	✓	✓	✓	✓	✓	✓	✓	?	High
Thong 2004	✓	✓	✗	✗	✓	✓	✓	✗	Moderate

Note: crosses refer to things that were not reported on in the article, that were not undertaken or that were undertaken poorly based on CASP criteria.

Table E3 Quality assessment of primary studies

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Overall quality assessment
Agata 1993	Non-random comparison	NA	?	?	?	✓	✓	Low
Alonso 1994	Non-random comparison	NA	✗	✗	✓	✓	✗	Low
Asero 1998	Non-random comparison	NA	✗	✗	✓	✓	✗	Low
BerniCanani 2012	RCT	✗	✗	✗	✓	✓	✓	Low
Bindslev-Jensen 1991	RCT	✗	✓	✓	✓	✓	✗	Low
Bolhaar 2004	RCT	✗	✗	✗	✓	✓	✗	Low
Boner 1986	RCT	✗	✓	✓	✓	✓	✗	Low
Brouwer 2006	RCT	✗	✓	✓	✓	✓	✓	Moderate
Bucher 2004	Non-random comparison	NA	✗	✗	✓	✓	✗	Low
Burks 1988	RCT	✗	✓	✓	✓	✓	✗	Low
Burks 2012	RCT	✓	✓	✓	✓	✓	✗	Moderate
Businco 1986	RCT	✓	✓	✓	✓	✓	✗	Low
Caminiti 2009	Non-random comparison	NA	✓	✓	✓	✓	✗	Low
Cantani 2006	Non-random comparison	NA	✗	✗	✓	✓	✗	Low
Cavagni 1989	RCT	✗	✓	✓	✓	✓	✗	Low
Ciprandi 1987	Non-random comparison	NA	?	✓	✓	✓	✗	Low
Ciprandi 1987 (terfenadine)	Non-random comparison	NA	?	✓	✓	✓	✗	Low
Cukrowska 2010	RCT	✗	✓	✓	✓	✓	✗	Moderate
Dannaeus 1977	RCT	✗	✓	✓	✓	✓	✗	Low
Daugbjerg 1984	RCT	✗	✓	✓	✓	✓	✗	Low
Ellul-Micallef 1983	RCT	✗	✓	✓	✓	✓	✗	Low
Enrique 2005	RCT	✗	✓	✓	✓	✓	✗	Low
Fernandez-Rivas 2009	RCT	✗	✓	✓	✓	✓	✗	Moderate

Table E3 (continued)

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Overall quality assessment
Flinterman 2007	RCT	x	✓	✓	✓	✓	x	Low
Galli 1996	Non-random comparison	NA	?	?	✓	✓	?	Low
Garcia 2010	RCT	✓	✓	✓	✓	✓	✓	Moderate
Gerrard 1979	RCT	x	✓	✓	✓	x	Low	
Halken 1993	Non-random comparison	NA	x	✓	✓	✓	x	Low
Hansen 2004	RCT	✓	✓	✓	✓	✓	✓	Moderate
Helin 2002	RCT	x	✓	✓	✓	✓	x	Low
Hol 2008	RCT	✓	✓	✓	✓	✓	✓	High
Isolauri 1995	RCT	x	✓	✓	✓	✓	x	Low
Jirapinyo 2007	RCT	?	✓	✓	✓	✓	x	Low
Keet 2012	RCT	x	x	x	✓	✓	x	Low
Kim 2011 (baked)	Non-random comparison	NA	x	x	✓	✓	✓	Low
Kim 2011 (peanut)	RCT	x	✓	✓	✓	✓	x	Low
King 1988	Controlled crossover	x	✓	✓	✓	✓	✓	Low
Kirjavainen 2003	RCT	x	✓	✓	✓	✓	x	Low
Klemola 2002	RCT	✓	✓	✓	✓	✓	✓	High
Kopac 2012	RCT	?	x	x	✓	✓	x	Low
Lee 2010	RCT	x	✓	✓	✓	✓	✓	Moderate
Leung 2003	RCT	✓	✓	✓	✓	✓	✓	High
Lever 1998	RCT	?	✓	✓	✓	✓	x	Low
Lin 2000	RCT	✓	✓	✓	✓	✓	x	Moderate
Majamaa 1997	Non-random comparison	NA	x	x	✓	✓	✓	Low
Martorell 2011	RCT	?	✓	✓	✓	✓	✓	Moderate
Mauro 2011	RCT	✓	x	x	✓	✓	x	Low
McLeish 1995	RCT	✓	✓	✓	✓	✓	x	Low
Miller 1977	Crossover	x	✓	✓	✓	✓	x	Low

Table E3 (continued)

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Overall quality assessment
Morisset 2007	RCT	✓	✗	✗	✓	✓	✓	Moderate
Niggemann 2001	RCT	✗	✗	✗	✓	✓	✓	Moderate
Niggemann 2008	RCT	✗	✗	✗	✓	✓	✓	Moderate
Oppenheimer 1992	RCT	?	✓	✗	✗	?	✗	Low
Ortolani 1983	RCT	✗	✓	✓	✓	✓	✗	Low
Pacor 1992	RCT	✗	✓	✓	✓	✓	✗	Low
Paino 2010	RCT	✗	✗	✓	✓	✓	✗	Low
Patriarca 1998	Non-random comparison	NA	✗	✗	✓	✓	✗	Low
Patriarca 2003	Non-random comparison	NA	✗	✗	✓	✓	✓	Low
Reche 2010	RCT	✗	✗	✗	✓	✓	✓	Moderate
Salpietro 2005	RCT	✗	?	✓	✓	✓	✗	Low
Savino 2005	RCT	?	?	?	✓	✓	?	Low
Sistek 2006	RCT	✓	?	✓	✓	✓	✓	Moderate
Skripak 2008	RCT	✓	✓	✓	✓	✓	✗	Low
Spira 1988	Non-random comparison	NA	?	?	?	✓	?	Low
Staden 2007	RCT	✗	✗	✓	✓	✓	✗	Low
Terracciano 2010	RCT	✗	✓	✓	✓	✓	✓	Moderate
van Hoffen 2011	RCT	✗	✓	✓	✓	✓	✗	Low
Varshney 2011	RCT	✗	✓	✓	✓	✓	✗	Low
Viljanen 2005	RCT	✓	✓	✓	✓	✓	✓	High
Vita 2007	RCT	?	✗	✓	✓	✓	✗	Low
Wang 2010	RCT	✗	✓	✓	✓	✓	✗	Low
Zur 2002	Non-random comparison	NA	?	?	✓	✓	?	Low

Note: RCT refers to a randomized controlled trial. Crosses refer to things that were not reported on in the article, that were not undertaken or that were undertaken poorly according to Cochrane EPOC criteria. Question marks denote where insufficient information was available to make a determination. NA refers to components of the study design that were not applicable (for example where no randomization took place).

Table E4 Unpublished and ongoing studies

Principal investigator, Title country	Study design	ClinicalTrials. gov identifier	Participants	Intervention	Primary outcome measures	Began complete date	Status
Aragones, Specific Oral Tolerance Induction to Cows' milk Allergy Spain	RCT	NCT01199484	60 children aged 24-36 months of age with IgE-mediated cows' milk allergy	Oral immunotherapy	Efficacy	2010	Unknown
Beyer, France, Germany and UK	A Prospective, Double Blind Randomized Controlled Trial to Evaluate the Immunological Benefits and Clinical Effects of an Elimination Diet Using an Amino Acid Based Formula	RCT	NCT01109966	228 infants aged up to 8 months with cows' milk allergy	Amino acid formula	Tolerance, Growth	2010 2014
Brennan, US	Oral Peanut Immunotherapy	RCT	NCT01324401	32 7-21 year olds with peanut allergy	Oral immunotherapy	Tolerance	2011 2015
Burks, US	Mucosal Immunotherapy for Peanut Allergy	RCT	NCT00597675	45 1-6 year olds with peanut allergy	Immunotherapy	Tolerance	2007 2013
Burks, US	Mucosal Immunotherapy for Peanut Allergy in Young Children	RCT	NCT00932828	60 9-36 month olds with peanut allergy	Oral immunotherapy	Tolerance	2009 2015
Burks, US	Oral Immunotherapy for Childhood Egg Allergy	RCT	NCT00461097	55 5=18 year olds with egg allergy	Oral immunotherapy	Tolerance	2007 2013
Burks, US	Oral Immunotherapy (OIT) for Peanut Allergy	RCT	NCT00815035	60 1-6 year olds with peanut allergy	Oral immunotherapy	Tolerance	2009 2015
Burks, US	Peanut Oral Immunotherapy	Unknown	NCT00598039	40 1-16 year olds with peanut allergy	Oral immunotherapy	Tolerance	2003 2014
Burks, US	Peanut Oral Immunotherapy and Anti-Immunglobulin E (IgE) for Peanut Allergy	RCT	NCT00932282	10 people older than 12 years with peanut allergy	Omalizumab plus immunotherapy	Tolerance	2009 2015
Burks, US	Peanut Sublingual Immunotherapy	RCT	NCT00580606	40 12-40 year olds with peanut allergy	Sublingual immunotherapy	Tolerance, safety	2007 2014
Canani, Italy	Tolerance to a New Free Amino Acid-based Formula in Children With IgE or Non-IgE-mediated Cows' milk Allergy	RCT	NCT01622426	60 1-168 month olds with cows' milk allergy	Amino acid based formula	Tolerance	2006 2011
Christie, US	Walnut Oral Immunotherapy for Tree Nut Allergy	RCT	NCT01546753	15 6-45 year olds with tree nut allergy	Oral immunotherapy	Tolerance	2012 2017

Table E4 (continued)

Principal investigator, Title country	Study design	ClinicalTrials. gov identifier	Participants	Intervention	Primary outcome measures	Began complete	Estimated date	Status	
Clark, England	Efficacy and Safety of High-dose Peanut Oral Immunotherapy With Factors Predicting Outcome	Non-random	NCT01259804	22 7-17 year olds with peanut allergy	Oral immunotherapy	Efficacy, safety	2008	2012	Active, not recruiting
DBV Tech- nologies, US	Safety of Epicutaneous Immunotherapy for the Treatment of Peanut Allergy	RCT	NCT01170286	100 6-50 year olds with peanut allergy	Epicutaneous immunotherapy	Safety, tolerance	2010	2012	Completed
Dupont, France	Epicutaneous Immunotherapy in Peanut Allergy in Children	RCT	NCT01197053	70 5-17 year olds with peanut allergy	Immunotherapy	Tolerance	2010	2012	Ongoing
Dupont, France	Sublingual Milk Immunotherapy in Children	RCT	NCT00874627	51 5-17 year olds	Sublingual immunotherapy	Tolerance	2008	2012	Completed
Iacono, Italy	Time-limited Specific Oral Tolerance Induction in Children With Severe Egg Allergy	RCT	NCT01379651	20 5-11 year olds with egg allergy	Oral immunotherapy	Tolerance	2008	2010	Completed
Kamilaris, US	Sublingual Immunotherapy for Peanut Allergy and Induction of Tolerance	RCT	NCT01373242	50 1-11 year olds with peanut allergy	Oral immunotherapy	Tolerance	2011	2021	Recruiting
Kinaciyan, Vienna	Sublingual Immunotherapy of Birch Pollen Associated Apple Allergy	RCT	NCT01449786	60 18-50 year olds with apple allergy	Sublingual immunotherapy	Tolerance	2011	2014	Not open for recruitment
Lollar, US	Sublingual Immunotherapy for Food Allergy	RCT	NCT00736281	Patients 4 years and older with multiple food allergies	Immunotherapy - food drops	Food allergen reactions	2008	2010	Unknown
Mäkelä, Finland	Nut Allergy Study: Double-blind Challenge and Oral Desensitization	Non-random	NCT01502878	200 3-18 year olds with nut allergy	Oral immunotherapy	Efficacy, safety	2011	2015	Recruiting
Nadeau, US	Efficacy and Safety of Several Doses of Viaskin Peanut in Adults and Children With Peanut Allergy	RCT	NCT01675882	220 6-55 year olds with peanut allergy	Oral immunotherapy	Tolerance, safety	2012	2013	Recruiting
Nurmatov, Scotland	Effectiveness, mechanisms of action and safety of orally-administered immunotherapy for food allergy: systematic review and meta-analysis	Systematic review	Not applicable	15 trials in people with food allergy	Oral immunotherapy	Desensitization, safety	2011	2013	Complete, awaiting publication
Paasilita, Finland	Safety of Oral Immunotherapy for Cows' milk Allergy in School-aged Children	RCT	NCT01361347	28 6-16 year olds with cows' milk allergy	Oral immunotherapy	Safety	2008	2014	Ongoing, recruitment complete

Table E4 (continued)

Principal investigator, Title country	Study design	ClinicalTrials. gov identifier	Participants	Intervention	Primary outcome measures	Began complete	Estimated date	Status	
Sampson, US	OIT and Xolair® (Omalizumab) in Cows' milk Allergy	RCT	NCT01157117	75 7-35 year olds with cows' milk allergy	Omalizumab vs immunotherapy	Tolerance	2010	2015	Ongoing
Sicherer, US	Peanut Allergy Vaccine Study in Healthy and Peanut-allergic Adults	RCT	NCT00850668	15 people aged 18 to 50 years with peanut allergy	Vaccine	Safety, desensiti- zation	2009	2010	Completed
Sussman, Canada	A Prospective, Randomized, Case Controlled, Pilot Study to Evaluate the Effect of Ketotifen on the Adverse Events Associated With Peanut Desensitization in Children With Peanut Allergies.	RCT	NCT01625715	6-8-12 year olds with peanut allergy	Ketotifen	Desensiti- zation	2011	2014	Ongoing, not recruiting
Waserman, Canada	Peanut Allergy Oral Immunotherapy Desensitization.	RCT	NCT01601522	50 5-10 year olds with peanut allergy	Oral immunotherapy	Tolerance	2012	2014	Recruiting
Wong, US	A Study of Xolair in Peanut-Allergic Subjects Previously Enrolled in Study Q2788g	RCT	NCT00382148	Unspecified number of children and adults with peanut allergy	Omalizumab	Safety, tolerance	2006	2008	Data analysis begun
Wood, US	A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Sublingual/Oral Immunotherapy for the Treatment of Peanut Allergy	RCT	NCT01084174	6-21 year olds with peanut allergy	Sublingual versus oral immunotherapy	Tolerance, safety	2010	Unknown	Active, not recruiting
Wood, US	A Randomized, Double-Blind, Placebo-Controlled Study of Oral Milk Immunotherapy for Cows' Milk Allergy	RCT	NCT00465569	20 6-21 year olds with cows' milk allergy	Oral immunotherapy	Tolerance	2006	2008	Completed
Wood, US	Omalizumab in the Treatment of Peanut Allergy	Non- random	NCT00949078	20 people 15 people aged 18 to 50 years with peanut allergy	Omalizumab	Efficacy	2009	2011	Unknown
Wood, US	The Safety and Efficacy of Sublingual/Oral Immunotherapy for the Treatment of Milk Protein Allergy	RCT	NCT00732654	30 6-21 year olds with cows' milk allergy	Oral and sublingual immunotherapy	Safety, tolerance	2008	2015	Ongoing, not recruiting
Xiu-Min, US	Therapeutic Effect of Chinese Herbal Medicine on Food Allergy (FAHF-2)	RCT	NCT00602160	People aged 12 to 45 years with food allergy	Chinese herbal medicine	Safety	2007	2012	Recruiting

DATA E1. SEARCH STRATEGIES

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1	exp Food Hypersensitivity/
2	foodallerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	or/1-5
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
8	exp animals/ not humans.sh.
9	7 or 8
10	6 not 9
11	MEDLINE.tw.
12	systematic review.tw.
13	meta analysis.pt.
14	or/11-13
15	Randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	Randomized.ab.
18	placebo.ab.
19	clinical trials as topic.sh.
20	randomly.ab.
21	trial.ti.
22	or/15-21
23	intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individual?e? or individual?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab.
24	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab.
25	(hospital\$ or patient?).hw. and (study or studies or care or health\$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.
26	demonstration project?.ti,ab.
27	(pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or (pre adj5 post)).ti,ab.
28	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.
29	trial.ti. or ((study adj3 aim?) or "our study").ab.
30	(before adj10 (after or during)).ti,ab.
31	("quasi-experiment\$" or quasiexperiment\$ or "quasi random\$" or quasirandom\$ or "quasi control\$" or quasicontrol\$ or ((quasi\$ or experimental) adj3 (method\$ or study or trial or design\$))).ti,ab,hw.
32	("time series" adj2 interrupt\$).ti,ab,hw.
33	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month\$ or hour? or day? or "more than")).ab.
34	pilot.ti.
35	Pilot projects/
36	(clinical trial or controlled clinical trial or multicenter study).pt. (589305)
37	(multicentre or multicenter or multi-centre or multi-center).ti. (24808)
38	random\$.ti,ab. or controlled.ti.
39	(control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or Randomized controlled trial).pt.
40	comment on.cm. orreview.ti,pt. or Randomized controlled trial.pt.
41	or/23-40
42	10 and 14
43	10 and 22
44	10 and 41
45	or/42-44

Database: EmbaseClassic+Embase<1990 to 2012 August 20>*Search Strategy:***Database: EmbaseClassic+Embase<1947 to 2012 September 17>***Search Strategy:*

1	exp Food Hypersensitivity/	18	*nutritional intolerance/
2	foodallerg*.mp.	19	*Food Hypersensitivity/
3	food hypersensitivity.mp.	20	((food\$ or nutrient\$) adj5 (allerg\$ or hypersensitiv\$ or sensitiv\$ or intoleran\$ or reaction\$)).ti,ab.
4	food hypersensitivities.mp.	21	oral allerg\$.ti,ab.
5	allergy, food.mp.	22	or/17-21
6	or/1-5	23	intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individual?e? or individual?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab.
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.	24	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4] (10005)
8	(animal\$ not human\$).sh,hw.	25	(hospital\$ or patient?).hw. and (study or studies or care or health\$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (1422994)
9	7 or 8	26	demonstration project?.ti,ab.
10	6 not 9	27	(pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or (pre adj5 post)).ti,ab. (78798)
11	intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individual?e? or individual?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab. (172132)	28	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (665)
12	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4] (10005)	29	trial.ti. or ((study adj3 aim?) or "our study").ab.
13	[or/11-36]	30	(before adj10 (after or during)).ti,ab.
14	[or/38-40]		
15	[or/42-56]		
16	[or/61-63]		
17	*food allergy/		

31	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month\$ or hour? or day? or "more than")).ab.	47	("quasi-experiment\$" or quasiexperiment\$ or "quasi random\$" or quasirandom\$ or "quasi control\$" or quasicontrol\$ or ((quasi\$ or experimental) adj3 (method\$ or study or trial or design\$))).ti,ab. [EM] (118829)
32	pilot.ti.	48	("time series" adj2 interrupt\$).ti,ab. [EM]
33	intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individuali?e? or individuali?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab.	49	or/23-48
34	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]	50	meta-analys:.mp.
35	(hospital\$ or patient?).hw. and (study or studies or care or health\$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.	51	search:.tw.
36	demonstration project?.ti,ab.	52	review.pt.
37	(pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or (pre adj5 post)).ti,ab.	53	or/50-52
38	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.	54	random\$.tw.
39	trial.ti. or ((study adj3 aim?) or "our study").ab.	55	factorial\$.tw.
40	(before adj10 (after or during)).ti,ab.	56	crossover\$.tw.
41	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month\$ or hour? or day? or "more than")).ab.	57	cross over.tw.
42	pilot.ti.	58	cross-over.tw.
43	(multicentre or multicenter or multi-centre or multi-center).ti.	59	placebo\$.tw.
44	random\$.ti,ab. or controlled.ti.	60	(doubl\$ adj blind\$).tw.
45	review.ti. [EM]	61	(singl\$ adj blind\$).tw.
46	*experimental design/ or *pilot study/ or quasi experimental study/ [EM] (5126)	62	assign\$.tw.
		63	allocat\$.tw.
		64	volunteer\$.tw.
		65	crossover procedure/
		66	double blind procedure/
		67	Randomized controlled trial/
		68	single blind procedure/
		69	or/54-68
		70	22 and 49
		71	22 and 53
		72	22 and 69
		73	or/70-72
		74	73 not 9

Database: CINAHL Search Strategy

S9	S1 or S8	S4	TI allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S8	S6 and S7	S3	AB food or nutrient
S7	S4 or S5	S2	TI food or nutrient
S6	S2 or S3	S1	(MM "Food Hypersensitivity")
S5	AB allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction		

Database: ISI Web of Science: Science Citation Index, Conference Proceedings

Citation search strategy:

2

Topic=(food or nutrient) AND Topic=(allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)

Refined by: Web of Science Categories=(ALLERGY OR IMMUNOLOGY) AND Document Types=(PROCEEDINGS PAPER OR MEETING ABSTRACT)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

1

Topic=(food or nutrient) AND Topic=(allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

Database: Cochrane Library

Search strategy:

#1 MeSH descriptor Food Hypersensitivity
explode all trees

#2 (food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*)))

#4 (#1 OR #2)

Database: TRIP Database

Search Stategy: (Advanced search screen)

area:"Allergies and Immunology"

any of these words: food allerg*

Downloaded: Evidence Based Synopses, Systematic Reviews, Guidelines

All years

Database: Clinicaltrials.gov

Search Strategy: (Advanced search screen)

Conditions: food allergy or food intoleran* or food reaction or food hypersensitiv* or food sensitiv*

all years

References

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SECTION 2

PRIMARY PREVENTION OF FOOD ALLERGY

**Supplementary
materials**

2.1

PRIMARY PREVENTION OF FOOD ALLERGY IN CHILDREN AND ADULTS SYSTEMATIC REVIEW

❖ Supplementary materials ❖

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EAACI Food Allergy and Anaphylaxis Group: CA Akdis, R Alvarez, K Beyer, C Bindslev Jensen, P Demoly, P Eigenmann, M Fernandez Rivas, G Lack, MJ Marchisotto, B Niggeman, C Nilsson, N Papadopoulos, I Skypala, M Worm.

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Table E1 Studies included in the systematic review

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
STRATEGIES TARGETING PREGNANT WOMEN: DIETARY AVOIDANCE							
Falh-Magnusson 1992	Sweden	RCT	198 infants at high-risk followed to 5 years	Mothers abstained from cow's milk and egg from gestational week 28 to delivery versus no diet	Food intolerance	Maternal elimination diet during late pregnancy did not prevent food intolerance or allergy in high-risk infants. Infants whose mothers had an avoidance diet were more likely to suffer persistent intolerance to egg (7% diet versus 0% control at 5 years, $p < 0.05$).	Low
Lilja 1991	Sweden	RCT	163 infants at high-risk followed to 18 months	High versus low intake of hen's egg and cow's milk by mother during final trimester of pregnancy. One third of the mothers with a reduced egg and milk intake during pregnancy continued this for two months after birth. All other mothers reverted to their usual diet	Sensitization to food allergens	Reducing dietary intake was not associated with differences in food sensitivity at two, six or 18 months.	Moderate
STRATEGIES TARGETING PREGNANT WOMEN: PROBIOTICS AND PREBIOTICS							
Sausenthaler 2007	Germany	Cohort	2641 children followed to 2 years	Maternal diet during the last 4 weeks of pregnancy	Sensitization	Foods rich in n-6 polyunsaturated fatty acids and al-lergenic foods during late pregnancy may increase childhood allergies whereas foods rich in n-3 polyunsaturated fatty acids may reduce allergies. High maternal celery and citrus fruit intake increased sensitization to food (significance not reported).	Low
Huurre 2008	Finland	RCT, double blind	171 infants followed to 1 year	Probiotics for mothers during pregnancy and dietary counseling versus placebo	Sensitization	Probiotic supplementation had a protective effect against sensitization in infants at high-risk who were breastfed. The risk of sensitization increased in infants with allergic mothers breastfeeding longer than six months ($OR\ 4.83, p = 0.005$) or exclusively breastfeeding for more than 2.5 months ($OR\ 3.4, p = 0.018$). Probiotic supplements appeared to protect against sensitization in infants with a high hereditary risk ($OR\ 0.3, p = 0.023$).	High

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
STRATEGIES TARGETING PREGNANT WOMEN: FISH OIL SUPPLEMENTS							
Dunstan 2003 and Denburg 2005	Australia	RCT, double blind	98 infants at high-risk due to maternal atopy, with follow up of 83 infants to 1 year	Pregnant women received fish oil capsules(3.7g per day) versus placebo from 20 weeks' gestation until delivery.	Clinical markers of allergy, food sensitization	This study was not designed or powered to examine clinical effects, but infants in the fish oil group were less likely to have a positive skin prick test to egg at one year (OR 0.34, 95% CI 0.11-1.02, p = 0.055). 37.8% of infants in the control group and 17.1% in the fish oil group were sensitized to egg. This equates to an absolute reduction of 21% and Moderate a relative risk reduction in this population of 54.6% (significance reported above). In the follow up study, fish oil was associated with improved clinical markers. There was a trend towards the fish oil group being three times less likely to be sensitized to egg at one year (OR 0.34, 95% CI 0.11-1.02, p = 0.055).	High
Palmer 2012	Australia	RCT	681 infants at high-risk followed to 1 year	Three 500mg fish oil capsules daily versus placebo for mothers from 21 weeks gestation until birth	Sensitization	There was no difference between groups in IgE-associated allergic disease (adjusted RR 0.7, 95% CI 0.45-1.09). There was a reduced risk of egg sensitization in the fish oil group (adjusted RR 0.62, 95% CI 0.41-0.93).	High
STRATEGIES TARGETING BREASTFEEDING WOMEN: DIETARY CHANGE							
Hattevig 1989	Sweden	Non-random comparison	1115 infants at high-risk followed to 18 months	In one group, mothers had a diet free from eggs, cow's milk and fish during the first three months after birth. Mothers in the other group had an ordinary diet. The diet of the infants was similar in both groups and involved avoiding cow's milk until six months and avoiding eggs and fish until nine months	Food allergy	There were no differences between groups in allergy to eggs, cow's milk or fish. 12% of the diet group versus 18% of the non-diet group experienced adverse reactions to food between birth and 18 months, but this was not a significant difference at 18 months or any age prior.	Low
Kramer 2012	Canada	Systematic review	Two trials with 523 families (plus other trials of other outcomes)	Allergen avoidance diet during pregnancy or lactation, or both	Sensitization	There was no significant effect of maternal allergen avoidance during lactation on the incidence of atop eczema / dermatitis during the first 18 months or on skin-prick tests to cow milk, egg, or peanut allergen at one, two, or seven years.	High

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Lovegrove 1994	England	Non-random comparison	22 infants at high-risk and 12 infants at normal-risk followed to 18 months	Mothers of high-risk infants had cow's milk-free diet versus unrestricted diet.	Allergy, including food	There was no difference between groups in allergy incidence at six months. However at 12 and 18 months, the milk-free diet was associated with reduced incidence of allergy (mean incidence was 5 for high-risk intervention group, 8 for control high-risk infants and 2 for normal-risk control infants). Data for specific food allergies were not reported separately.	Low
STRATEGIES TARGETING BREASTFEEDING WOMEN: FISH OIL SUPPLEMENTS							
Furuhjelm 2011	Sweden	RCT, double blind	143 infants followed to 2 years The mothers had at least one family member with current or previous allergic disease.	Daily maternal supplementation with omega 3 long chain polyunsaturated fatty acid versus placebo from 25th gestational week to 3.5 months of breastfeeding	Sensitization	There was no difference between groups in the prevalence of allergic symptoms or food allergies, but there were some positive trends. 11% of those in the omega 3 group versus 25% of controls had food reactions ($p = 0.06$). The omega 3 group were less likely to have egg allergies (13% versus 30% Moderate controls, 0.04), but there was no difference in milk, wheat or overall food allergy based on skin prick tests. At one year 6% in the intervention group versus 22% in the control group had IgE mediated food allergy, but this did not last until two years.	High
Klemens 2011	USA	Systematic review of RCTs and meta-analysis	5 randomized trials	Maternal supplementation with omega 3 long chain polyunsaturated fatty acid versus placebo during pregnancy and lactation	Food allergy, sensitization	Fish oil supplements during pregnancy were associated with reduced prevalence of infant sensitivity to egg at one year. Supplements during lactation were not associated with prevention of food allergy.	High
Manley 2011	Australia	RCT	614 preterm infants followed to 18 months	Expressed breast milk from mothers taking tuna oil, six 500mg capsules daily versus soy oil (control) capsules	Food allergy	This study was designed to investigate the improvement of neuro-developmental outcomes in preterm Infants. Data about a wide range of possible symptoms were obtained, including food allergy, at 12 and 18 months using structured interviews only rather than food challenges. Although the study design was high quality based on the structured grading scales used, when considering the relevance to food allergy prevention, the study and its methods were of low quality. There were no differences in most allergy outcomes. For example, at 18 months food allergy was evident in 12% of the tuna oil group and 13% of the soy oil group (adjusted RR 0.99, 95% CI 0.42-2.33).	High

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
STRATEGIES TARGETING INFANTS: BREASTFEEDING							
Kramer 2009	Belarus	Cohort	2951 children followed from birth to 6.5 years	Exclusively breastfeeding for six months versus those exclusively breastfeeding for three months and then partially breastfeeding for around another three months	Sensitization	There were no differences between groups in allergen skin prick tests, but these tests were focused on inhalant allergens and no numerical data were provided about food allergy.	Low
Kull 2010	Sweden	Cohort	3825 children followed from birth to 8 years	Exclusively breastfeeding for at least 4 months	Sensitization to food and other allergens	Children exclusively breastfed for four months or more had reduced risk of sensitization (adjusted OR 0.79, 95% CI 0.64-0.99) during the first eight years of life compared to those not exclusively breastfed for four months. Data were not presented separately for food allergens.	Low
Matheson 2007	Australia	Cohort	5659 people followed from age 7 to 44 years	Exclusive breastfeeding for at least 3 months	Food allergy	Exclusively breastfed children had a reduced risk of food allergy at 7 years (OR 0.75, 95% CI 0.62-0.92) but an increased risk of food allergy at 44 years (OR 1.25, 95% CI 1.1-1.5). Data were collected using self-report only and data were only prospectively collected from seven years onwards (prior data were collected retrospectively).	Low
Mehrshahi 2007	Australia	Cohort	516 infants with a family history of asthma, followed to 5 years	Randomized in 4 groups to house dust mite avoidance and supplement of omega-3 fatty acids for primary prevention of asthma Breastfeeding for longer than 6 months and delayed introduction of solids evaluated in the total group.	Atopy, including sensitization to food and inhalant allergens	After adjusting for confounding factors there was no significant association between the duration of breastfeeding or timing of introduction of solid foods and incidence of allergic disease. Breastfeeding for six months or more and introducing solid foods after three months were both associated with an increased risk of sensitization at age five. No separate data on sensitization to food allergens or food allergy.	Low
Pesonen 2006	Finland	Cohort	164 infants followed to 20 years, 42% at high-risk	Exclusive breastfeeding for at least 9 months	Food hypersensitivity	Exclusive breastfeeding for more than nine months was associated with increased risk of food hypersensitivity at five years (OR 5.3, 95% CI 1.2-24.1) and 11 years (OR 7.9, 95% CI 1.4-50) in children with a family history of allergy, but not for those with no family history. Data were collected using self-report surveys only.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Saarinen 1995	Finland	Cohort	150 children followed to 17 years	Breastfeeding for more than 6 months versus breastfeeding for 1-6 months versus limited or no breastfeeding	Food allergy	Those with little or no breastfeeding had the highest rates of atopy. Food allergy was highest in this group, with 65% of those aged 17 not breastfed having food allergy.	Low
Saarinen 1999and 2000	Finland	Cohort	6209 infants followed to 1 year	Breastfeeding, formula feeding and environmental factors	Cows' milk allergy	Prolonged exclusive breastfeeding may increase the risk of cow's milk allergy in infants at high-risk (OR 3.9, 95% CI 1.6-9.8). Other risk factors for cow's milk allergy included exposure to cow's milk in hospital shortly after birth (OR 3.5, 95% CI 1.2-10.1) and breastfeeding exclusively (OR 5.1, 95% CI 1.6-16.4) or with infrequent small exposure to cow's milk in the first two months (OR 5.7, 95% CI 1.5-21.6). A large number of children were excluded from the analyses.	Low
STRATEGIES TARGETING INFANTS: COW'S MILK FORMULA ALTERNATIVES							
Chandra 1997	Canada	Non-random comparison, double blind	216 infants at high-risk fed formula and 72 breastfed followed to 5 years	Exclusive breastfeeding for 5 months or more	Sensitization to eggs	Neither maternal dietary intake during pregnancy or the duration of breastfeeding influenced the development of sensitization to food allergens or food allergy at one year. Those weaned prior to 16 weeks were less likely have food sensitization at one year (OR 0.26, 95% CI 0.05-0.94) or three years (OR 0.33, 95% CI 0.11-0.86) and less likely to have food allergy at one year (OR 0.41, 95% CI 0.18-0.89) or three years (OR 0.51, 95% CI 0.28-0.92).	Low
Wetzig 2000	Germany	Cohort	265 infants at high-risk followed to 2 years	Exclusive breastfeeding for 5 months or more	Sensitization to eggs	At one year, those who were breastfed for five months or more were more likely to be sensitized to eggs (OR 4.9, 95% CI 1.2-20.4). This association did not last to two years.	Low
This series of studies has been discredited. It is included here for completeness, but is not included in the summary of results. Exclusive breastfeeding or feeding with partial whey hydrolyzate formula and not soy formula did not reduce incidence. The whey in results hydrolyzate group was less likely to suffer food summary allergy than the other formula groups.							

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Chirico 1997	Italy	Non-random comparison	51 infants at high-risk and 23 infants at normal-risk followed to 6 months	Breastfeeding versus partially hydrolyzed whey formula versus usual cow's milk formula	Sensitization	Partially hydrolyzed formula was less immunogenic and allergenic than traditional formula. Infants at high-risk fed hydrolyzed formula had IgE concentration the same as high and low-risk breastfed infants and IgE concentration much lower than high and low-risk infants fed usual formula.	Low
D'Agata 1996	Italy	Non-random comparison	125 infants at high-risk followed to 4 years	Exclusive breastfeeding versus hypoallergenic milk versus soy milk versus conventional formula	Food allergy symptoms	14% of infants using hypoallergenic milk had allergic symptoms compared with 53% eating conventionally.	Low
de Seta 1994	Italy	Non-random comparison	108 infants at high-risk followed to 2 years	Exclusive breastfeeding versus hypoallergenic formula versus conventional formula. No other food was introduced until 6 months	Allergic diseases, including food allergy	There were no significant differences between groups in the incidence of allergic disease.	Low
Halken 1993	Denmark	RCT	154 infants at high-risk followed to 18 months	Extensively hydrolyzed whey formula versus partially hydrolyzed whey formula versus extensively hydrolyzed casein formula to supplement breastfeeding in the first 4 months	Cows' milk allergy	2% of those fed casein hydrolyzate, 5% of those fed ultrafiltrated whey hydrolyzate and 5% of those breastfed had cow's milk allergy.	High
Halken 2000	Denmark	RCT, double blind	478 infants at high-risk followed to 18 months	Partially hydrolyzed whey formula versus extensively hydrolyzed whey formula versus extensively hydrolyzed casein formula to supplement breastfeeding in the first 4 months. 232 of the sample were exclusively breastfed	Cows' milk allergy	At 12 and 18 months, parental-reported and documented cow's milk allergy was greater in breastfed children and those fed partially hydrolyzed formula compared to extensively hydrolyzed formula. At 18 months, the cumulative incidence of parental reported food allergy was 19% for those exclusively breastfed for four months, 7% for extensively hydrolyzed casein formula, 5% for extensively hydrolyzed whey formula and 13% for partially hydrolyzed whey formula.	High
Hays 2005	USA	Systematic review	22 randomized trials	Extensively or partially hydrolyzed infant formula versus breastfeeding, cow's milk formula or soy formula	Allergic diseases, including food allergy	There were reductions in the cumulative incidence of atopic disease from 12 to 60 months in high-risk infants fed extensively hydrolyzed casein formula or partially hydrolyzed whey formula versus cow's milk formula. Data about food allergy outcomes were not reported separately, only as part of cumulative figures.	Moderate

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Kjellman 1979	Sweden	RCT	48 infants at high-risk followed to 4 years	Soy formula versus cow's milk formula from weaning to 9 months	Food allergy, sensitization	There was no difference between groups in symptoms, allergy or cow's milk intolerance. Withholding cow's milk and replacing with soy during the first nine months did not reduce the incidence of cow's milk intolerance from birth to four years of age.	Low
Lowe 2011	Australia	RCT	620 infants at high-risk followed to 7 years	At cessation of breastfeeding, cow's milk formula versus partially hydrolyzed whey formula versus soy formula	Food allergy	Use of partially hydrolyzed whey formula or soy formula did not decrease the risk of allergic symptoms or food allergy in infancy or up to seven years. At two years, 3.8% of those fed traditional formula, 1.4% of those fed partially hydrolyzed whey formula and 5.5% of those fed soy formula had cow's milk allergy. Differences were not statistically significant.	Moderate
Lucas 1990 and 1999	England	RCT	777 preterm infants followed to 18 months	Trial 1: banked donor milk versus preterm formula as sole diet versus preterm formula as supplement to breast milk. Trial 2: term versus preterm formula	Food allergy	Feeding preterm babies formula based on cow's milk, including formula with high protein content, did not increase the overall risk of food allergy. At 18 months there were no differences between groups regarding cow's milk allergy (15% term formula versus 5% preterm formula) or all food allergies (13% term formula versus 8% preterm formula, $p > 0.05$). Among high-risk children, those fed human milk had a significant lower risk for atopic reactions inclusive documented food allergy as compared to those fed pre-term formula. Combining the two trials the prevalence of documented cow's milk protein allergy at 18 months was significantly lower among high-risk children fed human milk compared with those fed term or preterm formula.	Moderate
Mallet 1992	France	RCT	125 infants at high-risk followed to 4 years	Extensively hydrolyzed formula versus adapted cow's milk formula (control)	Cows' milk allergy alone or with breastfeeding for 4 months	At one year the prevalence of food allergy was too low to show significant differences between groups (1% hydrolyzed formula alone versus 0% hydrolyzed formula plus breastfeeding versus 0% adapted cow's milk formula alone or with breastfeeding). In this study the diagnostic criteria or food challenges were not described.	Moderate

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Odelram 1996	Sweden	RCT	91 infants at high-risk followed to 18 months	Extensively hydrolyzed-cow's milk whey formula versus usual cow's milk formula for 12 months, started after exclusive breastfeeding ended. Lactating mothers avoided milk, egg and fish as did infants up to one year. 20 infants were exclusively breastfed for more than 9 months so acted as a control	Cows' milk allergy	The incidence of food allergy was similar between groups. The incidence of reactions to cow's milk on skin prick tests was 12% for those fed whey hydrolyzate, 9% for those fed cow's milk formula and 15% for those breastfed for more than 9 months ($p > 0.05$).	Moderate
Oldaeus 1997	Sweden	RCT	155 infants at high-risk followed to 18 months	At weaning, extensively versus partially hydrolyzed-cow's milk formula versus regular formula. No cow's milk was given during the first 9 months and no egg or fish up to 12 months. Breastfeeding mothers avoided these foods	Food allergy	At 18 months, the cumulative incidence of atopic symptoms was 51% in the extensively hydrolyzed group, 64% in the partially hydrolyzed group and 84% in the regular formula group. The extensively hydrolyzed formula was more effective than partially hydrolyzed formula up to six and nine months. There was no difference between groups in food allergy outcomes (sensitization to milk or egg).	Moderate
Osborn 2006	Australia	Systematic review with meta-analysis	18 randomized or quasi-randomized trials	Hydrolyzed formula versus usual feeding	Any allergy, cows# milk allergy, food intolerance	In high-risk infants who were unable to exclusively breastfeed, prolonged feeding with hydrolyzed formula may reduce allergy compared to cow's milk. No trials compared long-term hydrolyzed formula to breast milk. Two studies of short-term feeding with hydrolyzed formula found no difference from breast milk regarding allergy generally or cow's milk allergy. There were no differences between short-term feeding with hydrolyzed formula versus cow's milk formula, although one study did suggest a possible reduction in cow's milk allergy among low-risk infants (RR 0.62, 95% CI 0.38-1.00). Meta-analysis of four studies of long-term feeding with hydrolyzed formula found reduced allergy incidence in infancy compared to cow's milk formula (RR 0.63, 95% CI 0.36-0.81). These studies also found reduced cow's milk allergy in infancy. All of these studies focused on infants at high-risk.	High

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Osborn 2009	Australia	Systematic review with meta-analysis	3 randomized or quasi-randomized trials with 80% or more follow-up of infants at high-risk	Soy formula versus cow's milk formula. Comparisons with breast milk or hydrolyzed protein formula were also eligible, but no studies were identified	Any allergy, food intolerance	Soy formula cannot be recommended for preventing allergy in infants. No article studied short-term feeding of soy formula. Meta-analysis of studies of prolonged feeding of soy formula found no significant difference compared to cow's milk formula in the incidence of infant or childhood allergies, asthma, atopic eczema / dermatitis or rhinitis. One study reported no significant difference between groups in cow's milk protein intolerance (RR 1.09, 95% CI 0.45-2.62) or cow's milk allergy (RR 1.09, 95% CI 0.24-4.86) in infants.	High
Szajewska 2010	Poland	Systematic review with meta-analysis	15 randomized trials with infants at high-risk	Partially hydrolyzed whey formula versus regular formula or extensively hydrolyzed whey or extensively hydrolyzed casein formula	Any allergy, including food	Partially hydrolyzed formula was associated with less risk of all allergic conditions combined compared to cow's milk formula. Meta-analysis of seven trials found reduced risk of allergic diseases with partially hydrolyzed formula. There were limited data specific to food allergy, but trends were positive for partially hydrolyzed formula. Risk ratios were calculated for different age groups. There were no significant differences between partially hydrolyzed formula and extensively hydrolyzed whey or casein formulas.	High
Vandenplas 1995	Belgium	RCT, double blind	58 high-risk non breastfed infants followed to 5 years	Partial whey hydrolyzate formula versus regular cow's milk formula for 6 months	Cows' milk protein sensitivity	Allergy prevention appears to be allergen specific. At six months, cow's milk protein sensitivity was lower in the hydrolyze group (7% versus 43% controls).	Moderate
van Odijk 2003	Sweden	Systematic review	120 studies, of which 56 were considered to have conclusive findings and were summarized	Breastfeeding, cow's milk formula, cow's milk formula alternatives	Allergy, including food allergy	Most findings did not differentiate food allergy from other forms of allergy and atopy. 14 out of 26 studies of breastfeeding and atopic manifestations in cross-sectional populations reported that breastfeeding reduced the risk of asthma, wheezing, atopic dermatitis, and cow's milk allergy. Two studies found no protective benefit for cow's milk allergy. 18 out of 19 studies of breastfeeding in children with atopic heredity found that breast milk had a protective effect up to at least 1-3 years. All 14 studies of formula feeding in children with atopic heredity found that replacing cow's milk formula with extensively hydrolyzed whey or casein formula had a protective effect. There was no evidence to suggest that whey hydrolyzate was better than casein hydrolyzate or vice versa. Three out of four studies suggested that introducing cow's milk in the first few days of life had a protective effect.	High

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
von Berg 2008	Germany	RCT, double blind	2252 infants at high-risk followed to 6 years	Partially hydrolyzed whey formula versus extensively hydrolyzed whey formula versus extensively hydro- lyzed casein formula versus cow's milk formula for first 4 months when breastfeed- ing was insufficient.	All allergy, including food allergy	Hydrolysed infant formulas may have a long-term protective effect for allergies. Partially hydrolyzed formula and extensively hydrolyzed casein formula were less likely to result in allergic symptoms than cow's milk formula. Outcomes specific to food allergy were not reported separately.	High
STRATEGIES TARGETING INFANTS: PROBIOTICS AND PREBIOTICS							
Gruber 2010	5 European countries	RCT	830 infants at low risk who were fed formula, plus 300 others breastfed	Regular cow's milk formula alone or supplemented with a mixture of neutral oligo- saccharides and pectin-de- rived acidic oligosaccha- rides (prebiotic formula)	Sensitization to cow's milk and hen's eggs	There was no difference between groups in sensitization to cow's milk or hen's eggs at one year.	Moderate
Kalliomaki, 2001	Finland	RCT, double blind	132 infants at high-risk followed to 2 years	Lactobacillus GG given to mothers daily for 2 to 4 weeks before delivery and afterwards if breastfeeding and to infants for 6 months versus placebo	Eczema and sensitization	There was no difference between groups in sensitization, including milk and egg allergy. No specific data on sensitization to food allergens.	High
Kukkonen 2011	Finland	RCT, double blind	688 infants at high-risk followed to 2 years	Probiotic mixture for mothers during last month of pregnancy plus probiotic and prebiotics for infants for 6 months versus placebo for mothers and infants	Allergic diseases, including food allergy	Probiotics and probiotics may have no immunomodulatory effect. Compared with placebo, probiotic treatment had no effect on food allergy at two years (6% probiotics plus prebiotics versus 7% controls).	High
Kuitonen 2009	Finland	RCT, double blind	891 infants at high-risk followed to 5 years	Probiotic mixture for mothers during last month of pregnancy plus probiotic and prebiotics for infants for 6 months versus placebo for mothers and infants	Food allergy	There was no significant difference between groups in overall allergy (87.9% probiotics versus 87.1% controls) or in food allergy (20.8% probiotics versus 23.5% controls, OR 0.85, 95% CI 0.62-1.17). Children delivered by caesarean section receiving probiotics were less likely to have allergy.	High
Marschan 2008	Finland	RCT, double blind	98 infants at high-risk followed to 2 years	Probiotic mixture for mothers during last month of pregnan- cy plus probiotic for infants for 6 months versus placebo for mothers and infants	Food allergy, sensitization	Probiotics may induce protective immune profiles for some forms of allergic disease, but there was no significant difference between groups in food allergy or sensitization.	Moderate

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Morisset 2011	France	RCT, double blind	110 infants at high-risk followed to two years	Non-hydrolyzed fermented infant formula containing heat killed <i>Bifidobacterium</i> C50 and <i>Streptococcus thermophilus</i> O65 versus standard infant formula for 2 years	Cows' milk allergy	Use of the special formula did not decrease the incidence of cow's milk allergy (13% versus 15% controls, $p = 1$), but was associated with reduced digestive and respiratory issues in the early months.	High
Osborn 2009	Australia	Systematic review	7 randomized and quasi-randomized trials with infants	Probiotic versus no probiotic or versus another probiotic in infant formula	Food hypersensitivity	There is insufficient evidence about the role of prebiotics in infant formula for preventing allergic disease and food hypersensitivity. Only two studies reported disease outcomes and these both focused on asthma rather than food allergy.	High
Osborn 2009	Australia	Systematic review with meta-analysis	12 randomized and quasi-randomized trials with infants	Probiotic versus no probiotic or versus another probiotic or versus prebiotic in infant formula	Food hypersensitivity	There is insufficient evidence about the role of probiotics for preventing allergic disease or food reactions. Meta-analysis of five studies found a significant reduction in infant atopic eczema / dermatitis but there was heterogeneity. All studies finding benefits used <i>Lactobacillus rhamnosus</i> with infants at high-risk. No other benefits were reported for other allergic disease or food hypersensitivity.	High
Prescott 2008	Australia	RCT, double blind	153 infants followed to 2.5 years	<i>Lactobacillus acidophilus</i> probiotic supplementation versus placebo for 6 months	Food allergy, allergen sensitization	Probiotic supplementation did not have any significant effect on food allergy. The incidence of food allergy was 14% in both groups at 2.5 years of age.	High
Tang 2012	China	Systematic review and meta-analysis of RCTs	15 randomized trials with 3604 infants	Probiotics versus placebo	Sensitization	There was no impact on food allergy or sensitization. Numerical data specific to food allergy were not reported.	High
STRATEGIES TARGETING INFANTS: OTHER SUPPLEMENTS							
Kull 2006	Sweden	Cohort	2614 infants followed to 4 years	Early life supplementation of vitamins A and D in water soluble form or in peanut oil	Food sensitization	98% of children received supplements, usually in peanut oil. Those receiving supplements in water soluble form had twice as much chance of food hypersensitivity (OR 1.89, 95% CI 1.45-3.28) and sensitization to common food and airborne allergens at four years (OR 1.88, 95% CI 1.34-2.64).	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
STRATEGIES TARGETING INFANTS: INTRODUCTION OF SOLID FOOD							
Zachariasen 2011	Denmark	RCT	324 very preterm infants followed to 1 year	Cows' milk-based human milk fortifier added to mother's breast milk versus exclusive breastfeeding versus (for those not breastfeeding) cow's milk-based preterm formula for 4 months after discharge.	Allergic diseases, including food allergy	There was no difference between feeding groups in various types of allergy. No infant developed food allergy.	Moderate
Joseph 2011	USA	Cohort	594 children followed to 2 years	Exposure to solid food or cow's milk prior to 4 months	Food sensitization	Introducing solid food prior to four months was associated with a reduced risk of peanut sensitization by two years, but only for children with a parental history of asthma or allergy (OR 0.2, 95% CI 0.1-0.7).	Low
Kajosaari 1994	Finland	Non-random comparison	1113 infants at high-risk followed to 5 years	Exclusive breastfeeding plus delayed introduction of solid foods until 6 months versus breastfeeding with solid foods introduced from 3 months	Food allergy	There was no difference between groups in food allergy (numbers not reported).	Low
Poysa 1991	Finland	Cohort	1119 children with and without a family history of atopy followed from birth to 10 years	Atopy-prone children were asked to follow a diet intended to prevent atopy. The diet involved breastfeeding to three months and introduction of solid food and formula based on cow's milk after three months	Allergy, including food allergy	Half the atopy-prone children kept to the diet. At age 9 to 10 years, 32% of all children had at least one atopic illness (bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic eczema / dermatitis or food allergy). There was no significant difference between groups. The authors concluded that preventive dietary measures in early infancy had no influence on atopic manifestations in childhood. However, families were self-selected in terms of choosing whether to adhere to the dietary guidelines.	Low
Sausenthaler 2011	Germany	Cohort	9088 infants from two cohort studies, including a subgroup of 2252 at high-risk followed to 6 years	Maternal diet, early introduction of solid foods, formula	Food allergen, sensitization	Delayed introduction of solid foods or avoiding highly allergic foods during the first year did not reduce allergy incidence but food allergy outcomes were not reported separately. Very early introduction of solid foods before week 17 may increase the risk of later allergy. Maternal diet during pregnancy may be associated with increased risk for food sensitization. For instance, maternal diet high in celery (OR 1.85, 95% CI 1.18-2.89) and citrus fruits (OR 1.73, 95% CI 1.18-2.53) was associated with increased sensitization to food allergens in infants.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Schoetzau 2002	Germany	Cohort	1121 infants followed to 1 year	Exclusive breastfeeding and avoiding solid food for at least 4 months	Sensitization to milk and egg	There was no relationship between the age at introduction of solid food or diversity of solid food and incidence of sensitization.	Low
Tarini 2006 USA	Systematic review		13 studies of infants followed up to various ages	Early introduction of solid foods prior to 4 months	Food allergy	There was no evidence of a relationship between early solid foods (prior to four months) and food allergy, asthma or allergic rhinitis.	High
STRATEGIES TARGETING INFANTS: EXPOSURE TO POTENTIAL FOOD ALLERGENS							
de Jong 1998 and 2002	The Netherlands	RCT, double blind	1108 breastfed infants followed to 5 years	Exposure to cow's milk protein versus protein-free placebo in first 3 days of life	Allergic symptoms, including food allergy	Early brief exposure to cow's milk in breastfed children did not increase the risk of allergic symptoms or atopic disease in the first five years. Allergy to cow's milk was 5.8% in the exposed group and 4.1% in controls at age 1 (RR 1.43) and 5.3% for the exposed group versus 3.0% controls at age 5 (RR 1.77). This study did not use controlled food challenges.	High
Host 1988	Denmark	Cohort	1749 infants followed to 1 year	Cows' milk formula during the first three days	Cows' milk allergy	2.2% of infants developed cow's milk allergy in the first year. Of these, 23% developed cow's milk allergy during exclusive breastfeeding in the first three months, 21% developed cow's milk allergy whilst combining breast and formula feeding and 56% were using cow's milk formula alone (significance not reported). All infants who developed cow's milk allergy had been given some cow's milk formula to supplement feeding within the first three days. Of the 1539 children who received some cow's milk formula during the first three days of life, 3% developed cow's milk allergy in the first year. Of the 210 who did not receive any cow's milk formula during the first three days, 0% developed cow's milk allergy ($p < 0.05$).	Low
Kull 2006	Sweden	Cohort	4089 children followed to 4 years	Fish consumption during the first year of life	Allergic symptoms and sensitization	Sensitization to fish was evident in a very small number of children. Regular fish consumption during the first year of life was associated with a reduced risk for allergic disease at age 4 (adjusted OR 0.76, 95% CI 0.61-0.94) and sensitization (adjusted OR 0.76, 95% CI 0.58-1.0).	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Lindfors 1992	Sweden	RCT	183 infants with slightly reduced birth weight followed to 5 years	Cows' milk formula during the first days of life before breast milk production started versus no formula before normal breastfeeding started	Allergic symptoms, including food allergy	At 18 months and 5 years there were fewer allergic symptoms in the group exposed early to cow's milk. This difference was mainly caused by a reduced incidence of mild symptoms in those at high-risk. There was no difference in moderate to severe symptoms. The authors concluded that early exposure to foreign protein has a protective effect on the development of allergic disease. However there was no difference between groups in confirmed food allergy when this data was separated from other allergic manifestations. Furthermore, the data were collected using self-report rather than food challenges.	Moderate
Merrett 1988	Wales	RCT	487 infants at high-risk followed to 1 year	Withholding cow's milk and foods containing cow's milk and substituting with soy substitute if required versus no intervention for 4 months. Mothers in the intervention group were asked to restrict their milk intake	Allergy symptoms	There was no benefit from withholding cow's milk. Allergy symptoms were higher in this group. Specific numerical data about food allergy were not reported.	High
STRATEGIES TARGETING INFANTS: MULTIFACETED STRATEGIES							
Arshad 2007 With update: Scott 2012	England	RCT	120 children at high-risk, followed from birth to 8 years, then to 18 years	Standard care versus reduction of food and dust mite allergen exposure through breastfeeding by a mother on a low allergen diet or feeding through extensively hydrolyzed formula and use of acaricide and mattress covers	Food allergy	At eight years, the prevalence of food allergy was lower in the intervention group, but the overall numbers were small so trends did not reach statistical significance (adjusted OR 0.75, 95% CI 0.27-2.1). Moderate However, by 18 years there was no significant difference between groups in the proportion of current or ever food sensitization (p all > 0.2)	Low
Bardare 1993	Italy	Non-random comparison	462 infants followed to 1 year	Standard care versus recommended breastfeeding for 6 months, restricted maternal diet, delay of solid food and advice about avoiding environmental allergens	Atopy, including food	Combining diet and environmental strategies may protect against or delay onset of food allergies during the first year of life. Those who complied with the prescribed maternal and infant diet had a lower incidence of atopy during the first year compared to families that ignored the diet (13% versus 55%) and those who were not offered dietary recommendations (29%). Data specific to food allergy were not available.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Bruno 1993	Italy	Cohort	174 infants at high-risk followed to 52 months	Dietary and environmental changes such as exclusive breastfeeding for the first 6 months supplemented if needed with soy formula, delayed weaning beyond 6 months and eliminating exposure to dust mites and passive smoking	Food allergy	Breastfeeding and environmental changes may help to keep the prevalence of food allergy low. The prevalence of food allergy was 1% and this remained stable between 6 and 52 months. Those fed breast milk or soy milk in the first six months were less likely than those receiving cow's milk to have any atopic disease at 52 months.	Low
Halken 1992	Denmark	Non-random comparison	159 infants at high-risk followed to 18 months	105 families were recommended breastfeeding or extensively hydrolyzed casein-based formula, avoidance of solid foods for 6 months and given advice about avoiding environmental allergens. 54 families acted as controls	Food allergy	Feeding with breast milk or hypoallergenic formula and avoiding solid foods for six months reduced atopic symptoms. At 18 months the prevalence of atopic symptoms was lower in the intervention group (32% versus 74% controls). There was reduced prevalence of wheezing, atopic dermatitis and colic. Food allergy was also lower (6% versus 17%, p < 0.05).	Low
Halmerbauer 2002	Austria, Germany, UK	RCT	696 infants at high-risk followed to 1 year	Advice to reduce exposure to food and environmental allergens e.g. using mattress encasings versus no intervention	Food sensitization	Sensitization to food and environmental allergens was lower in the intervention group (6% versus 11% control).	High
Marini 1996	Italy	Non-random comparison	279 infants at high-risk and 80 infants at normal-risk followed to 3 years	Exclusive and prolonged breastfeeding followed by hypoallergenic weaning diet and environmental measures versus no intervention. In the intervention group, those who could not breastfeed were randomly assigned to a partially hydrolyzed formula or conventional formula	Allergy, including food allergy	At one year, two and three years, allergic conditions were fewer in the intervention group. In the intervention group, those breastfed were least likely to develop food allergies, followed by the hydrolyzed formula group (figures not provided). Those fed cow's milk were most likely to develop allergies. Of the factors tested, the following seemed most likely to result in allergic symptoms: beginning formula in the first week of life; weaning before four months; feeding beef before six months; cow's milk before six months; parental smoking in the presence of babies and day care before two years.	Low

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
Schneider Chafen 2010	USA	Systematic review of reviews and RCTs	6 systematic reviews and 27 additional randomized trials (plus additional studies on other topics)	Breastfeeding and delayed introduction of solids, maternal diet during pregnancy or lactation, exclusive breastfeeding, special diets for children, probiotics	Food allergy	Three studies about maternal diet during pregnancy or lactation found mixed effects, but atopy rather than food allergy was the main outcome studied. Three studies about exclusive breastfeeding found conflicting evidence. The focus was on atopy rather than food allergy as an outcome.	
Schneider Chafen 2010	USA	Systematic review	16 studies of preventing food allergy in children and adults (plus additional studies on other topics)	Breastfeeding, maternal diets, children's diets, formula and probiotics	Food allergy	One study found that delaying the introduction of solids and continuing breastfeeding reduced the incidence of food intolerance (reported by parents). Two systematic reviews and five additional RCTs evaluated hydrolyzed formulas. Partially and extensively hydrolyzed formulas may reduce cow's milk allergy in infants at high-risk compared to cow's milk formula.	
Zeiger 1989, 1992 and 1995	USA	RCT		Mothers avoided cow's milk, egg and peanut during the last trimester and infants avoided cow's milk to 1 year, with casein hydrolyzate formula supplements as needed	Food allergy	One systematic review and one additional RCT suggested that soy formula had little impact.	
				and infants also avoided egg, peanut and fish until 2 years versus no dietary restrictions for mothers or infants.		There is evidence that hydrolyzed formulas, particularly extensively and partially hydrolyzed formula, may reduce infant and childhood allergy, asthma, and cow's milk allergy syndrome in high-risk infants compared with cow milk formula. Soy milk made little difference. There is insufficient evidence to determine the effect of breastfeeding, restricting maternal diet during pregnancy or lactation or delayed introduction of solid foods for infants. Probiotics have mixed results.	
						The cumulative incidence of food allergy and intolerance was lower in the intervention group. This remained through to four years, but the protective effect occurred in the early years. There was no difference between groups at seven years (13.9% Moderate versus 15.4% controls). This may be due to the natural course of food allergy, which children often 'grow out of.' There was also a high dropout rate over time.	

Table E1 (continued)

First author	Country	Design	Sample	Intervention	Relevant outcomes	Key findings	Quality
STRATEGIES TARGETING CHILDREN AND ADULTS							
Anandan 2009	Scotland	Systematic review and meta-analysis of RCTs	Six double blind randomized trials of children or adults at high or low-risk	Omega 3 or omega 6 supplementation versus placebo	Food allergy	There was no evidence that omega 3 supplements reduced the risk of food allergy. Meta-analysis of data from two studies found no impact (RR 0.51, 95% CI 0.10-2.55). No studies about omega 6 had food allergy as an outcome.	High
Arnoldus-sen 2011	Scotland	Systematic review and meta-analysis	17 studies of infants	BCG vaccination	Allergic disease, including food allergy and sensitization	Meta-analysis found that BCG vaccination had no protective effect against the risk of sensitization, as judged by specific IgE tests (OR 1.31, 95% CI 1.07-1.60) or skin prick testing (OR 0.87, 95% CI 0.67-1.13).	High
Marmsjo 2009	Sweden	Cohort	2423 children followed to 8 years	Multivitamin supplements	Atopic sensitization, including food allergy	There were no strong associations between current multivitamin use and atopic sensitization (including food allergy). Children who began taking vitamins prior to five years had reduced risk of sensitization to food allergens (OR 0.61, 95% CI 0.39-0.97).	Low

Note: 'Relevant outcomes' relate to outcomes of interest to this systematic review. The articles commonly included other outcomes in addition.

Table E2 Quality assessment of systematic reviews

First author	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Adequateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits versus harms / costs	Overall quality assessment
Anandan 2009	✓	✓	✓	✓	✓	✓	✓	✓	✗	High
Arnoldussen 2011	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Hays 2005	✓	✓	✗	✓	✓	✓	✓	✓	✓	Moderate
Klemens 2011	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Kramer 2012	✓	✓	✓	✓	✓	✓	✓	✓	✗	High
Osborn 2006	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Osborn 2009 (probiotics)	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Osborn 2009 (prebiotics)	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Osborn 2009 (soy)	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Schneider Chafen 2010 (article)	✗	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Schneider Chafen 2010 (report)	✗	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Szajewska 2010	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Tang 2012	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Tarini 2006	✓	✓	✓	✗	✓	✓	✓	✓	✓	High
van Odijk 2003	✓	✓	✗	✓	✓	✓	✓	✓	✓	High

Note: Crosses refer to things that were not reported on in the article, that were not undertaken or that were undertaken poorly.

Table E3 Quality assessment of primary studies

First author and update:	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Other method notes	Overall quality assessment
Arshad 2007 and update: Scott 2012	RCT	x	✓	✓	✓	✓	x	Testing two things: dust mites and food	Moderate
Bardare 1993	Non-random comparison	NA	x	x	✓	✓	x	Comparing those who complied and those who didn't, with a control group	Low
Bruno 1993	Cohort	NA	NA	NA	✓	✓	x	Testing multiple variables	Low
Chirico 1997	Non-random comparison	NA	x	x	✓	✓	✓	Allocation unclear Small sample	Low
D'Agata 1996	Non-random comparison	NA	x	x	?	✓	✓	Allocation unclear Confounders not accounted for	Low
de Jong 1998 and 2002	RCT	x	✓	✓	✓	✓	✓	High dropout	Moderate
de Seta 1994	Non-random comparison	NA	NA	x	✉	?	?	Allocation unclear Small sample in each group	Low
Dunstan 2003 and Denburg 2005	RCT	✓	✓	✓	✓	✓	✓	Clinical outcomes not prime focus Some dropout was due to adverse effects	Moderate
Falh- Magnusson 1992	RCT	x	x	x	✓	✓	x	Allocation protocol unclear Not blinded Some crossover in groups	Moderate
Furuholm 2011	RCT	x	✓	✓	✓	✓	✓	Some dropout Allocation protocol unclear	Low
Gruber 2010	RCT	x	?	?	✓	✓	x	Allocation protocol unclear	Moderate
Halken 1992	Non-random comparison	NA	NA	x	✓	✓	✓	Subsample of larger study	Low
Halken 1993	RCT	✓	✓	x	✓	✓	✓		High
Halken 2000	RCT	✓	✓	✓	✓	✓	✓	Some dropout Different class status of those breastfed	High
Halmerbauer 2002	RCT	?	✓	✓	✓	✓	✓	Testing variety of interventions Compliance uncertain	High
Hattevig 1989	Non-random comparison	NA	x	x	✓	✓	✓		Low

Table E3 (continued)

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Other method notes	Overall quality assessment
Host 1988	Cohort	NA	NA	NA	✓	✓	✗	Low
Huurre 2008	RCT	?	✓	✓	✓	✓	Studied multiple variables	High
Joseph 2011	Cohort	NA	NA	NA	✓	✓	High proportion of ethnic minorities High dropout	Low
Kajosaari 1994	Non-random comparison	✗	✗	✗	✓	✗	Randomization unclear	Low
Kalliomaki, 2001	RCT	✓	✓	✓	✓	✓	Some dropout	Low
Kjellman 1979	RCT	✗	✗	✗	✓	✓	Some dropout	High
Kramer 2009	Cohort	NA	NA	NA	✗	✓	Allocation protocol uncertain	Low
Kuitonen 2009	RCT	✗	✓	✓	✓	✓	Allocation protocol unclear	Low
Kukkonen 2011	RCT	✓	✓	✓	✓	✓	High dropout Allocation protocol unclear	High
Kull 2006 (vitamins)	Cohort	NA	NA	NA	✗	✓	High dropout Allocation protocol unclear	High
Kull 2006 (fish)	Cohort	NA	NA	NA	✓	✓	Dropout Most received supplements	Low
Kull 2010	Cohort	NA	NA	NA	✗	✓	Incomplete data May not have accounted for confounders	Low
Lilja 1991	RCT	NA	✗	✗	✓	✓	Not focused on symptoms	Moderate
Lindfors 1992	RCT	✗	✓	✗	✓	✓	High dropout	Moderate
Lovegrove 1994	Non-random comparison	✗	✓	✗	✓	✓	Purpose of non-atopic control uncertain Participants not blind	Low
Lowe 2011	RCT	✗	✓	✓	✓	✓	Two trials conducted in different areas Unclear if subgroup analyses were preplanned	Moderate
Lucas 1990 and 1999	RCT	✓	✓	✓	✓	✗	No blinded High dropout	Moderate
Mallet 1992	RCT	✗	✗	✗	✓	✓	Allocation protocol unclear	Moderate

Table E3 (continued)

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Other method notes	Overall quality assessment
Manley 2011	RCT	✓	✓	✓	✓	✓	✗	Allergy data incomplete	High
Marini 1996	Non-random comparison	NA	✓	✗	✓	✓	✗	Multiple variables introduced	Low
Marmsjö 2009	Cohort	NA	NA	NA	✓	✓	✗	Different supplements examined Symptoms based on self-report questionnaire	Low
Marschan 2008	RCT	✓	✓	✓	✓	✓	✗	Subgroup analysis	Moderate
Matheson 2007	Cohort	NA	NA	NA	✓	✓	✗	Retrospective data collection for breastfeeding Loss to follow up	Low
Merrett 1988	RCT	✓	✓	✓	✓	✓	✓	Some dropout Intervention group less likely to breastfeed, perhaps because given free soy substitute	High
Mehrshahi 2007	Cohort	NA	NA	NA	✓	✓	✓		Low
Morisset 2011	RCT	✓	✓	✓	✗	✓	✓	Some dropout	High
Odelram 1996	RCT	✓	✓	✓	✗	✓	✓	Breastfeeding group created ad hoc Sample too small for significance Not blinded	Moderate
Oldaeus 1997	RCT	✓	✗	✗	✓	✓	✓	Cows' milk formula not masked High dropout	Moderate
Palmer 2012	RCT	✓	✓	✓	✓	✓	✓	Some dropout More infants in fish oil group were initially breastfed and more in the placebo group received cow's milk formula	High
Pesonen 2006	Cohort	NA	NA	NA	✗	✓	✓	Small sample High dropout	Low
Poysa 1991	Cohort	NA	NA	NA	✓	✓	✗		Low

Table E3 (continued)

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Other method notes	Overall quality assessment
Prescott 2008	RCT	✓	✓	✓	✓	✓	✓	High dropout Incomplete blood sample data	High
Saarinen 1995	Cohort	NA	NA	NA	✗	✓	✓	Food allergy defined by history rather than gold standard tests	Low
Saarinen 1999 and 2000	Cohort	NA	NA	NA	✓	✓	✓	Unclear accounting for confounders	Low
Sausenthaler 2007	Cohort	NA	NA	NA	✓	✓	✗	Retrospective collation of diet data	Low
Sausenthaler 2011	Cohort	NA	NA	NA	✓	✓	✗	High dropout Combining multiple populations	Low
Schoetzau 2002	Cohort	NA	NA	NA	✓	✓	✓	Some dropout Allocation protocol unclear	Low
Vandenplas 1995	RCT	✗	✗	✗	✓	✓	✓	Allocation protocol unclear	Moderate
von Berg 2008	RCT	✓	✓	✓	✓	✓	✗		Moderate
Venter 2009	Cohort	NA	NA	NA	✓	✓	✗		
Wetzig 2000	Cohort	NA	NA	NA	✗	✓	✓	High dropout	Low
Zachariassen 2011	RCT	✗	✗	✗	✓	✓	✗	Not fully randomised Limited participation rate Allocation protocol unclear	Moderate
Zeiger 1989, 1992 and 1995	RCT	✓	✗	✗	✓	✓	✗	High dropout Unequal loss to follow up	Moderate

Note: RCT refers to a randomized controlled trial. Crosses refer to things that were not reported on in the article, that were not undertaken or that were undertaken poorly
NA refers to components of the study design that were not applicable (for example randomization in cohort studies).

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SECTION 3

QUALITY OF LIFE IN FOOD ALLERGY

**Supplementary
materials**

3.1

DISEASE-SPECIFIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENTS FOR IgE-MEDIATED FOOD ALLERGY SYSTEMATIC REVIEW

❖ Supplementary materials ❖

SA Salvilla¹, AEJ Dubois², BMJ Flokstra-de Blok³, SS Panesar¹, A Worth¹, S Patel⁴, A Muraro⁵, S Halken⁶, K Hoffmann-Sommergruber⁷, A DunnGalvin⁸, JO B'Houirhane⁸, L Regent⁹, NW de Jong¹⁰, G Roberts¹¹⁻¹³, A Sheikh^{1, 14}, on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines Group

On behalf of the EAACI Food Allergy and Anaphylaxis Group: C Bindslev-Jensen, V Cardona, P Eigenmann, N Papadopoulos, B Vlieg-Boerstra, CA Akdis

DATA E1. SEARCH STRATEGIES

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1	exp Food Hypersensitivity/
2	foodallerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	or/1-5
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
8	(animal\$ not human\$).sh,hw.
9	7 or 8
10	6 not 9
11	Quality of Life/
12	QOL.ti,ab.
13	Health Status/
14	Health Status Indicators/
15	Activities of Daily Living/
16	Quality-Adjusted Life Years/
17	(quality adj4 life).ti,ab.
18	(well adj4 being).ti,ab.
19	HRQL.tw.
20	QALY\$.tw.
21	(Health\$ adj2 state).ti,ab.
22	(Life adj3 quality).ti,ab.
23	(Health\$ adj2 year\$ adj2 equivalent\$).ti,ab.
24	(subjective adj2 health adj2 status).ti,ab.
25	(Health Care)"/
26	(patient adj2 reported adj2 outcome adj2 measure\$).ti,ab. (530)
27	(patient adj2 outcome).ti,ab.
28	patient preference\$.ti,ab.
29	*Patient Participation/
30	*"Patient Acceptance of Health Care"/
31	consumer satisfaction.ti,ab.
32	*Patient Satisfaction/
33	*Questionnaires/
34	*Health Surveys/
35	tool\$.ti,ab.
36	*Psychometrics/
37	Utilit\$.ti,ab.
38	Short form 36.mp.
39	Short form 12.mp.
40	(SF 12 or SF 36 or SF-12 or SF-36).ti,ab.
41	Euroqol.mp.
42	EQ-5D.tw.
43	Health Utilities Index.mp.
44	HUI.mp.
45	Medical Outcomes Survey.mp.
46	MOS.tw.
47	QWB.tw.
48	Rosser.mp.
49	*"Reproducibility of Results"/
50	valid\$.ti,ab.
51	reliab\$.tw.
52	(effect adj1 size).ti,ab.
53	(Sensitiv\$ adj2 change).tw.
54	Reproduc\$.ti,ab.
55	Utility measure\$.ti,ab.
56	or/11-55
57	10 and 56

Database: Embase<1980 to 2012 Week 32>*Search Strategy:*

1	exp Food Hypersensitivity/	30	*"Patient Acceptance of Health Care"/
2	foodallerg*.mp.	31	consumer satisfaction.ti,ab.
3	food hypersensitivity.mp.	32	*Patient Satisfaction/
4	food hypersensitivities.mp.	33	or/11-32
5	allergy, food.mp.	34	*Questionnaires/
6	or/1-5 (21168)	35	*Health Surveys/
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1586460)	36	tool\$.ti,ab.
8	(animal\$ not human\$).sh,hw.	37	*Psychometrics/
9	7 or 8	38	Utilit\$.ti,ab.
10	6 not 9	39	Short form 36.mp.
11	Quality of Life/	40	Short form 12.mp.
12	QOL.ti,ab.	41	(SF 12 or SF 36 or SF-12 or SF-36).ti,ab.
13	Health Status/	42	Euroqol.mp.
14	Health Status Indicators/	43	EQ-5D.tw.
15	Activities of Daily Living/	44	Health Utilities Index.mp.
16	Quality-Adjusted Life Years/	45	HUI.mp.
17	(quality adj4 life).ti,ab.	46	Medical Outcomes Survey.mp.
18	(well adj4 being).ti,ab.	47	MOS.tw.
19	HRQL.tw.	48	QWB.tw.
20	QALY\$.tw.	49	Rosser.mp.
21	(Health\$ adj2 state).ti,ab.	50	*"Reproducibility of Results"/
22	(Life adj3 quality).ti,ab.	51	valid\$.ti,ab.
23	(Health\$ adj2 year\$ adj2 equivalent\$).ti,ab.	52	reliab\$.tw.
24	(subjective adj2 health adj2 status).ti,ab.	53	(effect adj1 size).ti,ab.
25	**"Outcome Assessment (Health Care)"/	54	(Sensitiv\$ adj2 change).tw.
26	(patient adj2 reported adj2 outcome adj2 measure\$).ti,ab.	55	Reproduc\$.ti,ab.
27	(patient adj2 outcome).ti,ab.	56	Utility measure\$.ti,ab.
28	patient preference\$.ti,ab.	57	or/34-56
29	*Patient Participation/	58	33 and 57
		59	10 and 58
		60	limit 59 to yr="1990 - 2012"

Database: CINAHL - Ebscohost*Search Strategy:*

S18	"Euroqol"	S8	S6 and S7
S17	"patient preferences"	S7	S4 or S5
S16	(MH "Health Status Indicators") OR (MH "Health Status")	S6	S2 or S3
S15	(MH "Quality-Adjusted Life Years")	S5	AB allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S14	"patient reported outcomes"	S4	TI allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S13	"proms"	S3	AB food or nutrient
S12	(MH "Outcomes (Health Care)") OR (MH "Outcome Assessment")	S2	TI food or nutrient
S11	(MH "Quality of Life")	S1	(MM "Food Hypersensitivity")
S10	S1 or S8		
S9	S1 or S8		

Database: ISI Web of Science: Science Citation Index, Conference Proceedings Citation*Search Strategy:*

Topic=((food or nutrient) AND (allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)) AND Topic=((PROMs or PROM or patient reported outcome measure* or questionnaire* or HRQL or QOL or HRQL of life or patient satisfaction or consumer satisfaction or patient preference or patient participation or “patient acceptance of healthcare” or patient outcome or patient based outcome or functional status or health status or subjective health status or health status indicator or health status assessment) AND (methodol* or psychometric* or validity or reliability or responsiveness or effect size or sensitivity to change or reproducibility or acceptability or utility measure*))

Timespan=All Years. Databases=CPCI-S.

Lemmatization=On

Table E1: Quality assessment tool for evaluation of patient reported outcome measures

Property	Definition	Quality Criteria*
DEVELOPMENT OF THE INSTRUMENT		
Pre-study hypothesis	The pre-study specification of the aim of the instrument and the intended population	<ul style="list-style-type: none"> ✓✓ A clear description is provided of the aim of the instrument and the intended population ✓ Only one of the above ✗ Neither reported
Intended population	The extent to which the instrument has been studied in the intended population	<ul style="list-style-type: none"> ✓✓ Indented population studied ✓ Partly studied only or sample size was smell (less than 50 patients) ✗ Not studied in the intended population, only genetic
Actual content area (face validity)	<p>The extent to which the study checked for face validity <i>The extent to which the content meets the pre-study hypothesis specifications</i></p>	<ul style="list-style-type: none"> ✓✓ A clear description is provided of how validity was checked within the intended population <i>Content as intended, and is relevant to the intended population</i> ✓ Some of the intended content areas missing ✗ Content area not relevant to intended population
Item identification	Selection of the items relevant to the target population for inclusion in the pilot instrument	<ul style="list-style-type: none"> ✓✓ Comprehensive consulting with patients, (focus groups or in-depth interviews), experts and a literature review ✓ Minimal consultation with patients end experts opinion and literature review ✗ No consultation with patients
Item selection	Determining the items included in the final instrument	<ul style="list-style-type: none"> ✓✓ A pilot instrument was developed and tested with Rasch or factor analysis or clinical impact and statistical justification provided for removing items, plus items with floor and ceiling effects removed and the amount of missing data considered. ✓ Only some of above techniques were used ✗ No pilot instrument OR no statistical justification of items included in the final instrument
Unidimensionality	Demonstration that all the items fit with a single underlying construct	<ul style="list-style-type: none"> ✓✓ Rasch analysis using fit statistics (0.7-1.3) or item-trait interaction or Factor analysis on Rasch scores (1st factor loadings > 0.4 for all items) or items scores ✓ Rasch fit statistic mostly within 0.7-1.3 range but some less well fitting items retained, or Cronbach's α > 0.7, and <0.9 or factor analysis on raw scores (1st factor loadings > 0.4 for all items) ✓ Rasch analysis, does not support unidimensionality or Factor analysis does not support unidimensionality or Cronbach's α <0.7, or >0.9 OR ✗ No checks for unidimensionality reported
Response scale	Categories used to rate the items	<ul style="list-style-type: none"> ✓✓ Response scale identified with a to/from range, any comments about missing data in the scales development ✓ Some, but not au of above ✗ Response scale not identified
Scoring	A description of how the instrument should be scored	<ul style="list-style-type: none"> ✓✓ Rasch scoring or summary scoring of a statistically justified response scale ✓ Summary score of a statistically justified response scale ✗ Scoring system not described or scoring of a statistically unjustified or faulty scale

Property	Definition	Quality Criteria*
Instrument translated and validated in English speaking population	The extent to which the instrument has been translated and validated in English speaking population	<ul style="list-style-type: none"> ✓✓ Instrument developed in English or translated into English and validated in English speaking population ✓ Instrument translated to English but not validated in English speaking population ✗ Instrument has not been translated to English nor validated in English speaking population
PERFORMANCE OF THE INSTRUMENT		
Convergent validity	Amount of correlation with a related measure	<ul style="list-style-type: none"> ✓✓ Tested against appropriate measure, correlates between 0.3 and 0.9 ✓ Debatable choice of measure, but correlation between 0.3 and 0.9 ✗ Tested and correlates <0.3 or >0.9
Discriminant validity	The degree to which an instrument is not similar to (diverges from) other instruments that it should not be similar to	<ul style="list-style-type: none"> ✓✓ Tested against appropriate measure, correlates <0.3 ✓ Debatable choice of measure, but correlation <0.3 ✗ Tested and correlates > 0.3
Predictive validity	The extent to which the instrument can predict a future event	<ul style="list-style-type: none"> ✓✓ Tested against appropriate measure, correlates >0.3 or significant difference between groups ✓ Debatable choice of measure, but correlation >0.3 or significant difference between groups ✗ Tested and correlates <0.3 or non-significant difference between groups
Other evidence for construct validity e.g. criterion, discriminant	Any other hypothesis driven testing	<ul style="list-style-type: none"> ✓✓ Hypothesis stated, tested and proven ✓ Construct validity claimed but debatable under scrutiny ✗ Construct validity claimed but does not hold up to scrutiny
Test-retest agreement	The extent to which the results are repeatable when taken by the same observer or same person if self-report	<ul style="list-style-type: none"> ✓✓ Bland Altman plot LOA appear tight and less than MID, or weighted Kappa or ICC ≥ 0.8 ✓ LOA broader but still close to MID, or weighted Kappa or ICC 0.60 to 0.79, or correlation ≥ 0.7 ✗ LOA >> MID, weighted Kappa or ICC < 0.60 or incorrect statistical test or inadequate sample (< 30 subjects)
Interobserver agreement/intermode agreement	The extent to which the results are repeatable between observers/the extent to which the results are repeatable between modes of administration	<ul style="list-style-type: none"> ✓✓ LOA appear tight and less than MID, or weighted Kappa or ICC ≥ 0.70 ✓ LOA broader but still close to MID, or weighted Kappa or ICC 0.50 to 0.69 ✗ LOA >> MID, weighted Kappa or ICC < 0.50 or incorrect statistical test or inadequate sample (< 30 subjects)
Person or item separation reliability	A Rasch analysis indication of reliability- the proportion of true variance in the observed variance	<ul style="list-style-type: none"> ✓✓ Reliability of ≥ 0.8 for both person and item separation or 3 G value or separation ratio > 2 ✓ Only one of person or item separation of ≥ 0.8, or a G value or separation ratio > 2 ✗ Person or item separation of < 0.8, or a G value or separation ratio < 2 O Not reported (not a Rasch scaled measure)

Property	Definition	Quality Criteria*
Interpretation	The extent which score differences are meaningful	<ul style="list-style-type: none"> ✓✓ Normative data (Mean scores and SD) and MID given for a representative target population, and test population demographic reported ✓ MID or normative data or demographic details of study populations, or ad hoc populations ✗ No normative data and no MID
Responsiveness	The extent to which the instrument can detect clinically important changes over time	<ul style="list-style-type: none"> ✓✓ Score changes > MID for measures of progression over time or changes with intervention. Effect size or responsiveness statistic given ✓ Changes over time but relationship to MID not reported, small sample, and inadequate time frame ✗ Score changes MID

Data E2: Excluded studies

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16. Mo F, Choi BC, Li FC, Merrick J. Using health utility index (HUI) for measuring the impact on health-related quality of life (HRQL) among individuals with chronic diseases. *Scientific World Journal* 2004;4:746-757.
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SECTION 4

ANAPHYLAXIS

**Supplementary
materials**

4.1

THE EPIDEMIOLOGY OF ANAPHYLAXIS IN EUROPE SYSTEMATIC REVIEW

❖ Supplementary materials ❖

SS Panesar¹, S Javad², D DeSilva³, B I Nwaru⁴, L Hickstein⁵, A Muraro⁶, G Roberts⁷⁻⁹, M Worm¹⁰, MB Bilò¹¹, V Cardona¹², AEJ Dubois¹³, A DunnGalvin¹⁴, P Eigenmann¹⁵, M Fernandez-Rivas¹⁶, S Halken¹⁷, G Lack¹⁸,
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Food Allergy and Anaphylaxis Group

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Search strategies

To retrieve systematic reviews, we used the systematic review filter developed at McMaster University Health Information Research Unit (HIRU; (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews)). We also adapted the search filter from York University Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/intertasc/epidemiological_studies.html) to retrieve incidence, prevalence, and other characteristics describing the epidemiology of anaphylaxis. Similarly, we also applied the McMaster filter for prognosis studies (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx#Prognosis).

The following databases were searched: MEDLINE(OVID), Embase (OVID), CINAHL (Ebscohost) and ISI Web of Science (Thomson Web of Knowledge). The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Boxes E1-4). In all cases, the databases were searched from January 1, 2000 to September 30, 2012. Searches were limited to literature from 2000 onwards because we wanted to understand and describe the

contemporary epidemiology of anaphylaxis, and ensure a pragmatic approach to dealing with the vast body of literature. Given the scope of the European guidelines, the search was limited to European evidence. European countries were based on the definitions provided by the Organisation for Economic Co-operation and Development (OECD) (<http://www.oecd.org/std/oecdmaineconomicindicators-countriescovered.htm>), i.e. Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom (UK). All references were collated into an EndNote Library and tagged with the name of the database. Additional references were located through searching the references cited by the identified studies, and unpublished work, and research in progress was identified through discussion with experts in the field. We also invited experts who are active in the field from a range of disciplines and geography to comment on our search strategy, and the list of included studies. There were no language restrictions and, where possible, all literature was translated.

Box E1 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1990 to Present>**Search Strategy:**

1	Anaphylaxis/	19	(incidence or prevalence or epidemiol\$).ti.
2	anaphylaxis react*.mp.	20	epidemiologic methods/
3	anaphylactic react*.mp.	21	*cohort studies/
4	anaphylactic shock*.mp.	22	controlled clinical trial.pt.
5	anaphylactoid syndrome*.mp.	23	*case-control studies/
6	anaphylactoid react*.mp.	24	exp Anaphylaxis/ep [Epidemiology]
7	anaphylactic syndrome*.mp.	25	exp Hospitalization/
8	anaphylactoid shock*.mp.	26	exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
9	acute systemic allergic react*.mp.	27	exp Mortality/sn, td [Statistics & Numerical Data, Trends]
10	idiopathic anaphylaxis.mp.	28	exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
11	systemic anaphylaxis.mp.	29	exp "Cause of Death"/
12	or/1-11	30	((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
13	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal\$).ti.	31	or/17-30
14	exp animals/ not humans.sh.	32	16 and 31
15	13 or 14	33	limit 32 to yr="1990 - 2012"
16	12 not 15		
17	*Incidence/		
18	*Prevalence/		

Box E2 Database: EmbaseClassic+Embase<1990 to 2012 August 19>*Search Strategy:*

1	Anaphylaxis/	19	(incidence or prevalence or epidemiol\$).ti.
2	anaphylaxis react*.mp.	20	epidemiologic methods/
3	anaphylactic react*.mp.	21	*cohort studies/
4	anaphylactic shock*.mp.	22	controlled clinical trial.pt.
5	anaphylactoid syndrome*.mp.	23	*case-control studies/
6	anaphylactoid react*.mp.	24	exp Anaphylaxis/ep [Epidemiology]
7	anaphylactic syndrome*.mp.	25	exp Hospitalization/
8	anaphylactoid shock*.mp.	26	exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
9	acute systemic allergic react*.mp.	27	exp Mortality/sn, td [Statistics & Numerical Data, Trends]
10	idiopathic anaphylaxis.mp.	28	exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
11	systemic anaphylaxis.mp.	29	exp "Cause of Death"/
12	or/1-11	30	((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
13	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal\$).ti.	31	or/17-30
14	exp animals/ not humans.sh.	32	16 and 31
15	13 or 14	33	limit 32 to yr="1990 - 2012"
16	12 not 15		
17	*Incidence/		
18	*Prevalence/		

Box E3 Database: CINAHL via Ebsco*Search Strategy:*

Query	
S16 S11 and S15	S8 (MH "Prescribing Patterns")
S15 S12 or S13 or S14	S7 "Epinephrine prescription"
S14 (MM "Anaphylaxis")	S6 "Epinephrine dispensing"
S13 "anaphylactic shock"	S5 (MH "Epinephrine/AD/SD")
S12 "anaphylactic"	S4 (MH "Epinephrine")
S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10	S3 (MM "Hospitalization")
S10 (MM "Prevalence")	S2 (MM "Disease Surveillance")
S9 (MH "Incidence")	S1 (MH "Epidemiology") OR (MH "Epidemiological Research")

Box E4 Database:ISI Web of Science: Science Citation Index, Conference Proceedings Citation*Search Strategy:*

Query
4 #2 AND #1 Refined by: Web of Science Categories=(ALLERGY OR IMMUNOLOGY OR MEDICINE GENERAL INTERNAL) AND Publication Years=(1990-2012) AND Document Types=(PROCEEDINGS PAPER OR REVIEW OR MEETING ABSTRACT) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
3 #2 AND #1 Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
2 Topic=((epidemiol* or incidence or prevalance or surveillance or death or mortality or survival or prescrib* or prescript*)) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
1 Topic=(anaphylaxis or anaphylactic) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On

Table E1 Key characteristics of included studies

Ref- er- ence	Study design	Study population		Age (range, mean)	Outcomes		Main findings	Frequency of occurrence (original)		Factors	Overall Quality
		Number / type	Source		Outcome(s)	Measure focus		Incidence	Prevalence	Case- fatality rate	
CAUSAL CATEGORY OF ANAPHYLAXIS: FOOD-INDUCED											
Alvarado MI 2006 ¹	Cross- sectional	506 adults and 168 children, 106 of whom had food allergy	Allergy unit years and adults	Children 0-14 years and adults 15+	Food allergy	Self-report survey Skin prick test Blood test	Period prevalence (May 2002 to October 2004)	15 / 674 (2.2%)	15 / 674 (2.2%)	Food	Weak
Asero R 2009 ²	Cross- sectional	1110 adults with food allergy	19 allergy centres	12-79 years, mean 31 years	Food-in- duced anaphy- laxis	Skin prick test, blood test, medi- cal record review	Period prevalence (1st Janu- ary 2007 to 31st December 2007)	58 / 1110 (5.2%)	58 / 1110 (5.2%)	Age Allergy type Geo- graphic area	Weak
Calvani M 2011 ³	Cross- sectional	163 chil- dren with complete records out of 237	29 outpa- tient allergy clinics	Median 4 years, range 0-18 years	Food induced anaphy- laxis	Self-report survey Skin-prick test	Risk factors			Age Gender Prev- ious ep- isodes Food Exercise Condi- tions Family history	Mod- erate

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings		Frequency of occurrence (original)		Factors	Overall Quality
		Number / type	Source		Outcome(s)	Methods		Incidence	Prevalence	Case-fatality rate	Risk	Prognostic	
Derby CJ 2005 ^a	Cross-sectional	400 surveys sent, 280 surveys returned, 257 surveys of adults and children valid	Members of anaphylaxis charity who avoided sesame	N/A	Sesame allergy	Self-report survey	Point prevalence (April 2002)	18% reported anaphylaxis as a reaction to sesame. 89% of people who reacted to sesame reported other atopics conditions. 91% reported other food allergies. 10% of first reactions, which usually happened in children, were potentially life threatening. 18% reported anaphylaxis due to sesame.	27 / 150 (18%)	Food	Other allergic conditions	Weak	
Kanny G 2001 ^b	Cross-sectional	33110 people up to 60 years. 1129 with food allergy received a second survey	General population	N/A	Food allergy	Self-report survey	Point prevalence (1997 and 1998)	The prevalence of food allergy was estimated at 3.24%. The main manifestations were atopic dermatitis for those under 6 years, asthma for those aged 4-6 years and anaphylactic shock for those 30+.	22 / 818 (2.7%)	Alcohol Medication Pollen	Alcohol Medication Pollen	Moderate	
Moneret - Vautrin DA 2001 ^c	Cross-sectional	Clinics of general practitioners, paediatricians, lung specialists and dermatologists	N/A	Anaphylaxis reactions to foods	Self-report survey	Point prevalence (April 2001 or May 2001)	163 serious food allergy incidents were identified. Serious food-allergy related accidents occurred in 46.6% of children under the age of 15 years of age and 53.4% of adults. Anaphylactic shock occurred in 39.9%. The most frequent allergens were peanuts and nuts (27.6%), food cross-reacting with latex (11%) and egg (8.6%).	100 members of the network responded to the questionnaire.	65 / 163 (39.9%)	Food	Weak		
Mulier S 2006 ^d	Cross-sectional	156 cases of food allergy	Allergy clinics	1 month to 14 years old, median age 26 months	Clinical history Response to elimination diet	Period prevalence (May 2002 to May 2005)	Anaphylactic shock occurred in 6/156 (3.8%) patients.	6 / 156 (3.8%)	Food Family history of atopic disease	Food Family history of atopic disease	Weak		

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings		Frequency of occurrence (original)		Factors		Overall Quality	
		Number / type	Source		Outcome(s)	Methods		Incidence	Prevalence	Case-fatality rate	Risk	Prognostic			
Rance F 2005 ⁸	Cross-sectional	2716 out of 3500 children surveyed	150 classes in 8 schools	2.5-14 years, mean 8.9 yrs	Food allergy	Self-report survey	Period prevalence (September 2002)	The point prevalence for food allergy was 4.7%. 4.9% of children had anaphylactic shock as a symptom of food allergy. Cow's milk, eggs and peanuts were the main reported causes of anaphylaxis. 182 had true food allergy and prevalence of true food allergy is 12/182=6.59% 196/796 (24.6%) patients reported adverse reactions to one or more foods. Anaphylaxis occurred in 146/796 (18.4%) of patients. The most common foods provoking reactions were strawberry (5.0%), cow's milk (3.3%) and tree nuts (3.2%).	12 / 2716 (0.44%)						Moderate
Rymarczuk B 2009 ⁹	Cross-sectional	796 adults	Allergy clinics	Mean age 41.5 (SD 13.9 years)	Clinical manifestations of food allergy	Self-report survey	Point prevalence	36 / 796 (4.52%)						Moderate	
Vetander M 2011 ¹⁰	Cohort	From 531 records reviewed, 383 children had anaphylaxis of which 371 had reactions to food	Three hospital A&E departments	0-18 years	Anaphylaxis and reactions to foods	Medical records review	Incidence rate (1st January 2007 to 31st December 2007)	32 per 100,000 children for all anaphylaxis, 29 per 100,000 person years (32*0.92 per 100,000 or 128/447739) for food related anaphylaxis. Food was involved in 92% of cases of anaphylaxis. Reactions to peanut and tree nuts were as common as reactions to egg and milk in the early years. Exposure to airborne allergens increased the risk of anaphylaxis due to food. Pollen allergic children were admitted due to food-related anaphylaxis more during pollen season.	32 per 100000 person years OR 143 / 1 (447739 * 1) (0.03%)	Age < 3 years Gender Allergic conditions	Food Drugs				

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors		Overall Quality Prognostic
		Number / type	Source		Outcome(s)	Methods			Incidence	Prevalence	Case-fatality rate	Risk	
CAUSAL CATEGORY OF ANAPHYLAXIS: GENERAL													
Calvani M 2008 ¹¹	Cohort	203 cases of anaphylaxis in children	Hospital	0-17 years, mean 6 years	Anaphylaxis	Hospital databases 2000-2003	Incidence rate (2000 to 2003)	203/3,454,208 cases of anaphylaxis in children were identified from hospital records. Anaphylactic shock accounted for 54% of all diagnoses of anaphylaxis and food induced anaphylaxis accounted for 43% of cases. Food induced anaphylaxis was more common in younger children, with an incidence of 12.5 per 100,000 resident children per year in the first year of life, dropping to 6.1 in the first two years and less than 3 per 100,000 resident children per year after the seventh year.	5.9 (95%CI 5.1 to 6.7) cases per 100,000 resident children OR 1.47 per 100,000 patient years	0.038 cases per 100,000 resident children OR 0.007 per 100,000 patient years	Age, gender, Allergic history, Foods, Medications, Intra-muscular adrena-line	Moderate	
Capps JA 2010 ¹²	Cross-sectional	816 of 401,152 incidents	General population	All ages, mean not stated	Anaphylaxis	Official records of emergency ambulance callouts	Period prevalence (1st June 2007 to 31st May 2008)	816 / 401152 (0.2%)	816 / 401152 (0.2%)	1253 individuals responded. 3 / 1253 (0.2%) reported anaphylaxis.	Weak		
Couto M 2011 ¹³	Cross-sectional	1253 individuals	Allergy clinics	15-65 years old	Prevalence of allergic disease	Self-report survey	Point prevalence (16 th April 2007 - 27 th April 2007)	3 / 1253 (0.2%)					

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors		Overall Quality Prognostic	
		Number / type	Source		Outcome(s)	Methods			Incidence	Prevalence	Case-fatality rate	Risk		
Gibbison B 2009 ¹⁴	Cohort	81 children and 1269 adults	Critical care units	Not stated	Anaphylaxis admissions to critical care units	Doc-tor-diagnosed cases over a five year period in national audit data	Cumulative Incidence (2005 to 2009) Risk factors	Anaphylaxis constitutes 0.1% of children's admissions, 0.3% of adult admissions. The number of admissions to critical care units for anaphylaxis is increasing year on year. Critical care units may have an average of one admissions per year for anaphylaxis. 5% of children and adults admitted with anaphylaxis died in hospital.	4 children and 60 adults died	4 children and 60 adults died	Age Gender	High		
Gonzalez -Perez A 2010 ¹⁵	Nested Case-control from asthma cohort	1777.00 children and adults with asthma and 200,000 without asthma	People enrolled with GP for at least one year who had at least one contact with the previous year	10-79 years	Anaphylaxis from all causes, and in asthma	National database spanning 10 year period	Cumulative incidence (1st January 1996 to 31st December 2005) Risk factors	21.28 per 100,000 person years for no asthma; 50.45 per 100,000 person years for overall asthma. The risk of anaphylaxis was greater in those with severe or non-severe asthma compared with no asthma. Incidence was higher in women (22.65 vs 19.56 for men per 100,000 person years). Other risk factors included atopic dermatitis, antibiotics and lipid lowering drugs.			Asthma Other conditions Gender Low Food medications			
Gupta R 2003 ¹⁶	Cohort	49,300 severe allergic conditions in adults and children	Hospital	N/A	Hospital admissions for systemic allergic disorders	National databases of hospital statistics for 11 years	Incidence rate 1990-91 to 2000-01	There were 13,230 admissions for anaphylaxis over an 11 year period. Relative risk for anaphylaxis was 7.5 (ranging from 6.6 to 8.6) and food-induced anaphylaxis was 5.8 (ranging from 5.1 to 6.8). Anaphylaxis rates rose from 6 to 41 per million admissions between 1990-1 and 2000-1.						
Gupta R 2004 ¹⁷	Cohort	N/A	General population	All ages	Allergic disease burden	Secondary analysis of official statistics and databases	Incidence rate (2000 to 2001)	In 2000, there were 3.8 per 100,000 admissions for anaphylactic shock. The rates differed by gender (3.4 males vs 4.1 females) and age (4.1 for 0-14 years, 3.9 for 15-44 and 3.5 for 45+). 12 deaths were attributed to anaphylaxis in the period 1991-5.	1964 / 53000000 (3.7 per 100,000 population)	1 / 53000000 (3.7 per 100,000 person years)	Age Gender Social class	High		

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors	Overall Prognostic Quality
		Number / type	Source		Outcome(s)	Methods			Incidence	Prevalence	Case-fatality rate	
Hebling A 2004 ¹⁸	Cohort	7739 adult and child patient records reviewed, 226 with anaphylaxis	Allergy clinics	Females 5-74 years, mean 41. Males 8 months - 85 years, mean 38 years	Life threatening anaphylaxis with circulatory symptoms.	Medical record review Reports from doctors and hospitals	Incidence rate (1 January 1996 to 31 December 1998)	Between 8 to 10 people per 100,000 per year suffer life threatening anaphylaxis with circulatory signs. Hymenoptera stings (58.8%), medications (18.1%) and foods (10.1%) were the most common causes. In 5.3% of cases, causes could not be identified.	8.9 (range 7.9 to 9.6) per 100,000 citizens OR 249 / 27978 (8.9 per 100 years)	3 out of 226 people over a 3 year period, equating to 0.442% per year in the region.	Food Insect venom Medication	Moderate
Pastorello EA 2001 ¹⁹	Cohort	38,685 children and adults attending A&E of which 140 had anaphylaxis	Accident and emergency department at one hospital	Anaphylaxis in a general hospital over a two year period	Anaphylaxis in a general hospital over a two year period	Medical record review	Period prevalence (1997 to 1998)	0.4% (1 in 300) had anaphylaxis symptoms. 1 in 3000 of the total population had severe anaphylaxis. Anaphylaxis was mainly linked to foods such as fruit and vegetables and non-steroidal anti-inflammatory drugs. Stings and other causes were less common. Females and atop patients were more likely to be admitted.	140 / 33685 (0.4%)	Food Atopy History Age Gender	Food Atopy History Age Gender	Low
Quercia O 2012 ²⁰	Cross-sectional	6676 out of 7201 adults returned surveys	General population	Mean 45.6 years	Allergic diseases	Self-report survey	Point prevalence	0.6% of participants had suffered anaphylaxis. There were no significant differences in the prevalence of allergies according to ethnicity.	37 / 6676 (0.55%)	Ethnicity Conditions		
Sheikh A 2000 ²¹	Cohort	32.4 million discharges of children and adults	Hospital	N/A	Hospital admissions for acute anaphylaxis	National hospital discharge statistics for 4 years	Study period (1994-95)	The incidence of hospital admissions for acute anaphylaxis increased from 5.6 per 100,000 discharges but for incidence rate is 10.2 in 1994-5. Key causes were medication (62%), food (15%) and insect venom (11%).	10.2 per 100,000 discharges. Incidence rate is 2424 / 32400000 (0.007%)	Medication Food Venom	High	

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings		Frequency of occurrence (original)		Factors	Overall Quality
		Number / type	Source		Incidence	Prevalence		Case-fatality rate	Risk	Prognostic			
Sheikh A 2001 ²²	Cohort	13.5 million emergency inpatient admissions for adults and children, 2323 cases of which with anaphylaxis	Hospital	All ages, mean not stated	Hospital admissions for anaphylaxis	Hospital records database 1991-95	Incidence rate (1991 to 1995)	There were variations in the incidence of inpatient admissions for anaphylaxis by age, gender, geographic area and socioeconomic factors. The risk of anaphylaxis was higher in women of childbearing age and those residing in southern, rural and affluent areas. 12 deaths from anaphylaxis were reported over a 4 year period.	2323 / 13500000	= 17 per 100,000 emergency admissions. Female rate ratio 1.19 (95% CI 1.09-1.29), South England rate ratio 1.35 (1.25-1.47), rural rate ratio 1.35 (1.17-1.59), non deprived area rate ratio 1.32 (1.19-1.44).	12 / 13500000	Age Gender Deprivation Geographic area	High
Sheikh A 2008 ²³	Cohort	2.9 million adults and children	People registered with a GP	Not stated	Anaphylaxis	National database derived from 422 general practices, 2001-2005	Incidence rate (2001 to 2005)	Lifetime age-sex standardised prevalence of recorded diagnosis of anaphylaxis was 50 per 100,000 in 2001, rising to 75.5 per 100,000 in 2005. By 2005, an estimated 37,800 people in England had experienced anaphylaxis at some point. This equates to 1 in 1333. The rate has been rising over time.	7.9 per 100000 person-years	37800 / 50066225 (75.5 per 100000 patients)			

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors		Overall Quality
		Number / type	Source		Incidence	Prevalence			Incidence	Prevalence	Case-fatality rate	Risk	
Crude cumulative incidence: 1.5 episodes per 5000 admissions.													
Tejedor Alonso MA 2011 ²⁴	Cohort	114,626 people admitted to hospital	Hospital	Mean 58 years	Anaphylaxis	Hospital database 1999-2005	Incidence rate (1st January 1998 to 31st December 2005)	34 / 850000 [0.2 (95% CI 0.2 to 0.3) per 5000 admission days]	34 / 850000 [0.2 (95% CI 0.2 to 0.3) per 5000 admission days]	34 / 114626 (0.03%)	34 / 114626 (0.03%)	Age Gender Hos- pit- depart- ment	High
Tejedor Alonso MA 2012 ²⁵	Cohort	150,000 adults and children	General popula- tion	0-85+	Anaphylaxis	Database review of clinical records for two years	Cumulative incidence (March 2004 - April 2004)	336 / 325046 (103.37 per 100000 patients)	336 / 325046 (103.37 per 100000 patients)	336 / 325046 (103.37 per 100000 patients)	Food Medica- tion Latex Exercise	Food Medica- tion Latex Exercise	High
Worm M 2012 ²⁶	Cohort	2012 adults and children, included from 2633	83 allergy clinics	1-87 years	Anaphylaxis	Registry survey of allergy centres	Risk factors (2006-2010)	The most common causes of anaphylaxis were insect venom (50%), food (24%) and medication (17%). Skin was the most commonly affected *84%, followed by cardiovascular (72%) and respiratory symptoms (68%). Older patients were more likely to suffer respiratory symptoms. 53% had one or more concomitant diseases.	Gender Age Other condi- tions	Gender Age Other condi- tions	Gender Age Other condi- tions	High	

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes	Measure focus	Main findings	Frequency of occurrence (original)		Factors	Overall prognostic quality
		Number / type	Source					Incidence	Prevalence		
CAUSAL CATEGORY OF ANAPHYLAXIS: LATEX-INDUCED											
Draisici G 2011 ²⁷	Cohort	294 women scheduled for caesarean section and 294 women undergoing gynaecological surgery	Hospital	Mean 33 years	Latex sensitisation	Self-report survey Blood test Skin-prick test	Cumulative incidence (July 2003 to September 2008)	15 tested positive in pregnant women and 5 non-pregnant women for latex sensitisation. 2/10= 10% experienced anaphylaxis given they were positive for latex sensitisation. There was a higher rate of latex sensitisation and anaphylaxis in pregnant women undergoing caesarean section compared to non-pregnant women undergoing surgery.		Allergy history Number of operations Age Weight	Low
CAUSAL CATEGORY OF ANAPHYLAXIS: MEDICATION-INDUCED											
Ayala F 2006 ²⁸	Cross-sectional	649 people hospitalised in the dermatology department for suspected adverse drug reactions	Hospital	N/A	Adverse drug reactions in dermatology patients	Clinical examination Biopsy if needed	Period prevalence (January 2001 to May 2002) Outcomes	Of those admitted with suspected adverse drug reactions, 2.5% had anaphylactic shock. There was no statistically significant relationship between gender and the type of adverse reaction.	16 / 649 (2.5%)	Weak	
Borch JE 2006 ²⁹	Cross-sectional case control	96 out of 3 642 adults and children, 13 of whom completed all investigations	Hospital	2-99 years, mean 61 years	Penicillin allergy	Self-report survey Challenge test Skin prick test	Period prevalence (2003)	In people with penicillin allergy, 14/96 (14.5%) had experienced immediate reactions such as anaphylaxis, hives or vomiting. 10/14 (71.4%) of these experienced anaphylaxis.	3 / 96 (3.1%)	Medication Family history	Moderate
Bousquet PJ 2007 ³⁰	Cohort study part of very large case and control cohort	210 out of 973 patients tested	Hospital	Mean 32.9 years	B-lactam hypersensitivity reactions	Provocation test Skin prick test Self-report survey over 8 year period	Period prevalence (1996 to 2004)	Anaphylaxis usually occurred in the first hour after drug administration. Later reactions included hives and maculopapular exanthema. 19.1% had anaphylaxis without shock and 17.6% had anaphylactic shock	40 / 973 (4.1%)		Moderate
Branelli A 2008 ³¹	Cross-sectional	1057 patients	General practice clinics	All ages, mean not stated	Prevalence of penicillin allergy	Self-report survey	Period prevalence (March 2005)	1057 patients participated, 11 reported anaphylactic shock.	11 / 1057 (1.04%)		Weak

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors	Overall Prognostic Quality
		Number / type	Source		Outcome(s)	Methods			Incidence	Prevalence	Case-fatality rate	
Dietrich W 2007 ³²	Cross-sectional	12,403 adults and children undergoing cardiac surgery with aprotinin	Hospital	Mean 3.5 years (SD 5.4 years) for children, mean 63.5 years (SD 16.9) for adults	Anaphylactic reactions to aprotinin	Hospital database completed by doctors	Period prevalence (1995 to 2003)	93% of cardiac operations were performed using aprotinin. The overall rate of hypersensitivity reactions / anaphylaxis was low (0.19%)	1/12403 12403 (0.2%) person per year	2.3 / 12403 (0.2%)	1/12403 = 8 per 100000 person per year	Strong
Hofp Y 2008 ³³	Cohort	1101 adults with emergency admission over a two week period	Hospital	Not stated	Adverse drug reaction related to pharmaceutical admissions	Screening of admissions by pharmacists and researchers	Cumulative Incidence (22nd May 2006 to 5th June 2006)	The prevalence of adverse drug reaction admissions was 2.7% (ranging from 1.8-3.7). Of these, anaphylaxis was noted as a symptom in only one case.	1/1101 (0.09%)	Low		
Lange L 2008 ³⁴	Cross-sectional	1446 children out of 1447	Tertiary hospital	0-211 months. Median 43 months	Allergic drug reactions	Self-report survey	Period prevalence (May 2004 to November 2004)	The reported lifetime prevalence of adverse drug reactions in children was 7.5%. 3 out of 1446 children (0.2%) had experienced an anaphylactic reaction.	3 / 1446 (0.2%)	Allergy history Medication type Age	Mod- erate	
Laporte J-R 2003 ³⁵	Case-control	184 cases and 1003 controls	Hospital	Median 52 years	Anaphylactic reactions to various medications in hospital	Review of hospital records	Incidence rate (1992 to 1997)	For most analgesics and antibiotics, incidence ranged between 5 and 15 cases per 100,000 exposed patients. There was wide variation in the incidence of anaphylaxis among different medications. For instance the rate per 100,000 exposed cases was 2.1 for aspirin, 32 for parenteral penicillin and 378 for parenteral plasma. There is a relatively low risk for dipyrone, diclofenac, paracetamol, ampicillin, cloxacillin and cephalosporins. Parenteral penicillin, dextran, contrast media. Blood and pentoxifylline have an intermediate risk. The highest incidence was observed in those receiving plasma and streptokinase.	3 / 1446 (0.2%)	Medica- tion	Mod- erate	

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors		Overall Quality Prognostic
		Number / type	Source		Incidence	Prevalence			Case-fatality rate	Risk			
Laxenaire MC 2001 ³⁶	Cohort	467 children and adults suffering anaphylaxis during anaesthesia	Hospital allergy centres	1-90 years	Anaphylaxis during anaesthesia	Self-report survey Clinical history Skin-prick test	Risk factors (2 years)	467 patients known to suffer from anaphylaxis. Women were more likely to suffer anaphylaxis during anaesthesia than men, relative to the overall number of operations for each gender. The most common causes were neuromuscular blocking drugs (69.2%), followed by latex (11.2%) and antibiotics (8%). Atopy was present in 25% of cases, asthma in 9% and food allergy in 3%.	Age Gender Medication Food atopy				
Lynch RM 2004 ³⁷	Case-control	15 - 91 years old	Emergency department	Incid- ence of anaphylaxis in patients receiving N-acetylcysteine	Cumulative incidence (January 1997 to June 1999)	64 patients received N-acetylcysteine infusions; 31 (48.4%) developed an anaphylactoid reaction. 19 patients who reacted were commenced on N-acetylcysteine prior to receipt of paracetamol concentrations and 15 (48.4%) were categorised as high-risk.					Medication Latex Atopy Gender	Mod- rate	
Mertes PM 2003 ³⁸	Cohort	789 adults and children	40 allergy centres	Not stated	Anaphylaxis during anaesthesia	Clinical history Self-report survey Skin-prick test Blood test	Risk factors	Women were more likely than men to experience anaphylaxis during anaesthesia. The most common causes were neuromuscular blocking agents, latex and antibiotics.			Medication Latex Atopy Gender	Low	
Mertes PM 2011 ³⁹	Cohort	2516 adults and children	General popula- tion	Not stated	Anaphylaxis during anaesthesia	National databases over an 8-year period	Cumu- lative incidence (1st January 1997 to 31 December 2004)	100.6 per million estimated annual incidence of IgE mediated allergic reactions during anaesthesia. The median annual incidence of anaphylaxis during anaesthesia was higher for adult women but not for female children. The most common causes were neuromuscular blocking agents (58%), latex (20%) and antibiotics (13%). Female hormones may also play a role.	Risk factors	Medication Latex	Gender	Mod- rate	

Table E1 (continued)

Ref- erence	Study design	Study population		Age (range, mean)	Out- come(s)		Measure focus	Main findings		Frequency of occurrence (original)		Factors Prog- nostic	Overall Quality
		Number / type	Source		Methods	Incidence		Prevalence	Case- fatality rate				
Mitch- ska - Krzanows- ka G 2006 ⁴⁰	Cohort	3560 patients who received anaesthesia	Hospital	N/A	Anaphylaxis due to anaesthetic agents	Medical record review	Cumulative incidence	130/3560 (3.6%)		NMBAs		Mod- erate	
Nybo M 2008 ⁴¹	Systematic review	25 studies with people undergoing cardiac surgery, total population not stated; only 2 studies met our inclusion criteria (Laxenaire MC 2001 and Mertes PM 2003)	Hospital	N/A	Anaphylactic reactions to protamine sulphate during cardiac surgery	N/A	Cumulative incidence	8/1165 (0.69%)	The incidence of anaphylactic reactions to protamine sulphate was 0.69% in 16 prospective studies and 0.19% in 9 retrospective studies. There was a low incidence of anaphylactic reactions to protamine sulphate during cardiac surgery, but studies included in the review tended to be of low quality.	8/1165 (0.69%)	Prospective Low		
Pakravan N 2008 ⁴²	Cohort	169 out of 193 people with acetaminophen overdose. 22 underwent more detailed study	Hospital	Mean 37 years	Anaphylactoid reactions to N-acetyl-cysteine	Records review Blood tests Other clinical tests	Risk factors	The most common reactions to intravenous N-acetyl-cysteine in people with acetaminophen overdose were nausea and vomiting, flushing and pruritus. Factors associated with moderate to severe adverse effects included female gender and family history of allergy.	Records review Blood tests Other clinical tests	Age Gender Dosage Drug allergy Family history	Low		

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Measure focus	Main findings	Frequency of occurrence (original)		Factors		Overall Quality
		Number / type	Source		Out-come(s)	Methods			Incidence	Prevalence	Case-fatality rate	Risk	
Quiralte J 2007 ⁴³	Cohort	174 out of 223 adults and children tested 49 referred due to history of anaphylaxis	Hospital records of NSAID-sensitive patients (NSAID = Nonsteroidal anti-inflammatory drug)	5-78 years, mean 32.2 years	NSAID reactions	Single blind placebo controlled oral challenge	Cumulative incidence Outcomes	16% of NSAID reactions involved anaphylaxis. In people reacting to NSAIDs, those experiencing anaphylaxis were more likely to be women.	50/317 (16%)			Atopy Conditions Gender	Low
Rasmussen TA 2012 ⁴⁴	Cohort	2300/227 children	General population	0-18 years	Outcomes from vaccination	National databases	Incidence rate (1st January 1980 to 31st December 2009)	Anaphylactic shock: 1.45 per 100,000 person years (95% CI 1.32 to 1.59). The incidence of anaphylactic shock following vaccination was higher for males. Incidence was predicted to be higher in the third quarter of the year.	1.45 per 100,000 person years (95% CI 1.32 to 1.59)		Age Gender Season	High	
Sandilands EA 2009 ⁴⁵	Systematic review	People given acetylcysteine comprising adults and children	Hospital	N/A	Adverse reactions from acetylcysteine	Varied between studies included in the review	Risk factors	Anaphylactoid reactions have been reported in 23% to 48% of patients receiving acetylcysteine. Nausea and vomiting are the most common manifestations. There have been few fatalities. Atopy is a risk factor. Only 3 studies included in this systematic review met our inclusion criteria. These studies were Waring WS 2008, Pakravan N 2008 and Lynch RM 2004.	Outcomes		Atopy	Moderate	
van Puijenbroek EP 2002 ⁴⁶	Case-control	190 cases and 26,720 controls, comprising adults and children	All aged reporting adverse drug reactions	10 years or more, mean 52.2 (SD 17.6) years	NSAID induced anaphylaxis	Drug reaction reports to pharmaceutical vigilance system	Risk factors (January 1985-2000)	The risk of reporting an anaphylactic reaction may be greater with NSAIDs than for other drugs (adjusted reporting odds ratio 9.4, 95% CI 6.9-12.7).			Age Gender Medication type	Moderate	
Waring WS 2008 ⁴⁷	Cohort	362 out of 1091 adults presenting to hospital after acute acetaminophen	Anaphylactoid reactions to N-acetylcysteine	Data collected by staff specifically for study	Cumulative incidence (March 2005 to June 2006)	Acetaminophen concentrations	14.9% of patients given N-acetylcysteine suffered anaphylactoid reactions. Anaphylactoid reactions were less common in people with high serum acetaminophen concentrations, suggesting some type of protective effect.			Acetaminophen concentrations	High		

Table E1 (continued)

Reference	Study design	Study population		Age (range, mean)	Outcomes		Main findings	Frequency of occurrence (original)		Factors	
		Number / type	Source		Out-come(s)	Methods		Incidence	Prevalence	Case-fatality rate	Risk
CAUSAL CATEGORY OF ANAPHYLAXIS: STINGING INSECT-INDUCED											
Celikel S 2006 ⁴⁸	Cross-sectional	494 out of 1245 surveys returned from adults	Bee-keepers	Mean 48.22 (SD 11.47)	Systemic reactions to bees and bee products in bee-keepers	Self-report survey	Period prevalence (December 2004 to June 2005) Risk factors	6.5% of beekeepers had a systemic reaction to bee sting in the past 12 months. 2% of these reactions involved anaphylaxis. The risk of systemic reactions increased when atopic disease was present.	9 / 494 (1.82%)	Age Duration of bee-keeping Atopy	Weak
CAUSAL CATEGORY OF ANAPHYLAXIS: VENOM-INDUCED											
Perez-Pimienta AJ 2007 ⁴⁹	Cohort	115 children and adults who had anaphylactic reaction to wasp sting	General population	10-80 years, mean 40.2 (SD 15.9) years	Anaphylactic reaction to wasp sting	IgE tests	Risk factors Outcomes	In people suffering anaphylaxis after a wasp sting, the most common symptoms involved the skin (90%), respiratory (55%), cardiovascular (34%) and gastrointestinal areas (22%). Age, gender and atopy were not related to the severity of the reaction.	Atopy Age Gender Gender	Atopy Age Gender Gender	Low

Table E2 Quality scoring of studies

Study design: Systematic reviews		Quality domains								
Reference	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Adequacy of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms/costs	Overall quality assessment
Nybo M 2008 ⁴¹	✓	✓	✓	✗	✓	✓	✓	✓	✗	Low
Sandilands EA 2009 ⁴⁵	✓	✓	✓	✓	✓	✓	✓	✓	✗	Moderate

Table E2 (continued)

Reference	Study design: Cohort													
	Quality domains													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7a	Q7b	Q8	Q9	Q10	Q11	Q12	Overall quality
Calvani M 2008 ¹¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Draisci G 2011 ²⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✗	Low
Gibbison B 2009 ¹⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Gupta R 2003 ¹⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Gupta R 2004 ¹⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Heibling A 2004 ¹⁸	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	Moderate
Hopf Y 2008 ³³	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	Low
Laxenaire MC 2001 ³⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Lynch RM 2004 ³⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	Moderate
Mertes PM 2003 ³⁸	✓	✓	✓	✓	✓	✓	✗	✗	✗	?	✓	✓	✓	Low
Mertes PM 2011 ³⁹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Michalska-Krzanowska G 2006 ⁴⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Pakravan N 2008 ⁴²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
Pastorello EA 2001 ¹⁹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Low
Perez Pimienta AJ 2007 ⁴⁹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Low
Quiralte J 2007 ⁴³	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Low
Rasmussen TA 2012 ⁴⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2000 ²¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2001 ²²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2008 ²³	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Tejedor Alonso MA 2011 ²⁵	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Moderate
Tejedor Alonso MA 2012 ²⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Vetander M 2011 ¹⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Waring WS 2008 ⁴⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Worm M 2012 ²⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High

Table E2 (continued)

Study design: Cross-sectional										
Reference	Quality domains									
	Selection bias	Study design	Confounding	Blinding	Data collection methods	Withdrawals and methods	Intervention integrity	Analyses	Overall quality	
Alvarado M 2006 ¹	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Asero R 2009 ²	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Ayala F 2006 ²⁸	Moderate	Moderate	Weak	Weak	Strong	Moderate	N/A	Moderate	Weak	
Borch JE 2006 ²⁹	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate	
Bousquet PJ 2007 ³⁰	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Strong	Moderate	
Branellec A 2008	Weak	Weak	Weak	Strong	Moderate	Moderate	N/A	Moderate	Weak	
Calvani M 2011 ³	Moderate	Weak	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate	
Capps JA 2010 ¹²	Moderate	Moderate	Weak	Weak	Strong	Moderate	N/A	Moderate	Weak	
Celikel S 2006 ⁴⁸	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Moderate	
Couto M 2011 ¹³	Moderate	Moderate	Weak	Weak	Moderate	Weak	N/A	Moderate	Weak	
Derby CJ 2005 ⁴	Weak	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Dietrich W 2007 ³²	Strong	Strong	Strong	Moderate	Strong	Moderate	N/A	Strong	Strong	
Kanny G 2001 ⁵	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate	
Lange L 2008 ³⁴	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate	
Moneret-Vautrin DA 2001 ⁶	Moderate	Moderate	Weak	Weak	Moderate	Weak	N/A	Moderate	Weak	
Mulier S 2006 ⁷	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Quercia O 2012 ²⁰	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate	
Rance F 2005 ⁸	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate	
Rymarczuk B 2009 ⁹	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate		

Table E2 (continued)

Reference	Study design: Case-control											Overall quality
	Q1	Q2	Q3	Q4	Q5	Q6a	Q6b	Q7	Q8	Q9	Q10	
Gonzalez-Perez A 2010 ¹⁵	X	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓
Laporte J-R 2003 ³⁵	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓
van Puijenbroek EP 2002 ⁴⁶	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	Moderate

Box E5 Key terms

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8 Reg number not available at present
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-8

Box E5 (continued)

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

APPENDIX 1: REASONS FOR EXCLUDING STUDIES

Pre-year 2000 or post year 2012 (n = 20)

1. Theissen JL, Zahn P, Theissen U, Brehler R. [allergic and pseudo-allergic reactions in anesthesia. I: Pathogenesis, risk factors, substances]. *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1995;30:3-12.
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Outside Europe (n = 86)

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4.2

MANAGEMENT OF ANAPHYLAXIS SYSTEMATIC REVIEW

☞ Supplementary materials ☞

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METHODS

Details of the methodology for the systematic review have been previously reported.

Search strategy

A highly sensitive search strategy was designed to retrieve all articles combining the concepts of anaphylaxis and epidemiology from electronic bibliographic databases. We focused on the acute management of anaphylaxis by assessing the effectiveness of epinephrine, H1-antihistamines (versus placebo), systemic glucocorticosteroids, methylxanthines or any other treatments for the emergency management of people experiencing anaphylaxis. The main interventions that have been studied in the context of long-term management are anaphylaxis management plans and allergen-specific immunotherapy.

Inclusion criteria for study design

Details of the methodology for the identification, selection, and inclusion of the studies have been previously reported (1). In summary, our inclusion criteria were systematic reviews with or without meta-analyses, randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before-after (CBA) designs, interrupted time series (ITS) studies, and case-series, with a minimum of 10 patients, for studies investigating the use of adrenaline (Figure 1).

We appraised the evidence by preferentially looking at higher levels of evidence such as systematic reviews and/or meta-analyses of RCTs and individual RCTs. However, in view of the anticipated limited information available, we decided *a priori* to include systematic reviews that included other non-RCT study designs (focusing on the studies that had used EPOC-endorsed study designs); quasi-RCTs and CCTs (i.e. where non-random allocation of patients had occurred); other EPOC study designs such as CBA studies (i.e. those in which observations were made before and after the implementation of an intervention) and ITS (i.e. where observations were made at multiple time-points before and after the intervention) (3). Despite their representing much weaker forms of evidence,

case series were eligible for inclusion in relation to adrenaline as expert advice pointed to the considerable ethical, scientific and logistical difficulties in mounting more rigorous study designs.

Exclusion criteria for study design

Reviews, discussion papers, non-research letters and editorials and case studies plus animal studies were excluded.

Study selection and quality assessment

The titles were independently checked by two reviewers according to the above criteria; any discrepancies were resolved by consensus and when necessary a third reviewer was consulted. Quality assessments of studies were undertaken using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews (4). We assessed the risk of bias of studies eligible for the review using the criteria suggested by EPOC (5). RCTs, CCTs and CBAs were assessed for: generation of allocation sequence; concealment of allocation; baseline outcome measurements; baseline characteristics; incomplete outcome data; blinding of outcome assessor; protection against contamination; selective outcome reporting; and other risks of bias. These assessments drew on the principles incorporated into the Cochrane EPOC guidelines for assessing intervention studies (6) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for assessing observational studies (7). Similarly, we drew on the quality assessment tool produced by the National Institute for Health and Clinical Excellence (NICE) to help critically appraise case series (8).

Analysis, data synthesis and reporting

All assessments and data extraction were carried out independently by two reviewers; any discrepancies were resolved through discussion amongst the reviewers and, where necessary, arbitration by a third reviewer. A descriptive summary with data tables was produced to summarize the literature. We preferentially extracted data on risk ratios and mean differences. Data were not suitable for meta-analysis (9) so a narrative synthesis of the data is reported.

RESULTS

Studies in progress

We are aware of two RCTs that are as yet unpublished (Table E4). The first is investigating the effectiveness of a 24-hour helpline offering direct access to specialist paediatric allergy advice in the context of supporting the management of allergic emergencies in children with life-threatening food allergies (10, 11). The second is a multicentre RCT investigating the effectiveness of two xthree hours standardised educational intervention aimed to increase practical knowledge on anaphylaxis, performance in a training anaphylaxis situation and reduce anxiety in patients with anaphylaxis and caregivers of affected children.

Table E1 Key characteristics of included studies

Ref-	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
ACUTE MANAGEMENT: EPINEPHRINE								
Bock, 2001 ¹²	USA	Case- series	n=32 2-33 years	Characteristics of anaphylaxis fatalities due to food	Numbers of food aller- gy-triggered deaths in the USA Treatment at the onset of reactions and emergen- cy response treatment, with a particular focus on epinephrine	32 deaths from anaphylaxis to food investigated from a national USA register between 1994 and 1999. 31 with known food allergy. Good data on 21 subjects, 20 (95%) had active asthma, 2 (10%) received prompt i.m. epinephrine but died, 19 (90%) had no/delayed epinephrine. Suggest better education, availability of epinephrine auto-injectors	Low	Most anaphylactic fatalities to food occurred in those with a known history of food allergy so potentially avoid- able. Suggestion that prompt administration of epineph- rine may avoid fatalities. High proportion of fatal cases had co-existent asthma.
Bock, 2007 ¹³	USA	Case- series	n=31 5-50 years	Characteristics of anaphylaxis fatalities due to food	Numbers of food aller- gy-triggered deaths in the USA Treatment at the onset of reactions and emergen- cy response treatment, with a particular focus on epinephrine	31 deaths from anaphylaxis to food investigated from a national USA registry between 2001 and 2006 26 were known to have food allergy but may have had a previous mild reaction. All (100%) subjects had asthma. Only 4/31 (13%) subjects had epinephrine prompt- ly administered	Low	Characteristics of deaths from anaphylaxis in food allergy patients remain largely unchanged. Still appears to be lack of adequate awareness of al- lergen avoidance and poor access to readily-available epinephrine. All fatal cases had co-existent asthma.
Jarvin- en, 2008 ¹⁴	USA	Case- series	n=78 0.5-17.5 years	Looking at use of multiple doses of epinephrine in chil- dren with food-in- duced anaphylaxis via anonymous questionnaires.	In food-induced anaphy- laxis requiring epineph- rine, how many doses were needed. Factors that may predis- pose to requiring multiple doses.	95 reactions treated with epinephrine in 78 chil- dren, from a food allergy referral centre, analyzed. 77 reactions needed one dose of epinephrine. (81%) 18 reactions needed multiple epinephrine doses (19%). The second dose was administered by a health professional in 17 of 18 reactions (94%). Patients needing multiple doses were more likely to have asthma ($p=0.027$). Symptom of 'throat closure' more common in those needing multiple doses of epinephrine ($p=0.055$). In those requiring multiple doses of epinephrine, the first dose was administered earlier ($p=0.07$), iv fluids were more commonly used ($p=0.031$) and observa- tion in hospital was longer ($p=0.09$). When 3 doses of epinephrine were administered, compared to two doses, features that were more frequently occurring were: hypotension ($p=0.022$); difficulty swallowing ($p=0.022$) and 'throat closure' ($p=0.014$). Peanut was the main trigger ($p=0.013$)	A fifth of children with anaphylaxis receive more than one epinephrine auto-injector. Most (94%) of second doses are given by health care professionals. Co-existent asthma was associated with using more than one auto-injector.	

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment	
Pum- phrey, 2000 ¹⁵	UK	n=164 Case- series 40-89 years	Anaphylaxis fatali- ties from any cause	Number of deaths due to anaphylaxis in the UK Circumstances leading to fatal anaphylaxis	164 deaths identified due to probable anaphylaxis from any cause from UK death certificates between 1992 and 1998 (20/year). Half were iatrogenic, a quarter food induced and a quarter insect venom related. Paramedics and doctors had difficulty diagnosing anaphylaxis which led to a delay in epinephrine treatment. Only 22% of patients with food allergy-triggered fatalities and 18% of venom allergy-triggered fatali- ties had experienced a previous severe reaction. Of the 14 who had experienced previous severe reactions, 9 (64%) had been issued epinephrine self-treatment. Of these 9; 3 (33%) used the epinephrine as instructed; the remaining 6 (67%) had a variety of reasons for non-use i.e. had not collected from pharmacy (n=1); non-carriage (n=1); found dead with unused epinephrine (n=2); used for someone else and not replaced (n=1); out-of-date (n=1). 56% of drug-triggered reactions occurred in hospi- tals with full resuscitative equipment available. 20% received epinephrine before cardiac arrest; the remaining 80% arrested before epinephrine administration. 2 patients given high dose i.v. epinephrine, both died.	Low	Fatalities may occur in those with only mild previous reactions. Diagnostic uncertainty, lack of issuing, carriage and use of epinephrine may increase risk of death. High dose i.v. epineph- rine may increase risk of death. B2-agonists may be particularly important in those with food aller- gy-triggered reactions to help deal with res- piratory compromise Death may still occur in those who have admin- istered epinephrine	Over half the deaths occurred in those who had a previous mild reaction, such that it would have been unlikely that a doctor would have recommended auto-injector carriage Suggest optimizing allergen avoidance, optimal asthma management, and continuing patient aware- ness of risk factors.

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Pum- phrey, 2007 ¹⁶	UK	Case- series	n=48 n=5 months to 85 years	Food-triggered ana- phylaxis fatalities	Number of deaths due to food-triggered anaphylaxis in the UK Circumstances leading to fatal anaphylaxis	48 deaths from anaphylaxis due to food in the UK between 1999 to 2006. 43 (90%) had asthma; 10 (21%) had a degree of exacerbation prior to death. 19 (40%) had been prescribed epinephrine auto-injectors. 9 correctly used; 2 had expired; 1 used 3 auto-injectors but still died. Auto-injectors were used too late, didn't have it with them or incorrectly used.	Low	Optimizing asthma control identified as important. Persisting issues with under-use of epinephrine. Overweight individuals may have epinephrine inadvertently administered s.c..
Safdar, World- wide 2001 ¹⁷	any	SR of any study design	Not known n=not known Older people (i.e. >35-40 years	Safety of use of epinephrine during anaphylaxis in older patients without coronary artery disease in pre-hospital setting epinephrine	Risk of cardiovascular side effects of epinephrine in older patients	Authors only able to find 3 case reports demonstrating adverse cardiac effects (i.e. 1 transient ischemia; 1 had a myocardial infarction; and the last patient died of a cerebral hemorrhage) associated with use of epinephrine in anaphylaxis. This led the authors to conclude that there was very little evidence to contradict the use of s.c. epinephrine in patients older than 35-40 years without coronary heart disease in the management of asthma or anaphylaxis.	Low	Poor quality SR that did not specify how many studies found.
Samp- son, 1992 ¹⁸	USA	Case- series	n=13 2 to 17 years	Fatal and near-fatal episodes of anaphylaxis to food in children were collated over a 14 month period.	Survey of severe food induced anaphylaxis in children	6 children died and 7 had near fatal episodes requiring intensive care admission, intubation, ventilation and vasopressor support. Of the 6 fatal cases, 5 accidentally ingested a known allergen, to which they had a previous mild reaction. All were atopic with asthma, allergic rhinitis and atopic dermatitis. Asthma was controlled on the day of death. Only 2 received epinephrine within 60 minutes of onset of symptoms, which began 3 to 30 minutes after ingestion of allergen Of the 7 near-fatal reactions, 6 of the children reacted to a known allergen the 7th had experienced several near fatal reactions in the past. All 7 had well controlled asthma: 2 had atopic dermatitis and 3 had allergic rhinitis. 6 of the children received epinephrine between 10 to 30 minutes after ingestion of the allergen; one received it 130 minutes after ingestion. All required intubation. 3 of the children who died had been prescribed self-injectable epinephrine but did not have it with them. Of the near fatal cases 3 had been prescribed epinephrine and one self-injected.	Low	Delayed administration of epinephrine can lead to fatality. All patients had asthma some had other atopic disorders. None of the patients were aware of the need for strict avoidance of their food allergen. Prescription of epinephrine auto-injectors is important but non-carriage of the medication can be fatal. Most of the fatal reactions took place in a public setting whereas all of the near-fatal reactions took place in a private home. Uniphasic (7/13), biphasic (3/13) and protracted (3/13) anaphylactic reactions were described.

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
				Primary: Death Secondary: Resolution of upper airway obstruction; Resolution of lower airway obstruction; Improvement in arterial blood pressure;	No RCT's or quasi-RCT's comparing epinephrine with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Recommend to continue use of epinephrine as first-line medication; such trials are unlikely to be forthcoming.
Sheikh, World- wide 2008 ¹⁹	RCT's and quasi- RCT's	N=O all ages eligible	Epinephrine vs no intervention, placebo or other adrenergic treatments	Resolution of urticaria; Requirement of second dose of epinephrine; Admission to hospital; Length of emergency department stay; Length of hospital stay; Re-presentation for therapy within 24 hours; Adverse events due to therapy, in either treatment arm	No RCT's or quasi-RCT's comparing epinephrine with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Updated review. Recommend to continue use of epinephrine as first-line medication; such trials are unlikely to be forthcoming.
Sheikh, ^a World- wide 2012 ²⁰	RCT's and quasi- RCT's	N=O all ages eligible	Epinephrine vs no intervention, placebo or other adrenergic treatments	Resolution of urticaria; Requirement of second dose of epinephrine; Admission to hospital; Length of emergency department stay; Length of hospital stay; Re-presentation for therapy within 24 hours; Adverse events due to therapy, in either treatment arm	No RCT's or quasi-RCT's comparing epinephrine with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Updated review. Recommend to continue use of epinephrine as first-line medication; such trials are unlikely to be forthcoming.

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Sheikh, ^b World- wide 2012 ²¹	RCT's n=0 all ages quasi- eligible RCT's	SR of RCT's World- wide 2012 ²¹	n=17 4-12 years	To assess the effectiveness of epi- nephine auto-in- jectors in relieving the symptoms of anaphylaxis that occur in the com- munity	Primary:Death Secondary: Proportion of par- ticipants carrying auto-injec- tor; Proportion correctly us- ing auto-injector; Proportion experiencing difficulty using auto-injector; Proportion who failed to use auto-injector in a timely and appropriate manner; Resolution of airway obstruction; Improvement in arterial blood pressure; Hospital attendance or ad- mission; Re-presentation for treatment within 72 hours; Cost-effectiveness; Adverse events due to treatment, in either arm	No RCT's or quasi-RCT's comparing epinephrine auto-injectors with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Recommend to continue regarding epinephrine auto-injectors as the first-line treatment for the community man- agement of anaphylaxis; such trials are unlikely to be forthcoming in economically-developed countries but may be possible in low resource settings.

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Simons, Cana- da 2000 ²³	RCT 6-14 years	n=19 Inhaled epinephrine vs placebo inhala- tions	Plasma epinephrine serially at baseline and up to 180 mins post-treatment. Blood glucose concentration se- rially at baseline and up to 180 mins post-treatment. Heart rate and blood pres- sure at baseline and up to 180 mins post-treatment. Blood glucose concentra- tion serially at baseline and up to 180 mins post-treat- ment. Adverse effects	Few children were able to take the required number of inhalations because of adverse effects. Mean plasma epinephrine concentrations not sig- nificantly higher in inhaled epinephrine group when compared to placebo inhalation group at any time point ($p>0.05$). Mean heart rate and diastolic blood pressure did not differ significantly between the two groups. Systolic blood pressure significantly higher at 30 mins in epinephrine group. Adverse effects were common in both groups, par- ticularly bad taste of inhalations; worse in treatment group: 10/11 vs 4/8 in placebo group. One child who nearly managed the required number of epinephrine inhalations had adverse effects last- ing for 50 minutes post inhalation; these included apprehension, nausea, pallor, shaking, and intermit- tent muscle twitching.	Small study with poor compliance because of adverse effects may have compromised abil- ity to detect differences in epinephrine concen- tration.	Mod- erate	High rate of adverse events indicates that unlikely to represent a viable alternative route of administration.
Simons, Cana- da 2001 ²⁴	RCT, cross over study	n=13 18-35 years	Epinephrine absorption in adults, i.m. vs s.c.; also site of injection, vastus lateralis vs deltoid muscle and epinephrine vs placebo in well adults with a history of anaphylaxis	Plasma epinephrine seri- ally at baseline and up to 180 mins post-treatment Heart rate and blood pressure Adverse effects	Mean plasma epinephrine concentration was sig- nificantly higher ($p<0.01$) after epinephrine i.m. in injection into the vastus lateralis vs. epinephrine i.m. or s.c. into the deltoid (or saline i.m. or s.c. into the thigh). Adverse effects reported were mild and transient: 21 after epinephrine, 3 after saline injection	Supports i.m. injection or epinephrine auto-in- jector into thigh Limitation is however that not performed dur- ing severe acute allergic reaction	Mod- erate
Simons, Cana- da 2002 ²⁵	RCT	n=12 4-8 years	Plasma epinephrine seri- ally at baseline and up to 180 mins post-treatment Blood glucose concentra- tion serially at baseline and up to 180 mins post-treatment	153 families approached, 12 agreed to participate; 2 children subsequently withdrew consent. Of 10 children randomized and treated: 5 received Epipen (0.3mgs) and 5 received Epipen Jr (0.15mgs). Max- imum plasma epinephrine concentration reached at 16 (SEM 3) minutes for Epipen 0.15mg, and 15 (3) minutes for Epipen 0.3mg; no significant difference. Mod- erate Mean systolic blood pressure and blood glucose significantly higher in those who received Epipen 0.3mg compared to Epipen 0.15mg. Adverse effects were experienced by all children, mild and transient significantly higher in Epipen 0.3mg arm. One child who received Epipen 0.3mg had prolonga- tion of QT interval lasting 120 mins post-injection.	No significant difference in peak plasma epi- nephrine concentration shown, may be due to small sample size. Children receiving Epipen Jr were signifi- cantly lower weight than those who received the Epipen.	Mod- erate	

Table E1 (continued)

Refere- nce	Coun- try	Design/ age	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Soreide, Nor- way 1988 ²⁶	n=27 5-74 years	Case- series	Etiology, symptoms and treatment of severe anaphylactic reactions outside hospital	Pre-hospital treatment Treatment delay Fatality	27 patients with anaphylaxis referred to air ambulance service over a 4-year period Epinephrine was the most commonly administered treatment, which was administered s.c., i.m. or i.v. 2 deaths, both occurring in women who waited for >45 minutes for emergency treatment.	Low		Suggestive evidence that delays in epinephrine treatment may have contributed to fatality.
ACUTE MANAGEMENT: GLUCOCORTICOSTEROIDS								
Choo, World- wide 2010 ²⁷	SR of RCTs and quasi- RCTs	n=0	Glucocorticoid use in the treatment of anaphylaxis compared with any control, placebo, epinephrine, anti- histamine or any combination.	Primary: Mortality rate Secondary: Prevention of biphasic or prolonged anaphylaxis; Incidence of cardiovascular manifesta- tions; Incidence of respiratory manifestations; Incidence of gastrointestinal manifes- tations; Incidence of other clinical manifestations; Hos- pitalization rate; Length of emergency department visit; Length of hospital stay; Rate of re-presentation to hospital	No RCT's or quasi-RCT's comparing glucocorti- costeroids with any control were identified for inclusion. No evidence from high quality studies for the use of steroids in the emergency management of anaphylaxis.	High	Cannot support or refute the use of gluco- corticosteroids in the treatment of anaphy- laxis.	
Choo, World- wide 2012 ²⁸	SR of RCTs and quasi- RCTs	n=0 all ages eligible	Glucocorticoster- oids use in those experiencing ana- phylaxis compared with any control, placebo, epineph- rine, antihistamine or any combination.	Primary: Mortality rate Secondary: Prevention of biphasic or prolonged anaphylaxis; Incidence of cardiovascular manifesta- tions; Incidence of respiratory manifestations; Incidence of gastrointestinal manifes- tations; Incidence of other clinical manifestations; Hos- pitalization rate; Length of emergency department visit	No RCT's or quasi-RCT's comparing glucocorti- costeroids with any control were identified for inclusion. No evidence from high quality studies for the use of steroids in the emergency management of anaphylaxis.	High	Cannot support or refute the use of gluco- corticosteroids in the treatment of anaphy- laxis.	

Table E1 (continued)

Refere- rence	Coun- try	Design/ age	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
ACUTE MANAGEMENT: ANTIHISTAMINES								
Lin, 2000 ²⁹	USA	RCT	n=19 Adults >18 years	Parenteral adminis- tration of 50mg of diphenhydramine and saline vs. 50mg of di- phenhydramine and 50mgs of raniti- dine in patients with acute allergic symptoms	Primary: Resolution of urticaria, angioedema or erythema at 2 hours Secondary: Areas of cutaneous involvement; Heart rate; Blood pressure; Respira- tory findings; Symptom scores	Less urticaria at 2 hours in the ranitidine + diphenhydramine group vs diphenhydramine ($p=0.02$). Fewer areas of urticaria in ranitidine + di- phenhydramine group vs diphenhydramine group ($p=0.02$). Less urticaria and angioedema at 2 hours in ranitidine + diphenhydramine group ($p=0.02$). Proportion of patients without angioedema at 2 hours did not differ between the 2 groups. No difference in proportion treated with epineph- rine.	Mod- erate	Unclear if H2-antihis- tamines beneficial in anaphylaxis as only 2 patients had hypoten- sion. Addition of H2-antihis- tamines to H1 use may improve cutaneous man- ifestations of acute aller- gic reactions, but benefit in more severe allergic reactions/ anaphylaxis remains unproven.
Runge, 1992 ³⁰	USA	RCT (3 arms)	n=39 18-50 years	300Mg i.v. cimetidine and placebo vs 50mg i.v. diphenhydramine and placebo vs. i.v. diphenhydramine plus i.v. ci- metidine in patients experiencing acute allergic symptoms	Change in patients and physicians assessment of severity of acute allergic reactions using a visual-analog scale before and 30 minutes after treatment Adverse effects	Only pruritus and urticaria occurred often enough to allow any formal analysis. Diphenhydramine only group had greater symp- tom relief from pruritus than cimetidine only group ($p=0.022$); use of combined diphenhy- dramine +cimetidine did not offer any greater symptom relief. Greater relief of urticarial symptoms was achieved in the combined treatment group vs diphenhydramine alone ($p=0.027$).	Mod- erate	Small sample size: 39 patients across 3 arms Diphenhydramine group had less severe initial symptoms than the other 2 groups. Offers little insights into the effectiveness of treatments for life-threatening features of anaphylaxis.
Sneikh, World- wide 2007 ³¹		SR of RCT's and quasi- RCT's	N=0 n=0 All ages quasi- eligible	H1 antihistamines vs placebo or no intervention in the treatment of ana- phylaxis.	Primary: Clinical improve- ment by any objective measure; Mortality rate Secondary: Hospitali- zation rate; Length of emergency department visit; Length of hospital stay; Representation rate to hospital; Iatrogenic ad- verse events; Rate of per- sistent/delayed/biphasic reactions; Costs to health services and patients	No RCT's or quasi-RCT's comparing H1-antihis- tamines with placebo or no intervention were identified for inclusion.	High	Unable to make any recommendations for clinical practice.

Table E1 (continued)

Ref- erence	Coun- try	Design/ try	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Sheikh, ³² World- wide 2012 ³²	SR of RCT's n=0 n=0 All ages eligible	N=0 vs placebo or no intervention in the treatment of ana- phylaxis	H1 antihistamines vs placebo or no intervention in the treatment of ana- phylaxis	Primary: Clinical improve- ment by any objective meas- ure; Mortality rate Secondary: Hospitalization rate; Length of emergency department visit; Length of hospital stay; Representation rate to hospital Iatrogenic adverse events; Rate of per- sistent / delayed / biphasic reactions	No RCT's or quasi-RCT's comparing H1-antihis- tamines with placebo or no intervention were identified for inclusion.	High	Unable to make any recommendations for clinical practice.	
ACUTE MANAGEMENT: METHYLXANTHINES								
Ernst, ³³ USA 1999 ³³	SR of con- trolled trials	N=0 All ages eligible	Methylxanthine use in anaphylaxis	Evidence to support or refute the use of methyl- xanthines in anaphylaxis Safety of use	No studies identified on the use of methylxan- thines in the treatment of anaphylaxis. Until data are available on humans methylx- anthines should not be recommended in the treatment of anaphylaxis.	High		
LONG-TERM MANAGEMENT: ANAPHYLAXIS MANAGEMENT PLANS								
Choo, ³⁴ World- wide 2007 ³⁴	SR of RCT's n=0 All ages eligible	N=0 All ages eligible	Effectiveness of anaphylaxis man- agement plans in self-management of anaphylaxis	Primary: Clinical improve- ment by any objective meas- ure; Hospitalization rate Emergency department attendance; Admission and readmission rates; Length of hospital stay; Mortality rate Secondary: Symptoms; Use of rescue medication; Quality of life, functional health sta- tus; Days off work/school Health service use; length of emergency department stay, primary care visits	No RCT's or quasi-RCT's of anaphylaxis manage- ment plans on the management of anaphylaxis were identified.	High	Need to consider broad- ening searches.	

Table E1 (continued)

Ref- erence	Coun- try	Design/ age	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Nur- matov, 2007 ³⁵	World- wide	All ages and eligible	n= 19	Acceptability, effec- tiveness, facilitators and barriers to the use of anaphylaxis management plans	Any description of com- ponents of AMP's, barriers and facilitators to their use, clinical effec- tiveness and acceptability.	Four studies indicate that anaphylaxis management plans plus training to parents, patients, school staff may greatly reduce the frequency and severity of further reactions.	Mod- erate	Weak but nonetheless encouraging evidence on the effectiveness of anaphylaxis manage- ment plans.
LONG-TERM MANAGEMENT: VENOM IMMUNOTHERAPY								
Boyle, 2012 ³⁶	World- wide	All ages eligible	N=7 n=392	Standardized venom extract vs. placebo, no treat- ment or back-up treatment	Primary: Systemic reac- tion (SR) to a 'field' insect sting or a sting challenge during treatment. Fatal SR due to a field or chal- lenge insect sting over the same period. Secondary: Large local reactions to a field sting or sting challenge during treatment or during the 10 years following treatment. Quality of life or anxiety score, assessed using a published scale. Adverse events to immu- notherapy	6 RCT's and 1 quasi-RCT included. Included ant, bee, and wasp immunotherapy in chil- dren and adults with previous systemic or large local reactions to a sting, using subcutaneous (six trials) or sublingual (one trial) VIT. VIT is effective in preventing systemic allergic reaction to an insect sting but subgroup analysis by route showed that only subcutaneous VIT was effective. Fewer patients treated with VIT had a severe systemic reaction to a subsequent sting compared with untreated patients risk ratio [RR] 0.10 (95%CI 0.03, 0.28).	High	Only subcutaneous VIT was shown to be effective. VIT reduced subsequent systemic reactions and improved quality of life.

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Brown, 2003 ³⁷	Aus- tralia	RCT cross- over design	n=68 20-63 years	Healthy patients with a previous Grade II-IV hyper- sensitivity to ant- were randomly allocated to semi- rush immunothera- py or placebo with crossover	Primary: Systemic reac- tion to a sting challenge defined by objective measures Secondary: any systemic symptoms in the absence of objective physical signs; a grade IV reaction; treatment with epineph- rine; changes in serum mast cell tryptase or plasma histamine after the sting challenge.	Only patients with positive skin tests were included. 33 in placebo group and 35 received VIT. After 52 sting challenges, objective reactions were found in 21 of 29 (72%) in the placebo group and none of 23 in the VIT group. ($p<0.0001$). In the placebo group 15 anaphylactic reactions occurred following the first sting challenge and 6 after the second. In the VIT group only one systemic reaction occurred on sting challenge, urticaria which settled without treatment. Of 30 patients from the placebo group who chose to crossover to VIT, 26 were sting challenged of these only one had a systemic reaction, Grade I urticaria.	Mod- erate	Venom immunotherapy, in those with positive intradermal skin tests, was effective in prevent- ing life threatening sting anaphylaxis. The severity of reaction to the deliberate sting in the placebo group could not be predicted from the worst Grade reaction in the field.
Golden, 1980 ³⁸	USA	RCT	n=64	Patients with a positive history of sting-an- aphylaxis and positive intradermal skin test were randomized to 3 treatment groups. Group I, slow im- munotherapy over 16 weeks, main- tenance reached at 14 weeks; Group II, rush immunotherapy 7 bimonthly injections, maintenance reached at 6 weeks; Group III stepwise increment of doses, maintenance dose reached at 11 weeks.	Efficacy: 52 patients had sting challenges in hospital 4 were accidentally stung, none had a systemic reaction. Adverse reactions- during immunotherapy from all groups, 50% had at least one large local reaction average rate of 9.6 reactions/100 injections; 16% of all patients had systemic reactions during immu- notherapy, 1.6 reactions per 100 injections. In both cases Group I, slow regime, had more reactions per patient as more injections were administered. IgG levels were significantly higher in Group II (rush) than the slow group $p<0.008$ at 18 weeks.	Low	Indicates that rush regimens of venom immunotherapy are equally as efficacious as more slower forms and are associated with less adverse effects due to the fewer number of injections administered. 7.8% of patients required epinephrine during treatment. Most local reactions oc- curred at doses of 15- 50ug and decreased at higher doses and maintenance dose.	

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Golden, 1981 ³⁹	USA	CBA	n=36	To prolong the interval between maintenance doses of VIT. 30 patients were randomly selected from a group of 81 patients who were already receiving the recommended maintenance dose of VIT following successful desensitization with whole-body extract therapy. 80% of the 81 had a history of previous anaphylaxis to insect sting. These 30 patients had the interval between maintenance doses increased from 4-6 weeks.	IgG venom specific antibody levels. Challenge stings. Adverse reactions	No increase in adverse reactions occurred between the 4 and 6 weekly maintenance dosing groups. At 6-9 months of maintenance therapy 29 of the 30 patients were sting challenged. 28 had no systemic effects and 1 had anxiety which settled with reassurance.	A 6 week maintenance interval should be considered in those who are successfully maintained on the conventional 4 week interval regime. Longer interval should be considered in those who are successfully maintained on the conventional 4 week interval regime.
SR of RCTs and quasi RCT's, 5 -RCT's quasi-ex- perimental health eco- nomic mod- eling Hock- enhull, 2012 ⁴⁰	UK	N=9, 4	Clinical effectiveness and cost effectiveness of Pharmalgen VIT for the treatment of bee and wasp venom allergy compared to other active treatment.	Clinical effectiveness outcomes: Systemic reactions Local reactions Mortality Anxiety related to the possibility of future reactions Health-related quality of life Adverse reactions to treatment	All trials small and of poor quality. Eight studies reported re-sting data after PhVIT, rate of systemic reactions ranged from 0-36.4%. AR's to PhVIT were recorded in 8 studies, systemic reactions between 0.0-38.1%, none was fatal. 17 non-comparative studies of PhVIT showed post VIT systemic reaction rates between 2-12.5%. Quality of life of people receiving VIT improved more than the quality of life of those using an Epipen ($p < 0.00001$). Cost effective only for high risk groups or if VIT is assumed to improve quality of life.	High	Evidence supports a decrease in reactions to stings following PhVIT. PhVIT is associated with AR's, these are treatable and may be acceptable due to the overall quality of life improvement perceived by the patients. Unable to assess impact on fatality because of small numbers of fatal events. Cost-effectiveness only likely in high-risk subgroups or if improved quality of life associated with VIT taken into account.

Table E1 (continued)

Reference	Country	Design	Sample/age	Intervention	Outcomes	Key findings	Quality	Comment
Hunt, 1978 ⁴¹	USA	RCT	n=59	Patients with a history of a generalized allergic reaction to a sting included, some had a previous anaphylactic reaction to a sting.	Challenge by hospital based stings after a series of immunotherapy injections had failed to cause a reaction.	Venom group after achieving a maintenance dose of 100µg VIT were stung challenged. 18 stung, one had mild urticaria. 1 patient was not challenged as failed to tolerate treatment. Whole-body extract group, of 11 patients 7 were stung, 64% had systemic symptoms to the challenge.	Of 59 patients, 58 successfully achieved desensitization with VIT Advocate use of venom immunotherapy over whole-body extract for the prevention of life-threatening reactions to insect stings.	
Mosbech, 1985 ⁴²	Denmark	RCT	n=32	Three matched groups were given placebo, whole-body extract or venom immunotherapy.	IgE antibody to honeybee and yellow jacket measured before and after the intervention.	Placebo group, of 12 patients 7 were challenged and 58% had systemic symptoms to the sting. Last two groups, no statistical difference but significantly greater than the venom treated group, p<0.01. Control arm of study was aborted when second patient experienced a severe systemic reaction 14 patients who were treatment failures from the placebo and whole-body extract group and a further 17 patients who were not challenged were then given VIT and re-stung. Of these, 1 patient had urticaria following sting challenge. IgG antibody level increased in all venom treated patients but not in the other 2 groups.	Low	Small number of patients distributed among 3 arms, Treatment regimens different, difficult to blind. No statistical values given.

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Muller, 1979 ⁴³	Swit- zer- land	CBA n=56	Patients with immediate type hypersensitivity (onset within 30 mins) to bee stings, and positive specific IgE antibodies to bee venom were randomized to immunotherapy with bee venom (BV) or whole-body extract (WBE). Half of each group had intra-cutaneous injections and half subcutaneous into the upper arm.	IgE and IgG antibodies levels to bee venom before treatment and at 1, 2, 6, and 12 months of treatment. Results of subsequent stings were compared.	31 patients received bee venom and 25 whole bee extract. 24 patients, 12 from each group were re-stung, 23 accidental and one controlled. 8 of the WBE patients and all of the BV patients had a reduced or no general reaction on re-sting. Difference between the 2 groups is significant ($p<0.05$). No general reaction on re-exposure ($p<0.025$). IgE levels of both groups were significantly lower at the end of treatment, greater reduction in the venom group. IgG levels increased significantly in the BV group, most pronounced in the first 2 months but maintained after 1 year of treatment ($p<0.001$). In the WBE group IgG levels decreased after 1 year of treatment. 8% of WBE and 39% of BV patients had severe local reactions during treatment; 16% of WBE and 39% of BV patients had general reactions. 4 had dyspnea needing epinephrine.	Low	Venom is more effective than whole body extract in successful desensitization of highly allergic patients. Maintenance dose of 100Ug is recommended.
Muller, 1985 ⁴⁴	Swit- zer- land	RCT n=24	Honey bee sting challenge.	Of 12 HBV patients, 1 had a systemic reaction and 4 local reactions were noted on sting challenge. On PEG-HBV of 12 patients 3 had systemic reactions and 7 local reactions. Specific HBV-IgE initially increased mildly in the HBV group no change illustrated in the PEG-HBV group.	Small sample size. No statistical analysis. Maintenance dose was changed during the study due to treatment failures.	Low	
Muller, 1987 ⁴⁵	South Africa	RCT n=35	Patients were randomized to honey bee venom (HBV) or monomethoxy polyethylene glycol-coupled honey bee venom (PEG-HBV)	Honey bee sting challenge. HBV specific IgE anti-bodies measured before treatment and at 1 and 3 months of treatment plus pre-sting and 2 weeks post-sting.	Increase in HBV specific IgG in both groups.	17 patients in each arm. Systemic reactions occurred in 2 of the PEG-HBV patients and 4 of the HBV.	

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Oude El- berink, 2002 ⁴⁶	Canada	RCT	n=74	The effect of VIT on health-related quality of life in patients allergic to yellow jacket venom. Patients block-randomized to VIT or Epipen	HRQL measured with a disease specific instrument (VQLQ) before and 1 year post treatment. Mean change in VQLQ in both groups compared	36 received VIT, 38 Epipen Mean change in VQLQ score in VIT group 1.07 (95% CI, 0.68-1.46). Mean change in VQLQ score in Epipen group -0.43 (95%CI, -0.71 to -0.16), significantly different from VIT group ($p<0.0001$). Expectation of outcome score, changed in the VIT group from 5.66 to 2.88 ($p<0.0001$), no change in the Epipen group. Improvement of VQLQ score of greater than 0.5 was 74% in VIT group and 9% in Epipen group. Overall proportion of patients benefiting from VIT over Epipen is 0.72 which corresponds to an NNT of 1.4. 94% rated VIT as extremely or very positive when taking into consideration the positive and negative effects of this treatment	Low	Half of patients approached refused to be randomized, 80% of whom chose VIT over Epipen. Improvement in HRQL scores indicates that this is clinically important and relevant to patients. NNT of 1.4 to achieve an improvement in VQLQ scores is favorable.
Oude El- berink, 2006 ⁴⁷	Canada	RCT	n=94 18 to 65	To examine negative aspects of the Epipen when compared to VIT in patients with anaphylaxis to yellow jacket stings by using a burden of treatment questionnaire (BOT) and statements about the Epipen. Patients were randomized to VIT or carry an Epipen for 1 year.	Measurement of VQLQ, BOT and Epipen statements at the onset of treatment and 1 year later. Epipen group given choice to continue with Epipen or have VIT.	47 received VIT and 47 had an Epipen. 2 patients were stung in the field during the study one from each group, VIT patient had no symptoms, and the other patient used the Epipen. 91.5% of the VIT group were positive about treatment, none were negative. 47.7% of the Epipen group were positive compared to 29.5% who were negative After 1 year of carrying the Epipen when given the choice 78% wanted to start VIT.	Moderate	Suggests that carrying an Epipen is more of a burden than VIT.
Quercia, 2001 ⁴⁸	Italy	RCT	n=55	Patients with systemic reactions Grade II or more, positive skin prick and RAST to <i>Apis Mellifera</i> were assigned to 1 of 3 groups: Aluminum hydroxide-adsorbed honey bee venom was used as an aqueous cluster, rush VIT or cluster depot VIT.	Tolerance of aqueous cluster or rush VIT vs cluster depot VIT. Adverse reactions during the induction phase.	20 patients had aqueous-rush VIT, 20 aqueous-cluster, 15 received depot-cluster VIT. Significantly lower number of patients with adverse events in both cluster arms compared to the rush arm ($p<0.009$). Frequency of adverse events also significantly lower in both cluster groups ($p<0.003$) No significant difference in both number of patients and frequency of adverse events between the two cluster groups.	Low	Aqueous cluster and depot cluster VIT have fewer side effects than rush schedule VIT. Small sample size may have influenced results. No reference to randomization of patients to various arms.

Table E1 (continued)

Ref- erence	Coun- try	Design/ Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Ross, 1999 ⁴⁹	SR World-wide	N=8 n=453	Meta-analysis of all studies to compare the effects of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity.	To assess the effectiveness of specific venom immunotherapy for Hymenoptera venom as a protection against a major systemic reaction.	Studies included involved patients with severe venom hypersensitivity. All 8 studies concluded that SiT was clinically effective. Significantly greater likelihood of a reduced rate of systemic symptoms on re-sting.	Low	Most of the studies were open with no placebo or control group.
Thurnheer, 1983 ⁵⁰	Swe- den	CBA n=42	Patients with previous systemic allergic reactions to hymenoptera stings were randomized to receive rush or conventional ViT. Patients received honeybee venom (HBV), yellow jacket venom (YJV) or both venom dependent on their allergy profile.	Primary outcomes were treatment tolerance; skin tests; specific IgE and IgG antibodies before treatment and at 3, 6, 12, 24 and 36 months after commencing treatment.	24 patients were re-stung, 22 accidental and 2 were challenged. 17 had no reaction, 6 had reduced systemic reactions and 1 had a prolonged delayed reaction and discontinued treatment. 96% success rate. Skin test to honeybee venom and yellow jacket venom decreased over the 3 year treatment period for all patients but more in the conventional treatment group. More became negative on conventional treatment but only statistically significant for YJV ($p<0.05$). After 3 years treatment, 3/30 were specific IgE negative to HBV, 17/29 negative to YJV and 5/30 negative to both who were on combined treatment. More patients negative on conventional treatment but only significant for those on YJV treatment ($p<0.01$).	Low	Patients were randomized to rush treatment if they lived at a distance to the hospital or had a high risk of re-sting. Skin tests and specific IgE antibodies became negative in 15 patients in whom desensitization was successful..
Watanabe, 2010 ⁵¹	World-wide	N=4 n=286 RCT's All ages eligible	VIT vs placebo or patient follow-up	Risk of systemic reactions after specific immunotherapy was evaluated using odds ratios and their 95% confidence intervals	4 RCTs satisfied inclusion criteria.	High	Lack of allocation concealment and the fact that the trials were not double-blind may have led to an over-estimation of the effects of treatments.

Table E1 (continued)

Refere- nce	Coun- try	Design/ age	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
LONG-TERM MANAGEMENT: EDUCATIONAL INTERVENTIONS								
Spina, 2012 ⁵²	USA	Quasi-experimental trial	n=77 14-18 years	Effectiveness of school nurse-delivered educational intervention to high-school students with food allergy vs standard checks	Primary: To increase carriage of epinephrine auto-injector. Secondary: To increase carriage of in-date epinephrine auto-injector	Ineffective at improving carriage rate ($p=0.189$). Suggestion that those who carry epinephrine may be more likely to carry unexpired auto-injectors.	Mod- erate	Within arm analysis of expired / unexpired auto-injectors.
LONG-TERM MANAGEMENT: PSYCHOLOGICAL INTERVENTIONS								
Manas- sis, 2012 ⁵³	World-wide	SR of studies of any design	Children and adolescents	Reviews anxiety and anaphylaxis in children and youth and principles to manage anxiety in children and parents.	Aspects of anxiety assessed: Physiological Cognitive Behavioral Parental anxiety	Physical, cognitive and behavioral aspects of anxiety related to anaphylaxis needs to be addressed to allow children to function well. Parents need to be involved in children's care. On-going follow up is needed of psychological as well as medical management.	Low	Poor quality SR with limited transparency of searches, assessment of quality of included studies. Conclusions drawn mainly from weak primary evidence.
LONG-TERM MANAGEMENT: PROPHYLACTIC INTERVENTIONS FOR SNAKE ANTI-VENOM								
De Silva, 2011 ⁵⁴	Sri Lanka	RCT	n=1007	Immediately before receiving snake anti-venom patients experiencing envenomation were randomized to either s.c. epinephrine (0.25mls 1:1000), i.v. promethazine 25mgs or i.v. hydrocortisone up to and including 48 hours after anti-venom administration. Hydrocortisone 200mgs alone or in combination or placebo. Patients were randomized to 8 possible groups using a 2x2x2 factorial blinded design.	The incidence of severe reactions following pre-treatment with epinephrine, promethazine or hydrocortisone up to and including 48 hours after anti-venom administration.	752(75%) patients had acute reactions to anti-venom within the 48 hour period; 43% of these were severe and 83% of the severe reactions took place in the first hour. Epinephrine reduced the rate of severe reactions compared to placebo significantly at 1 hour ($p<0.001$) and at 48 hours ($p<0.001$). No significant benefit was seen by using hydrocortisone or promethazine in the incidence of adverse effects at 1, 6, 24 or 48 hours. Combination of hydrocortisone with epinephrine appeared to negate the beneficial effects of epinephrine ($p=0.013$).	High	Pretreatment with epinephrine significantly reduces the incidence of acute adverse effects following administration of anti-venom. A dose of epinephrine 0.25mls given s.c. appears to be safe and no adverse effects of the pretreatment were noted. Routine pretreatment with glucocorticosteroids and antihistamines was not shown to significantly reduce adverse effects. There is a need to produce better anti-venoms to reduce the incidence of adverse reactions.

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Fan, 1999 ⁵⁵	Brazil	RCT	n=101 >2 years	Patients bitten by bothrops snakes needing anti-venom were randomized to i.m. promethazine (25mgs for adults, 0.5kg for children) or placebo, 15-20 mins prior to iv infusion of anti-venom.	Incidence and severity of anaphylactic reactions occurring within 24 hours of anti-venom treatment.	Anaphylactic reactions occurred early in 25 patients, 12 from the treatment group 13 from the placebo group. All needed epinephrine. A further 8 developed anaphylaxis 1-2 hours after the anti-venom infusion, 3 from the treatment group and 5 from the placebo group. No difference in the severity of reactions between the two groups. No statistical difference illustrated in between the 2 groups.	High	No evidence to suggest use of H1 antihistamine to reduce severe adverse reactions to snake anti-venom.
Gawar- am- manna, 2004 ⁵⁶	Sri Lanka	RCT	n=52 >12 years	Patients with snake envenoming randomized to hydrocortisone infusion (n=15), hydrocortisone infusion with chlorpheniramine bolus (n=21) or placebo (n=16) prior to and during treatment with snake anti-venom.	Occurrence and severity of adverse reactions to anti-venom	Adverse reactions in 80% receiving hydrocortisone alone; in 52% receiving hydrocortisone and chlorpheniramine and in 8.1% of the placebo group. No significant difference in the severity of reactions between groups. 21 patients needed treatment with epinephrine. Hydrocortisone infusion with a 10mg chlorpheniramine bolus had significantly less adverse effects when compared to placebo ($p=0.04$). Using hydrocortisone alone did not significantly reduce adverse reactions when compared to placebo.	High	Evidence that a combination of hydrocortisone and chlorpheniramine reduces the likelihood of adverse reactions with anti-venom.
Habib, 2011 ⁵⁷	World- wide	SR of RCTs	n=833 All ages eligible	N=7 Effect of pre-medication following anti-venom use in snake bite	Risk of early adverse reactions Epinephrine pre-medication	3 randomized and 4 non-randomized trials Epinephrine pre-medication resulted in a reduced risk of early adverse reactions: overall RR=0.32 (95%CI 0.18, 0.58). No significant reduction in early adverse reactions associated with use of H1-antihistamines and glucocorticosteroids.	High	Only one author, unclear whether quality assessment of studies carried out by more than one person.
Pre- maward- hena, 1999 ⁵⁸	Sri Lanka	RCT	n=105 12-70 years	Patients with envenomation randomized to receive epinephrine 0.25mls (1:1000) s.c. into the forearm or placebo prior to treatment with snake anti-venom serum.	Acute adverse reactions to snake anti-venom serum. Side-effects associated with use of epinephrine.	56 patients received epinephrine and 49 placebo. No of patients experiencing mild, moderate or severe adverse reactions significantly reduced in the epinephrine group ($p=0.00002$). No adverse effects noted due to epinephrine use.	High	Treatment so effective study had to be aborted after recruiting 105 patients, power calculations stated needed 228 patients but results at halfway point so significant. Patients at high risk of adverse effects with epinephrine excluded e.g. people with atopy, wheezing, ischemic heart disease.

Table E1 (continued)

Reference	Coun-try	Design	Sample/age	Intervention	Outcomes	Key findings	Quality	Comment
LONG-TERM MANAGEMENT: PROPHYLACTIC INTERVENTIONS FOR CONTRAST MEDIA								
Bertrand, France 1992 ⁵⁹	n=400 >18 years	RCT	oral: Hydroxyzine (H1 antihistamine) 100mg 12 hours before i.v. contrast media or placebo	Adverse reactions to i.v. contrast media	No anaphylactic reactions occurred in either group. Hydroxine compared to placebo reduced the number of mild adverse reactions occurring significantly ($p<0.0001$).	Hydroxine compared to placebo reduced the number of mild adverse reactions occurring significantly ($p<0.0001$).	Low	Patients with any allergy, atopy, drug sensitivities or previous allergic reaction to contrast media were excluded. Patient numbers too small to show if effective to prevent anaphylaxis plus high risk patients actively excluded.
Chevrot, France 1988 ⁶⁰	n=221	RCT	Assess the protective effect of betamethasone 8 mg injected or not (1:1) to patients at the same time as the contrast media. 221 patients, 68 had the steroid injected with the contrast medium.	Occurrence of an allergic reaction	133 patients had allergic reactions, weak difference between the treatment and no treatment group, 6.1% versus 7.9%.	133 patients had allergic reactions, weak difference between the treatment and no treatment group, 6.1% versus 7.9%.	Low	Open randomization.
Ginsberg, UK 1996 ⁶¹	n=86	RCT	Patients requiring myelography were randomized to receive oral dexamethasone 4mgs, 4 times a day or placebo 24 hours before and after myelography with intra-thecal contrast medium.	To investigate the usefulness of glucocorticosteroids to alleviate adverse reactions to contrast media	Analysis of post-myelography symptom pathogenesis.	No significant difference was illustrated between the 2 groups in terms of adverse effects.	Low	Patient size small may have contributed to lack of difference illustrated between treatment and control group.

Table E1 (continued)

Ref- erence	Coun- try	Design/ Study	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Lasser, 1987 ⁶²	USA	RCT	n=6763 >18 years	Patients undergoing x-rays with iv contrast media were randomized to 4 arms: 1. Oral methylprednisolone 32mg, 12 and 2 hours prior to iv contrast media 2. Oral methylprednisolone 2 hours prior to i.v. contrast media or 3. Placebo 2 tablets to match group 1 4. Placebo 1 tablet to match group 2	Reduction of adverse events with pretreatment with corticosteroids prior to iv contrast media administration	No significant difference was found in the adverse reaction rate between the two placebo groups, or between placebo and one dose of methylprednisolone. The two dose methylprednisolone group had a reduced adverse reaction rate ($p<0.05$), compared to the other 3 groups.	Low	Patients with previous severe reactions to contrast media were excluded.
Lasser, 1994 ⁶³	USA	RCT	n=1155 18 years or older	To determine whether patients receiving 2 doses of corticosteroids before i.v. injection of non-ionic contrast media would have reduced adverse effects.	107 patients had a history of previous adverse reaction to contrast media, 12 (11%) had an adverse reaction in this study.	Patients excluded if they had used antihistamines in the previous 12 hours	Low	Patients with previous reactions to contrast media were included in the study. Previous adverse reaction is associated with a greater risk of a further adverse reaction ($p<0.0001$). Study was aborted early due to lack of funding, ideal patient size was 6000. Methylprednisolone failed to show any reduction in severe adverse reactions such as those fulfilling the criteria for anaphylaxis.

Table E1 (continued)

Ref- erence	Coun- try	Design	Sample/ age	Intervention	Outcomes	Key findings	Quality	Comment
Small, 1982 ⁶⁴	Canada	RCT	n=220	Patients requiring an IVP were randomized to 3 arms: 1. no pre-medication, 2. s.c. of saline 15 minutes prior to receiving i.v. contrast media or 3. s.c. chlorpheniramine 10mg 15 minutes prior to receiving i.v. contrast media.	Incidence of allergic and non-allergic reactions. Changes in serum total hemolytic complement and immune complexes at 0, 1, 5, 10, 20 minutes after injection of contrast media.	42 patients had a reaction. Reduced number of reactions in chlorpheniramine group compared to other 2 groups ($p<0.05$). No statistical difference between the 2 control groups.	Low	Patients currently taking antihistamines were not included in the study. Allergic reactions which occurred were mild no cardiovascular or respiratory compromise occurred.
Tramer, 2006 ⁶⁵	World-wide	SR of RCTs	n = 10011 All ages eligible	Efficacy of pharmacological prevention of anaphylactic reactions to iodinated contrast media vs placebo or no treatment	Distinct allergy related symptoms Symptom categories (grades) Non-specific symptoms Adverse drug-reactions	H1-antihistamines, H1+H2-antihistamines and glucocorticosteroids trialled. Anaphylactic reactions to iodinated contrast media were rare, e.g. no deaths or cardio-pulmonary resuscitation Oral prednisolone reduced the risk of less severe cardio-respiratory outcomes OR=0.28 (95%CI 0.13, 0.60) Overall risk of serious adverse reactions was low, so the NNT to treat even with effective interventions is likely to be very high	High	Prophylactic premedication in unselected patients to prevent allergic reactions is of doubtful value This approach may however be useful in selected high risk patients who have a history of allergy but no trials in such high risk groups.
Wicke, 1975 ⁶⁶	Germany	RCT	n=208 adults	Patients requiring urography (148) or cholangiography (60) were randomised to receive an antihistamine, Clemastine iv (92) or placebo (116) with contrast media	Does the intervention reduce side effects for the patients while/after diagnostic x-ray examination	Side effects with the contrast material Uravision and Clemastine were 13% Side effects with the contrast material Uravision and placebo were 25%	Low	Side effects are significantly reduced with use of clemastine ($p<0.1$) Side effects with the contrast material Biligrain and clemastine were 4% Side effects with the contrast material Biligrain and placebo were 24% Side effects are significantly reduced with use of clemastine ($p<0.05$)

N=no. of studies; n=no. of participants.

Table E2 Quality assessment of systematic reviews

Author, year	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Appropriateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms / costs	Overall quality assessment
Boyle, 2012 ³⁶	✓	✓	✓	✓		✓	✓	✓	✓	High
Choo, 2007 ³⁴	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Choo, 2010 ²⁷	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Choo, 2012 ²⁸	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Ernst, 1999 ³³	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Habib, 2011 ⁵⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Hockenhull, 2012 ⁴⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Manassis, 2012 ⁵³	✓	X	✓	X	✓	✓	✓	✓	✓	Low
Nurmatov, 2008 ³⁵	✓	X	✓	✓	✓	✓	✓	✓	✓	Moderate
Ross, 1999 ⁴⁹	✓	X	✓	X	X	✓	✓	✓	✓	Low
Safdar, 2000 ¹⁷	X	X	X	✓	✓	✓	✓	✓	✓	Low
Sheikh, 2007 ¹⁹	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Sheikh, 2009 ²⁰	✓	✓	✓	N/A	N/A	✓	✓	✓	N/A	High
Sheikh, ^a 2012 ³¹	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Sheikh, ^b 2012 ³²	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Sheikh, ^c 2012 ³²	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Tramer, 2006 ⁶²	✓	✓	✓	Unclear	✓	✓	✓	✓	✓	High
Watanabe, 2010 ⁵¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	High

Table E3 Quality assessment of original studies

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding/ patient-related outcomes	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Bertrand, 1992 ⁵⁹	RCT	Unclear	Unclear	Yes	Yes	Yes	No	Low
Bock, 2001 ¹²	Case series	No	No	No	No	No	No	Low
Bock, 2007 ¹³	Case series	No	No	No	No	No	No	Low
Brown, 2003 ³⁷	RCT	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Chevrot, 1988 ⁶⁰	RCT	Unclear	No	No	Unclear	Unclear	Unclear	Low
De Silva, 2011 ⁵⁵	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Fan, 1999 ⁵⁶	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Gawarammana, 2004 ⁵⁷	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Ginsberg, 1996 ⁶¹	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Golden, 1980 ³⁸	RCT	Unclear	Unclear	No	No	No	Yes	Low
Golden, 1981 ³⁹	CBA	No	No	No	Unclear	No	Yes	Low
Hunt, 1978 ⁴¹	RCT	Yes	Unclear	No	Yes	Unclear	No	Low
Jarvinen, 2008 ¹⁴	Case series	No	No	No	No	No	No	Low
Lasser, 1987 ⁵⁹	RCT	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Lasser, 1994 ⁶⁰	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Lin, 2000 ²⁹	RCT	Yes	Yes	Yes	Yes	Yes	No	Moderate
Mosbech, 1986 ⁴²	RCT	Unclear	Unclear	No	Yes	Yes	Yes	Low
Muller, 1979 ⁴⁵	CBA	No	No	No	Unclear	Unclear	No	Low

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding/patient-related outcomes	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Muller, 1985 ⁴³	RCT	Unclear	Unclear	No	Yes	Yes	No	Low
Muller, 1987 ⁴⁴	RCT	Unclear	Unclear	Unclear	No	Yes	No	Low
Oude Elberink, 2002 ⁴⁶	RCT	Yes	Yes	No	Yes	Yes	Yes	Moderate
Oude Elberink, 2006 ⁴⁷	RCT	Unclear	Unclear	No	Yes	Yes	No	Low
Premawardhene, 1999 ⁵⁸	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Pumphrey, 2000 ¹⁵	Case series	No	No	No	No	No	No	Low
Pumphrey, 2007 ¹⁶	Case series	No	No	No	No	No	No	Low
Quercia, 2001 ⁴⁸	RCT	No	No	No	Yes	Yes	No	Low
Runge, 1992 ³⁰	RCT	Yes	Yes	Yes	Yes	No	No	Moderate
Sampson, 1992 ¹⁸	Case series	No	No	No	No	No	No	Low
Simons, 1998 ²²	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2000 ²³	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2001 ²⁴	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2002 ²⁵	RCT	Yes	Yes	Yes	Yes	Yes	No	Moderate
Small, 1981 ⁶⁴	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Soreide, 1988 ²⁶	Case series	No	No	No	No	No	No	Low
Spina, 2012 ⁵²	Quasi-RCT	No	Yes	No	Yes	No	No	Moderate
Thurnheer, 1983 ⁵⁰	CBA	No	No	No	No	No	No	Low
Wicke, 1975 ⁶⁶	RCT	No	Yes	No	No	Yes	No	Low

Table E4 On-going/unpublished studies

PI, country	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
EFFECTS OF A STRUCTURED EDUCATIONAL INTERVENTION ON KNOWLEDGE AND EMERGENCY								
Brockow, Germany	RCT	None	130	Two 3-hour schooling modules of group education; the waiting control group received no intervention	Knowledge of anaphylaxis and emergency management competence at baseline and 3 months after	2009	2011	Closed, submitted for publication
A 24-HOUR HELPLINE FOR ACCESS TO EXPERT MANAGEMENT ADVICE FOR FOOD ALLERGY-RELATED ANAPHYLAXIS IN CHILDREN: PROTOCOL FOR A PRAGMATIC RCT								
Hourihane, Ireland	RCT	ISRCTN 29793562	47	24-hour telephone access to specialist paediatric allergy expert advice for children <16 years with food allergy who carry an epinephrine auto-injector vs. usual care	To compare the difference in food allergy related quality of life between the 24-h telephone access and usual care at 1 and 6 months post-randomization	July 2012	Early 2013	Closed, data as yet unpublished

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