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Title: The march from early life food sensitisation to allergic disease: A systematic review and meta-analyses of birth cohort studies.

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SA designed the systematic review and meta-analysis with input from **SD**, **CL** and **AL** and wrote the first draft of the paper, **BC** conducted the parallel systematic search and data entry check. **BE** provided input to the meta-analysis methods, **CL**, **KA**, **BE**, **AL** and **SD** revised and edited the manuscript, and approved the final version.

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Short title: The march from food sensitisation to allergic disease

Abstract

Background: There is growing evidence for an increase in food allergies. The question of whether early life food sensitisation, a primary step in food allergies, leads to other allergic disease is a controversial but important issue. Birth cohorts are an ideal design to answer this question.

Objectives: We aimed to systematically investigate and meta-analyse the evidence for associations between early food sensitisation and allergic disease in birth cohorts.

Methods: MEDLINE and SCOPUS databases were searched for birth cohorts that have investigated the association between food sensitisation in the first 2 years and subsequent wheeze/asthma, eczema and/or allergic rhinitis. We performed meta-analyses using random-effects models to obtain pooled estimates, stratified by age group.

Results: The search yielded fifteen original articles representing thirteen cohorts. Early life food sensitisation was associated with an increased risk of infantile eczema, childhood wheeze/asthma, eczema and allergic rhinitis and young adult asthma. Meta-analyses demonstrated that early life food sensitisation is related to an increased risk of wheeze/asthma (pooled OR 2.9; 95%CI 2.0-4.0), eczema (pooled OR 2.7; 95%CI 1.7-4.4), and allergic rhinitis (pooled OR 3.1; 95%CI 1.9-4.9) from 4 to 8 years.

Conclusion: Food sensitisation in the first 2 years of life can identify children at high risk of subsequent allergic disease who may benefit from early life preventive strategies. However, due to potential residual confounding in the majority of studies combined with lack of follow-up into adolescence and adulthood, further research is needed.

Key words: Allergic rhinitis, Asthma, Atopic march, Eczema and Food sensitisation.

Introduction

Over the past 50 years there has been a global epidemic of asthma, eczema and allergic rhinitis (1) with an exponential increase since early 1990. This global epidemic of allergies has posed a substantial public health burden on affected individuals, their families and healthcare resources (2-4). Recent evidence suggests a 'second wave' of the allergy epidemic, which is related to an increase in food allergies (5-7). This is supported by a recent European systematic review of three UK based studies which found weak evidence for an increasing prevalence of food allergy

since the 1990s (6). Additionally, Branum *et al.* (8) recently showed an increase in self-reported food allergy and health care utilisation during the period 1997 to 2007 among US children.

Atopic dermatitis (eczema) and food allergy are the most common allergic diseases during the first 2 years of life, with some evidence that they are temporally interrelated (9, 10). While it is acknowledged that both early life eczema and food allergy may progress into asthma and allergic rhinitis, a concept known as the ‘atopic march’ (11), whether food sensitisation induces or is a consequence of eczema is controversial (12, 13). The progression from eczema to other allergic disease has been documented and systematically synthesised (14). However, few studies have assessed the evidence for the atopic march in relation to cow’s milk allergy (15-18). Given the increase in childhood food allergy, it is important to evaluate whether food allergy marches towards other allergies.

Although the gold standard for diagnosis of food allergy is oral food challenge, there are relatively few epidemiological studies that measure food allergy in this way. Food sensitisation is one of the first steps in the defining the pathogenesis of food allergy and is the measure most commonly used in allergy birth cohorts. The aim of this systematic review and meta-analyses was to assess and quantify the role of early food sensitisation on risk of allergic disease from infancy to young adulthood. We limited the review to birth cohort studies only, as this design provides the ideal opportunity to investigate early life determinants.

Methods

Search strategy

The protocol of this systematic review was developed and approved by all co-authors prior to commencement of the search. We systematically searched Medline (Web of Knowledge) and Scopus databases for English language peer-reviewed original articles, published from 1950 to

2014 by linking three groups of keywords (MeSH HEADING in Medline and TITLE-ABS-KEY in Scopus). The first group of keywords was related to food sensitisation (the exposure), the second group to allergic diseases outcomes, and the third group to birth cohorts (Table E1 in Supplementary documents). We also searched the reference lists of all included articles to find potentially other relevant articles.

Inclusion criteria and definitions

Birth cohort studies were considered eligible for inclusion if they met the following criteria: 1. Presented the association between food sensitisation, as defined by skin prick testing (SPT) or serum specific immunoglobulin E (s-IgE), in early life (i.e. in the first 2 years) and the subsequent development of asthma, eczema and/or allergic rhinitis outcomes during late infancy (1-2 years), childhood (>2-12 years), adolescence (>12-18 years) or adulthood (>18 years); 2. Defined asthma as either doctor diagnosed or parent or self-reported wheeze (1-5 years) or asthma (>5 years); 3. Defined eczema as either doctor diagnosed or parent or self-reported eczema or “atopic dermatitis”; and 4. Defined allergic rhinitis as either doctor diagnosed or parent or self-reported allergic rhinitis or hay fever.

Selection of included articles

Abstracts of all articles were assessed for eligibility by two authors independently (SA, BC). The same authors then further assessed the full-text articles of selected abstracts to determine article inclusion.

Data extraction and assessment

A standardised form was used for data extraction. The following information was extracted from each included article: author, year of publication, country/study location, name of the cohort, years of enrolment, original sample size, number included in the analysis, study population, food allergens tested and methods used to define food sensitisation. Findings from eligible articles were tabulated according to the outcome assessed and included the following data: timing of sensitisation and allergic outcomes assessment, risk estimates along with 95%CI/p value and assessed confounders. Corresponding authors of the included articles were contacted for further information if the reported data were incomplete.

The quality of each included article was assessed using Newcastle-Ottawa Scale (NOS) criteria (19). This scale assesses evidence of study quality based on selection of sample, comparability and the quality of outcome assessment. Each article was scored using a standard “starring (*)” system. In addition, three confounders were predetermined as being necessary for inclusion in adjusted models. These were family history of atopic disease (in population based studies), concurrent eczema and/or wheezing, and centre (in multi-centre studies). Concurrent eczema and wheeze were considered essential confounders to control for co-manifestation of the relevant phenotypes.

Statistical Methods

Meta-analysis methods

We computed separate forest plots for all three allergic outcomes during infancy, childhood and adulthood. We conducted meta-analyses when effect estimates from three or more studies were available and when the heterogeneity across the studies, as assessed by I^2 (20), was less than 80%. To evaluate conflicting results, more studies are needed for a meta-analysis. We chose a minimum of three as this allowed us to evaluate the robustness due to studies from different

populations, regions, follow-ups and co-varying factors. If we were to include only two studies, it would be challenging to estimate any between-study variations, since we assume a moderate degree of heterogeneity. We used random-effects model in all meta-analysis. All analyses were performed using Stata 13 (StataCorp, College Station Texas).

Results

The electronic search yielded 1225 articles. After abstract review, the full texts of 106 articles were retrieved for assessment, from which 15 articles were eligible for inclusion (Figure 1).

Study Characteristics

The 15 included articles represented 13 birth cohort studies, of which seven cohorts were conducted in Europe (21-29), two in United States (30, 31), two in Australia (13, 32) and two in Asia (33, 34). Of the 13 birth cohorts, five were population based (21, 22, 30, 33, 34) and eight were defined as high-risk (i.e. infants who had first degree relatives with history of asthma, eczema, allergic rhinitis or food allergy, children of mothers with allergies, parents or siblings with current asthma or wheezing, parent positive SPT) (13, 23-27, 31, 32) (Table E2 in Supplementary documents). The original number of enrolled participants in each cohort ranged from 100 (27) to 2252 (23) (Table 1).

Exposure assessment

Food sensitisation was assessed by SPT in five cohorts (25, 27, 31, 32, 35), s-IgE in seven cohorts (23, 24, 26, 29, 30, 33, 34) or both SPT and s-IgE in one cohort (22). The earliest age for assessment of food sensitisation was 3 months (22). Hen's egg and cow's milk sensitisation were investigated in all included cohorts, peanut in five (13, 26, 30-32), soy in four (21, 23, 26, 33), wheat in three (21, 33, 34), codfish in two (26, 31), and shrimp and walnut in one (31).

Among cohorts that assessed sensitisation using s-IgE, the definition of a positive test (i.e. the level of specific IgE ≥ 0.35 kU/l) was consistent across all cohorts except one. The Swedish cohort (26) defined sensitisation as low (i.e. s-IgE between 0.1 and 0.7 kU_A/l) and very low (i.e. s-IgE <0.1 kU_A/l). For the purpose of this review, we define low s-IgE as <0.1 kU_A/l.

Additionally, all studies that assessed sensitisation by SPT defined a positive test as the mean wheal diameter of ≥ 3 mm, with the exception of the Poole birth cohort (27) where a positive test was defined as a mean wheal diameter ≥ 2 mm in subjects less than 2 years and as ≥ 3 mm for subjects older than 2 years.

Outcome assessment

The age at which allergic outcomes were reported varied between articles, ranging from 14 months to 22 years.

Among the 13 articles that investigated wheeze/asthma as an outcome, two were from the same cohort with outcomes presented at both 5 years (21) and 7 years (29). The definition of wheeze/asthma varied between articles and the majority defined it using data from parent questionnaires. Only three articles defined wheeze/asthma using information from a paediatric allergist or bronchial hyperresponsiveness (BHR) (27, 31, 33). Seven articles defined wheeze/asthma as current (21-24, 27, 29, 32) and six as ever (25, 26, 30, 31, 33, 34). (Table E3 in Supplementary documents).

Eczema as an outcome was assessed in 9 articles from different cohorts. Eczema was defined according to Hanifin and Rajka's criteria (22, 26, 33, 34), presence of eczematous rash during physical assessment (31, 32) or parental report of child's eczema or use of any topical treatment (13, 23, 25, 32).

The development of allergic rhinitis was investigated in six articles, representing five cohorts.

Two articles were from one cohort, with outcomes presented at age 5 (21) and 7 years

(28). Allergic rhinitis was defined as parental report of child's nasal symptoms or doctor diagnosis of allergic rhinitis in all studies (21-23, 28, 32).

Quality assessment of included articles

Study quality was assessed using the NOS for cohort studies. The majority of articles reported satisfactory selection of participants, in which exposed individuals were truly representative of the intended study population and non-exposed individuals were from the same community. The ascertainment of exposure in all included articles was from laboratory or medical records. Only one Danish population-based cohort (22) and two, Australian and German, high-risk cohorts considered all key confounders listed in the methods section of this review (13, 23). Five articles presented several statistical models with different levels of adjustment for other potential confounders (24, 28, 31-33). The remaining articles did not adjust for any confounders. The majority of included articles assessed asthma, eczema and allergic rhinitis based on reported data. Loss to follow-up was a potential source of bias given that the included studies were longitudinal in design. However, as we assessed the outcome at different age, the follow-up rate at the age of outcome was determined to be satisfactory in the majority of articles, with adequate comparability between included and non-included participants. Only two studies did not provide comparisons between included and non-included participants (24, 34). Overall, according to the suggested criteria for selection, comparability and outcome in NOS, the articles included in this review were of acceptable quality (Table E4 in Supplementary documents).

Studies included in the meta-analyses

Due to insufficient number of studies and methodological heterogeneity, we meta analysed only studies that reported the association between food without inhalant allergens sensitisation and allergic diseases from 2 to 12 years.

One of the included studies reported results for both egg and milk sensitisation separately (24).

In the meta-analysis model, we included the results for egg and milk separately and observed no significant differences between the two models. Thus, egg sensitisation results were plotted in the final models.

Two of the included studies investigated food sensitisation at age 6, 12 and 24 months (26, 34).

When conducting the meta-analysis, we computed separate models for each of the different time points and found no significant differences in the pooled estimates. Therefore 6 month SPT results were included in the final meta-analyses models.

The association between food sensitisation and wheeze/asthma (Table 2)

In infancy (1-2 years)

One population based (33) and one high-risk cohorts (26) assessed the association between food sensitisation and wheeze in the first 2 years of life (Table 2). The high-risk cohort showed an increase in the risk of ever wheezing at 2 years in children with an increased serum level of the sum of egg and milk s-IgE (26). The population based cohort showed no statistical significant associations.

In childhood (>2-12 years)

Ten articles representing nine birth cohorts examined the association between food sensitisation (with or without inhalant sensitisation) and subsequent wheeze/asthma in childhood (Table 2).

Of these, only five were from population based cohorts (21, 22, 29, 30, 34).

Overall, positive associations were demonstrated in three articles from population based (21, 22, 34) and four articles from high-risk cohorts (23-25, 31). The population based MAS cohort found that food sensitisation at both 1 and 2 years of age increased the risk of current wheeze/asthma at 5 (21) but not significantly at 7 years (29) (Table 2).

The results of seven articles that met the inclusion criteria for meta-analysis (22-25, 29, 30, 34) showed that food sensitisation in the first 2 years was associated with an increased risk of asthma during childhood (OR=2.8, 95%CI=2.1-3.9) (Figure 2). The pooled estimates remained almost the same when studies that assessed wheeze/asthma before the age of 5 were excluded from the final model, (OR=3.2, 95%CI=2.2-4.8).

The association between co-sensitisation to food and inhalant allergens and subsequent wheeze/asthma was reported in five studies (22, 29, 30, 32, 34) (Table 2). All cohorts, except two populations based (22, 34), demonstrated a positive relationship.

Specific food allergen sensitisation in relation to wheeze/asthma was assessed in three high-risk cohorts (24, 25, 31) (Table 2). Hen's egg sensitisation in the first 2 years of life was found to be associated with increased risk of wheeze/asthma in early childhood in three high-risk cohorts (24, 25, 31). Conversely, the evidence for the association between cow's milk sensitisation and wheeze/asthma was inconsistent. Cow's milk sensitisation at 1 year was not related to wheeze/asthma from 3 to 11 years in Bekkers, et al. (20) but significantly increased the risk of asthma at 7 years in Zeiger, et al. (31) .

In adolescence (12-18 years)

None of the included articles investigated the association between food sensitisation and subsequent asthma in this age group.

In adulthood (>18 years)

Only one birth cohort (27) assessed the association between early food sensitisation and subsequent asthma in adulthood. In this high-risk cohort, sensitisation to milk, egg or both before the age of 1 year was associated with an increased risk of asthma at 22 years (Table 2).

The association between food sensitisation and eczema (Table 3)

In infancy (1-2 years)

One population based (33) and one high-risk cohort (26) assessed the association between food sensitisation and eczema during late infancy. Although both cohorts showed a positive association, no adjustment for concurrent eczema was made at the time of sensitisation assessment (Table 3). Egg white, milk or wheat sensitisation at 6 months was found to be associated with eczema at 14 months in the population based cohort (33). However in the high risk cohort, that used the same eczema definition, found that milk but not egg sensitisation at 6 months was significantly associated with eczema at 2 years (26).

In childhood (>2-12 years)

Eight articles representing eight cohorts investigated the association between food sensitisation with or without inhalant sensitisation and subsequent eczema at age 4 to 8 years (13, 22, 23, 25, 26, 31, 32, 34) (Table 3). Overall, two population based (22, 34) and five out of six high-risk cohorts reported positive associations (13, 23, 25, 31, 32). Conversely, a Swedish high-risk cohort (26) that assessed egg and milk sensitisation at 3 time points (6, 12 and 24 months) found no significant association between s-IgE to egg or milk in the first year and the development of eczema at 5 years (Table 3).

Results from one population based study (34) showed that only food sensitisation at 6 but not at 12, 18 or 24 months was significantly related to increased risk of eczema at 4 years. Also, no confounders were considered in their analysis. Findings from a high-risk cohort observed a significant association between food sensitisation at 12 months and eczema at 6 years (23), but this association was no longer present when children who had eczema in their first year of life were excluded from the analysis.

Five of the eight articles assessing early food sensitisation and eczema during childhood met the meta-analyses inclusion criteria (22, 23, 25, 26, 34). Pooling of the findings showed that food sensitisation in the first 2 years was associated with an increased risk of eczema during childhood (OR=2.5, 95%CI=1.8-3.6) (Figure 2).

Co-sensitisation to food and inhalant allergens and subsequent eczema during childhood was investigated in two population based and one high-risk cohort (22, 32, 34). Two of these studies found positive associations (22, 32) (Table 3), while the third study (34) showed significant positive associations when sensitisation was assessed at 18 and 24 months, but not at 6 or 12 months.

In adolescence and adulthood (>12 years)

None of the included articles examined the association between food sensitisation and subsequent eczema in this age group.

The association between Food sensitisation and allergic rhinitis (Table 4)

In infancy (1-2 years)

None of the included articles examined the association between food sensitisation and subsequent allergic rhinitis during infancy.

In childhood (>2-12 years)

Three population based (21, 22, 34) and two high-risk cohorts (23, 32) examined the association between food with or without inhalant sensitisation and subsequent allergic rhinitis at age 4 to 8 years (Table 4). Overall, positive associations were observed in five (21, 23, 28, 32, 34) out of six articles (21-23, 28, 32, 34). Two articles from the MAS cohort assessed allergic rhinitis at 5 years (21) and seasonal allergic rhinitis at 7 years (28). These articles showed that the risk of

allergic rhinitis at 5 years and seasonal allergic rhinitis at 7 years in food sensitised compared to non-food sensitised children were similar (OR=4.7 and 4.6 at 5 and 7 years, respectively) however, 95%CI was not reported in the former.

Four of the six articles met the inclusion criteria to be included in meta-analysis of articles assessing early food sensitisation and allergic rhinitis during childhood (22, 23, 28, 34). Our meta-analyses showed that food sensitisation in the first 2 years of life was associated with an increased risk of allergic rhinitis during childhood (OR=3.0, 95%CI=2.1-4.2) (Figure 2). After excluding studies that assessed allergic rhinitis before the age of 5, there was no significant change in pooled estimates (OR= 2.9, 95%CI=2.0-4.1).

Co-sensitisation to food and inhalant allergens and subsequent allergic rhinitis during childhood was investigated in two population based and one high-risk cohort (22, 32, 34) (Table 4).

Although a significant association was reported in the high-risk cohort (32), a non-significant association was found in one population based cohort (22). The second population based cohort showed significant positive associations when food and inhalant sensitisation were assessed at 18 and 24 months but not at 6 or 12 months (34).

In adolescence and adulthood (>12 years)

None of the included articles assessed the association between food sensitisation and subsequent allergic rhinitis in this age group.

Dose-response relationship between food sensitisation and allergic diseases:

Only in MACS study (13) was the association between number and size of SPT reactions to food allergens and risk of developing eczema examined. The authors found that infants with the largest SPT wheal (≥ 6 mm) had the greatest risk of eczema (HR=2.28, 95%CI=1.34-3.87) and those who were sensitised to three food allergens had the greatest risk of developing eczema

(HR= 4.73, 95%CI=2.10-10.66) when compared to those sensitised to only one food allergen (HR=1.53, 95%CI= 1.10-2.12).

Three articles (21, 22, 29) investigated the association between specific patterns of food sensitisation and subsequent allergic diseases. However, the patterns were different across the articles. The MAS study (21) found that long lasting food sensitisation (i.e. food sensitisation at age 1 and 2 years) was associated with increased risk of asthma and allergic rhinitis compared to transient (i.e. food sensitisation at only at age 1 or 2 years) and never food sensitised (Table 2&3). While articles from the MAS (29) and DARC studies (22) have found that early food sensitisation was associated with increased risk of subsequent asthma, the definition of early sensitisation varied between the two studies. Early food sensitisation was defined as sensitisation before the age of 2 years in the MAS study (29) and between 3 and 18 months in the DARC study (22).

Discussion

This is the first systematic review and meta-analyses that assessed the association between food sensitisation and subsequent allergic diseases in birth cohort studies. We found that early life food sensitisation was related to eczema in late infancy, wheeze/asthma, eczema or allergic rhinitis in childhood and asthma in young adults. Meta-analyses confirmed these relationships for childhood wheeze/asthma, eczema, and allergic rhinitis. Association in relation to infant wheeze was inconsistent and associations with adult eczema and allergic rhinitis have not been investigated.

Although a formal protocol was not registered, we developed an informal protocol prior to commencement of the search to ensure the review methodology was not altered based on the findings from individual studies. Two independent authors selected papers for inclusion by

searching two large databases along with the reference lists of included papers. Two authors also independently performed data extraction and quality assessment. However, there is potential for publication bias affecting the pooled estimates. We chose not to include unpublished literature as we could not properly assess the quality of papers that have not been published in full.

Some of the included papers were from interventional studies (13, 23-25, 31, 32) where the intervention might influence the occurrence of food sensitisation (such as dietary intervention) or allergic outcomes (such as HDM avoidance). The presented associations in these studies were from both control and intervention groups with only three studies (23, 24, 31) having considered the intervention in their statistical analyses. In a sensitivity analysis, excluding the studies that had not considered the intervention from our meta-analyses did not appreciably change the pooled estimates.

The quality of included articles was acceptable as assessed by the NOS. However in the majority of articles, there was no control for important confounding factors such as family history of allergy, concurrent eczema and wheezing. Most articles were from high-risk allergy cohorts, where it is not necessary to account for a family history of atopy. Family history of atopy was considered as a potential confounder in only two out of five population-based cohorts. Eczema in the first 12 months is commonly associated with high levels of food specific IgE (12), and has been associated with increased risk of asthma (35). Similarly wheeze has been co-associated with food specific IgE levels (or food allergy) (36). Thus, considering early life eczema and wheeze as potential confounders is essential for investigating the consequences of food sensitisation. Only three articles, however, investigated this. One population-based cohort adjusted for early atopic dermatitis and early wheeze, and this showed a positive association even after these adjustments (22). Conversely, a high-risk cohort(23) reported a null association

between food sensitisation at 12 months and eczema at 6 years after excluding all children with eczema in the first year. However, this may have underestimated the true association as those who developed food sensitisation before eczema may have been excluded. Another high-risk study (13) showed an increase in the incidence rate of eczema up to 7 years in children who had food sensitisation at 6 months compared to non-sensitised children among those who did not have eczema in the first six months.

The majority of articles in our review were from high-risk cohorts (eight out of fifteen), limiting the generalisability of findings. However, we observed positive associations in five articles from population-based cohorts (21, 22, 28, 33, 34) and the effect estimates from the high-risk vs. general population studies were almost always similar. Another limitation is that the number of tested food allergens varied across studies. We cannot exclude the possibility of non-differential misclassification of the exposure, which may push the estimates towards null in cohorts with fewer tested food allergens. However, cow's milk and hen's egg, which are considered common food sensitisations in the first 2 years of life (37), were tested in all cohorts. A small number of articles defined outcomes as "ever" (25, 26, 30, 31) instead of "current" allergic disease. This may lead to imprecise estimation for the effect of early food sensitisation since the outcome of interest may develop before, after, or at the time of testing food sensitisation status. If the disease is not current, the relevance of the observed association with long-term disease burden is also questionable.

The influence of early food sensitisation on subsequent eczema and allergic rhinitis has not been investigated beyond childhood in any birth cohorts. Only one British birth cohort investigated the association with subsequent asthma in adulthood, finding an increased risk. However, small sample size and loss to follow-up (only 63 out of 100 participants were included in analysis), limited number of food allergens (cow's milk and egg white), and being an atopy high-risk cohort might limit its generalisability (27). Given that the prevalence of asthma and allergic

rhinitis increases with age (38), investigating the subsequent effect of early life food sensitisation on allergic diseases in birth cohorts over a long period of follow-up is required.

In conclusion, our systematic review supports the hypothesis that food sensitisation marches towards other allergies especially childhood wheeze/asthma, eczema and allergic rhinitis.

Therefore early life food sensitisation can be used as an early indicator for identifying children at risk of subsequent allergic disease who may benefit from early life preventive strategies.

However, due to lack of inclusion of key confounders in many of these studies, lack of follow-up data into adulthood and unclear data on the role of specific food allergens and specific pattern of sensitisation, further research is needed to confirm these findings.

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Table 1 Birth cohort studies that assessed the association between food sensitisation and subsequent development of allergic disease.

Name of the cohort, Country	Years of enrolment (Original sample size)	Study population*	Tested food allergens (Methods for assessment)	Publication(s); First author (year), Ref.	Number of analysed participants (% from total cohort)	Allergic outcomes Assessed	Quality Score**
The German Multicenter Allergy Study (MAS), Germany	1990 (1314)	Population- based atopy enriched study (40%)	Egg, Milk, Wheat, Soy (s-IgE)	Kulig (1998), (21)	-	Asthma, Allergic rhinitis	6/9
				Kulig (2000), (28)	-	Seasonal allergic rhinitis	5/9
				Illi (2001), (29)	1062 (80.8%)	Asthma	6/9
The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort, United States	2003 – 2007 (1258)	Population-based	Egg, Milk, Peanut (s-IgE)	Havstad (2014), (30)	594 (47%)	Asthma	5/9
The Danish Allergy Research Centre cohort (DARC birth cohort), Denmark	1998 – 1999 (562)	Population-based	Egg, Milk (SPT and s-IgE)	Kjaer (2009), (22)	S-IgE → 325 (57.8%) SPT → 382 (68%)	Asthma, Eczema, Allergic rhinitis	7/9
The Gifu Allergy and Immunology Cohort Study (GAICS), Japan	2004 – 2005 (314)	Population-based	Egg, Milk, Wheat, Soy bean (s-IgE)	Kawamoto (2012), (33)	171 (54.5%)	Asthma, Eczema	5/9
The Prediction of Allergies in Taiwanese Children study (PATCH), Taiwan	2007 – 2010 (258)	Population-based	Egg, Milk, Wheat (s-IgE)	Chiu (2014), (34)	182 (70.5%)	Asthma, Eczema, Allergic rhinitis	5/9
German Infant Nutritional Intervention	1995 – 1998 (2252)	High-risk of atopy	Egg, Milk, Soy (s-IgE)	Brockow (2009), (23)	1290 (57.3%)	Asthma, Eczema, Allergic rhinitis	7/9

(GINIplus) study, Germany							
The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, Netherlands	1996 – 1997 (855)	High-risk of atopy	Egg, Milk (s-IgE)	Bekkers (2013), (24)	-	Asthma	6/9
The Melbourne Atopy Cohort Study (MACS), Australia	1990 – 1994 (620)	High-risk of atopy	Egg, Milk, Peanut (SPT)	Lowe (2007), (13)	552 (89%)	Eczema	7/9
The Childhood Asthma Prevention Study (CAPS), Australia	1997 – 2000 (616)	High-risk of asthma	Egg, Milk, Peanut (SPT)	Garden (2013), (32)	509 (83%)	Asthma, Eczema, Allergic rhinitis	6/9
No specific name was given, Referred to South Wales Birth Cohort, UK	- (497)	High-risk of atopy	Egg, Milk (SPT)	Burr (1997), (25)	437 (88%)	Asthma, Eczema	6/9
No specific name was given, Referred to as Swedish Birth Cohort, Sweden	1997 – 2000 (268)	High-risk of atopy	Egg, Milk, Peanut, Soybean, Codfish (s-IgE)	Söderström (2011), (26)	-	Asthma, Eczema	6/9
No specific name was given, Referred to as Poole Birth Cohort, UK	1976 – 1977 (100)	High-risk of atopy	Egg, Milk (SPT)	Rhodes (2001), (27)	63 (63%)	Asthma	6/9
No specific name was given, Referred to as San Diego Birth Cohort, USA	-	High-risk of atopy	Egg, Milk, Peanut, Cod, Shrimp, Walnut (SPT)	Zeiger (1995), (31)	-	Asthma, Eczema, Allergic rhinitis	6/9

S-IgE= serum specific IgE, SPT= skin prick testing

* For definition of high- risk cohort refer to Table E2 at supplementary documents

** For details of the quality assessment refer to Table E4 at supplementary document

Table 2 The association between food sensitisation and subsequent development of wheeze/Asthma in birth cohort studies stratified by the age of wheeze/asthma development.

Name of the cohort (Ref.)	Age at assessment of Asthma /wheezing ¹	Age at assessment of food sensitisation	Main Findings OR (95% CI)	Assessed confounders
Late infancy				
GAICS (33)	14 months	6 months Egg white Wheat	1.8 (0.4 - 7.1) 1.5 (0.1 - 13.9)	The level of cord blood IgE and other immunological biomarkers.
Swedish Birth Cohort (26)	2 years	12 months Egg + Milk	2.6 (1.0–6.7)	No adjustment
Childhood				
PIAMA (24)	Yearly from 3 to 8 years and then at 11 years	12 months Hen's egg Cow's milk	Later asthma → 2.5 (1.2 - 5.1) At 6 years → 3.9 (1.6 - 9.4) At 7 years → 4.3 (1.8 - 10.5) At 8 years → 3.9 (1.6 - 9.5) Later asthma → 1.0 (0.6 - 1.6)	Sex, Maternal smoking during pregnancy, Breast-feeding, Presence of older siblings, Paternal allergy
WHEALS (30)	4 years	2 years Highly sensitised ² Egg + Milk Peanut + any inhalant ³	5.3 (1.6 -17.4) 1.6 (0.8 - 3.0) 1.8 (0.6 - 4.9)	-
PATCH (34)	4 years	6, 12, 18 & 24 months Food only (6M) Food + inhalant (6M) Food only (12M) Food + inhalant (12M) Food only (18M) Food + inhalant (18M) Food only (24M) Food + inhalant (24M)	7.5 (1.7–33.0) 2.8 (0.2–48.8) 3.0 (0.8–10.4) 4.8 (0.7–31.1) 9.0 (1.0–78.1) 57.0 (4.3–744.7) 7.4 (0.8–68.1) 38.4 (3.9–373.1)	-
MAS (21)	5 years	1,2 and 5 years Long lasting ⁴ vs. transient ⁵ Long lasting vs. No	5.5 (No 95% CI), p<0.0001 10.6 (No 95% CI)	-

		sensitisation		
DARC (22)	6 years	Early food (3-18M) Early food + inhalant	4.0 (1.1 - 12.5) 3.8 (0.8 - 14.0)	Early atopic dermatitis, Family history of allergy, Elevated cord blood IgE, Early wheeze, Male gender, Maternal history of allergy
GINIplus(23)	6 years	12 month	3.9 (1.9-7.7) Adjusted; 3.9 (1.9-7.9)	Family history of atopic disease, Parental education, Siblings, Gender, Study region, and Type of milk feeding during the first 4 months of life
MAS (29)	7 years	1 and 2 years Food only before 2 Yrs. Food + inhalant before 2 Yrs.	2.2 (0.7 – 6.2) 11.1 (4.7 – 26.1)	-
South Wales Birth Cohort (25)	7 years	6 months. Egg	2,6 (1.2 - 5.5)	-
San Diego Birth Cohort (31)	7 years	12 months Egg Milk Peanut	1.7 (No 95% CI) Adjusted; 6 (1.3 - 28) Adjusted; 11.2 (1.2 - 107)	Male gender, Maternal ethnicity, Parental atopic disease, Maternal smoking
CAPS (32)	8 years	18 months, 3, 5 and 8 years Mixed food and inhalant ⁶	16.4 (5.2 - 51.7) Adjusted; 14.3 (4.7 - 44.1)	Sex, The study intervention groups.
Adulthood				
Poole Birth Cohort (27)	22 years	3,6 and 12 months Egg or milk before 1 year	12.3 (2.5 - 77.1)	-

¹The definitions of outcome are listed in Table E3 at supplementary documents.

² Sensitisation to at least 4 of the same allergens: milk, egg, peanut, and timothy grass, as determined by latent class analysis

³Inhalant allergens were Dermatophagoides farinae, dog, cat, timothy grass, ragweed and Alternaria alternate.

⁴Long lasting sensitisation: sensitisation at both 1 and 2 years.

⁵Transient sensitisation: sensitisation at 1 or 2 years.

⁶Mixed food and inhalant (as determined by latent class analysis): Characterized by early and persistently sensitisation to peanut, early, but decreasing sensitisation to egg; and an increasing sensitisation to HDM, Alternaria and grass.

Table 3 The association between food sensitisation and development of eczema in birth cohort studies, stratified by the age of eczema development.

Name of the cohort (Ref.)	Age at assessment of Eczema/atopic dermatitis ¹	Age at assessment of food sensitisation	Main Findings OR (95% CI)	Assessed confounders
Late infancy				
GAICS (33)	14 months	6 months Egg white Cow's milk Wheat	14.9 (4.1 - 53.2) Adjusted; 23.2 (2.8 - 192.9) 8.1 (2.7 - 24.2) 10.2 (2.3 - 44.5)	The level of cord blood IgE and other immunological biomarkers.
Swedish Birth Cohort (26)	2 years	6 and 12 months Egg (6M) Egg (12M) Milk (6M) Milk (12M) Egg +/-or Milk (6M) Egg +/-or Milk (12M)	1.7 (0.7 - 4.0) 3.3 (1.5 - 7.1) 4.8 (1.8 - 12.8) 3.5 (1.4 - 8.3) 3.1 (1.4 - 6.5) 3.3 (1.6 - 6.9)	No adjustments
Childhood				
PATCH (34)	4 years	6, 12, 18 & 24 months Food only (6M) Food + inhalant (6M) Food only (12M) Food + inhalant (12M) Food only (18M) Food + inhalant (18M) Food only (24M) Food + inhalant (24M)	8.2 (1.7–39.5) 8.2 (0.6–101.0) 3.0 (0.7–11.6) 6.0 (0.8–40.8) 1.0 (0.2–4.0) 7.6 (1.1–54.1) 1.1 (0.2–5.1) 5.6 (1.1–27.3)	-
Swedish Birth Cohort (26)	5 years	6 and 12 months Egg (6M) Egg (12M) Egg (24M) Milk (6M) Milk (12M) Milk (24M) Egg +/-or Milk (6M) Egg +/-or Milk (12M)	1.0 (0.4 – 2.4) 1.1 (0.5 – 2.6) 1.5 (0.8 – 2.8) 0.7 (0.2 – 1.9) 0.8 (0.3 – 2.1) 1.1 (0.6 – 2.0) 1.1 (0.5 – 2.6) 0.9 (0.4 – 2.1)	No adjustments

		Egg +/-or Milk (24M)	1.2 (0.6 – 2.1)	
DARC (22)	6 years	Early food (3-18M) Early food + inhalant	4.0 (1.6 - 9.9) 6.2 (2.2 - 17.1)	Early atopic dermatitis, Family history of allergy, Elevated cord blood IgE, Early wheeze, Male gender, Maternal history of allergy
GINIplus(23)	6 years	12 month	2.3 (1.4 - 3.7) Adjusted; 2.1 (1.2 - 3.6) <i>Excluding children with a physician's diagnosis of eczema within the first year of life</i> →Adjusted; 0.8 (0.3 - 2.1)	Family history of atopic disease, Parental education, Siblings, Gender, Study region, and Type of milk feeding during the first 4 months of life
MACS (13)	6 and 7 years	6 months Any food Egg Milk Peanut	1.6* (1.1 - 2.3) 1.6* (1.1 - 2.5) 2.1* (1.1 - 3.7) 1.7* (0.9 - 2.9)	Maternal or paternal history of eczema, Gender and Presence of older siblings
South Wales Birth Cohort (25)	7 years	6 months Egg	3.5 (1.7 - 7.4)	-
San Diego Birth Cohort (31)	7 years	1 year Egg Peanut	15 (No 95% CI) Adjusted; 34 (1.5-794)	Male gender, Maternal ethnicity Parental atopic disease, Maternal smoking
CAPS (30)	8 years	18 months, 3, 5 and 8 years Mixed food and inhalant ²	5.6 (1.8 - 17.2) Adjusted; 5.6 (1.9 - 16.8)	Sex, study intervention groups

¹The definitions of outcome are listed in Table E3 at supplementary documents..

² Mixed food and inhalant (as determined by latent class analysis): Characterized by early and persistently sensitisation to peanut, early, but decreasing sensitisation to egg; and an increasing sensitisation to HDM, Alternaria and grass.

*Hazard Ratio (HR)

Table 4 The association between food sensitisation and subsequent development of allergic rhinitis in birth cohort studies stratified by the age of allergic rhinitis development.

Name of the cohort (Ref.)	Age at assessment of Allergic rhinitis ¹	Age at assessment of food sensitisation	Main Findings OR (95% CI)	Assessed confounders
Childhood				
PATCH (34)	4 years	6, 12, 18 & 24 months Food only (6M) Food + inhalant (6M) Food only (12M) Food + inhalant (12M) Food only (18M) Food + inhalant (18M) Food only (24M) Food + inhalant (24M)	5.2 (1.4–19.8) 2.1 (0.1–24.3) 1.1 (0.4–2.8) 1.8 (0.3–8.5) 1.8 (0.6–4.8) 8.6 (1.5–46.8) 2.4 (0.8–7.1) 8.4 (2.3–30.6)	-
MAS (21)	5 years	1,2 and 5 years Long lasting ² vs. Transient ³ Long lasting vs. No sensitisation	3.4 (No 95% CI), p<0.0001 4.7 (No 95% CI)	-
DARC (22)	6 years	Early food (3-18M) Early food + inhalant	2.0 (0.7 - 5.0) 2.7 (0.9 - 7.5)	Early atopic dermatitis, Family history of allergy, Elevated cord blood IgE, Early wheeze, Male gender, Maternal history of allergy
GINIplus(23)	6 years	12 month	2.2 (1.3- 3.7) Adjusted; 2.1 (1.2 - 3.7)	Family history of atopic disease, Parental education, Siblings, Gender, Study region, and Type of milk feeding during the first 4 months of life
MAS (28)	7 years	1 and 2 years	4.6 (2.6 - 8.1) Adjusted; 3.3 (1.7 - 6.5)	Parental educational level and Study center
CAPS (32)	8 years	18 months, 3, 5 and 8 years Mixed food and inhalant ⁴	5.1 (1.8 - 14.8) Adjusted; 4.2 (1.5 - 11.7)	Sex, study intervention groups

¹ The definitions of outcome are listed in Table E3 at supplementary documents.

² Long lasting sensitisation: sensitisation at both 1 and 2 years.

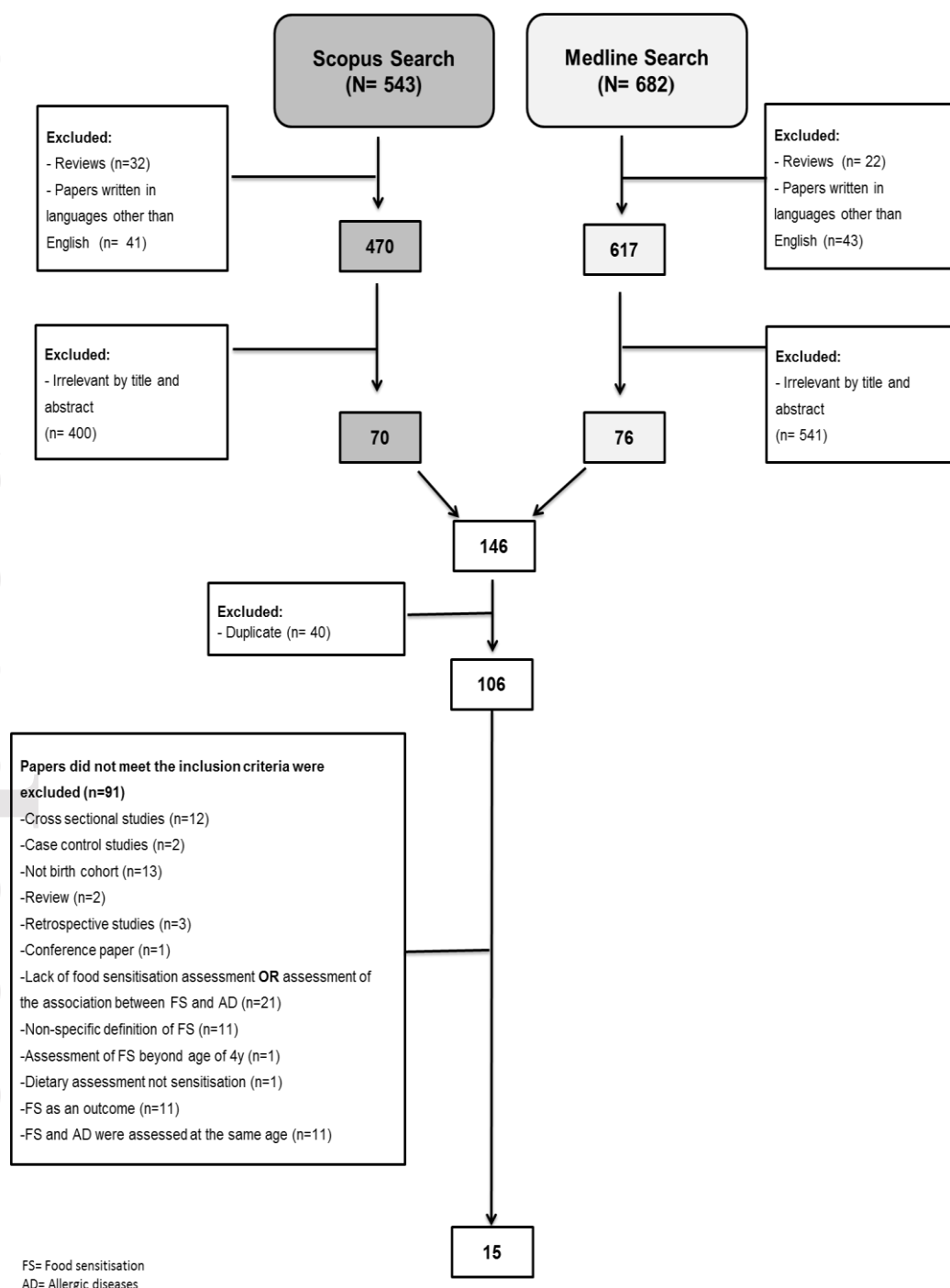
³ Transient sensitisation: sensitisation at 1 or 2 years.

⁴ Mixed food and inhalant (as determined by latent class analysis): Characterized by early and persistently sensitisation to peanut, early, but decreasing sensitisation to egg; and an increasing sensitisation to HDM, Alternaria and grass.

Figure legends

Figure 1 Flow chart for systematic searching process

Figure 2 Association between early life food sensitisation and asthma, eczema and allergic rhinitis during childhood (>2-12 years). Risk estimates and 95% confidence intervals estimated with random effects modelling.



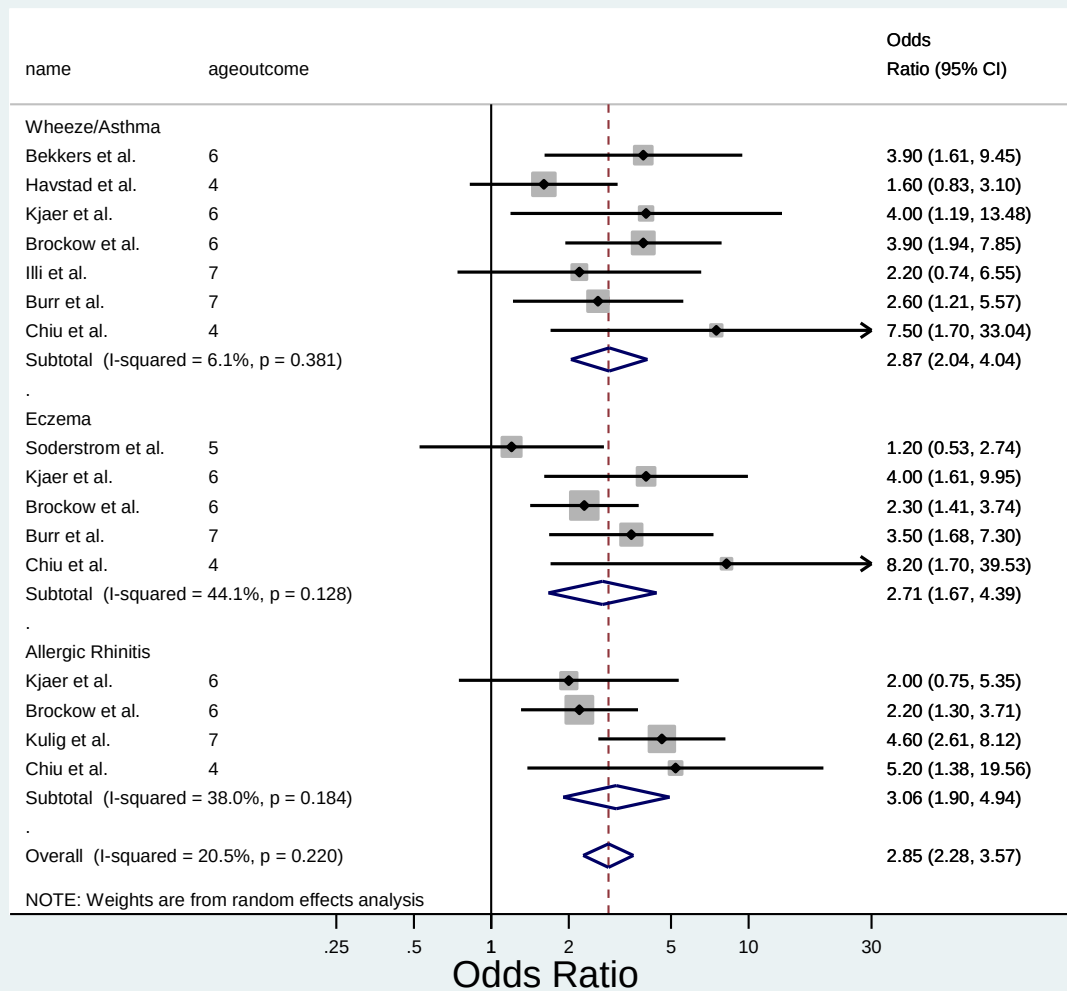


Table E1: Search terms in Medline and Scopus databases

Medline Years: 1950 - 2014	Exposure Group: (MeSH heading) Food or milk or egg or peanut or fish or wheat or soy <i>and</i> sensitisation or specific immunoglobulin E or skin prick test AND Outcome Group: (MeSH heading) Asthma or wheeze or eczema or "hay fever" or "allergic disease*" AND Inclusion Group: Cohort or prospective or longitudinal
Scopus Years: All years published	Exposure Group: (Title, abstract and keywords) Food or milk or egg or peanut or fish or wheat or soy <i>and</i> sensitisation or specific immunoglobulin E or skin prick test or SPT AND Outcome Group: (Title, abstract and keywords) Asthma or “asthma symptoms” or wheeze or eczema or “atopic dermatitis” or "hay fever" or “allergic rhinoconjunctivitis” or “allergic rhinitis” or "allergic disease*" AND Inclusion Group: Cohort or prospective or longitudinal

Table E 2: Definitions of high-risk cohort

Cohort	Definition
GINIplus (23)	Positive family history of atopic diseases
PIAMA (24)	Children of mothers with ever asthma, pet allergy, HDM allergy or nasal allergy
MACS (13)	At least one 1 st degree relative with history of asthma, eczema, hay fever or food allergy
CAPS (32)	Parents or siblings with current asthma or wheezing
South Wales Birth Cohort (25)	Parental or siblings history of asthma, eczema or hay fever
Swedish Birth Cohort (26)	Positive SPT in parents
Poole Birth Cohort (27)	One or both parents having a history of asthma, hay fever or both
San Diego Birth Cohort (31)	Atopic parents

Table E 3: Definitions of outcomes in included studies.

Name of the cohort	Outcomes definition
MAS (21, 28, 29)	Asthma at 5Y → The presence of one of the following criteria throughout the fifth year of life; 1. At least two reported episodes of wheezing or shortness of breath within the last 12 months, 2. Asthma diagnosed by the family practitioner or the study physician (considering that symptoms were not related to infections or were present especially in pollen season). Asthma at 7Y → Doctor's diagnosis of asthma and current wheeze at the age of 7 years Allergic rhinitis at 5Y → The presence of ≥1 throughout the 5th year of life: 1. Reported symptoms of blocked nose and rhinorrhoea not related to infections for 2 to 8 consecutive months and /or 2. Allergic rhinitis diagnosed by the family practitioner or the study physician (considering that symptoms, see above, were not related to infections or were present especially in pollen season) Seasonal Allergic rhinitis → Reported seasonal symptoms had to be associated with the respective seasonal sensitization to birch or grass pollen
WHEALS (30)	Asthma → Parental report of child's doctor's diagnosis of asthma
DARC (22)	Asthma → A clear subjective or objective response to treatment with b2-agonists and/or inhaled corticosteroids AND The presence of one of the following criteria;(i) recurrence of at least two of the three symptoms cough, wheeze and shortness of breath within the previous 12 months (symptoms not triggered only by infections), (ii) doctor's diagnosis of asthma prior to follow-up visit (in combination with ongoing treatment), and (iii) symptoms suggestive of asthma within the previous 12 months in combination with a positive exercise or bronchodilator test. Eczema → According to Hanifin-Rajka criteria Allergic rhinitis → Two or more separate episodes of one or more typical symptoms from eyes and/or nose (not related to common colds)
GAICS (33)	Asthma → Recurrent wheezing (RW) diagnosed by a pediatric allergist based on a history of more than 2 episodes of physician-diagnosed wheezing Eczema → diagnosed by a pediatric allergist according to Hanifin and Rajka's minor criteria
PATCH (34)	Asthma → Ever having asthma with the occurrence of wheeze or current use of asthma medication. Eczema → Pruritic rash over the face and/or extensors with a chronic relapsing course as described by Hanifin and Rajka Allergic rhinitis → Ever having sneezing, nasal congestion, itching, rhinorrhea or current use of medication for these symptoms
GINIplus (23)	Asthma → Parental report of a physician's diagnosis of asthma in the 12

	months Eczema → Parental report of a physician's diagnosis of eczema in the 12 months prior to their child turning 6 years Allergic rhinitis → Parental report of a physician's diagnosis of allergic rhinitis in the 12 months prior to their child turning 6 years)
PIAMA (24)	Asthma → The presence of at least 2 of 3 parental-reported criteria: (1) a doctor's diagnosis of asthma ever, (2) wheezing during the last 12 months, and (3) a prescription of inhaled corticosteroids in the last 12 months.)
MACS (13)	Eczema → Either a doctor diagnosis of eczema or any rash (excluding rash that only affected the nappy region or scalp) that was treated with topical steroid-based preparations
CAPS (32)	Asthma → Wheeze in the last 12 months AND either ever-diagnosed asthma (reported at ages 18 months and 3, 5 or 8 years) or airway hyperresponsiveness (at 8 years) Eczema → Flexural rash at the time of physical assessment or a history of recurrent itchy rash and use of topical treatments in the last 12 months Allergic rhinitis → Positive response if the child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu in the past 12 months.
South Wales Birth Cohort (25)	Asthma → Parental report of child's wheezing or asthma at 3, 6 and 12 months then annually up to the age of 7 years Eczema → Parental report of child's eczema at 3, 6 and 12 months then annually up to the age of 7 years)
Swedish Birth Cohort (26)	Asthma → Any episode of wheezing or signs of hyper-reactivity reaction or wheezing after exposure to an allergen or respiratory symptoms treated with inhaled Eczema → According to Hanifin and Rajka criteria
Poole Birth Cohort (27)	Asthma → Current wheeze (yes answer to the question, "Have you had wheezing (loud breathing with a whistling sound coming from the chest) at any time in the last 12 months) AND BHR (the maximum cumulative dose of 7.8 µmol of histamine that caused a reduction in FEV1 by 20%)
San Diego Birth Cohort (31)	Asthma → Physician-documented lower respiratory disorder with reversible bronchospasm, occurring at least twice and unassociated with other anatomic, congenital, or immunologic causes Eczema → An eczematous eruption associated with at least three of the following four criteria: (1) Pruritis, (2) typical appearance and distribution, (3) a tendency toward chronicity or recurrence, and (4) concurrent specific IgE

Table E 4: NOS quality assessment for included studies.

First author (Cohort)		S. Havstad (WHEALS)	C. Chiu (PATCH)	M. Bekkers (PIAMA)	F. Garden (CAPS)	N. Kawamoto (GAICS)	L. Söderström	I. Brockow (GINIplus)	H. Kjaer (DARC)
<u>Selection</u>	<u>1) Representativeness of the exposed cohort</u>								
	a) truly representative	★ Children born between 2003 and 2007 in Detroit and surrounding suburbs, USA	★ Children born between 2007 and 2010 in Taiwan	★ Children born between 1996 and 1997 in Netherland	★ Children born between 1997 and 2000 in Sydney, Australia	★ Children born between 2004 and 2005 in Gifu, Japan	★ Children born between 1997 and 2000 in Stockholm, Sweden	★ Children born between 1995 and 1998 in Germany	★ Children born between 1998 and 1999 in Germany
	b) somewhat representative	NA	NA	NA	NA	NA	NA	NA	NA
	c) selected group of users	NA	NA	NA	NA	NA	NA	NA	NA
	d) no description of the derivation of the cohort	NA	NA	NA	NA	NA	NA	NA	NA
	<u>2) Selection of the non-exposed cohort</u>								
	a) drawn from the same community as the exposed cohort	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community
	b) drawn from a different source	NA	NA	NA	NA	NA	NA	NA	NA
	c) no description of the derivation of the non-exposed cohort	NA	NA	NA	NA	NA	NA	NA	NA
	<u>3) Ascertainment of exposure</u>								
	a) secure record (eg surgical records)	★ Laboratory records for	★ Laboratory records for	★ Laboratory records for	★ Clinical records for	★ Laboratory records for	★ Laboratory records for	★ Laboratory records for	★ Laboratory and clinical

		blood samples	blood samples	blood samples	SPT	blood samples	blood samples	blood samples	records for blood samples
	b) structured interview	NA	NA	NA	NA	NA	NA	NA	NA
	c) written self-report	NA	NA	NA	NA	NA	NA	NA	NA
	d) no description	NA	NA	NA	NA	NA	NA	NA	NA
	<u>4) Demonstration that outcome of interest was not present at start of study</u>								
	a) yes	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life
	b) no	NA	NA	NA	NA	NA	NA	NA	NA
<u>Comparability</u>	<u>1) Comparability of cohorts on the basis of the design or analysis</u>								
	a) Family history of atopy	Not adjusted for family history of atopy	Not adjusted for family history of atopy	★ Adjusted for parental allergy	★ Asthma high risk cohort	Not adjusted for family history of atopy	★ Atopy high risk cohort	★ Adjusted for family history of atopy	★ Adjusted for maternal history of allergy
	b) Early life eczema or wheezing	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	★ Early life eczema was considered	★ Early life eczema was considered
<u>Outcome</u>	<u>1) Assessment of outcome</u>								
	a) independent blind assessment	-	-	-	-	-	-	-	-

	b) record linkage	-	-	-	-	-	-	-	-
	c) self-report	Data on asthma extracted by parental-reported questionnaires	Data on allergic diseases extracted by questionnaires and pediatric pulmonologist	Data on asthma extracted by parental-reported questionnaires	Data on allergic diseases extracted by parental-reported questionnaires	Data on allergic diseases extracted by pediatric allergist	Data on allergic diseases extracted by pediatric allergist	Data on allergic diseases extracted by parental-reported questionnaires	Data on allergic diseases extracted by parental-reported questionnaires
	d) no description	NA	NA	NA	NA	NA	NA	NA	NA
	<u>2) Was follow-up long enough for outcomes to occur</u>								
	a) yes	★ 4 years follow up	★ 4 years follow up	★ 11 years follow up	★ 8 years follow up	★ 14 months follow up	★ 5 years follow up	★ 6 years follow up	★ 6 years follow up
	b) no	NA	NA	NA	NA	NA	NA	NA	NA
	<u>3) Adequacy of follow up of cohorts</u>								
	a) complete follow up	Loss to follow up	Loss to follow up	NA	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up
	b) subjects lost to follow up unlikely to introduce bias	Both analyzed and non-analyzed children were comparable	NA	NA	Lost to follow-up had younger and less educated parents	Both included and non-included children were comparable	NA	Lost to follow-up were from less educated parents with more siblings	NA
	c) follow up rate	47% included in the analysis	NA	NA	83% at 8 years	54% included in the analysis	90% at 5 years	57% included in the analysis	68% included in the analysis
	d) no statement	NA	No statement	No statement	NA	NA	NA	NA	NA

First author (Cohort)		S. Illi (MAS)	H. Rhodes	M. BURR	R. Zeiger	M. Kulig (MAS)	M. Kulig (MAS)	A. Lowe (MACS)
<u>Selection</u>	<u>1) Representativeness of the exposed cohort</u>							
	a) truly representative	★ Children born during 1990 in 5 German cities.	★ Children born between 1976 and 1977 in Poole, UK	★ Children born in two areas of south Wales	★ Families from the Kaiser Foundation Health Plan of San Diego, USA	★ Children born during 1990 in 5 German cities.	★ Children born during 1990 in 5 German cities	★ Children born between 1990 and 1994 in Melbourne, Australia
	b) somewhat representative	NA	NA	NA	NA	NA	NA	NA
	c) selected group of users	NA	NA	NA	NA	NA	NA	NA
	d) no description of the derivation of the cohort	NA	NA	NA	NA	NA	NA	NA
	<u>2) Selection of the non-exposed cohort</u>							
	a) drawn from the same community as the exposed cohort	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community	★ Exposed group from the same community
	b) drawn from a different source	NA	NA	NA	NA	NA	NA	NA
	c) no description of the derivation of the non-exposed cohort	NA	NA	NA	NA	NA	NA	NA
	<u>3) Ascertainment of exposure</u>							

	a) secure record (eg surgical records)	★ Laboratory records for blood samples	★ Clinical records for SPT	★ Clinical records for SPT	★ Clinical records for SPT	★ Laboratory records for blood samples	★ Laboratory records for blood samples	★ Clinical records for SPT
	b) structured interview	NA	NA	NA	NA	NA	NA	NA
	c) written self-report	NA	NA	NA	NA	NA	NA	NA
	d) no description	NA	NA	NA	NA	NA	NA	NA
	<u>4) Demonstration that outcome of interest was not present at start of study</u>							
	a) yes	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life	★ Birth cohort and outcomes appear later in life
	b) no	NA	NA	NA	NA	NA	NA	NA
<u>Comparability</u>	<u>1) Comparability of cohorts on the basis of the design or analysis</u>							
	a) Family history of atopy	★ Stratified the analysis by family history of atopy or asthma	★ Atopy high risk cohort	★ Atopy high risk cohort	★ Adjusted for history of parental atopy	★ Stratified the analysis by family history of atopy or asthma	Not adjusted for family history of atopy	★ Adjusted for parental history of eczema
	b) Early life eczema or wheezing	Not adjusted for early life wheezing or eczema	Effect of early life wheezing and eczema was assessed separately from exposure	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Not adjusted for early life wheezing or eczema	Effect of early life wheezing and eczema was assessed separately from exposure	★ Early life eczema was considered

<u>Outcome</u>	<u>1) Assessment of outcome</u>							
	a) independent blind assessment	-	-	-	-	-	-	-
	b) record linkage	-	-	-	-	-	-	-
	c) self-report	Data on asthma extracted by parental-reported questionnaires	Data on asthma extracted by parental-reported questionnaires	Data on allergic diseases extracted by parental-reported questionnaires	Data on allergic diseases extracted by parental-reported questionnaires	Data on allergic diseases extracted by pediatric allergist	Data on allergic rhinitis extracted by parental-reported questionnaires	Data on eczema extracted by parental-reported questionnaires
	d) no description	NA	NA	NA	NA	NA	NA	NA
	<u>2) Was follow-up long enough for outcomes to occur</u>							
	a) yes	★ 7 years follow up	★ 22 years follow up	★ 7 years follow up	★ 7 years follow up	★ 5 years follow up	★ 7 years follow up	★ 7 years follow up
	b) no	NA	NA	NA	NA	NA	NA	NA
	<u>3) Adequacy of follow up of cohorts</u>							
	a) complete follow up	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up	Loss to follow up
	b) subjects lost to follow up unlikely to introduce bias	Lost to follow-up were from less educated and smoker parents and without history of atopy.	Lost to follow-up had parental history of asthma	NA	Both included and non-included children were comparable	Both analyzed and non-analyzed children were comparable	Both analyzed and non-analyzed children were comparable	NA

	c) follow up rate	81% included in the analysis	63% included in the analysis	88% at 7 years	NA	NA	71% included in the analysis	89% included in the analysis
	d) no statement	NA	NA	NA	NA	NA	NA	NA