Does atopic dermatitis cause food allergy? A systematic review

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Abstract

Background

The association between atopic dermatitis (AD) and food allergy (FA) is not fully understood, although a causal relationship has been suggested. This has important implications for prevention and treatment.

Objective

We aimed to review associations between AD and FA; the impact of FA on AD severity, chronicity, age of onset and the temporal relationship between the two.

Methods

Medline and Embase were systematically searched from inception to November 2014 for studies investigating both AD and FA.

Results

66 studies were identified. 18 were population-based, 8 utilized high-risk cohorts, and the rest comprised patients with either established AD or FA. In population-based studies, the likelihood of food sensitization was $\leq$6 times higher in AD patients versus healthy controls at 3 months of age (OR=6.18, 95% CI 2.94-12.98, p<0.001). Other population-based studies reported the prevalence of food sensitization in AD patients as $\leq$53%, and $\leq$15% for challenge-proven FA. Meanwhile, studies including only patients with established AD have reported the prevalence of food sensitization as $\leq$66%, and $\leq$81% for challenge-proven FA. 16 studies suggested that FA is associated with a more severe AD phenotype. 6 studies indicated that AD of earlier onset or increased persistence is particularly associated with FA. Finally, one study found that AD preceded the development of FA.

Conclusions

This systematic review confirms a strong and dose-dependent association between AD, food sensitization and FA. AD of increased severity and chronicity is particularly associated with FA. There is also evidence that AD precedes the development of food sensitization and allergy, in keeping with a causal relationship.

Keywords

atopic dermatitis, eczema, food allergy, food sensitization

Key Messages

- There is a strong association between AD, food sensitization and FA
- AD of increased severity and chronicity is particularly associated with FA
- AD arises before the development of food sensitization in most cases, supporting a causal relationship

Capsule Summary

This systematic review suggests a strong association between AD and FA**.** AD of increased severity and chronicity appears to be particularly associated with FA. Finally, AD may arise before the development of food sensitization, supporting a causal relationship.

Abbreviations

AD – atopic dermatitis
aOR – adjusted odds ratio
DBPCFC – double blind placebo controlled food challenge

FA – food allergy
FLG – filaggrin gene
fx1 – mixed sensitization to peanut, hazelnut, brazil nut, almond & coconut
fx5 – mixed sensitization to milk, egg, wheat, soy, cod & peanut
kU/L – kilounits per litre
OFC – open food challenge
OR – odds ratio
PPV – positive predictive value
SD – standard deviation
SCORAD – SCORing Atopic Dermatitis
sIgE – specific IgE
SPT – skin prick test

Introduction

Atopic dermatitis (AD, syn. 'atopic eczema', 'childhood eczema') is the commonest chronic inflammatory disorder of the skin, affecting over 20% of children in industrialized countries (1-3) and up to 3% of adults (4). Although up to two thirds of patients with AD do not show sensitization to environmental allergens, including foods (5), AD is often associated with other atopic diseases such as IgE-mediated food allergy (FA) (6), and around one third of all children with early onset AD progress through the so-called 'atopic march' (7). It has been suggested that food allergen recognition via antigen-presenting cells in eczematous skin may act as an important mediator of food sensitization and FA (8,9). To further assess a potential causal pathway between AD and IgE-mediated FA, this systematic review critically appraises the current body of evidence according to the Bradford Hill (10) principles of inferring causality from clinical studies. These principles take into account i) the strength of the association between AD and FA in selected and unselected populations, ii) whether a dose-response effect is demonstrated, with more severe AD showing a greater association with FA, and equally whether FA may predict age of onset or chronicity of AD, as well as iii) the temporal sequence of events - in other words, whether AD or FA arises first amongst infants.

Methods

This systematic review was registered on PROSPERO (11), and PRISMA guidance (12) was followed throughout. Medline and Embase were searched from inception to the end of November 2014, with no language limits imposed. Search terms included the Cochrane Skin Group strategy for AD, combined with terms describing FA, food hypersensitivity and food sensitization overall, as well as to specific foods (including milk, egg, peanut, tree nuts, wheat, sesame and seafood). The full search strategy is available in the Online Repository. This online search was supplemented by an extensive hand search of the literature, and communication with individual authors where necessary. The Medline search identified 339 articles, the Embase search 1,704 articles, and the hand search a further 34 articles (Figure 1 Online Repository). Two authors (TT and MM) independently screened all abstracts for suitability, resulting in 164 papers that were read in full. Discrepancies in the assessment were resolved through discussion with CF. Paper selection for further analysis was based upon the following inclusion criteria: 1. The majority of subjects comprising patients <18 years of age 2. At least a proportion of subjects having AD and an overlapping proportion of subjects having food sensitization and/or FA, evidenced by at least one of skin prick testing (SPT, standard cutoff 3mm wheal), serum specific IgE (sIgE, standard cutoff 0.35 kU/L), open food challenge (OFC), or double-blind placebo-controlled food challenge (DBPCFC). Exclusion criteria were: 1. AD diagnostic criteria including SPT/sIgE sensitization to common allergens, as well as typical skin findings 2. FA evidenced only by parent or patient-reported symptoms 3. Data referring to mixed food and aeroallergen sensitization, with no separate values provided for food

allergens. Furthermore, we excluded management guidance documents, reviews, intervention trials and studies in animal models.

Data was extracted from 66 selected papers using a predefined pro forma. Formal meta-analysis was considered neither feasible nor appropriate due to marked heterogeneity in study design, participants, and diagnostic criteria for both FA and AD. We therefore assigned a quality score to each paper (maximum score three points) based on: AD diagnostic criteria (1: clear validated criteria or physician diagnosis, 0: unclear diagnostic criteria or process); study size (1: $\geq$500 subjects, 0: <500 subjects); and a modified Newcastle-Ottawa score (13) (1: $\geq$4 out of 5 points, 0: <4 points). Papers were then ranked by quality score. Those with the same quality score were further ranked by number of participants.

Results

The strength of association between AD and FA

Population-based studies (Table I Online Repository)

Eleven population-based studies scored three points for quality, and their results closely reflect the age groups of the children they investigated (Figure 2).

The largest study (14) utilized a case-control design nested within the consecutively recruited BAMSE birth cohort (n=2256), reporting that 27% of AD cases at 2 years were SPT positive to food (egg 21%, peanut 15%, milk 8%, cod 2%). The second-largest study (15) investigated SPT sensitization amongst much older children aged 12-16 years, who were participating in the Danish Adolescent Odense Cohort (TOACS, n=1501). Whilst a strongly positive association was demonstrated between current AD and peanut sensitization (16.2% of AD patients vs. 0.5% of controls, $p<0.05$) during adolescence, no significant differences persisted for milk and egg sensitization. Investigations amongst younger children reflected the higher prevalence of milk and egg allergies within that age group (Figure 2).

Two high quality population-based papers were based on the Isle of Wight allergy birth cohort (n=1456), with Arshad et al. (16) reporting that at 4 years of age, the highest independent risk factor for AD was SPT sensitization to peanut (OR 4.65, 95% CI 1.02-21.34). There was also a positive association with egg sensitization; this just missed statistical significance (OR 6.08, 95% CI 0.88-42.01), likely due to a lack of power whilst a proportion of children were outgrowing their egg allergy.

Meanwhile, Peroni et al.'s cross-sectional study (17) of 1,402 UK children aged 3-5 years found that egg sensitization on SPT was strongly associated with AD (OR 9.53, 95% CI 2.40-37.82), whilst milk sensitivity was not (OR 1.26, 95% CI 0.27-6.00).

The Danish Allergy Research Cohort (DARC) (18) monitored babies from the age of 3 months to 6 years, undertaking food challenges in children with food-specific SPT ≥3mm/sIgE ≥class 1, and also in children with parent-reported adverse reactions to food. The investigators reported that 18/122 (15%) of children with AD demonstrated symptoms on food challenge, and that 52% of the remainder were food sensitized. More recently, Flohr et al. analyzed those undergoing SPT at 3 months within the EAT Study UK birth cohort (n=619) (9), reporting that children with AD were significantly more likely than healthy controls to be sensitized to at least one of six foods (milk, egg, sesame, peanut, wheat or cod), with an adjusted OR (aOR) of 8.53 (95% CI 3.51-20.65, p<0.001). This association was independent of filaggrin (FLG) loss-of-function mutation inheritance. Equally, there was a positive association between AD and sensitization to individual foods, including egg (aOR 9.48, 95% CI 3.77-23.83, p<0.001), milk (aOR 9.11, 95% CI 2.27-36.59, p=0.002), and peanut (aOR 4.09, 95% CI 1.00-13.16.76, p=0.05).

In Figures 3-5, ORs for each of the major food allergens are presented in order of ascending age of participants at cross-sectional analysis. Pooling of results between allergens and beyond the first six years of childhood was not considered appropriate in view of the contrasting natural history of individual allergens, as well as the changes in association seen for each individual food allergen as a child becomes older.

High-risk cohort studies (Table II Online Repository)

Eight papers were based on high-risk cohorts, recruiting according to parental atopy. Burr et al.'s UK study (n=497) (19) reported a significant association between AD arising before the first birthday and positive SPT to egg at 6 months (OR 5.57, 95% CI 2.70-11.5); this was even stronger at 1 year (OR 7.57, 95% CI 3.57-16.05) (20). Three papers utilized the Melbourne Atopy Cohort Study cohort (MACS, n=552), including Lowe et al.'s report (21) that food SPT sensitization at 6 months was associated with an increased risk of developing AD (HR 1.63, 95% CI 1.13–2.35) up to 7 years of age. This was in line with other MACS data from Hill et al. (22), who found that more AD patients had positive SPT to milk, egg, or peanut at 6 months (22% vs. 5%, $p<0.001$) and at 12 months (36% vs. 11%, $p<0.001$) than those without AD (Figure 6 Online Repository). Four years later, the same group reported that 36% of infants with AD had positive food SPT, compared with 12% of infants without AD ($p<0.001$) (23). Recently, Brough et al. (24) investigated whether AD and disease severity modified the strength of the association between environmental peanut protein exposure and the risk of peanut sensitization and peanut allergy. 512 American infants (<15 months old) with egg/milk SPT sensitization plus either parent-reported egg/milk allergy or parent-reported AD, were recruited from the Consortium of Food Allergy Research study (CoFAR, n=512). Environmental peanut exposure was quantified from dust on the living room floor. An association between environmental peanut exposure and the likelihood of peanut sensitization or allergy was only seen in participants with a history of AD. Indeed, history of AD and increased environmental peanut exposure in participants was found to increase the risk of both peanut sensitization (OR 1.97, 95% CI 1.26-3.09, $p<0.01$) and peanut allergy (OR 2.34, 95% CI 1.31-4.18) per $\log_2$ unit environmental peanut exposure

147 increase. The effect for peanut sensitization was further augmented with a history of
148 severe AD (OR 2.41, 95% CI 1.30-4.47, p<0.01), although this was not observed for
149 peanut allergy.

150 *Studies investigating FA and food sensitization amongst children with established AD*
151 *(Table III Online Repository)*

152 Thirty-four studies selected groups of patients with established AD rather than
153 taking a population-based approach, and therefore are likely to have inflated
154 prevalence estimates of atopy. Two investigations (25,26) comprising >2,000
155 subjects aged 11.8-25.8 months from 12 countries were derived from the Early
156 Prevention of Asthma in the Atopic Child (EPAAC) study cohort. Hill et al. (25)
157 reported that 64% of those with AD commencing before 3 months of age were
158 sensitized to egg and/or milk and/or peanut, based on sIgE >95% PPV. The following
159 year, De Benedictis et al. (26) compared the allergic sensitization patterns associated
160 with AD between the 12 countries, reporting that positive sIgE to egg predominated
161 in each country (53% in the UK), whereas milk sensitization was highest in Italy (48%)
162 and peanut sensitization was highest in Australia (45%).
163 Of note, 16 studies in patients with established AD reported oral food challenge data
164 as well as sensitization data. However, many failed to apply systematic criteria in
165 determining who was eligible for food challenges, limiting their insight. One of the
166 largest studies (27) in this category was performed in Finland, and reported a
167 prevalence of 54% for milk allergy amongst 183 children with AD up to 3 years old.
168 Burks et al. (28) proposed a standard food SPT panel for AD patients recruited from a
169 paediatric allergy clinic in the USA. This group reported that out of 165 participants

aged between 4 months and 22 years, 60% had at least one positive SPT response. The investigators then performed 266 DBPCFCs, and 39% of patients reacted to seven foods (milk, egg, peanut, soy, wheat, cod/catfish, cashew), accounting for 89% of the positive challenges.

Finally, Gray et al. (29) investigated 100 black or mixed race children who attended an urban Cape Town clinic with moderate to severe AD. The authors reported high rates of food sensitization (66%) and challenge-confirmed FA (44%), with egg and peanut being the most common allergens.

Studies investigating AD amongst children with established FA (Table IV Online Repository)

Four investigations selected patients with established FA, then measured the prevalence of AD. Two of these were particularly enlightening, and both focused on children with peanut allergy.

Fox et al. (30) compared 133 patients with peanut allergy, 160 high-risk controls with allergy to egg but not peanut, and 150 low-risk controls with no known allergy. Cases and high-risk controls were recruited from food allergy clinic, whereas low-risk controls were recruited from children attending general paediatric clinic with a non-allergic complaint. A parent-reported history of AD in the first year of life was highly prevalent amongst both cases (92%) and high-risk controls (88%), but significantly less so amongst low-risk controls (42%; $p<0.001$).

More recently, Brown et al. (8) investigated the role of FLG mutations as a risk factor for peanut allergy. The study design comprised 71 patients aged up to 18 years from the UK, Ireland and the Netherlands with challenge-proven peanut allergy, and 1000 non-peanut sensitized population controls. Covariate analysis using both AD and FLG

as predictors in the logistic regression model demonstrated a strong association between AD and peanut allergy in challenge-positive patients, with an OR of 7.4 (95% CI 4.1-13.7). The association between FLG mutation inheritance and peanut allergy remained significant, even after adjustment for a history of AD in early life (OR 3.8, 95% CI 1.7-8.3, p<0.001).

The association between AD severity and FA

22 papers addressed the question of whether FA impacts on AD severity. Flohr et al.'s UK population-based study (9) amongst 619 exclusively breastfed 3 month old infants was the highest quality paper in this area, showing that the association between AD and sensitization to milk, raw egg, cod, sesame, and peanut was significantly stronger in AD with SCORAD >20 (aOR 25.60, 95% CI 9.03-72.57, p<0.001) than AD with SCORAD <20 (aOR 3.91, 95% CI 1.70-9.00, p=0.001). Four papers were awarded 2 quality points; for instance, Lack et al.'s case control study (31) found a trend towards an association between the severity of a flexural rash (as determined by topical steroid usage) in the first 6 months, and a history of peanut allergy and a positive peanut challenge (p<0.001 for both associations). When the same research group performed screening assessments amongst 834 infants, in order to enroll those with egg allergy and/or severe eczema into the Learning Early About Peanut (LEAP) trial, a strong association between food sensitization and AD severity was evident (32). When the infants were split into three SCORAD severity groups, increasing AD severity was associated with a higher likelihood of sensitization to peanut (p_{trend}<0.001), raw egg (p_{trend}<0.001), pasteurized egg (p_{trend}<0.001), milk (p_{trend}=0.001) and 'any food' (p_{trend}<0.001).

In a group of Australian infants whose AD did not respond to topical steroid therapy, the equivalent rates of SPT food sensitization were 83% at 6 months and 65% at 12 months. The relative risk estimates for SPT food sensitization also rose with increasing AD severity as defined by topical steroid use in the first year of life (23). In a later study by the same group, based on the EPAAC cohort of 2084 infants with AD, the authors used regression analysis to show that children with sIgE to milk, egg or peanut >95% PPV were more likely to have severe eczema of early onset up to one year of age ($p<0.001$) (25). Lastly, data from the South African paediatric cohort (n=100) (29) showed that 15/50 (30%) children with moderate AD were food allergic, compared to 25/50 (50%) in those with severe AD ($p=0.04$).

Is FA associated with earlier onset of AD and greater chronicity?

Six papers examined whether FA is associated with AD of early onset or increased chronicity, including Hill et al.'s 2008 paper as mentioned above (25). The best quality study (33) assessed the relationship between FLG status, AD, food sensitization and FA (inferred from symptom-based diagnosis) in patients up to 18 years of age on the Isle of Wight (n=1456). AD at 1 and 2 years of age was associated with both FA (OR 6.04, 95% CI 1.25-29.9, $p<0.001$) and food sensitization (OR 20.1, 95% CI 4.40-54.50, $p<0.001$) at 4 years, and sensitization at 18 years (OR 18.2, 95% CI 5.47-65.3, $p<0.001$). In addition, AD at 4 years was linked to food sensitization at 10 years (OR 6.9, 95% CI 3.65-13.04, $p<0.001$) and 18 years (OR 3.82, 95% CI 2.44-5.99, $p<0.001$), suggesting longer-term FA sequelae.

Supportive papers in this area include Ricci et al.'s retrospective analysis (34) of 252 infants with AD, in which egg sensitization was associated with more prolonged AD

(egg sensitized: mean 11.1 ±6.9 years vs. non egg-sensitized: 8.3 ±6.9 years, p<0.02). As described above, Fox et al.'s case control study (30) examining peanut allergy showed that parent-reported AD in the first year of life was significantly less prevalent amongst low-risk controls recruited from general as opposed to food allergy clinics; furthermore, AD in low-risk controls was significantly later in onset and also less severe (p<0.001).

The Belgian ETAC cohort (n=397) (35) showed that egg and milk sIgE sensitization at enrolment was associated with persisting AD (SCORAD>7) at 18 months follow-up (p=0.006). Burks et al. (28) showed that children with both positive SPTs and DBPCFCs had a significantly lower age of AD onset than patients without (2 months vs. 7 months, p=0.003). Finally, Gray et al.'s South African study (29) reported that onset of AD before 6 months was a significant risk factor for FA (p=0.002).

Is there a temporal relationship between the development of AD and FA?

Two papers (18,33) repeatedly examined for AD and food sensitization throughout childhood, and one of these (18) initiated this early enough to discriminate between the emergence of AD and FA. 562 participants were recruited at birth in the Danish general population, and were followed up at 3, 6, 9, 12, 18, 36 and 72 months of age. All follow-ups except the 9-month visit included an interview, clinical examination, and SPT/sIgE measurements. Where food related symptoms were declared, OFCs were undertaken. By three months of age, 2% of the cohort was found to have signs of AD on examination, and yet none of the participants demonstrated symptoms on OFC at that age (Figure 7).

Unfortunately, the Isle of Wight cohort (33) only investigated food sensitization amongst children whose families reported adverse food reactions before 4 years of age, preventing a population-based comparison.

Of note, Soderstrom et al.'s high-risk birth cohort study (36) was unique in that it focused solely on low levels of sIgE, in an attempt to capture allergic sensitization at the earliest possible stage. All IgE levels exceeding 0.7 kUA/l were therefore omitted in the risk analysis. AD at 2 years of age was associated with increased low-level sensitization to egg and/or milk at 6 months (OR 3.07, 95% CI 1.44-6.55), 12 months (OR 3.33, 95% CI 1.60-6.96) and 24 months (OR 1.74, 95% CI 1.01-3.01). However, 35% of 6 month old infants already had AD and were not excluded from the analysis, meaning that low-grade sensitization may relate more to the persistence of AD that is already established, as opposed to newly arising AD. Furthermore, no follow-up data on clinical FA status was reported.

Four papers investigated cord blood sIgE, attempting to assess the possibility that food sensitization precedes the development of AD. The ALSPAC cohort study (31) followed children until they developed challenge-proven peanut allergy, but found no relationship with cord blood peanut sIgE levels. Likewise in the DARC cohort (37), food sIgE proved no better than total cord IgE in predicting AD within the first 18 months of life. Overall, the key message from these studies is that cord blood sIgE is rarely detectable and not a significant risk factor, in line with the hypothesis that AD precedes and is likely to drive food sensitization.

Discussion

This review interrogates whether AD causes FA according to the established Bradford Hill principles (10). We found a significant association between FA, food sensitization and AD in both selected and unselected populations. FA is associated with AD of increased severity and chronicity. In addition, there is tentative evidence from one study suggesting that AD may arise before FA.

Our systematic review protocol was registered online in advance, in keeping with PRISMA guidelines (12). Cognizant of the potential for bias in literature searching, we supplemented the online search strategy with an extensive hand search to maximize capture of relevant publications. However, this would not overcome inherent limitations such as publication bias. 66 publications fulfilled our selection criteria, of which 12 scored 3 out of 3 in our *a priori* independent quality grading. The 66 selected papers represent 3% of the total number of articles identified via our online search and hand search. Amongst these, substantial methodological differences and study heterogeneity (different age groups, sIgE/SPT cutoffs, and food challenge protocols) precluded formal meta-analysis. Only 49/66 (74%) studies stated the use of doctor diagnosis and/or validated diagnostic criteria for AD, and only 26/66 (39%) studies used food challenges to determine FA status. Furthermore, the rationale for investigating certain subgroups of participants was often unclear, with numerous studies employing food challenges only in selected patients. Where food sensitization was investigated, only four papers used values equating to the 95% PPV cutoff as part of their methodology for diagnosing food allergy (see summary of study limitations, Table V Online Repository).

It is a challenge for any study to capture the emergence of both AD and FA, partly

because AD characteristically waxes and wanes. In addition, clinical FA, in particular to egg and peanut, often arises without the child having ever specifically ingested the food in question. Therefore, the only way of investigating the emergence of FA is to prospectively screen for food sensitization at regular intervals, and perform OFCs throughout infancy. Given the strong association found between early onset, and also moderate-to-severe AD and food sensitization, as well as the low content of food allergens in breast milk and lack of sIgE in cord blood, it is likely that food sensitization occurs across the inflamed skin barrier in eczematous skin, potentially leading to the development of clinical FA. Brough et al. have recently shown that food protein content in dust samples collected from the infant's environment, such as the living room floor, predisposes towards early food sensitization, especially in the presence of eczematous skin inflammation (24). Indeed, carrying a FLG mutation additionally raised this risk, further supporting the evidence that a disrupted skin barrier predisposes towards sensitization. However, detailed work from our own birth cohort demonstrated that it is the presence of AD and its severity, rather than FLG mutation carriage per se, that relates to food sensitization risk in early life (9). When investigating the role of food allergen ingestion as a prevention strategy, the interplay between environmental versus oral food allergen exposure alongside AD status and management becomes of crucial importance. Fallon et al. used the FLG-deficient flaky tail mouse model to demonstrate that the application of ovalbumin to intact yet FLG-deficient mouse skin was sufficient to induce cutaneous inflammation and increase ovalbumin sIgE (38). Bartnikas et al. (39) contrasted the physiological effect of epicutaneous sensitization with that of oral tolerance induction. BALB/c mice were epicutaneously sensitized with repeated applications of ovalbumin to

tape-stripped skin over 7 weeks, or orally immunized with ovalbumin and cholera toxin over 8 weeks. Both the epicutaneous and orally exposed groups of mice demonstrated specific IgE antibody responses, and yet only those without oral immunization developed signs in keeping with anaphylaxis on oral challenge. Thus the determination of food allergy or tolerance depends not only upon a period of cutaneous sensitization, but also the timing and likely dose of GI tract allergen exposure.

The design of methodologically sound studies examining the dynamic and interrelated nature of AD and FA will facilitate the generation of future therapeutic and preventative interventions (Table V Online Repository). Recent data in humans has shown that carrying a FLG mutation disrupts the infant skin barrier by 3 months of age, even before AD emerges (40). Two small intervention studies (41,42) suggest that the regular application of emollients from birth reduces the risk of AD development and may thus impact upon FA, although the study investigating egg sensitization did not find a significant reduction (41).

Finally, it is important to remember that FA can develop in patients without a prior diagnosis of AD. Lack et al.'s seminal paper showed that 5/8824 (0.06%) children without a history of a rash over joints or skin creases were peanut-allergic on DBPCFC (31). However, even in the absence of AD, skin barrier alterations of a different nature may play a role in the development of FA. For instance, Flohr et al.'s previously discussed study also found an independent positive association between skin barrier impairment (raised TEWL) and food sensitization, even in the absence of clinically visible skin inflammation (9). Other environmental factors, such as water hardness, the use of soaps and detergents and the frequency of washing, could

361 further contribute to skin barrier permeability and thus food sensitization (1). These
362 are all areas that warrant further research.
363 The evidence presented in this systematic review provides further support for skin
364 barrier repair, early proactive AD treatment, and reduction of environmental food
365 allergen exposure in the prevention of food sensitization and allergy. Large
366 population-based intervention studies, using validated diagnostic criteria and gold
367 standard food challenges, are required to test this hypothesis further.
368
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374
375

Figure/Table legends

Figure 1. Flowchart of study selection process

Table I. Data extraction for papers based on whole populations

Table II. Data extraction for papers using high-risk birth cohorts

Table III. Data extraction for papers using selected populations of AD patients

Table IV. Data extraction for papers using selected populations of FA patients

Figure 2. Milk/egg/peanut SPT sensitization amongst AD and control subgroups in population-based cohorts

Figure 3: ORs of milk sensitization in AD, ascending age order

Figure 4: ORs of egg sensitization in AD, ascending age order

Figure 5: ORs of peanut sensitization in AD, ascending age order

Figure 6. Food sensitization amongst AD and control subgroups in the MACS high-risk cohort (22)

Figure 7. Temporal sequence of AD and FA onset in the Danish DARC cohort (18)

Table V. Methodological issues complicating interpretation of studies investigating AD and FA

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