Atopic dermatitis and skin disease

Does atopic dermatitis cause food allergy? A systematic review

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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 the association between AD and FA, the effect of FA on AD severity, chronicity, and 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: Sixty-six studies were identified. Eighteen were population-based, 8 used high-risk cohorts, and the rest comprised patients with either established AD or FA. In population-based studies, the likelihood of food sensitization was up to 6 times higher in patients with AD versus healthy control subjects at 3 months of age (odds ratio, 6.18; 95% CI, 2.94-12.98; \( P < .001 \)). Other population-based studies reported that up to 53% of subjects with AD were food sensitized, and up to 15% demonstrated signs of FA on challenge. Meanwhile, studies including only patients with established AD have reported food sensitization prevalences up to 66%, with challenge-proven FA prevalences reaching up to 81%. Sixteen studies suggested that FA is associated with a more severe AD phenotype. Six 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. (J Allergy Clin Immunol 2016;137:1071-8.)

Key words: Atopic dermatitis, eczema, food allergy, food sensitization

Atopic dermatitis (AD; synonyms: atopic eczema and eczema) is the most common chronic inflammatory disorder of the skin, affecting more than 20% of children in industrialized countries and up to 3% of adults. Although up to two thirds of patients with AD do not show sensitization to environmental allergens or foods, AD is often associated with other allergic diseases, such as IgE-mediated food allergy (FA), and around one third of all children with early-onset AD progress through the so-called atopic march. It has been suggested that food allergen recognition via antigen-presenting cells in eczematous skin might act as an important mediator of food sensitization and FA.

This systematic review critically appraises the current body of evidence according to the Bradford Hill principles of inferring causality from clinical studies, to further assess a potential causal pathway between AD and IgE-mediated FA. These principles take into account (1) the strength of the association between AD and FA in selected and unselected populations; (2) whether a dose-response effect is demonstrated, with more severe AD showing a greater association with FA, and equally whether FA can predict age of onset or chronicity of AD; and (3) the temporal sequence of events—in other words, whether AD or FA arises first among infants.

METHODS

This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance 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 both overall and to specific foods (including milk, egg, peanut, tree nuts, wheat, sesame, and seafood). The full search strategy is available in the Methods section in this article's Online Repository at www.jacionline.org. 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 identified 1704 articles, and the
hand search identified a further 34 articles (see Fig E1 in this article’s Online Repository at www.jacionline.org).

Two authors (T.T. and M.M.) independently screened all abstracts for suitability, resulting in 164 articles that were read in full. Discrepancies in the assessment were resolved through discussion with a third author (CF). Article selection for further analysis was based on the following inclusion criteria: (1) the majority of subjects being less than 18 years old and (2) at least a proportion of subjects having AD and an overlapping proportion of subjects having food sensitization and/or FA, as evidenced by at least one of skin prick testing (SPT; standard cutoff, 3-mm 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 as follows: (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; and (3) data referring to mixed food allergens, as well as the changes in association seen for each food allergen as a child becomes older.

Data were extracted from 66 selected articles using a predefined pro forma. Formal meta-analysis was considered neither feasible nor appropriate because of marked heterogeneity in study design, participants, and diagnostic criteria for both FA and AD. Therefore we assigned a quality score to each article (maximum score, 3 points) based on AD diagnostic criteria (1 = clear validated criteria or physician’s diagnosis, 0 = unclear diagnostic criteria or process), study size (1 = ≥500 subjects, 0 = <500 subjects), and a modified Newcastle-Ottawa score13 (1 = ≤4 of 5 points, 0 = <4 points). Articles were then ranked by quality score. Those with the same quality score were further ranked by number of participants.

RESULTS

Strength of association between AD and FA

Population-based studies (see Table E1 in this article’s Online Repository at www.jacionline.org).

Eleven population-based studies scored 3 points for quality, and their results closely reflect the age groups of the children they investigated (Fig 1).

The largest study14 used a case-control design nested within the consecutively recruited Barn (Children’s) Allergy Milieu Stockholm Epidemiology (BAMSE) birth cohort (n = 2256), reporting that 27% of patients with AD at 2 years had positive SPT responses to food (egg, 21%; peanut, 15%; milk, 8%; and cod, 2%). However, the investigators did not compare this with sensitization amongst children without AD. The second-largest study15 investigated SPT sensitization among 1501 older children aged 12 to 16 years who were participating in the Danish Adolescent Odense Cohort (TOACS). Although a strongly positive association was demonstrated between current AD and peanut sensitization (16.2% of patients with AD vs 0.5% of control subjects, P < .05) during adolescence, no significant differences persisted for milk and egg sensitization.

Investigations among younger children reflected the higher prevalence of milk and egg allergies within that age group (Fig 1).

Two high-quality population-based articles were based on the Isle of Wight atopy birth cohort (n = 1456), with Arshad et al16 reporting that at 4 years of age, the highest independent risk factor for AD was SPT sensitization to peanut (odds ratio [OR], 4.65; 95% CI, 1.02-21.34). There was also a positive association with egg sensitization that just missed statistical significance (OR, 6.08; 95% CI, 0.88-42.01), likely because of a lack of power while a proportion of children were outgrowing their egg allergy.

Meanwhile, the United Kingdom (UK) cross-sectional study by Peroni et al17 of 1402 children aged 3 to 5 years found that egg sensitization on SPTs was strongly associated with AD (OR, 9.53; 95% CI, 2.40-37.82), whereas milk sensitivity was not (OR, 1.26; 95% CI, 0.27-6.00).

The Danish Allergy Research Cohort18 (DARC) monitored children from the age of 3 months to 6 years, undertaking food challenges in children with food-specific SPT responses of 3 mm or greater/sIgE levels of class 1 or greater, and also in children with parent-reported adverse reactions to food. The investigators reported that 18 (15%) of 122 children with AD demonstrated symptoms on food challenge, and that 52% of the remainder were food sensitized. More recently, Flohr et al19 analyzed those undergoing SPTs at 3 months within the Enquiring About Tolerance (EAT) study UK birth cohort (n = 619), reporting that children with AD were significantly more likely than healthy control subjects to be sensitized to at least 1 of 6 foods (milk, egg, sesame, peanut, wheat, or cod), with an adjusted odds ratio (aOR) of 8.53 (95% CI, 3.51-20.65; P < .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 < .001), milk (aOR, 9.11; 95% CI, 2.27-36.59; P = .002), and peanut (aOR, 4.09; 95% CI, 1.00-13.16; P = .05).

In Figs 2 to 4, 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 6 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 food allergen as a child becomes older.

High-risk cohort studies (see Table E2 in this article’s Online Repository at www.jacionline.org).

Eight articles were based on high-risk cohorts that recruited according to parental atopy. The UK study (n = 497) by Burr et al20 reported a significant association between AD arising before the patient’s first birthday and a positive SPT response 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).

Three articles used the Melbourne Atopy Cohort Study (MACS) cohort (n = 552), including the report by Lowe et al21 that food SPT-determined sensitization at 6 months was associated with an increased risk of AD (hazard ratio, 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 patients with AD had positive SPT responses to milk, egg, or peanut at 6 months (22% vs 5%, P < .001) and at 12 months (36% vs 11%,
than those without AD (see Fig E2 in this article’s Online Repository at www.jacionline.org). Four years later, the same group reported that 36% of infants with AD had a positive food-related SPT response compared with 12% of infants without AD (P < .001).23

Recently, Brough et al24 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. Five hundred twelve American infants (<15 months old) with egg/milk SPT-determined sensitization plus either parent-reported egg/milk allergy or parent-reported AD were recruited from the Consortium of Food Allergy Research (CoFAR) study (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, a 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 < .01) and peanut allergy (OR, 2.34; 95% CI, 1.31-4.18) per log2 unit environmental peanut exposure increase. The effect for peanut sensitization was further augmented with a history of severe AD (OR, 2.41; 95% CI, 1.30-4.47; P < .01), although this was not observed for peanut allergy.

Studies investigating FA and food sensitization among children with established AD (see Table E3 in this article’s Online Repository at www.jacionline.org). Thirty-four studies selected groups of patients with established AD rather than taking a population-based approach, and therefore are likely to have inflated prevalence estimates of atopy. Two investigations25,26 comprising more than 2000 subjects up to 3 years old from Finland were performed. Hill et al25 reported that 64% of those with AD commencing before 3 months of age were sensitized to egg and/or milk and/or peanut, based on sIgE values greater than 95% of positive predictive value (PPV). The following year, de Benedictis et al26 compared the allergic sensitization patterns associated with AD between the 12 countries, reporting that positive sIgE levels to egg predominated in each country (53% in the UK), whereas milk sensitization was highest in Italy (48%) and peanut sensitization was highest in Australia (45%).

Of note, 16 studies in patients with established AD reported both oral food challenge and sensitization data. However, many failed to apply systematic criteria in determining who was eligible for food challenges, limiting their insight. One of the largest studies27 in this category was performed in Finland and reported a prevalence of 54% for milk allergy among 183 children with AD up to 3 years old.

Burks et al28 proposed a standard food SPT panel for patients with AD recruited from a pediatric allergy clinic in the United States. This group reported that of 165 participants aged between 4 months and 22 years, 60% had at least 1 positive SPT response. The investigators then performed 266 DBPCFCs, and 39% of patients reacted to 7 foods (milk, egg, peanut, soy, wheat, cod/catfish, and cashew), accounting for 89% of the positive challenge results.

Finally, Gray et al29 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 among children with established FA (see Table E4 in this article’s Online Repository at www.jacionline.org). Four investigations selected patients with established FA and then measured the

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![Figure 1](image-url)
prevalence of AD. Two of these focused on children with peanut allergy and were particularly enlightening.

Fox et al\(^3\) compared 133 patients with peanut allergy, 160 high-risk control subjects with allergy to egg but not peanut, and 150 low-risk control subjects with no known allergy. Cases and high-risk control subjects were recruited from an FA clinic, whereas low-risk control subjects were recruited from children attending a general pediatric clinic with a nonallergic complaint. A parent-reported history of AD in the first year of life was highly prevalent among both peanut allergic patients (92%) and high-risk control subjects (88%) but significantly less so among low-risk control subjects (42%, \(P < .001\)).

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 control subjects. Covariate analysis using both AD and\(FLG\) as predictors in the logistic regression model demonstrated a strong association between AD and peanut allergy in patients with positive challenge results (OR, 7.4; 95% CI, 4.1-13.7). The association between\(FLG\) mutation inheritance and peanut allergy remained significant, even after adjusting for a history of AD in early life (OR, 3.8; 95% CI, 1.7-8.3; \(P < .001\)).

Is FA associated with AD of increased severity?

Twenty-two articles addressed the question of whether FA affects AD severity. A UK population-based study\(^9\) among 619 exclusively breast-fed 3-month-old infants was the highest quality article in this area, showing that the association between AD and sensitization to milk, raw egg, cod, sesame, and peanut was significantly stronger in AD patients with SCORAD scores of greater than 20 (aOR, 25.60; 95% CI, 9.03-72.57; \(P < .001\)) than in patients with SCORAD scores of less than 20 (aOR, 3.91; 95% CI, 1.70-9.00; \(P = .001\)).

Four articles were awarded 2 quality points; for instance, the case-control study by Lack et al\(^3\) found a trend toward an association between the severity of a flexural rash (as determined by topical steroid use) in the first 6 months, and a history of peanut allergy and a positive peanut challenge result (\(P < .001\) for both associations). When the same research group performed screening assessments in 834 infants to enroll those with egg allergy and/or severe AD into the Learning Early About Peanut (LEAP) trial, a strong association between food sensitization and AD severity was evident.\(^2\) When the infants were split into 3 SCORAD severity groups, increasing AD severity was associated with a higher likelihood of sensitization to peanut (\(P_{\text{trend}} < .001\)), raw egg (\(P_{\text{trend}} < .001\)), pasteurized egg (\(P_{\text{trend}} < .001\)), milk (\(P_{\text{trend}} = .001\)), and “any food” (\(P_{\text{trend}} < .001\)).

In a group of Australian infants whose AD did not respond to topical steroid therapy, the equivalent rates of SPT-determined food sensitization were 83% at 6 months and 65% at 12 months. The relative risk estimates for SPT-determined food sensitization also rose with increasing AD severity as defined by topical steroid use in the first year of life.\(^2\)

In a later study by the same group, based on the Early Prevention of Asthma in the Atopic Child (EPAAC) cohort of 2084 infants with AD, the authors used regression analysis to show that children with sIgE to milk, egg, or peanut (greater than 95% PPV cutoff) were more likely to have severe AD of early onset up to 1 year of age (\(P < .001\)).\(^2\) Lastly, data from the South African pediatric cohort (n = 100)\(^2\) showed that 15 (30%) of 50 children with moderate AD had FA, compared with 25 (50%) of 50 of those with severe AD (\(P = .04\)).

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

Six articles examined whether FA is associated with AD of early onset or increased chronicity, including the 2008 EPAAC article by Hill et al,\(^2\) as mentioned above. The best quality study\(^3\) 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 = 1,456). AD at 1 and 2 years of age was associated with both FA (OR, 6.04; 95% CI, 1.25-29.9; P < .001) and food sensitization (OR, 20.1; 95% CI, 4.40-54.50; P < .001) at 4 years and sensitization at 18 years (OR, 18.2; 95% CI, 5.47-65.3; P < .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 < .001) and at 18 years (OR, 3.82; 95% CI, 2.44-5.99; P < .001), supporting the hypothesis that early childhood AD raises the risk of food sensitization as a subsequent complication.

Further support in this area comes from the retrospective analysis by Ricci et al. of 252 infants with AD, in which egg sensitization was associated with more persistent AD (egg sensitized: 11.1 ± 6.9 years mean duration vs non–egg-sensitized: 8.3 ± 6.9 years mean duration; P < .02). As described above, the case-control study by Fox et al. examining peanut allergy showed that parent-reported AD in the first year of life was significantly less prevalent among low-risk control subjects recruited from general as opposed to FA clinics; furthermore, AD in low-risk control subjects was significantly later in onset and also less severe (P < .001).

The Belgian Early Treatment of the Atopic Child (ETAC) cohort (n = 397) showed that egg and milk sIgE sensitization at enrollment was associated with persisting AD (SCORAD score > 7) at 18 months’ follow-up (P = .006). Burks et al. showed that children with both positive SPT and DBPCFC responses had a significantly lower age of AD onset than patients without positive responses (2 vs 7 months, P = .003). Finally, the South African study by Gray et al. reported that onset of AD before 6 months was a significant risk factor for FA (P = .002).

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

Two articles described repeatedly examining for AD and food sensitization throughout childhood, and the DARC cohort initiated this early enough to discriminate between the emergence of AD and FA. Five hundred sixty-two participants were recruited at birth in the Danish general population and 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 3 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 OFCs (Fig 5).18

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

Of note, the high-risk birth cohort study by Soderstrom et al. was unique in focusing solely on low sIgE levels in an attempt to capture allergic sensitization at the earliest possible stage. Therefore all IgE levels exceeding 0.7 kU/L were omitted in the risk analysis. AD at 2 years of age was associated with increased low-level sensitization to egg, milk, or both 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 might relate more to persistence of AD that is already established, as opposed to newly arising AD. Furthermore, no follow-up data on clinical FA status were reported.

Four articles investigated cord blood sIgE, attempting to assess the possibility that food sensitization precedes the development of FA. The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort followed children until they had challenge-proven peanut allergy, but found no relationship with cord blood peanut sIgE levels. Likewise, in the DARC cohort, food sIgE levels proved no better than total cord IgE levels 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 for FA, in line with the hypothesis that AD precedes and is likely to drive food sensitization.

### DISCUSSION

This review investigates whether AD causes FA, according to the established Bradford Hill principles. 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 evidence from a Danish population cohort showing that AD arises before FA, as well as data from the Isle of Wight demonstrating associations between early childhood AD and later food sensitization and allergy.

Our systematic review protocol was registered online in advance, in keeping with PRISMA guidelines. 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. Sixty-six publications fulfilled our selection criteria, of which 12 scored 3 of 3 in our a priori independent quality grading. The 66 selected articles represent 3% of the total number of articles identified through our online search and hand search. Among these, substantial methodological differences and study heterogeneity (different age groups, sIgE/SPT cutoffs, and food challenge protocols) precluded formal meta-analysis. Only 49 (74%) of 66 studies stated the use of a doctor’s diagnosis, validated diagnostic criteria for AD, or both, and only 26 (39%) of 66 studies used food challenges to determine FA status. Furthermore, the rationale for investigating certain subgroups of...
participants was often unclear, with numerous studies using food challenges only in selected patients. Where food sensitization was investigated, only 4 articles used values equating to the 95% PPV cutoff as part of their methodology for diagnosing FA (see the summary of study limitations in Table E5 in this article’s Online Repository at www.jacionline.org).

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 directly ingested the food in question. Therefore the only way to investigate 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 lack of sIgE in cord blood, it is likely that food sensitization occurs primarily across the inflamed skin barrier in eczematous skin, potentially leading to the development of clinical FA. Brough et al24 have recently shown that food protein content in dust samples collected from the infant’s environment (such as the living room floor) predisposes toward early food sensitization—especially in the presence of eczematous skin inflammation. Indeed, carrying a FLG mutation also increases this risk, further supporting the evidence that a disrupted skin barrier predisposes to 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 al38 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 levels. Bartnikas et al39 contrasted the physiologic 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 sIgE antibody responses, and yet only those without oral immunization had signs in keeping with anaphylaxis on oral challenge. Thus the determination of FA or tolerance depends not only on a period of cutaneous sensitization, but also the timing and likely dose of gastrointestinal 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 (see Table E5). Recent data in human subjects have shown that carrying an FLG mutation disrupts the infant skin barrier by 3 months of age, even before AD emerges.40 Two small intervention studies41,42 suggest that the regular application of emollients from birth reduces the risk of AD development and might thus affect FA, although a pilot 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. The seminal article by Lack et al21 showed that 5 (0.06%) of 824 children without a history of a rash over joints or skin creases had peanut allergy on DBPCFCs. However, even in the absence of AD, skin barrier alterations of a different nature might play a role in the development of FA. For instance, the previously discussed study by Flohr et al9 also found an independent positive association between skin barrier impairment (increased transepidermal water loss) and egg sensitization in children.
loss) and food sensitization, in the absence of clinically visible skin inflammation. Other environmental factors, such as water hardness, the use of soaps and detergents, and the frequency of washing, could further contribute to skin barrier permeability and thus food sensitization.1 These are all areas that warrant further research.

The evidence presented in this systematic review provides further support for skin barrier repair, early proactive AD treatment, and reduction of environmental food allergen exposure in the prevention of food sensitization and allergy. Large population-based intervention studies using validated diagnostic criteria and gold standard food challenges are required to test this hypothesis further.

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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.

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11. PROSPERO International prospective register of systematic reviews. Available at: http://www.crd.york.ac.uk/PROSPERO/.

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