New insights into the phenotypes of atopic dermatitis linked with allergies and asthma in children: an overview

Running head: phenotypes of atopic dermatitis in children

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Abstract (251/300 words)

Atopic dermatitis (AD) is a complex disease with multiple causes and complex mechanistic pathways according to age of onset, severity of the illness, ethnic modifiers, response to therapy, and triggers. A group of difficult-to-manage patients characterized by early-onset AD and severe lifelong disease associated with allergic asthma and/or food allergy, has been identified. In this paper, we focus on these severe phenotypes, analyzing their links with other atopic comorbidities, and taking into account the results from recent cohort studies and meta-analyses. The main hypothesis that is currently proposed to explain the onset of allergic diseases is an epithelial barrier defect. Thus, the atopic march could correspond to an epithelial dysfunction, self-sustained by a secondary allergenic sensitization, explaining the transition from AD to allergic asthma. Furthermore, AD severity seems to be a risk factor for associated food allergy. Results from population-based, birth and patient cohorts show that early-onset and severe AD, male gender, parental history of asthma, and early and multiple sensitizations are risk factors leading to the atopic march and the development of asthma. The importance of environmental factors should be recognized in these high-risk children and prevention programs adapted accordingly. Effective targeted therapies to restore both barrier function and to control inflammation are necessary; early emollient therapy is an important approach to prevent AD in high-risk children. Clinicians should also keep in mind the specific risk of atopic comorbidities in case of filaggrin loss-of-function mutations and the rare phenotypes of orphan syndromes due to heritable mutations in skin barrier components.

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Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory disorder of the skin in children. Although not life-threatening, AD hugely alters quality of life due to pruritus that may constitute a disabling condition affecting sleep as well as daily or social activities [1, 2]. Furthermore, the financial burden of the disease should not be underestimated: for example, in the United Kingdom AD costs the healthcare system around £125 million annually[2]. Evidence from the ISAAC Study and other population-based cohorts shows that AD affects more than 20% of children in industrialized countries[3,4]. Although primarily defined by clinical criteria[5,6], it is now recognized that AD is a complex disease with multiple causes and complex mechanistic pathways according to age of onset, severity of the illness, ethnic modifiers, response to therapy, and triggers (including infections, allergens, stress, and irritants). Approximately one third of patients with AD have sensitization to allergens[4]. Most infants who present with mild AD will outgrow their skin disease later in life, and overall less than 5% of childhood AD will persist into adulthood[4]. However, a group of difficult-to-manage patients with early-onset and severe lifelong AD associated with allergic asthma and/or food allergy (FA) has been identified[7]. In this general review, we will focus on these severe phenotypes, analyzing their links with other atopic comorbidities, and taking into account the results from recent cohort studies and meta-analyses. We will first describe the criteria mainly used to define AD, then the pathophysiological pathways suspected to lead to sensitization and asthma, the particular phenotypes due to ethnic background, the epidemiological links between AD, other atopic comorbidities, and some orphan genetic diseases, and finally the last results on prevention and treatment.

Methodology

We searched the Medline database for terms included in the Cochrane Skin Group strategy for AD[8] and terms describing FA, food hypersensitivity, and food/aeroallergen sensitization, respiratory allergies, and asthma. The terms used to identify studies focusing on AD are described in Table 1.

Four authors (F.A., A.S., A.D., and J.J.) then independently screened the studies to select those published in international peer-reviewed journals. Discrepancies in the assessment were resolved through discussion among the four authors.

Particular issues due to various definitions of AD

The United Kingdom Working Party (UKWP) defined the following diagnostic criteria for clinical research: "AD is an itchy skin disease (located on bending folds in children older than 4 years, or on limb convexities, cheeks and forehead in younger children), accompanied by xerosis, and a personal or familial history of atopy"[6]. These diagnostic criteria have been validated both in hospital and community settings and have been used in many epidemiological studies worldwide. They constitute a refinement of the Hanifin and Rajka diagnostic criteria, developed in the 1980s, which defined AD as having at least three of the following criteria: pruritus, lichenification, a chronically relapsing course, personal or familial history of atopy[5].

However, some of the epidemiological studies included in this review have used other criteria to define AD or atopic eczema, and readers should be aware of these methodological differences while interpreting the findings.

Finally, a multidisciplinary team of experts addressing therapies for moderate-to-severe AD has recently reached aa high level of consensus to define AD as a chronic, relapsing, noncontagious, pruritic inflammatory skin disease that occurs more commonly in children. They go further in stating that AD is often, but not exclusively, associated with allergenic sensitization with elevated serum IgE levels and a personal or family history of atopic

background (i.e., allergic asthma, allergic rhinoconjunctivitis, and/or FA). The experts state that a diagnosis of AD should not be ruled out in individuals lacking evidence of sensitization, and that allergic or irritant contact dermatitis and other forms of eczematous dermatitis (dyshidrotic eczema, nummular dermatitis, seborrheic eczema, etc.) may occur concomitantly or independently with AD[9].

The main criteria used to define AD throughout the studies retained for this review are summarized in Table 2.

The main studies cited in this review are summarized in Tables 3 and 4.

Pathophysiology of AD and link with sensitization

The main current accepted hypothesis to explain the onset of AD is an epithelial barrier defect associated with a dysfunction of the skin's innate and adaptive immune systems, and dysbiosis. Thus, the atopic march could correspond to an epithelial dysfunction, self-sustained by a secondary allergenic sensitization, explaining the transition from AD to allergic asthma. The skin represents the interface between the body, especially lymphoid tissues, and the surrounding environment, preventing antigens from irrupting into circulating blood. Injuries induced by scratching or irritant topics could increase the absorption of allergens through the skin[10] thus facilitating sensitization and promoting skin inflammation. Skin barrier dysfunction is due to multiple abnormalities, including in particular a low level of lipids (ceramides and sphingosines) facilitating dysbiosis[11], and abnormal keratinization due to dysfunctional filaggrin. Filaggrin, a protein that surrounds the keratin filaments, and keratinocytes are essential components of the stratum corneum[12], which acts as a barrier to water loss. Corneocytes, resulting from a keratinocyte differentiation process, are anucleated cells filled with keratin filaments as well as amino acids and other small molecules (collectively referred to as natural moisturizing factor: NMF) derived from the breakdown of filaggrin.

Filaggrin gene expression is linked to skin barrier function and is associated with the risk of AD. Ziyab *et al* found that increased filaggrin expression was associated with a reduced risk of AD during the first year of life[13].

Early studies[14-16] reported filaggrin loss-of-function mutations in about 20% of European patients with AD, but other filaggrin mutations have been detected in people of Asian origin[17]. The presence of filaggrin mutations has been related to more severe phenotypes (as measured by the SCORAD index) and to allergic sensitization to house dust mites and cat dander, for example[18].

During AD, both lesional and non-lesional skin exhibit a defective permeability barrier reflected by an increase in transepidermal water loss (TEWL) that persists even between flares[19]. TEWL is associated with a reduction in hydration of the stratum corneum and is positively correlated with AD severity[20]. In a mouse model, dysfunction of the epidermal barrier, and especially the stratum corneum, has been shown to induce transcutaneous sensitization and increase production of interleukin-4 and specific IgE independently of allergens or genetic background[21]. Furthermore, Kelleher *et al* have demonstrated that TEWL at birth is linked to food sensitization and food allergy at 2 years of age, supporting the concept of transcutaneous sensitization[22].

In AD, keratinocytes also respond abnormally to environmental irritants by producing Th2 cytokines such as interleukin-13 (IL-13) and thymic stromal lymphopoietin (TSLP)[23]. This production of Th2 cells contributes to a decreased expression of filaggrin and of antimicrobial peptides promoting colonization of *Staphylococcus Aureus* (*S Aureus*)[24] which in turn promotes excessive production of TSLP[25]. TSLP may act as a trigger of bronchial hyper-reactivity; when deleted in mice, the atopic march is stemmed, suggesting that TSLP may be a link between AD and asthma[26].

Finally, there is a specific interaction between AD and microorganisms. This is reflected by the strong relationship between AD severity and the toxins secreted by *S Aureus*. In a mouse model, staphylococcal enterotoxin B has been shown to have a synergic effect with allergenic exposure in AD severity leading to increased bronchial hyper-reactivity after inhaled challenge[27]. Furthermore, abnormal cutaneous response to microorganisms in children with AD could be involved in the pathways leading to asthma and allergies[28].

Specific phenotypes due to ethnic background

It is becoming increasingly accepted that there are ethnic differences in the phenotypic expression of AD. Noda *et al*, for instance, compared genomic profiling and immunohistochemistry on lesional and non-lesional biopsy specimens from 27 patients of Asian descent and 25 of European American descent. Although disease severity was similar between the groups, prominent epidermal hyperplasia, frequent parakeratosis, higher Th17 activation, and a strong Th2 component were characteristic of lesional epidermis in the Asian patients[29]. These histological and immunological differences are reflected in phenotypic differences in clinical practice: patients of Asian descent have more well-demarcated, erythematous, plaque-like skin lesions; patients of European descent have ill-defined, less elevated erythematous skin lesions; and patients of African descent have more lichenified skin lesions[30]. Furthermore, the prevalence of atopic diseases varies according to ethnic background. Severe AD has a higher prevalence in African Americans than in European Americans[31,32]. Whether this disparity stems from true genetic or ethnic-specific environmental risk factors or both, is unknown. Thus far, most genetic studies on atopic diseases have used populations of European descent, limiting their generalizability. It has been well demonstrated that filaggrin mutations are population specific, and that common filaggrin mutations in patients with severe AD of European descent are absent in patients of African descent. The fact that ethnic minorities often have a lower socio-economic status and

are more often associated with poor environmental conditions, may also have a direct effect on the development of atopic disorders and this needs to be carefully adjusted for in statistical analyses[33].

Link between AD phenotypes and food sensitization and FA

AD phenotypes and risk of food sensitization

AD is often linked with IgE-mediated FA: it is thought that food allergen recognition through antigen-presenting cells in eczematous skin is an important mediator of food sensitization. A recent meta-analysis performed by Tsakok *et al* showed that food sensitization was 6 times higher at 3 months of age in children with AD compared to controls[34] in population-based studies. This risk has been shown to persist throughout infancy in high-risk cohort studies[35,36]. In the ORCA (Observatory of Risks linked with Cutaneous Atopy) Study, hen's egg, cow's milk, and peanut accounted for 95% of overall food sensitization [37]. Birth cohort studies show similar results, although the order of allergens differ slightly from one country to another and from one age range to another: mainly egg (21%) in 2-year-olds from the Barn (Children's) Allergy Milieu Stockholm Epidemiology (BAMSE) cohort[38]; mainly milk (48%) in Italy and peanut (45%) in Australia in children from the Early Prevention of Asthma in Atopic Children Study Group cohorts (mean age 17.6 months)[39]. Peanut sensitization seems to be more strongly associated with AD in older children[40], or if AD is severe[41] or associated with previous egg sensitization[42]. Egg sensitization is associated with AD in most of the studies[43,44], with ORs ranging from 4.73 to 12.76[34]. Food sensitization is particularly frequent when AD is severe[35], as demonstrated in the LEAP Study[42]. Loo *et al* have also shown in the Growing Up in Singapore Towards healthy Outcomes birth cohort (GUSTO), including 792 infants, that an onset of AD before the age of 6 months was significantly associated with food sensitization at 18 months (OR 46.51; IC95%: 3.44-628.81, $p<0.01$)[45]. These results are consistent with a previous Swedish patient cohort study[46].

AD phenotypes and risk of FA

Although food sensitization is frequent in children with early-onset AD, FA is not systematic. In the ORCA Study, where all the children had early-onset (< 12 months) moderate to severe AD, 57.5% of them had food sensitization at baseline, whereas FA was reported in only 11.7%[47]. In this study, FA was not defined by food challenge but by relevant allergic symptoms following consumption of a food allergen, associated with an IgE sensitization to the same allergen, and confirmed by an allergist. Nevertheless, the results were very similar to those from the Danish Allergy Research Cohort (DARC) which monitored children from the age of 3 months to 6 years. Children with positive skin prick tests or with positive specific IgEs to food allergens, or with a history of reported adverse reactions to food, were investigated with food challenges: of the 122 children with AD, 52% were sensitized to food but only 15% of these children had a positive food challenge[44]. Results from the Isle of Wight birth cohort support the finding of a temporal sequence between AD and FA, with the prevalence of FA in10-year-olds being twice as high as in 1-year-olds in children with filaggrin loss-of-function mutations[48].

Severe AD seems to be a risk factor for associated FA, as demonstrated recently in a South African patient cohort[49]. Early childhood AD increases the risk of food sensitization during life as a subsequent complication in genetically predisposed children carrying filaggrin loss-of-function mutations[48,50]. The risk of sensitization through the skin is higher when filaggrin is absent or deficient in murine models[51]. Thus, filaggrin genetic deficiency should be explored in children with early-onset and severe AD[52]. Independently from filaggrin genetic deficiencies, genetic and ethnic predispositions for a particular form of AD linked with food sensitization and then FA are probable. Gray *et al* in South Africa, showed high rates of food sensitization and, most of all, high rates of challenge-confirmed FA (44%) in a cohort of black or mixed-race children with moderate to severe AD[49]. Ashley *et al* recently showed that the

rs9325071 variant of the skin barrier function gene SPINK5 may be a risk factor for both FA and AD[53].

Risk factors for the "atopic march", a "particular phenotype of AD" (Figure 1)

AD is considered to be the first step towards asthma. The term "atopic march" suggests a chronological sequence during childhood, with AD predating other manifestations of atopy such as asthma and allergic rhinitis. Many studies describe this particular trajectory[52]. In a birth-cohort study, Rhodes *et al* demonstrated the time course of atopic diseases from childhood to adulthood [54]. Abnormal reactivity to environmental triggers, present both in AD and asthma, suggest shared pathophysiological pathways. However, whether it is a temporal sequence between the diseases or a predetermined phenotype of multiple atopic comorbidities remains a matter of debate[55]. Results from the German Multicenter Atopy Study (MAS) birth cohort do not support the hypothesis of a chronological sequence of atopic diseases[56]. In this study, 1314 infants were recruited including 499 at risk of atopy due to familial history. Among them, only those who had early-onset AD (before 2 years), and early-onset wheezing (before 3 years), had an increased risk of asthma at 7 years. Conversely, most of the children who had early-onset AD without wheezing did not have an increased risk of asthma. Half of the children with early-onset AD already had recurrent wheezing far before the onset of AD. Thus, the link between AD and asthma seems more complex than ever thought before.

Furthermore, it has been well established that the atopic march only concerns from one third to a half of the children with AD[7]. Early-onset, severity, gender, multiple sensitization, environmental and genetic factors have been identified as risk factors.

Early onset of AD

Early-onset AD is a risk factor for school-age asthma. In a cohort of 373 children with a familial history of asthma, an onset of AD before the age of 2 years was significantly associated with bronchial hyper-reactivity at 7[57]. Von Kobyletzki *et al* found a 3-fold risk of

asthma if onset of AD occurred before the age of 12 months, while the risk became non-significant after this age[58]. In the Prevention of Allergy among Children in Trondheim (PACT) case-control study, the risk of asthma increased conversely with age of onset of AD: when AD onset occurred before 3 months, the risk of asthma at the age of 6 years was 4 times higher than for an onset of AD after 3 months[59]. These results could be explained by a higher risk of sensitization in children with early-onset AD[36,60]. Results from the Children's HEalth and Environmental Research (CHEER) population-based cohort suggest that early-onset AD is associated with a higher risk of asthma if linked with sensitization[61]. Furthermore, in this study, this phenotype of early-onset AD was also linked with persistent AD at school-age, suggesting a particular entity grouping early-onset persistent AD, sensitization and asthma.

Severity of AD

In a patient cohort, Gustafsson *et al* showed that the risk of asthma at school age increased with the severity of AD[46]. Illi *et al* demonstrated a 6-fold increase in the risk of school age asthma in children with severe AD in the MAS birth cohort[56]. However, it is important to note that this severe phenotype was infrequent, representing only 1% of this birth cohort.

An Italian retrospective study, conducted in a cohort of 3-year-old children with AD, found consistent results in terms of AD severity[62]. These results have since been confirmed in birth cohorts[58,63].

Recently, a national survey in the United States showed a strong association between severe and persistent AD, and asthma: the prevalence of asthma was 36.9% in patients with severe AD while it was only 24.3% for those with mild to moderate AD ($p=0.02$); and the prevalence of severe asthma was also higher in cases of severe AD compared with mild AD (36% *versus* 5.5%, respectively, $p<0.0001$). Once again, the prevalence of severe AD was low in the overall population, at around 1%[64].

Finally, in a prospective Swedish study of a cohort of 115 children with AD aged under 2 years, AD severity was not only associated with a higher risk of asthma at 10 years (p=0.01), but also with a higher risk of allergic rhinitis (p=0.01)[65].

Male gender

In the Melbourne Atopic Cohort Study (MACS), a birth cohort of 620 children with a parental history of atopy, Lowe *et al* showed that only boys were prone to the atopic march[63]. According to the authors, one explanation is that AD is more severe in boys than in girls (p=0.012). The effect persisted after adjustment on sensitization profile and was higher if AD was early-onset and/or severe.

Finally, von Kobyletzki *et al* in the Dampness in Building and Health (DBH) population-based study have also shown an excess risk of asthma and allergic rhinitis in boys with AD compared to girls[58].

AD with early and multiple sensitizations

The results from the ORCA Study describe the natural history of sensitization during the first 6 years of age in children with early-onset moderate to severe AD. In this cohort, food sensitization decreased over time, from 58% to 34%, whereas aeroallergen sensitization increased from 17% to 67%. Initial multiple food sensitization was the most predictive factor for the risk of developing aeroallergen sensitization at 6 years (OR 3.72 [1.68-8.30] p<0.001)[37]. The cohort was then investigated using an unsupervised statistical hierarchical clustering method. One cluster was characterized by a higher AD severity and frequent food (98.9%) or aeroallergen (26.2%) sensitization, often multiple (96.4% for food allergens). This cluster, called “AD with multiple sensitizations”, was the most likely to be associated with allergic asthma at the age of 6 (36.1%, p<0.01)[47]. In the same way, Lazic *et al*[66] recently suggested that allergic phenotypes change little over time, and that one infrequent phenotype

with sensitization to a wide variety of allergens was much more likely to give rise to asthma during childhood.

Furthermore, the age of onset of these multiple sensitisations seems to affect the subsequent severity of respiratory symptoms, as demonstrated by Belgrave *et al* in the Manchester Asthma and Allergy population-based study. In this study, children with persistent wheeze, frequent asthma exacerbations, and multiple early atopy have diminished lung function throughout childhood and are at risk of a progressive loss of lung function from age 3 to 11 years. This is especially true for boys[67].

The AD phenotype characterized by serum IgE levels ≥200 kU/L and food or aeroallergen sensitization is associated with greater disease severity[68]. This form of AD may be considered as the initial step of the atopic march[69], with severity and early sensitization as major prognostic determinants[46, 70]. In this group of patients, immune dysregulation, including higher sensitization levels and increased Th2 cytokine expression in eczematous lesions, may be the underlying pathway leading to the expression of atopic diseases such as allergic asthma[71]. To support this hypothesis, it has been suggested that concomitant early wheeze and AD does not explain the increased risk of childhood asthma associated with AD, but rather that sensitization is the primary confounding factor in this association[63].

Genetic factors

Gene expression seems to differ according to the phenotype, particularly in the genes involved in human keratinocyte and filaggrin expression which is down-regulated in IgE-related AD[68]. Independently from the well-known role of filaggrin loss-of-function mutations in epithelial dysfunction[72], other gene mutations in the epidermal differentiation complex could be involved in the severity of AD and risk of subsequent sensitization to allergens[73,74]. It is also suspected that some polymorphisms of Th2 cytokines interfere with epidermal

differentiation[73]. In a multi-stage genome-wide association study on infantile eczema followed by childhood asthma including 12 different populations, Marenholz *et al* identified seven susceptibility loci that could be involved in the atopic march: rs9357733 located in EFHC1 on chromosome 6p12.3 (OR 1.27; p<0.0001), rs993226 between TMTC2 and SLC6A15 on chromosome 12q21.3 (OR 1.58; p<0.0001), FLG (1q21.3), IL4/KIF3A (5q31.1), AP5B1/OVOL1 (11q13.1), C11orf30/LRRC32 (11q13.5) and IKZF3 (17q21)[75].

Familial history is not always considered as a risk factor for the atopic march, although it has been demonstrated to be a risk factor for the transition from early wheezing to asthma[58]. In the ORCA Study, the cluster with the highest rate of parental history of asthma was significantly associated with asthma at the age of 6 years[47]. One hypothesis to explain this result could be a specific genetic susceptibility, involving both inflammation and epithelial barrier pathways.

Role of environmental factors in AD phenotypes

The role of environmental factors in high risk children should not be minimized.

For instance, many studies have demonstrated a relationship between the content of peanut in house dust and the development of peanut allergy in patients with AD[41, 76]. In highly atopic children recruited from the Consortium of Food Allergy Research Observational Study, environmental peanut exposure was significantly associated with likely peanut allergy (OR 2.34; 95% CI, 1.31-4.18; p<0.01)[41].

Different triggers of AD have been identified such as *S. aureus*, the herpes simplex virus, stress, and allergens[30]. It is also known that environmental factors play a major role in the development of childhood asthma. However, their relative importance in triggering the atopic march in children with AD has not yet been determined[77]. Studies on pet fur exposure, house dust mites and breastfeeding give contrasting results[78, 79]. Recent studies suggest a harmful effect of tobacco smoke exposure, volatile organic compounds, formaldehyde, toluene, nitrogen dioxide and fine particles[80]. These pollutants are suspected to induce a cutaneous

oxidative stress leading to barrier dysfunction. *In utero* tobacco smoke exposure seems to be particularly noxious regarding the risk of occurrence of AD for some children[81], while it could be protective for others[82]. These apparent discrepancies may be due to complex interactions between genetic background and the exposome[83].

On the borderline between genetics, dysimmunity and AD

Some orphan syndromes due to heritable mutations in skin barrier components, apart from filaggrin loss-of-function mutations in ichthyosis vulgaris[84], have been described. These syndromes associate AD with other various symptoms corresponding to specific entities.

Among these syndromes, the autosomal recessive disorder, Netherton syndrome, is the most well-known. This syndrome is the result of homozygous or compound heterozygous loss-of-function mutations in the SPINK5 gene and is characterized by severe AD associated with a high level of total IgE, and a high frequency of IgE-mediated food allergies[85].

The recently described severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome is caused by mutations in the desmoglein 1 (DSG1) or desmoplakin (DSP) gene[86]. SAM syndrome is rare and only five familial cases have been reported to date. It associates erythrodermia in early-life, developmental delay, severe palmoplantar keratoderma, keratitis, severe *S Aureus* infections, and multiple FAs. Transcriptomic analysis in these patients has revealed high cytokine expression in keratinocytes, especially TNF, IL-5 and TSLP.

Autosomal dominant hyper-IgE syndrome (also known as STAT3 deficiency), is a primary immunodeficiency disease characterized by severe eczema, recurrent infections, and multiple connective tissue, skeletal and vascular abnormalities[87]. Although not all patients with STAT3 deficiency experience FA, a high rate of eosinophilic esophagitis has been described in these patients[88].

In practice: Prevention and treatment of AD during childhood

Recent studies focusing on the prevention of AD in infancy and early childhood have shown an effect of the use of skin barrier creams to prevent AD[89,90]. Simpson *et al*[89] performed a randomized controlled trial including 124 neonates at high risk of AD. Parents in the intervention arm were instructed to apply full-body daily emollient therapy as from 3 weeks of birth. Their results showed a statistically significant 50% reduction in relative risk on the cumulative incidence of AD at 6 months with daily use of emollient. Horimukai *et al*[90] in another randomized controlled trial with early moisturizer application conducted in 116 neonates at high familial risk for AD, showed a significant decrease of 40% of the risk of AD at 32 weeks of age. These studies suggest that early intervention with emollient therapy from birth is an effective way of preventing AD and support the concept of skincare respecting the natural barriers from birth. However, data are lacking about a possible effect on food sensitization. Low *et al* have shown that a twice-daily application of a ceramide-dominant emollient for the first 6 months of life may have an effect on the incidence of sensitization to food at 12 months, but only in a per-protocol analyses (only including infants who received ≥ 5 days per week of treatment)[91]. Thus, the effectiveness of this approach in the prevention of sensitization in children remains to be demonstrated.

Taken together, the sum of the pathophysiological facts, observational studies on sensitization risk, and interventional studies, pleads for an active management approach in AD, especially if severe, early-onset, and associated with familial history and early food sensitization. Among the available biotherapies, dupilumab blocks the interleukin-4 receptor thereby inhibiting interleukins 4 and 13. It has been demonstrated to be effective in adults with moderate-to-severe AD and/or asthma and could be a promising therapy in selected children with severe AD[9]. However, further studies are needed to show that dupilumab is safe and effective in slowing or preventing the atopic march.

Conclusion

AD should not be seen as a single entity but rather as a condition requiring a translational approach. Clinicians should be aware of specific phenotypes which are linked with subsequent risks of asthma or other associated atopic comorbidities, such as FA. Physicians should be particularly on the lookout for the phenotype comprising severe, early-onset AD, associated with multiple sensitization, because of a poorer respiratory prognosis during life. Association with FA should be carefully investigated in children with difficult-to-treat AD. A dysfunction in filaggrin or Th2-related cytokines or rare genetic syndromes may also explain some severe phenotypes.

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Table 1 – Terms used to identify studies focused on AD, adapted from Cochrane Skin Group guidelines

Definite AD	**Possible AD (AD retained if additional features obtained in the original paper as a good clinical description)**	**Not atopic eczema**
Atopic eczema **Atopic dermatitis**	Childhood eczema Infantile eczema Eczema (unspecified) Dyshidrotic eczema Nummular dermatitis Pityriasis alba	Seborrheic dermatitis/eczema Contact dermatitis/eczema Occupational dermatitis/eczema Hand dermatitis/eczema Allergic contact dermatitis/eczema Irritant contact dermatitis/eczema

Table 2 – Main definitions for atopic dermatitis, atopic eczema and eczema

Authors, date	Definition
Hanifin & Rajka, 1980	***Atopic dermatitis*** (syn. atopic eczema), defined by at least three of the following features: - Pruritus, - Lichenification, - Chronically relapsing course, - Personal of familial history of atopy Plus 3 or more minor features: -Xerosis - Ichtyosis/palmar hyperlinearity -Immediate skin test reactivity - Elevated serum IgE - Early age of onset - Tendency toward cutaneous infections/impaired cell-mediated immunity - Tendency toward non-specific hand or foot dermatitis - Nipple eczema -Cheilitis -Recurrent conjunctivitis - Dennie-Morgan infraorbital fold - Keratocornus - Anterior subscapular cataracts - Orbital darkening - Facial pallor/facial erythema - Pytiriasis alba - Anterior neck folds - Itch when sweating - Intolerance to wool and lipid solvents - Perifollicular accentuation - Food intolerance - Course influenced by environmental/emotional factors - White dermographism/ delayed blanch
Williams et al (UKWP), 1994	***Atopic dermatitis***, defined by: Evidence of itchy skin (or parental report of scratching or rubbing) plus three or more of the following: - History of involvement of the skin creases (e.g. fronts of elbows, backs of knees, fronts of ankles, and areas around the neck or eyes)

	- History of asthma or hay fever (or history of atopic disease in a first-degree relative if the child is under four years of age) - History of generally dry skin in the past year - Onset in a child under 2 years of age (criterion not used if the child is under four years of age) - Visible flexural dermatitis (including dermatitis affecting the cheeks or forehead and outer aspects of limbs in children under four years)
ISAAC Study Group, 1998	***Current atopic eczema***, defined if answered "Yes" to the questions: - "Have you ever had an itchy rash which was coming and going for at least 6 months? If yes: - "Have you had this itchy rash at any time in the last 12 months?" If yes: - "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"

UKWP: United Kingdom Working Party; ISAAC: International Study of Asthma and Allergies in Childhood

Table 3 – Role of filaggrin variants in AD expression: summary of main results

Authors, date	**Terms and definitions used***	**Type of study**	**Population**	**Aim**	**Main results**	**Conclusions**
Palmer et al, 2006	AD, eczema (UKWP)	Case-control with replication in 2 population-based cohorts	Children 189 controls, 52 cases with AD 21 cases with AD + asthma Replication: 1008 and 604 subjects	To assess the role of FLG R501X and 2282del4 variants in predisposition for AD in Irish, Scottish and Danish populations	Risk of AD for carriers of at least one allele: - in Irish subjects: OR13.4 [6.2-27.5] - in Scottish subjects: OR 1.8 [1.3-2.5] - in Danish subjects: HR 2.8 [1.7 – 4.5]	Key role of impaired skin barrier function in the development of atopic disease
Weidinger et al, 2006	AD (UKWP)	Family-based	476 families	To assess the role of R510X and 2282del4 variants in predisposition for AD	Risk of AD while carrying - 2282del4 variant: OR 2.5[1.4-4.3] - R501X variant: OR 4.1[2.2-7.9] -combined genotype: OR 3.3[2.1-5.4] Particular association with "extrinsic" AD, characterized by high total serum IgE levels and concomitant allergic sensitizations	FLG is the first really strong genetic factor identified in a common complex disease Crucial role of the skin barrier in preventing allergic sensitization
Ruether et al, 2006	AD (Hanifin & Rajka)	Case-control and family-	Children 272 cases 276	To explore further the relevance of	Risk of AD while carrying R501X variant:	FLG variants are specific to the epidermal

		based	controls 338 families	the variants in Northern Germany	OR 3.39 [1.75-6.58] AD risk while carrying 2282del4 variant = OR 7.1 [3.41-14.78]	barrier, and are major predisposing factors for AD in Western European populations
Nomura et al, 2009	AD (not specified)	Case-control	Children and adults 118 cases 134 controls	To assess the link between FLG mutations and AD in a Japanese population	Seven variants described:R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X Risk of AD if combined genotype: OR 6.8[2.5-18.5]	FLG mutations are population-specific
Nemoto-Hasebe et al, 2009	AD (Hanifin & Rajka)	Case-control	Adults 24 cases 12 controls	Main hypothesis: skin barrier defects caused by FLG deficiency is a primary abnormality leading to the AD symptoms	In filaggrin-related AD, objective score of atopic dermatitis correlated with - TEWL r = 0.81, p<0.005 - SC hydration: r=0.65,p<0.05 - SC thickness: r = 0.59, p<0.05	Skin barrier defects due to FLG mutations may play a crucial role in the pathogenesis of AD
Venkatarama n et al, 2014	AD (Hanifin & Rajka)	Population-based birth cohort	1313 children at the end of the follow-up	To explore the longitudinal relationship between 3 common FLG-LOF variants and FA	Effect of FLG-LOF variants on the risk of FA: - at 10 years: OR 31.46 [2.86->100 - at 18 years: 4.25[1.55-11.61] Indirect effect of FLG variants on FA at all ages through eczema and FS	FLG-LOF mutations are associated with FA in older children through eczema and FS during early childhood. Biologically plausible pathway suggesting that skin barrier function is important in the development and persistence of FA.
Ziyab et al, 2017	Eczema (Hanifin & Rajka)	Population-based birth cohort	94 children	To assess whether FLG expression in UCB associates with and predicts the development	RR of eczema during the first year of life if increased level of FLG expression:0.60 [0.38-0.95] RR of eczema	FLG expression in UCB is associated with eczema development in infancy

				of eczema in infancy	during the first year of life if increased level of FLG antisense transcripts : 2.02[1.10-3.72]	

AD: atopic dermatitis; UKWP: United Working Party Criteria; FLG: filaggrin; OR: odds ratio, 95% confidence interval expressed [-]; HR: hazard ratio; TEWL: transepidermal water-loss; SC: subcutaneous; LOF: loss-of-function; RR: relative risk; UCB: umbilical cordon blood

*Terms between brackets specify the criteria used to define AD

Table 4 –Link between AD, food sensitization and food allergy: summary of main results

Authors, date	Terms and definitions used*	Type of study	Population	Aim	Main results	Conclusions
Carlsten et al, 2013	AD (presence of a pruritic rash on the face or extensor surface of the arms or legs and flexural lichenification at the time of examination by the allergist investigators)	High-risk cohort	373 children	To evaluate the natural history of AD and its association with other allergic outcomes	Risk of FS at 2 years if associated AD: OR 2.52 [1.11-5.74] (if non persistent) OR 5.92 [2.23-15.7] (if persistent) Risk of FA at 7 years if early-onset persistent AD: OR13.4[2.94-61.4] Non significant risk of FS or FA if late-onset	Only early-onset, persistent AD is associated with atopic sensitization
Du Toit et al, 2013	AD (Hanifin & Rajka)	High-risk cohort	834 children	To characterize a population screened for the risk of PA.	PS was associated with severe eczema: OR 2.47 [1.14-5.34]	Severe eczema useful criterium for identifying PA high-risk infants
Gray et al, 2014	AD (UKWP)	Patient cohort	100 children	To determine the prevalence of, and risk factors for, IgE-mediated FA in South African children with AD	66 % of associated FS 40% of associated FA: egg 25% , PS 24% Comparable FS rates between Blacks and mixed race patients, but	Unexpectedly high prevalence of FA in South African children with AD Ethnic background differences

					lower PA rates in Blacks Risk factors for FA: early-onset AD (<6 months), severe eczema, and age <2 years	
Just et al, 2015	AD (UKWP and ISAAC)	Patient cohort	229 children	To describe the natural history of sensitization in a cohort of children with early-onset AD	FS decreased from 58% to 34% from 1 to 6 years Risk of developing sensitization to inhaled allergens if initial multiple FS: OR 3.72 [1.68–8.30]	Multiple FS conveys a higher risk of sensitization to inhaled allergens than single FS
Brough et al, 2015	AD (Hanifin & Rajka)	Patient cohort	512 children	To assess whether EPE is a risk for PS and PA	Effect of EPE on PS: - if history of AD: OR 1.97 [1.26-3.09] - if history of severe AD OR 2.41 [1.30-4.47] Effect of EPE on PA if history of AD: OR 2.34 [1.31-4.18]	Exposure to peanut antigen in dust through an impaired skin barrier in atopic inflamed skin is a plausible route for PS and PA
Kelleher et al, 2016	AD (UKWP)	Population-based birth cohort	1903 children	To examine whether early skin barrier disruption, based on TEWL assessment, is associated with increased rates of FS or FA at 2 years of age.	FS 6.27% FA 4.45% Egg: most prevalent allergen (2.94%), then peanut (1.75%), and cow's milk (0.74%) Day 2 TEWL>9 g water/m^2/h significant predictor of FA at age 2 years: OR 4.1 [1.5-4.8]	Neonatal skin barrier dysfunction predicts FA at 2 years of age, supporting the concept of transcutaneous allergen sensitization
Tsakok et al, 2016	AD, atopic eczema, eczema (exclusion of sensitization-based AD)	Systematic review	Children 11 population-based studies	To review the association between AD and FA, the effect	Likelihood of FS in patients with AD at 3 months of age = OR	Strong and dose-dependent association between AD, food

	8 high-risk cohorts	of FA on AD severity, chronicity, and age of onset, and the temporal relationship between the two.	6.18[2.94-12.98] Up to 53% of subjects with AD had FS, and up to 15% demonstrated FA in population-based studies 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 One study found that AD preceded the development of FA.	sensitization, and FA. AD of increased severity and chronicity particularly associated with FA AD precedes the development of food sensitization and allergy

AD: atopic dermatitis; FS: food sensitization; FA: food allergy; PS: peanut sensitization; OR: odds ratio, 95% confidence interval expressed [-]; PA: peanut allergy; UKWP: United Working Party Criteria; ISAAC: International Study of Asthma and Allergies in Childhood; TEWL: transepidermal water-loss; EPE: environmental peanut exposure.
*Terms between brackets specify the criteria used to define AD

Table 5 – Link between AD and asthma: summary of main results

Authors, date	Terms and definitions used*	Type of study	Population	Aim	Main results	Conclusions
Illi et al, 2004	AD (at least one of the following 3 criteria applied at any follow-up visit in the first 2 years of life: 1. a reported diagnosis by the family physician-pediatrician; 2. parental reporting of dry skin and at least 3 of 4 relevant symptoms (cheek eczema, eczema at other sites, infra-auricular fissuring, and scaly or itchy rash for a longer time period); or 3. visible AD at skin examination, as defined above)	Population-based birth cohort	1314 children	To investigate the natural course of AD and to analyze the relationship of AD with childhood asthma.	Risk factors of AD persistance: - initial severity:OR 5.86 [3.04-11.29] and - atopic sensitization OR2.76[1.29-5.91] Early wheeze and a specific sensitization pattern: significant predictors for wheezing at school age, irrespective of AD.	Children with AD and asthma represents a distinct phenotype
Ricci et al,	AD (Hanifin	Patient	205	To evaluate	Factors	Egg

2006	& Rajka)	cohort	children	the natural course of AD and the factors influencing its healing or persistence, and the appearance of asthma	significantly associated with asthma at 6 years old: higher initial severity of AD, hen's egg sensitization	sensitization is a particular profile amongst children with AD
van der Hulst et al, 2007	Atopic eczema (criteria not specified)	Systematic review	5384 children, 13 studies (birth cohorts, outpatients and inpatients studies)	To assess the risk of developing asthma in children with atopic eczema during the first 4 years of life	OR for asthma in children with atopic eczema: 2.14 [1.67-2.75] Prevalence of asthma at the age of 6 years in patients cohort studies: approx. 30%	Only 1 in every 3 children with eczema develops asthma during later childhood
Lowe et al, 2008	Eczema (parental report of either a doctor diagnosis of eczema or any rash that was treated with topical steroid preparation)	High-risk cohort	620 children	To examine the role of infantile eczema as a predictor of risk of childhood asthma	Eczema within the first 2 years of life associated with an increased risk of childhood asthma in boys: OR 2.45[1.31-4.46], but not in girls OR 0.88 [0.43-1.77]	Eczema in the first 2 years of life is associated with an increased risk of childhood asthma in boys, but there is no evidence of this in girls.
von Kobyletski et al, 2012	AD, eczema (ISAAC)	Population based birth cohort	3 214 children	To estimate the association between eczema in early childhood and the onset of asthma and rhinitis later in life	Risk of asthma : - if AD: OR3.07[1.795.27] - if moderate to severe AD :OR 3.56[1.62–7.83] -if early onset AD: OR 3.44[1.94–6.09] -if persistent AD: OR5.16[2.62–10.18]	Eczema in early childhood is strongly associated with the development of asthma
Saunes et al, 2012	Eczema (ISAAC)	Birth control cohort of an interventional study	2 192 children	To study the risk of current asthma and the co-existence of allergy-related diseases at 6 years of age among children with and	Estimate for the association between eczema at 2 years and current asthma at 6 years: OR=1.80[1.10-2.96]	Early eczema is associated with an increased risk of developing childhood asthma.

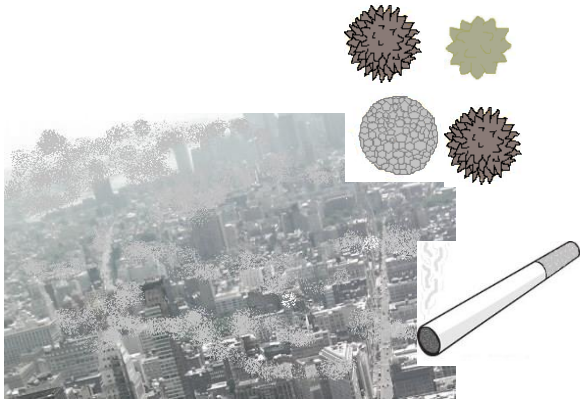
				without eczema at 2 years of age.		
Carlsten et al, 2013	AD (presence of a pruritic rash on the face or extensor surface of the arms or legs and flexural lichenification at the time of examination by the allergist investigators)	High-risk cohort	373 children	To evaluate the natural history of AD and its association with other allergic outcomes	Risk of sensitization to aeroallergens at 2 years if associated AD: OR2.97[1.25-7.08](non persistent) and 4.06 [1.52-10.9] (persistent) Risk of asthma at 7 years if early-onset persistent AD: OR 7.48[2.53-22.2] Non-significant risk of sensitization or asthma if late-onset	Early-onset persistent AD is highly associated with atopic sensitization and increases the risk of atopic diseases in later childhood
Silverberg et al, 2013	Eczema, AD (if "Yes" to the question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?")	National survey	79 667 children	To determine the impact of eczema severity on the development of other comorbid conditions	Severe eczema was associated with a higher prevalence of comorbid chronic health disorders, including asthma, hay fever, and food allergies ($p < 0.0001$)	Severe eczema is associated with multiple comorbid chronic health disorders, impaired overall health, and increased healthcare utilization
Nissen et al, 2013	Eczema (Areas of scaly, erythematous and itchy eczematous rash primarily of the face and scalp, behind the ears and at the flexural folds, diagnosed by a doctor. Only eczema localized to at least two typical areas and chronically	Population-based birth cohort	276 children (193 at the 26 years follow-up)	To investigate the natural course of sensitization and allergic diseases in a random population-based sample of Danish children	Prevalence of current eczema stable during childhood Prevalence of current eczema decreased in adulthood Rates of sensitization increased from childhood to adulthood	Allergic diseases not only occur in childhood but persist into adulthood.

	relapsing with duration of at least 3 months were recorded.)					
Eckbäck et al, 2014	Eczema (Hanifin & Rajka)	Patient cohort	123 children	To follow infants with eczema and suspected food allergy over time, focusing on sensitization to allergens, severity of eczema and the development of allergic airway symptoms at 4.5 and 10 years of age	Higher SCORAD on inclusion correlated with the risk of developing asthma: β=10.17 (p=0.01) If AD and wheezing before 2 years: OR for developing asthma 4.05 (p = 0.01)	Increased risk of asthma in case of severe AD Increased risk of asthma if concomitant early-onset AD and wheezing
Amat et al, 2015	AD (UKWP and ISAAC)	Patient cohort	217 children	To define early-onset AD phenotypes leading to asthma	Three clusters: - AD with low sensitization - AD with multiple sensitization - AD with familial history of asthma The two latter associated with higher frequency of asthma at age 6 (p<0.001)	Multiple sensitization and familial history of asthma convey a higher risk of developing asthma during childhood in infants with early-onset, moderate to severe AD.
Lee et al, 2016	AD (ISAAC)	Patients from a population-based cohort	242 children	To define AD phenotypes in children aged 6–8 years	Four phenotypes: 'early onset with low atopy' (26.4% of the sample; group 1) 'early onset with high atopy and high eosinophil percentages' (48.3%; group 2) 'late onset with low atopy' (9.9%; group 3) 'late onset with high atopy and normal eosinophils' (15.3%; group 4) Persistence of AD, eosinophilia	An allergic march-associated AD phenotype exists that is characterized by early-onset, persistent AD and high atopy.

		and asthma associated with group 2

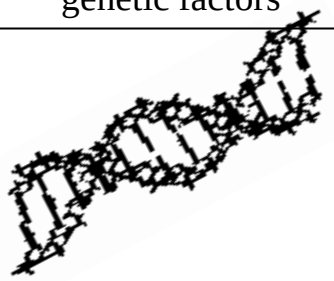
AD: atopic dermatitis; FS: food sensitization; FA: food allergy; PS: peanut sensitization; OR: odds ratio, 95% confidence interval expressed [-]; PA: peanut allergy; UKWP: United Working Party Criteria; ISAAC: International Study of Asthma and Allergies in Childhood; TEWL: transepidermal water-loss; EPE: environmental peanut exposure
*Terms between brackets specify the criteria used to define AD

Figure 1 – Main risk factors involved in the atopic march



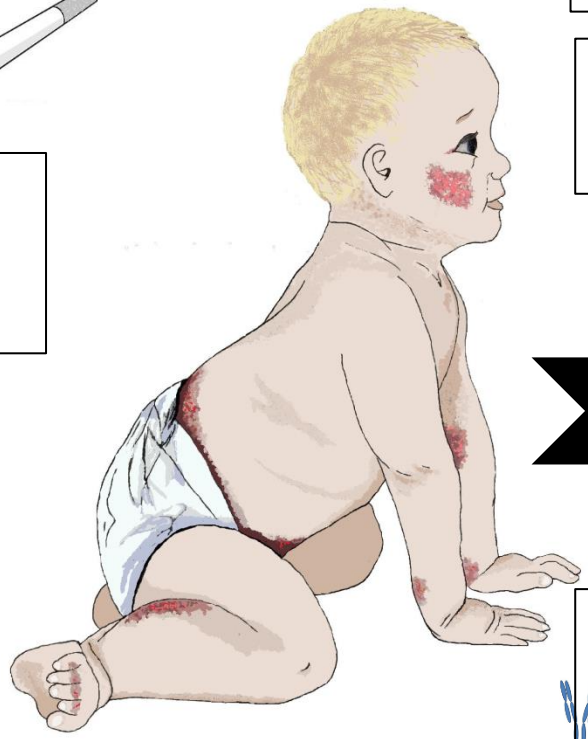
Environmental factors exposure: pollutants/irritants, allergens…

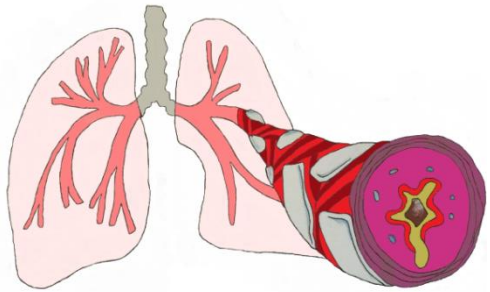
Familial history and genetic factors



Male gender

Early-onset and severe atopic dermatitis





Early-onset and multiple sensitizations

Staphylococcus aureus toxins

ATOPIC MARCH

Table 1 – Terms used to identify studies focused on AD, adapted from Cochrane Skin Group guidelines

Definite AD	**Possible AD (AD retained if additional features obtained in the original paper as a good clinical description)**	**Not atopic eczema**
Atopic eczema	Childhood eczema	Seborrheic dermatitis/eczema
Atopic dermatitis	Infantile eczema	Contact dermatitis/eczema
	Eczema (unspecified)	Occupational dermatitis/eczema
	Dyshidrotic eczema	Hand dermatitis/eczema
	Nummular dermatitis	Allergic contact dermatitis/eczema
	Pityriasis alba	Irritant contact dermatitis/eczema

Table 2 – Main definitions for atopic dermatitis, atopic eczema and eczema

Authors, date	Definition
Hanifin & Rajka, 1980	***Atopic dermatitis*** (syn. atopic eczema), defined by at least three of the following features: - Pruritus, - Lichenification, - Chronically relapsing course, - Personal of familial history of atopy Plus 3 or more minor features: -Xerosis - Ichtyosis/palmar hyperlinearity -Immediate skin test reactivity - Elevated serum IgE - Early age of onset - Tendency toward cutaneous infections/impaired cell-mediated immunity - Tendency toward non-specific hand or foot dermatitis - Nipple eczema -Cheilitis -Recurrent conjunctivitis - Dennie-Morgan infraorbital fold - Keratocornus - Anterior subscapular cataracts - Orbital darkening - Facial pallor/facial erythema - Pytiriasis alba - Anterior neck folds - Itch when sweating - Intolerance to wool and lipid solvents - Perifollicular accentuation - Food intolerance - Course influenced by environmental/emotional factors - White dermographism/ delayed blanch
Williams et al (UKWP), 1994	***Atopic dermatitis***, defined by: Evidence of itchy skin (or parental report of scratching or rubbing) plus three or more of the following:

	- History of involvement of the skin creases (e.g. fronts of elbows, backs of knees, fronts of ankles, and areas around the neck or eyes) - History of asthma or hay fever (or history of atopic disease in a first-degree relative if the child is under four years of age) - History of generally dry skin in the past year - Onset in a child under 2 years of age (criterion not used if the child is under four years of age) - Visible flexural dermatitis (including dermatitis affecting the cheeks or forehead and outer aspects of limbs in children under four years)
ISAAC Study Group, 1998	***Current atopic eczema***, defined if answered "Yes" to the questions: - "Have you ever had an itchy rash which was coming and going for at least 6 months? If yes: - "Have you had this itchy rash at any time in the last 12 months?" If yes: - "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"

UKWP: United Kingdom Working Party; ISAAC: International Study of Asthma and Allergies in Childhood

Table 3 – Role of filaggrin variants in AD expression: summary of main results

Authors, date	Terms and definitions used*	Type of study	Population	Aim	Main results	Conclusions
Palmer et al, 2006	AD, eczema (UKWP)	Case-control with replication in 2 population-based cohorts	Children 189 controls, 52 cases with AD 21 cases with AD + asthma Replication: 1008 and 604 subjects	To assess the role of FLG R501X and 2282del4 variants in predisposition for AD in Irish, Scottish and Danish populations	Risk of AD for carriers of at least one allele: - in Irish subjects: OR13.4 [6.2-27.5] - in Scottish subjects: OR 1.8 [1.3-2.5] - in Danish subjects: HR 2.8 [1.7 – 4.5]	Key role of impaired skin barrier function in the development of atopic disease
Weidinger et al, 2006	AD (UKWP)	Family-based	476 families	To assess the role of R510X and 2282del4 variants in predisposition for AD	Risk of AD while carrying - 2282del4 variant: OR 2.5[1.4-4.3] - R501X variant: OR 4.1[2.2-7.9] -combined genotype: OR 3.3[2.1-5.4] Particular association with "extrinsic" AD, characterized by high total serum IgE levels and concomitant allergic sensitizations	FLG is the first really strong genetic factor identified in a common complex disease Crucial role of the skin barrier in preventing allergic sensitization
Ruether et al, 2006	AD (Hanifin & Rajka)	Case-control and family-based	Children 272 cases 276 controls 338 families	To explore further the relevance of the variants in Northern Germany	Risk of AD while carrying R501X variant: OR 3.39 [1.75-6.58] AD risk while carrying 2282del4 variant = OR 7.1 [3.41-14.78]	FLG variants are specific to the epidermal barrier, and are major predisposing factors for AD in Western European populations
Nomura et al, 2009	AD (not specified)	Case-control	Children and adults 118 cases 134 controls	To assess the link between FLG mutations and AD in a Japanese population	Seven variants described:R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X Risk of AD if combined	FLG mutations are population-specific

					genotype: OR 6.8[2.5-18.5]	
Nemoto-Hasebe et al, 2009	AD (Hanifin & Rajka)	Case-control	Adults 24 cases 12 controls	Main hypothesis: skin barrier defects caused by FLG deficiency is a primary abnormality leading to the AD symptoms	In filaggrin-related AD, objective score of atopic dermatitis correlated with - TEWL r = 0.81, p<0.005 - SC hydration: r=0.65,p<0.05 - SC thickness: r = 0.59, p<0.05	Skin barrier defects due to FLG mutations may play a crucial role in the pathogenesis of AD
Venkataraman et al, 2014	AD (Hanifin & Rajka)	Population-based birth cohort	1313 children at the end of the follow-up	To explore the longitudinal relationship between 3 common FLG-LOF variants and FA	Effect of FLG-LOF variants on the risk of FA: - at 10 years: OR 31.46 [2.86->100 - at 18 years: 4.25[1.55-11.61] Indirect effect of FLG variants on FA at all ages through eczema and FS	FLG-LOF mutations are associated with FA in older children through eczema and FS during early childhood. Biologically plausible pathway suggesting that skin barrier function is important in the development and persistence of FA.
Ziyab et al, 2017	Eczema (Hanifin & Rajka)	Population-based birth cohort	94 children	To assess whether FLG expression in UCB associates with and predicts the development of eczema in infancy	RR of eczema during the first year of life if increased level of FLG expression:0.60 [0.38-0.95] RR of eczema during the first year of life if increased level of FLG antisense transcripts : 2.02[1.10-3.72]	FLG expression in UCB is associated with eczema development in infancy

AD: atopic dermatitis; UKWP: United Working Party Criteria; FLG: filaggrin; OR: odds ratio, 95% confidence interval expressed [-]; HR: hazard ratio; TEWL: transepidermal water-loss; SC: subcutaneous; LOF: loss-of-function; RR: relative risk; UCB: umbilical cordon blood

*Terms between brackets specify the criteria used to define AD

Table 4 –Link between AD, food sensitization and food allergy: summary of main results

Authors, date	Terms and definitions used*	Type of study	Population	Aim	Main results	Conclusions
Carlsten et al, 2013	AD (presence of a pruritic rash on the face or extensor surface of the arms or legs and flexural lichenification at the time of examination by the allergist investigators)	High-risk cohort	373 children	To evaluate the natural history of AD and its association with other allergic outcomes	Risk of FS at 2 years if associated AD: OR 2.52 [1.11-5.74] (if non persistent) OR 5.92 [2.23-15.7] (if persistent) Risk of FA at 7 years if early-onset persistent AD: OR13.4[2.94-61.4] Non significant risk of FS or FA if late-onset	Only early-onset, persistent AD is associated with atopic sensitization
Du Toit et al, 2013	AD (Hanifin & Rajka)	High-risk cohort	834 children	To characterize a population screened for the risk of PA.	PS was associated with severe eczema: OR 2.47 [1.14-5.34]	Severe eczema useful criterium for identifying PA high-risk infants
Gray et al, 2014	AD (UKWP)	Patient cohort	100 children	To determine the prevalence of, and risk factors for, IgE-mediated FA in South African children with AD	66 % of associated FS 40% of associated FA: egg 25% , PS 24% Comparable FS rates between Blacks and mixed race patients, but lower PA rates in Blacks Risk factors for FA: early-onset AD (<6 months), severe eczema, and age <2 years	Unexpectedly high prevalence of FA in South African children with AD Ethnic background differences
Just et al, 2015	AD (UKWP and ISAAC)	Patient cohort	229 children	To describe the natural history of sensitization in a cohort of children with early-onset AD	FS decreased from 58% to 34% from 1 to 6 years Risk of developing sensitization to inhaled allergens if initial multiple FS:	Multiple FS conveys a higher risk of sensitization to inhaled allergens than single FS

					OR 3.72 [1.68–8.30]	
Brough et al, 2015	AD (Hanifin & Rajka)	Patient cohort	512 children	To assess whether EPE is a risk for PS and PA	Effect of EPE on PS: - if history of AD: OR 1.97 [1.26-3.09] - if history of severe AD OR 2.41 [1.30-4.47] Effect of EPE on PA if history of AD: OR 2.34 [1.31-4.18]	Exposure to peanut antigen in dust through an impaired skin barrier in atopic inflamed skin is a plausible route for PS and PA
Kelleher et al, 2016	AD (UKWP)	Population-based birth cohort	1903 children	To examine whether early skin barrier disruption, based on TEWL assessment, is associated with increased rates of FS or FA at 2 years of age.	FS 6.27% FA 4.45% Egg: most prevalent allergen (2.94%), then peanut (1.75%), and cow's milk (0.74%) Day 2 TEWL>9 g water/m^2/h significant predictor of FA at age 2 years: OR 4.1 [1.5-4.8]	Neonatal skin barrier dysfunction predicts FA at 2 years of age, supporting the concept of transcutaneous allergen sensitization
Tsakok et al, 2016	AD, atopic eczema, eczema (exclusion of sensitization-based AD)	Systematic review	Children 11 population-based studies 8 high-risk cohorts	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.	Likelihood of FS in patients with AD at 3 months of age = OR 6.18[2.94-12.98] Up to 53% of subjects with AD had FS, and up to 15% demonstrated FA in population-based studies 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	Strong and dose-dependent association between AD, food sensitization, and FA. AD of increased severity and chronicity particularly associated with FA AD precedes the development of food sensitization and allergy

					One study found that AD preceded the development of FA.

AD: atopic dermatitis; FS: food sensitization; FA: food allergy; PS: peanut sensitization; OR: odds ratio, 95% confidence interval expressed [-]; PA: peanut allergy; UKWP: United Working Party Criteria; ISAAC: International Study of Asthma and Allergies in Childhood; TEWL: transepidermal water-loss; EPE: environmental peanut exposure.

*Terms between brackets specify the criteria used to define AD

Table 5 – Link between AD and asthma: summary of main results

Authors, date	Terms and definitions used*	Type of study	Population	Aim	Main results	Conclusions
Illi et al, 2004	AD (at least one of the following 3 criteria applied at any follow-up visit in the first 2 years of life: 1. a reported diagnosis by the family physician-pediatrician; 2. parental reporting of dry skin and at least 3 of 4 relevant symptoms (cheek eczema, eczema at other sites, infra-auricular fissuring, and scaly or itchy rash for a longer time period); or 3. visible AD at skin examination, as defined above)	Population-based birth cohort	1314 children	To investigate the natural course of AD and to analyze the relationship of AD with childhood asthma.	Risk factors of AD persistance: - initial severity:OR 5.86 [3.04-11.29] and - atopic sensitization OR2.76[1.29-5.91] Early wheeze and a specific sensitization pattern: significant predictors for wheezing at school age, irrespective of AD.	Children with AD and asthma represents a distinct phenotype
Ricci et al, 2006	AD (Hanifin & Rajka)	Patient cohort	205 children	To evaluate the natural course of AD and the factors influencing its healing or persistence, and the appearance of asthma	Factors significantly associated with asthma at 6 years old: higher initial severity of AD, hen's egg sensitization	Egg sensitization is a particular profile amongst children with AD
van der Hulst et al, 2007	Atopic eczema (criteria not specified)	Systematic review	5384 children, 13 studies (birth cohorts, outpatients and inpatients	To assess the risk of developing asthma in children with atopic eczema during the first 4	OR for asthma in children with atopic eczema: 2.14 [1.67-2.75] Prevalence of asthma at the age of 6 years in patients	Only 1 in every 3 children with eczema develops asthma during later childhood

			studies)	years of life	cohort studies: approx. 30%	
Lowe et al, 2008	Eczema (parental report of either a doctor diagnosis of eczema or any rash that was treated with topical steroid preparation)	High-risk cohort	620 children	To examine the role of infantile eczema as a predictor of risk of childhood asthma	Eczema within the first 2 years of life associated with an increased risk of childhood asthma in boys: OR 2.45[1.31-4.46], but not in girls OR 0.88 [0.43-1.77]	Eczema in the first 2 years of life is associated with an increased risk of childhood asthma in boys, but there is no evidence of this in girls.
von Kobyletski et al, 2012	AD, eczema (ISAAC)	Population based birth cohort	3 214 children	To estimate the association between eczema in early childhood and the onset of asthma and rhinitis later in life	Risk of asthma : - if AD: OR3.07[1.795.27] - if moderate to severe AD :OR 3.56[1.62–7.83] -if early onset AD: OR 3.44[1.94–6.09] -if persistent AD: OR5.16[2.62–10.18]	Eczema in early childhood is strongly associated with the development of asthma
Saunes et al, 2012	Eczema (ISAAC)	Birth control cohort of an interventional study	2 192 children	To study the risk of current asthma and the co-existence of allergy-related diseases at 6 years of age among children with and without eczema at 2 years of age.	Estimate for the association between eczema at 2 years and current asthma at 6 years: OR=1.80[1.10-2.96]	Early eczema is associated with an increased risk of developing childhood asthma.
Carlsten et al, 2013	AD (presence of a pruritic rash on the face or extensor surface of the arms or legs and flexural lichenification at the time of examination by the allergist investigators)	High-risk cohort	373 children	To evaluate the natural history of AD and its association with other allergic outcomes	Risk of sensitization to aeroallergens at 2 years if associated AD: OR2.97[1.25-7.08](non persistent) and 4.06 [1.52-10.9] (persistent) Risk of asthma at 7 years if early-onset persistent AD: OR 7.48[2.53-22.2] Non-significant risk of sensitization or asthma if late-	Early-onset persistent AD is highly associated with atopic sensitization and increases the risk of atopic diseases in later childhood

					onset	
Silverberg et al, 2013	Eczema, AD (if "Yes" to the question: "During the past 12 months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?")	National survey	79 667 children	To determine the impact of eczema severity on the development of other comorbid conditions	Severe eczema was associated with a higher prevalence of comorbid chronic health disorders, including asthma, hay fever, and food allergies ($p < 0.0001$)	Severe eczema is associated with multiple comorbid chronic health disorders, impaired overall health, and increased healthcare utilization
Nissen et al, 2013	Eczema (Areas of scaly, erythematous and itchy eczematous rash primarily of the face and scalp, behind the ears and at the flexural folds, diagnosed by a doctor. Only eczema localized to at least two typical areas and chronically relapsing with duration of at least 3 months were recorded.)	Population-based birth cohort	276 children (193 at the 26 years follow-up)	To investigate the natural course of sensitization and allergic diseases in a random population-based sample of Danish children	Prevalence of current eczema stable during childhood Prevalence of current eczema decreased in adulthood Rates of sensitization increased from childhood to adulthood	Allergic diseases not only occur in childhood but persist into adulthood.
Eckbäck et al, 2014	Eczema (Hanifin & Rajka)	Patient cohort	123 children	To follow infants with eczema and suspected food allergy over time, focusing on sensitization to allergens, severity of eczema and the development of allergic airway symptoms at 4.5 and 10 years of age	Higher SCORAD on inclusion correlated with the risk of developing asthma: $\beta=10.17$ ($p=0.01$) If AD and wheezing before 2 years: OR for developing asthma 4.05 ($p = 0.01$)	Increased risk of asthma in case of severe AD Increased risk of asthma if concomitant early-onset AD and wheezing
Amat et al,	AD (UKWP and ISAAC)	Patient cohort	217 children	To define early-onset	Three clusters:	Multiple sensitization and

2015				AD phenotypes leading to asthma	- AD with low sensitization - AD with multiple sensitization - AD with familial history of asthma The two latter associated with higher frequency of asthma at age 6 ($p<0.001$)	familial history of asthma convey a higher risk of developing asthma during childhood in infants with early-onset, moderate to severe AD.
Lee et al, 2016	AD (ISAAC)	Patients from a population-based cohort	242 children	To define AD phenotypes in children aged 6–8 years	Four phenotypes: 'early onset with low atopy' (26.4% of the sample; group 1) 'early onset with high atopy and high eosinophil percentages' (48.3%; group 2) 'late onset with low atopy' (9.9%; group 3) 'late onset with high atopy and normal eosinophils' (15.3%; group 4) Persistence of AD, eosinophilia and asthma associated with group 2	An allergic march-associated AD phenotype exists that is characterized by early-onset, persistent AD and high atopy.

AD: atopic dermatitis; FS: food sensitization; FA: food allergy; PS: peanut sensitization; OR: odds ratio, 95% confidence interval expressed [-]; PA: peanut allergy; UKWP: United Working Party Criteria; ISAAC: International Study of Asthma and Allergies in Childhood; TEWL: transepidermal water-loss; EPE: environmental peanut exposure

*Terms between brackets specify the criteria used to define AD