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Eczema in early life: Genetics, the skin barrier, and lessons learned from birth cohort studies

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Abstract

Eczema is a chronic inflammatory disorder of the skin that affects up to 30% of children. It often afflicts infants in the first few months of life and can be the first indicator of the atopic march. Recent results from birth cohort studies have uncovered novel information regarding genetic and environmental factors that promote the development of eczema. Birth cohort studies provide an optimal study design to elucidate these associations and prospectively track longitudinal data including exposure assessment and health outcomes from birth into early life and childhood. This is especially relevant for eczema given the age specific emergence of this disease. In this review, we will provide a general overview of pediatric eczema and discuss the important findings in the literature with respect to genetics and environmental exposures, highlighting those derived from birth cohort studies. Additionally, we will review how these relate to the atopic march, the hygiene hypothesis and the integrity of the skin barrier.

Keywords

atopic march; hygiene hypothesis; genetics; skin barrier; environment; birth cohort study

Eczema Definition, Prevalence and Epidemiology

Eczema is a multi-factorial inflammatory skin disease, arising from the interplay of both genetic pre-disposition and environmental exposures. It a form of dermatitis, which constitutes local inflammation of the skin characterized by itching and redness. This chronic skin disorder is often associated with cutaneous hyper-reactivity and other atopic disorders such as allergic rhinitis and asthma (1,2). Also known as atopic dermatitis, eczema is the preferred term for skin inflammation associated with itchiness and rash according to the World Allergy Organization, because not all eczema is associated with IgE mediated sensitivity to allergens (3).

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The prevalence of eczema differs between developing and industrialized nations (4). In the past three decades, prevalence rates in industrialized nations have increased to as much as 15–30% of children and 2–10% of adults (1). As part of the International Study of Asthma and Allergies in Childhood (ISAAC), data on eczema prevalence was collected during phase one (1994–1995) and phase three (5–10 years after phase one) in 56 countries (5). These data revealed that, although 58% of participating centers reported an increase in eczema prevalence among older children (13–14 years), it has since seemed to plateau or decrease in nations with historically high eczema prevalence, such as Northwest Europe and New Zealand (5,6). Large increases in eczema prevalence, however, are now observed in developing countries such as Mexico, Chile, Kenya and southeast Asia among this age group (5). However, of younger children (6–7 years), 84% of participating centers reported increased prevalence of eczema among, with the highest increases seen in Western Europe, Canada, South America, Australasia and the Far East (5). These substantial differences argue that environmental factors and genetic predisposition are key players for eczema development worldwide (5). Further, the recent plateau in eczema prevalence in countries with historically high rates suggests there may be a finite number of persons susceptible to eczema development (5,7).

Pathology, Clinical Features and Immune Function in Eczema

The development of eczema has been described in three distinct stages defined by age of onset (infancy, childhood and adolescence/adulthood). Sixty percent of all eczema cases will appear during the first year of life (infantile eczema) (1). A total of 45% of all eczema develops in infants two to six months of age with itching, redness, and small bumps on the cheeks, forehead or scalp that may later spread to the trunk (1,8). The childhood phase of eczema eruption commonly occurs between the ages of four and ten, and is characterized by raised, itchy, scaly bumps on the face and/or trunk also accompanied by dryness and thickening of the skin (8). The adolescent/adult phase appears at or after the time of puberty and is distinguished by itchy, dry, scaly skin that may continue into adulthood (8). Despite the life stage, pruritic erythematous papules and plaques with secondary skin peeling are common to all stages.

Among individuals with eczema, there is considerable evidence for immune dysregulation, including increased serum IgE and allergen sensitization, increased T-helper cell 2 (Th2) cytokine expression in eczematous lesions, increased T-cells expressing cutaneous lymphocyte-associated antigen, increased FcεRI on Langerhans cells and inflammatory dendritic epidermal cells, and decreased expression of antimicrobial peptides (9–12). Atopic keratinocytes have a reduced ability to synthesize antimicrobial peptides, contributing to an increased susceptibility to bacterial and viral infection (9). Although there are many unanswered questions concerning the interplay of skin barrier dysfunction, immune dysregulation and susceptibility to microbial colonization in eczema, genetic pre-disposition is known to play a central role the pathophysiology of eczema (10,13).

Genetics of Eczema

Strong evidence exists in the literature to support a genetic predisposition to eczema. The risk of childhood eczema is two to three times higher in children with a maternal or paternal history, irrespective of parent sex or body region affected (14,15). Twin studies show high concordance rates for eczema among monozygotic twins, ranging from 72 to 86% (16,17).

Genome wide scans have identified several possible eczema related loci on chromosomes 1q21, 3q21, 16q, 17q25 and 3p26, most notably 1q21 which harbors a family of epithelium related genes called the epidermal differentiation complex (EDC) (1,18–21). Genes in the EDC have been reported to have significantly altered expression in the skin of patients with eczema (20,22). Recent research has highlighted the importance of the skin barrier and genes related to barrier dysfunction in the pathogenesis of skin disorders (1,23–27).

The single most replicated gene in eczema studies is filaggrin (FLG), reported in 21 independent studies (27,28). FLG is a keratinocyte protein which is a key component in the granular cell layer of the skin (29,30). The FLG gene was first cloned in 1989 and hypothesized to have an important role in disorders of keratinazation because of its key role in the terminal differentiation of the epidermis (27,31,32). Smith et al. were the first group to identify two mutations in FLG (R501X and 2282del4) in patients with ichthyosis vulgaris (33). Data from eight pedigrees of families with ichthyosis vulgaris strongly supported that FLG null alleles predispose to eczema (34), and these results have been confirmed many times over in multiple ethnic populations including Caucasians from multiple European countries as well as the Japanese (27). FLG null alleles have also been shown to predispose to early onset eczema that persists into adulthood (35). It has been estimated that 50% of all eczema cases can be explained by the presence of one FLG null allele (29).

Among individuals with eczema, studies suggest that the FLG null alleles predispose to asthma (34,36–40), allergic rhinitis (36,39) and allergen sensitization (38). Thus, the FLG null alleles may predispose to the sequential eruption of allergic rhinitis and asthma, supporting the atopic march theory (36). Skin inflammation associated with eczema is typically associated with increased cytokine expression, mainly IL-4 and IL-13, which reduces FLG function and expression (41).

During formation of the cornified cell envelope, profilaggrin is dephosphorylated and cleaved by serine proteases ending in the release of functional FLG (42). A series of inhibitors control the protease activity, and serine peptidase inhibitor Kazal-type 5 (SPINK5) is the best characterized of these inhibitors (42). Genetic variation in SPINK5 has also been associated with eczema in multiple studies (43–45), although its physiological functions are not completely understood. Therefore, immune and skin barrier related genetic variations may work synergistically to increase susceptibility to eczema.

Indeed, there are two predominant groups of genes that have been associated with eczema: genes that encode epidermal or epithelial structural proteins, such as FLG and SPINK5, and genes that encode for major elements in the immune system, such as interleukin (IL) 4, IL5, and IL13, which promote allergic inflammation (1). The most replicated immune genes associated with eczema are *IL-4*, *IL-4* Receptor alpha (*IL4R*), *IL-13*, mast cell chymase 1 (*CMA1*) and CD14 (36,46–49). IL-4 promotes the development of Th2 cells in allergic inflammation and decreases gene expression in the EDC that contribute to barrier function and innate immune defense (41,50–52). *IL-13* promotes tissue inflammation and is up-regulated in eczematous skin lesions (9,50). Multiple SNPs in *IL-13* have been significantly associated with eczema in Canadian, Japanese, Dutch, and German populations. Furthermore, *IL-13* haplotypes have been associated with eczema in Caucasian infants during the first year of life (49,53–56). *IL-4* and *IL-13* also share a common receptor subunit, *IL4Rα* (57), and SNPs in *IL4Rα* have also been identified in subjects with eczema (46,49,58–63).

Mast cell chymase has numerous activities that contribute to inflammation including activation of interstitial pro-collagenase (64), process pro-collagen into collagen (65), and release of transforming-growth-factor beta 1 (TGF-β1) from the extracellular matrix of epithelial cells (66). Mao et al. observed a significant association between *CMA1* genetic variation and eczema in 851 Japanese school children aged 12–13 years (67), and these results have since been replicated in several studies (67–71). Functional studies are still needed to determine if this polymorphism has a role in the expression of chymase, which is increased in chronic eczematous skin lesions (68,72).

CD14 is a surface protein preferentially expressed on monocytes and macrophages (73,74). It binds lipopolysaccharide (LPS) binding protein, which activates these cells to produce pro-

inflammatory cytokines such as TNFα, IL-1 and IL-6 (73,75). Recently, the role of CD14 and dog exposure, as a surrogate for LPS, were evaluated with eczema outcomes in the first three years of life (76). Children who were carriers of the CC genotype of the CD14 −159C/T SNP were significantly more likely to have developed eczema by age three and have eczema at both ages two and three (76). This effect was most pronounced among children that did not have a pet dog. Similarly, Lange et al. found that the CT genotype of the −159C/T polymorphism conferred protection from eczema development (77). Of the three studies assessing the association of eczema and CD14 with respect to dog exposure, two reported significant gene by environment interactions (76,78) and one showed no association (79). These inconsistent findings may be due to the presence of additional environmental modifiers, as well as differences in the inclusion criteria.

The Importance of the Skin Barrier

The upper epidermal layer of human skin functions as a physical and chemical barrier, consisting of a brick an mortar like structure called the stratum corneum (1). There is a great deal of evidence in the literature that support a role for skin barrier dysfunction in eczema (80). As discussed above, mutations in the FLG gene, which contributes to the assembly of the stratum corneum, are associated with development of eczema (1). Assessment of transepidermal water loss (TEWL) is one method that has been used to quantify skin barrier function. Changes in the epidermal lipids caused by water loss allow cracks to develop in the stratum corneum, allowing penetration of external antigens, irritants and microbial pathogens, that can trigger further inflammation (81,82). In one recent study, a cohort of children aged 5–18 were assessed for eczema based on diagnostic criteria previously described (83) and the SCORAD index (84). TEWL measurements were taken from non-lesional skin on the cheek, forearm, and lower leg (84). TEWL measurements among eczema cases were significantly higher compared to allergic and non-allergic controls (84). Further, TEWL measured on the forearm correlated with disease severity. Thus, skin barrier function as assessed by TEWL is intrinsically compromised in children with AD but not in children with other allergic conditions, and the magnitude of skin barrier dysfunction correlates with AD disease severity (84). A 2009 study evaluated TEWL within the context of FLG mutations in 24 adults. The authors observed significant correlations between eczema severity (assessed by SCORAD score and TEWL measurements) and FLG-related eczema, but not with non-FLG related eczema, supporting a role for FLG as a determinant of skin barrier function and eczema severity (85).

In subjects with early-onset eczema, IgE sensitization often occurs weeks or months after eczematous lesions appear, suggesting the skin as the initial site of allergen introduction (1). Compromised skin can allow pollen and food allergens to penetrate the cornified envelope and interface with antigen-presenting cells, which can lead to initiation of a Th2 response by dendritic cells depending on the cytokine environment and intrinsic properties of the host (86). Once this cascade is initiated, the response is long-lasting and can result in sensitization of the host, with subsequent exposures leading to symptoms of allergic rhinitis and asthma (86).

In addition to permeability barrier dysfunction, subjects with eczema also have compromised antimicrobial barrier function, leading to increased skin infections. The skin is equipped with toll-like receptors that activate the epithelial cells upon binding to fungal, bacterial or viral structures and stimulate production of antimicrobial peptides (1,87). However, the allergic inflammation in patients with eczema leads to down-regulation of several antimicrobial peptides (1,12,51,88).

Environmental Factors and the Hygiene Hypothesis

Environmental factors have been implicated in allergic disease, including eczema. The role of environmental tobacco smoke (ETS) in allergic disease has been an area of extensive study. There is a clear association between lower airway disease and ETS exposures (89), but the association between ETS and eczema is not as consistent. Studies have reported associations between eczema and the number of cigarettes smoked in the home with urine cotinine (90), and maternal smoking during pregnancy (91). A 2008 study of 261 infant mother pairs evaluated the association of eczema at age two with cord and maternal serum cotinine levels (92). The authors observed that the risk of eczema increased with maternal and cord blood cotinine levels in a dose-dependent manner (92). Other studies have reported no associations between ETS and eczema (93–95). There is some evidence that ETS exposure may impact skin barrier function. In one study, investigators measured TEWL on the cheek area of 100 volunteers that were either active, passive, or non-smokers (96). The authors observed a lower TEWL measurements in non-smokers compared to both active and passive smokers, independent of age and sun exposure ($p<0.001$) (96). Thus, ETS exposure may have a role in the breakdown of the skin barrier that is associated with eczema development.

Polycyclic aromatic hydrocarbons (PAH), an environmental pollutant found in cigarette smoke and automobile exhaust, have also been investigated for associations with eczema. PAHs bind to the aryl-hydrocarbon receptor (AhR) and activate transcription (97). Tauchi et al. demonstrated that transgenic mice expressing the constitutively active form of AhR in keratinocytes developed severe skin lesions and itching accompanied by inflammation that resembled eczema (98). This suggested that PAH may have a direct effect on keratinocytes as well as indirect effects on cutaneous inflammation (98).

Allergic diseases, including eczema, are more prominent among peoples living in western, industrialized countries rather than in developing nations (99). Eczema is also more common in urban versus rural communities, and tends to target children growing up in smaller families of higher socioeconomic status (99–103). The hygiene hypothesis, conceived in 1989 by Strachan and Cook (104), theorizes that larger family size and increased exposures to early life infections lead to a decreased risk of allergic disease development (102,105).

Studies have demonstrated associations between increased risk of eczema with daycare attendance, and there was a decreased risk among children with a higher number of siblings and those living with a dog (99). Although evidence suggts that dog exposure may confer protection from disease development, there is no clear association with cat or any other furry animal exposure (106).

Studies on differences in intestinal flora in children with and without allergies are inconsistent, although differences have been observed. Wang et al. found a reduced diversity of early fecal microbiotica in infants aged 18 months with eczema compared to healthy controls (107). Children that do not develop allergies during the first two years of life are more likely to be colonized with enterococci and bifidobacteria (108), and colonization by clostridia is associated with allergy development (108–110). These results support the hygiene hypothesis and suggest that diversity in the early microbiotica might be important in allergy development and prevention (107).

The Atopic March and Birth Cohort Studies

Several prospective longitudinal studies have provided evidence for the atopic march from eczema to the development of allergic rhinitis and asthma (111–113). A systematic review of the risk of asthma development in children with eczema during the first four years of life reported a pooled odds ratio of 2.14 (95%CI 1.67–2.75) for asthma (114), which is lower than

originally estimated, but still supports the hypothesis of the atopic march from eczema to asthma.

Given the natural history of eczema, birth cohorts provide an optimum study design to evaluate eczema development and progression in early life. Many birth cohort studies designed to examine asthma and allergic diseases have been implemented in both European countries and the US. Although almost all of these studies aim to evaluate environmental contributions to asthma and allergic diseases, only a few of these cohorts are designed to evaluate both environment and genetics concurrently, which is important given the well-documented genetic contributions to these complex diseases. The birth cohorts discussed in this review are summarized in the Table.

One of the first birth cohort studies to evaluate eczema began in Denmark in 1985 (115). The children (n=276) were followed up at 6, 12 and 18 months and at 5, 10, and 15 years of age to investigate the natural course of sensitization and development of atopic diseases in childhood (115). Their results mirrored the progression of the atopic march. Since then, many other larger birth cohort studies have been implemented.

The largest of these is the Avon Longitudinal Study of Parents and Children (ALSPAC) study (15,116). ALSPAC is an ongoing birth cohort study that initially enrolled 14,541 mothers in their eighth week of pregnancy in the county of Avon, UK, between 1991 and 1992. The study collected parental and child completed questionnaires, biological samples including cord blood, a piece of the umbilical cord and placenta, hair and toe nail samples, teeth, blood, urine and saliva, as well as clinical assessments on a myriad of health outcomes including asthma, eczema, atopy and allergies (116). The study has also collected measurements from environmental monitors placed in the home regarding air pollutants and radiation (116). This birth cohort was designed to evaluate the genetic influences on disease as well; the ALSPAC DNA bank is comprised of 10,232 child samples, 10,364 mothers and 700 validated trios (117). Parental lifetime histories of eczema, asthma and hay fever as well as the child's eczema symptoms at 6, 18, 30 and 42 months were collected (15). Children whose mothers reported itchy rash in the joints or creases or oozy crusty rashes on the face, forearms or shins at least two times in the follow-up questionnaires were defined as having eczema (15). The authors found a strong association between parental and childhood eczema, regardless of which parent had eczema. There was no association of childhood eczema with parental asthma and hay fever (15). Their findings support the hypothesis that eczema has a polygenic etiology and suggests genes associated with parental eczema are more strongly associated with child eczema than genes related to asthma and hay fever (15). The ALSPAC group has also confirmed the importance of filaggrin mutations in the development of eczema and 'eczema plus asthma' phenotypes in children (38) and observed an association of the Il4R gene with eczema in children without infections requiring antibiotics, supporting the hygiene hypothesis (58). In the future, this study is well poised to contribute greatly to the literature in the area of genetics and allergic diseases.

Another large birth cohort evaluating allergic diseases is the BAMSE (B=barn (children), A=allergy, M=milieu (environment), S=Stockholm, E=epidemiology) (118,119) project with a sample size of 4089 children. BAMSE aims to evaluate the role of genetics, socio-economics, environment, diet and infections on the development of asthma, eczema and allergic diseases in children (120). The authors of the BAMSE cohort have published a protective effect for eczema with breast feeding (121) an increased risk with symptoms to pollen and fruit exposure in early life (119), and no relationship between eczema and anthropometric measures (122).

Other large birth cohorts (n > 1000) evaluating allergic diseases in children include the Isle of Wight Study (N=1456) (123), the Prevention and Incidence of Asthma and Mite Allergy

(PIAMA) study in the Netherlands (n=3291) (124), the Environment and Childhood Asthma (ECA) study in Norway (n=3754) (125), the German Infant Nutritional Intervention Study (GINI) (n=3739) (126), the Lifestyle-related Factors in the Immune System/Development of Allergies in Children (LISA) study in Germany (n=3097) (127) and the Study of Eczema/Asthma to Observe Influence on Nutrition (SEATON) study in the UK (n=1924) (128). In the Isle of Wight study, atopy, rhinitis, food allergy and maternal asthma have all been identified as independent risk factors for eczema at age 10 (129). Infants participating in the PIAMA study were at an increased risk of eczema if they had a higher birth weight or attended daycare, and exclusive breastfeeding for at least three months was protective (130). The GINI study has reported an increase in eczema risk in 6 year olds with early sensitization foods and aeroallergens (131), as well as an increase in eczema risk at age four with avoidance of eggs in the first year of life (132). In contrast, children who avoided soybeans and nuts in the first year of life had a decreased risk of eczema at age four (132). In 2008, Morgenstern et al. evaluated air pollution exposures and allergic disease development in children aged four and six participating in either the GINI or LISA cohorts. The authors found strong positive associations between distance to the nearest main road and asthmatic bronchitis, hay fever, eczema and sensitization, with the highest odds ratios observed for those living within 50 meters of a busy street (133). An association was also observed between eczema and nitrogen dioxide levels at the residential address, assessed by regression models of air pollution measurements (133). An increase in eczema development has also been reported with margarine consumption (134) and early life stressors such as parental divorce (135) in children participating in the LISA study. In the SEATON cohort, children born to atopic mothers that consume higher amounts of vitamin E during pregnancy were less likely to develop eczema and wheeze without a cold in the first two years of life (136), consistent with the hypothesis that antioxidant intake during pregnancy may modulate susceptibility to allergic diseases (137).

Some birth cohort studies have selected high-risk populations, which enrich allergy-associated alleles, thereby increasing power to detect genetic and gene-environment interactions (120). The German Multicenter Allergy Study (GMAS) was developed in 1990 and includes 1314 children, 499 of which are considered high risk due to having two atopic first-degree relatives and/or cold blood IgE $\geq$ 0.9kU/l, as discussed above (138). The children are followed-up several times until age two, and annually thereafter until the age of ten. GMAS participants also undergo pulmonary function testing and bronchial challenges at age seven, and DNA samples, cord blood and IgE measurements are collected. Questionnaires results provide data regarding atopic symptoms, nutrition, environmental factors, housing conditions, psychological problems and demographics. This study aims to assess the impact of immunizations, allergen exposures, early sensitization and upper airway infections on development of allergy and atopy in children (138,139). The GMAS investigators have evaluated the natural course of eczema and how it relates to asthma development in the participating children at age seven. They observed that the association of atopic sensitization and early eczema (onset in the first two years) was strongest when the onset of sensitization was before age one (140). The authors also found early eczema development to be significantly associated with wheeze and bronchial hyper-reactivity at age seven (140). Food sensitization was a strong predictor of asthma development and airway hyperresponsiveness until school age, regardless of inhalant sensitization (140). Interestingly, food allergen sensitivity usually develops in the first few months of life until age 2 years, and inhalant allergen sensitization develops later (141) another indicator that early life atopic status may be more predictive of asthma development than childhood allergy.

The Childhood Origins of Asthma (COAST) study is a birth cohort studying wheezing and subsequent asthma development in high risk children enrolled in 1998–2000 (142,143). Eligible participants in COAST (n=287) had at least one parent with a positive SPT and/or a

physician diagnosis of asthma (142). The children are examined annually and undergo pulmonary function tests including eNO, post-bronchodilator reversibility, impulse oscillometry and spirometry, SPT testing, DNA and nasal mucus collection, sputum induction and plethysmography. The aims of the COAST study are to evaluate associations of cytokine dysregulation response at birth as well as lower respiratory tract viral infection, specifically respiratory syncytial virus, with development of persistent wheezing in children. With regards to the atopic march, COAST has evaluated risk factors for the expression and persistence of eczema. Of the 65 high-risk infants that developed eczema during infancy, 46% had persistence of the disease to age five (144). The persistent expression of eczema into early childhood was associated with differences in immunological profiles, measured from cord and peripheral blood, and the presence of wheezing (144). As in the GMAS study, there was a strong association between food allergen sensitization, specifically egg, and asthma development by age six (145), however, this group also found a associations with aeroallergen sensitization and asthma (146) and persistent wheezing (147). As this cohort ages and additional objective measures of asthma are collected annually, this study is well designed to evaluate not only the atopic march in high-risk children, but also the early life predictors of persistent asthma and severity of disease in children and adolescents.

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is a high-risk birth cohort (n=762) uniquely poised to evaluate environmental and genetic associations with the development and progression of allergic disease and asthma. Newborns identified from birth records were enrolled if at least one parent had an allergy symptom and a positive skin prick test (SPT) (148). This study was designed in 2001 to determine the effects of environmental exposures, specifically diesel exhaust, on asthma and allergy development in children, and how these associations are modified by genotype and other factors. At annual visits starting at age one, children are examined for clinical symptoms of asthma and allergic disease, parents report detailed information on allergy and asthma symptoms, medical history, environmental exposures, diet and demographics, skin prick testing is performed and DNA, nasal swabs for eosinophils and hair samples for nicotine and cotinine analysis are taken (149). Dust samples are taken from the children's primary activity room and bedroom to determine home allergen levels and endotoxin exposures. The children are currently being evaluated for definitive asthma at age seven and pulmonary function tests including spirometry, exhaled nitric oxide (eNO) measurements, post-bronchodilator reversibility and methacholine challenge tests are being performed. The CCAAPS investigators have reported significant associations between SPT results and eczema. Children that were SPT+ by the age of three were significantly more likely to have eczema at age three or at both ages two and three (76). Further, those children that had a SPT+ to milk or egg allergen were at the highest risk for eczema development at ages one, two and three (76). This same study also reported that children with exposure to dog (s) were significantly less likely to develop eczema at age one or at both ages two and three, and this finding was most significant among children carrying the CC genotype of the CD14 −159C/T SNP. Even though the children in this study are still being examined for definitive diagnosis of asthma, this study is well-suited to dissect the associations of allergic sensitization, eczema, allergic rhinitis and asthma as they pertain to the atopic march in the future.

The Urban Environment and Childhood Asthma (URECA) birth cohort study was implemented in 2004 and enrolled 560 inner-city children who have at least one parent with allergic disease or asthma during the prenatal period (150). The overall aim of this study is to determine how specific urban exposures, including immune response (genetics), allergens, pollution, infection, microbes, stress, diet, altered innate and adaptive immune responses and lower respiratory infection affect childhood persistent wheeze and asthma. The participants will be followed-up until the age of seven. This study proposes the most inclusive environmental and genetic factors currently studied by CCAAPS, COAST and GMAS, and expands to include unique measures of urban life during pregnancy and throughout the study such as anxiety,

depression, life circumstances, neighborhood conditions, and support networks, as well as measurements of bioelectrical impedance analysis and airborne nicotine and NO_2 in the home. This study is also unique in that they enrolled a concurrent non-allergic control group (n=49). Although this cohort is still in the early stages, it is poised to analyze the natural course of allergic diseases up to age seven, specifically in high-risk, urban, low-income children, a population which had not been specifically targeted by previous asthma cohorts.

These unique resources have and will continue to allow researchers to better understand the environmental and genetic factors that lead to allergic disease development. Further, these studies also serve to generate new hypotheses exploring the underlying mechanisms of all allergic diseases, including eczema, as well as the atopic march.

Summary

Eczema is a heterogeneous disease that is highly prevalent in populations worldwide. Birth cohort studies have been instrumental in advancing our knowledge of eczema and uncovering genetic and environmental factors that promote its development. The literature thus far implicates two distinct groups of genes involved in eczema. These include genes that contribute to the skin barrier and integrity of the cornified envelope and genes involved in innate and adaptive immunity. Early sensitization through the skin may be the first step in the atopic march, leading from eczema and food allergy in infancy to allergic rhinitis and asthma in childhood and adolescence. Birth cohort studies, which are designed to evaluate environmental and genetic risk factors simultaneously, are the key to unraveling the mechanistic basis of eczema development.

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Abbreviations

ISAAC	International Study of Asthma and Allergies in Childhood
Th2	T-helper Cell 2
EDC	Epidermal Differentiation Complex
SPINK5	Serine peptidase inhibitor Kazal-type 5
IL	Interleukin
IL4Rα	Interleukin 4 Receptor Alpha
TNFα	Tumor Necrosis Factor Alpha
CMA1	Mast Cell Chymase 1
SNP	Single Nucleotide Polymorphism
LPS	Lipopolysaccharide
LEKTI	Lymphoepithelial Kazal-type Inhibitor
SSCE	Stratum Corneum Chymotryptic Enzyme
FLG	Filaggrin
TEWL	Transepidermal Water Loss
S.aureus	Staphylococcus aureus
ETS	Environmental Tobacco Smoke

PAH	Polycyclic Aromatic Hydrocarbons
AhR	Aryl-hydrocarbon Receptor
ALSPAC	Avon Longitudinal Study of Parents and Children
BAMSE, B	children, A=allergy, M=environment, S=Stockholm, E=epidemiology
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
ECA	Environment and Childhood Asthma
GINI	German Infant Nutritional Intervention Study
LISA	Lifestyle-related Ractors in th Immune System/Development of Allergies in Children
SEATON	Study of Eczema/Asthma to Observe Influence on Nutrition
GMAS	German Multicenter Allergy Study
COAST	Childhood Origins of Asthma
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
SPT	Skin Prick Test
eNO	Exhaled Nitric Oxide
URECA	Urban Environment and Childhood Asthma

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Table 1

Select birth cohort studies evaluating atopic diseases.

Study Name	Start	N	Age at Follow-up	Outcome Measures	Predictors of Disease	Main Eczema Findings
Denmark	1985	276	6, 12, 18 months; 5, 10, 15 years	asthma, allergic rhinitis, eczema	environmental factors	results mirrored atopic march
ALSPAC	1991	14541	6, 18, 30 and 42 months	asthma, eczema, atopy and allergies, food allergy	environmental and genetic factors	parental eczema, FLG and IL4R are associated with childhood eczema
BAMSE	1994	4089	1, 2, 4 and 8 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	increased risk of eczema with early symptoms to pollen and fruit exposures, protective effect from breastfeeding
Isle of Wight	1989	1456	10 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	atopy, rhinitis, food allergy and maternal asthma predict childhood eczema
PIAMA	1996	3291	3 months, annually after birth until age 8	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	increased risk of eczema with higher birth weight and daycare attendance; protective effect from breastfeeding
ECA	1992	3754	2 and 10 years	asthma, allergic rhinitis, eczema	environmental and genetic factors	children with eczema had decreased time to peak tidal expiratory flow/total expiratory time at age 2
GINI	1995	5991	1, 2, 3, 4, 6 and 10 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	increased risk of eczema observed with shorter distance to a main road* and NO(2) exposure; decreased risk of eczema with hydrolyzed infant formula consumption; early sensitization increases eczema risk at age 6.
LISA	1997	3097	0.5, 1, 1.5, 2, 4, and 6 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	decreased risk of eczema with endotoxin exposure and maternal fish intake; increased risk with personal and maternal margarine/butter consumption and parental divorce.
SEATON	1997	1924	0.5, 1, 2, 5 years	asthma, allergic rhinitis, eczema	environmental factors	maternal consumption of vitamin E and fish during pregnancy decreases eczema risk
GMAS	1990	1314	3, 6, 12, 18 and 24 months; annually thereafter	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	early onset of sensitization, food sensitization, wheeze and bronchial hyper-responsiveness and parental eczema is associated with increased risk of eczema
COAST	1998	287	birth and then annually to age 13	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	dog exposure associated with decreased risk of eczema; viral respiratory illness, wheezing, sensitization to food or aeroallergen or food allergy in the first year associated with persistent atopic eczema
CCAAPS	2001	762	1, 2, 3, 4 and 7 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	aeroallergen and food sensitization associated with increased risk of eczema; dog ownership decreases eczema risk; associations with CD14 and IL4Ra genes
URECA	2004	560	3 months, 1, 2, 2.75, 3, 4, 5, 6, 6.75 and 7 years	asthma, allergic rhinitis, eczema, food allergy	environmental and genetic factors	not yet published

*This finding also includes subjects in the LISA cohort.