Early Childhood Atopic Phenotypes and the Development of Allergic Respiratory Disease

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To the Editor,

Pediatric atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disorder that affects up to 20% of children worldwide[1]. Often the earliest sign of atopy, AD has been recognized as the start of the "atopic march", described as the progression of AD to allergic respiratory diseases (ARD) including asthma and allergic rhinitis[2]. Although these atopic conditions often share a common T2 enriched pathway influenced by both genetic and environmental factors, not all children with AD have subsequent risk of ARD. Additionally, recent investigations dispute the theory that the temporal progression of the atopic march occurs in a sequential pattern[3]. Early AD can facilitate allergen sensitization due to a dysfunctional skin barrier[4]. Both aeroallergen and food sensitization has been associated with risk of ARD[5], but it is less clear whether AD may partially mediate that risk. Additionally, food allergy has been recognized to be part of the atopic march, however its role in the march to ARD is less well identified. It is also unclear how these risks may appear in ethnically diverse populations. Distinct atopic phenotypes may better predict risk of ARD. Our objective was to identify whether associations between early food sensitization, aeroallergen sensitization, or food allergy (FA) and the subsequent risk of ARD by age 10 was modified by the development of early AD by age 2 years.

We analyzed data from our racially and socioeconomically diverse birth cohort, Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) that enrolled pregnant women 21–45 years of age and their offspring. Recruitment period was from September 2003–December 2007. Eligibility and recruitment are described in previous publications [6] and all study protocols were approved by the Henry Ford Health System Institutional Review Board.

Offspring sensitization to aeroallergens (*Alternaria,* cat, cockroach, dog, *Dermatophagoides farina,* ragweed, timothy grass), milk, egg, or peanut was determined at 2 years of age by sIgE[?]0.35 IU/mL and skin prick testing (SPT; wheal size [?]3 mm larger than the saline control defined a positive test). As sensitization does not always translate to clinical allergy, we also formed an algorithm to determine those most likely to have true IgE-mediated food allergy[7]. Two allergists reviewed subjects with at least one of the following criteria: (1) at least one food (milk, egg or peanut) with sIgE [?]0.35 IU/mL; (2) a positive SPT; or (3) parental report of infant symptoms potentially related to food allergy plus at least one sIgE >0.10 IU/mL. To standardize classifying infants to the presence of IgE-mediated food allergy (IgE-FA), physicians were asked to combine professional experience with investigator-developed protocols based on the Guidelines for the Diagnosis and Management of Food Allergy in the United States[8]. A third allergist independently reviewed and ruled on discordant decisions. Data on asthma and AR by age 10 diagnosed by the study physician was collected

using clinical history, physical exam, spirometry, and methacholine test.

Adjusted relative risk (aRR) was calculated using Poisson regression with robust error variance and following adjustment for sex, child's race, parental history of asthma, parental history of AR, BMI z-score at age 2, delivery mode, 1-month breastfeeding status, prenatal indoor dog exposure, prenatal indoor cat exposure, and 1-month daycare status.

Of the 1258 mother-child pairs enrolled in WHEALS, 347 had sufficient data for analyses (Supplemental Figure 1). Demographics are shown in Table 1. The overall rate of early AD by age 2 years was 25.4% (88 out of 347 subjects). Supplemental Table 1 shows the overall rates of asthma and allergic rhinitis by age 10 by 2-year AD status. AD by age 2 years significantly modified the association between FA at 3-5 years and the risk of ever having asthma by age 10 (p=0.027) (Figure 1). In the absence of AD, FA to milk, egg, or peanut was associated with an increased risk of ever having asthma (aRR 3.36(1.71, 6.58), p<0.001), while no difference was observed in the presence of AD (aRR 1.24(0.57, 2.68), p=0.99). Food sensitization in the absence of AD was associated with increased risk of ever asthma (aRR 2.04(1.03, 4.05), p=0.038), but was not associated with ever AR (aRR 1.10(0.81, 1.48), p=0.97). Food sensitization in the presence of AD was not associated with ever asthma (aRR 0.89(0.45,1.78), p=0.99) or ever allergic rhinitis (aRR 1.45(0.97-2.16), p=0.078).

In terms of aeroallergen sensitization, AD by age 2 did not significantly modify the association between aeroallergen sensitization at age 2 and the risk of ARD by age 10. This was true for aeroallergen sensitization overall and when sub-analyzed by seasonal versus perennial (Table 2, Figure 1). However, among those without AD by age 2, perennial aeroallergen sensitization was associated with an increased risk of ever having asthma by age 10 (aRR 2.15 (1.06, 4.36), p=0.031). This association was not significant for those with AD by age 2 (aRR 1.68 (0.78, 3.63), p=0.26).

Our findings among a racially and socioeconomically diverse birth cohort suggest that early AD modifies the relationship between FA and the risk of ever having asthma by age 10. However, the association between FA and increased risk of ever having asthma was only seen among those without AD by age 2, which does not support the previously reported atopic progression of disease as described by the atopic march. This held true after correcting for several environmental and parental factors that may increase risk of ARD in our cohort. Our findings may represent a distinct atopic phenotype more characteristic among non-White subgroups, as our cohort is 67% self-identified Black. Previous reports have highlighted the differences in AD phenotypes among ethnically diverse subgroups[9]. Additionally, recent reports highlight atopic trajectories differ among White and Black children, with Black children more likely to have asthma without FA, AR, or allergen sensitization[10]. Due to sample size, we were unable to assess the differing trajectories in whites versus blacks. However, because our cohort is composed of 64.8% black children, we believe that black race may be contributing to the outcomes of our study as previous studies have reported atopic trajectories that are different in Black children[10]. Future studies investigating these endotypes that differ by ethnicity would be beneficial to identify potential immunological markers that would guide therapies for ethnically diverse populations and allow appropriate anticipatory guidance.

Keywords : Atopic march, atopic dermatitis, food allergy, food sensitization, aeroallergen sensitization, asthma, allergic rhinitis

Key message: Identifying early atopic phenotypes may help identify later ARD risk. This study reiterates that the "march" is not always a chronological process, but rather a complex relationship between heterogenous allergic phenotypes.

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Table 1. Demographics of WHEALS Sub-Cohort

Variable	Response	N (%) (N=347)
Child's Race	Not Black	122 (35.2%)
	Black	225 (64.8%)
Child Sex	Male	187 (53.9%)
	Female	160 (46.1%)
Parental History (Mom or Dad) of Doctor Diagnosed Hay Fever or Allergic Rhinitis Ever	Yes	75 (26.0%)
	No	213 (74.0%)
Parental History (Mom or Dad) of Doctor Diagnosed Asthma Ever	Yes	96 (30.7%)
	No	217 (69.3%)
BMI Z-Score at age 2	Mean ± SD	0.2 ± 1.1
Mode of Delivery	Vaginal	224 (64.6%)
	C-section	123 (35.4%)
Breastfeeding Status at 1-month	Never Breastfed	69 (20.2%)
	Breastfed + Formula	224 (65.7%)
	Breastfed Exclusive	48 (14.1%)
Prenatal Indoor Dog Exposure	Yes	96 (27.7%)
	No	251 (72.3%)
Prenatal Indoor Cat Exposure	Yes	55 (15.9%)
	No	292 (84.1%)
Daycare Attendance at 1-month	Yes	9 (2.7%)
	No	326 (97.3%)

Figure 1: Effect modification of AD between early life exposures and ARD

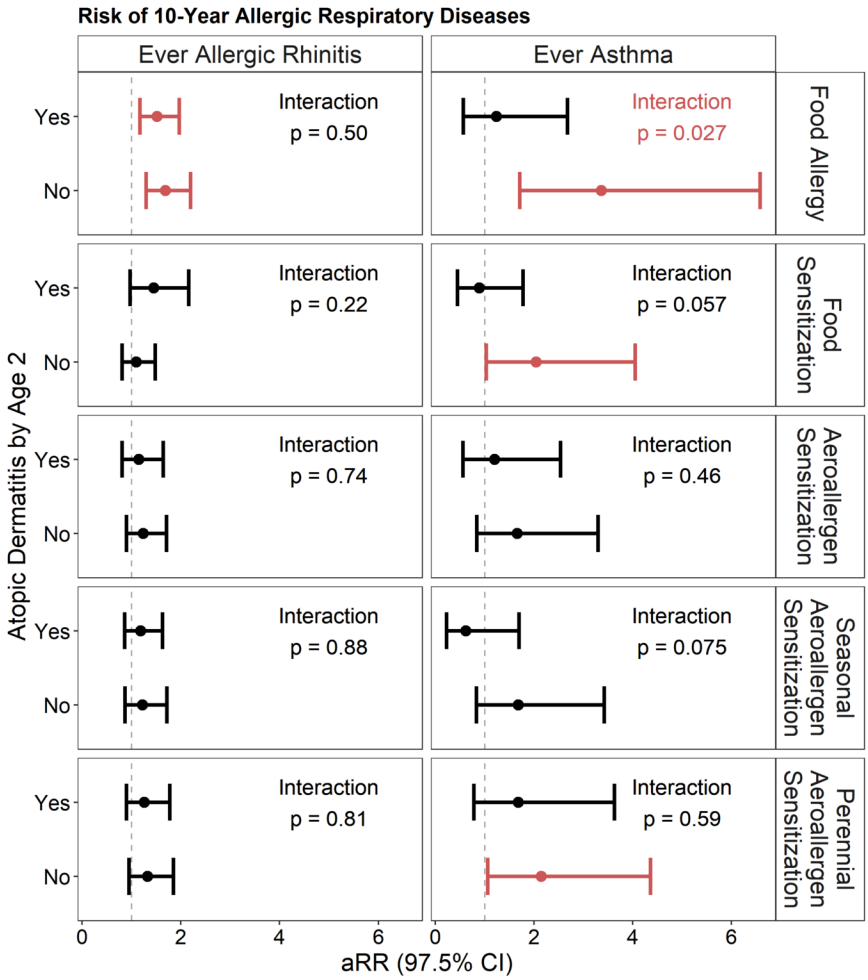

Table 2. Effect modification of AD between early life exposures and ARD

10-Year Outcome	Early Life Exposure	AD by age 2 years	aRR (97.5% Confidence Inte
Ever Asthma	**Physician-panel food allergy**	**Yes**	**1.24 (0.57, 2.68)**
		No	**3.36 (1.71, 6.58)**
Ever AR		**Yes**	**1.52 (1.17, 1.97)**
		No	**1.69 (1.30, 2.20)**
Ever Asthma	**Food sensitization**	**Yes**	**0.89 (0.45, 1.78)**
		No	**2.04 (1.03, 4.05)**
Ever AR		**Yes**	**1.45 (0.97, 2.16)**
		No	**1.10 (0.81, 1.48)**
Ever Asthma	**Aeroallergen sensitization**	**Yes**	**1.20 (0.56, 2.54)**
		No	**1.66 (0.84, 3.30)**
Ever AR		**Yes**	**1.15 (0.81, 1.64)**
		No	**1.24 (0.90, 1.71)**
Ever Asthma	**Seasonal Aeroallergen Sensitization**	Yes	0.62 (0.23, 1.70)
		No	1.68 (0.83, 3.42)
Ever AR		Yes	1.19 (0.86, 1.63)
		No	1.22 (0.87, 1.72)

Ever Asthma	**Perennial Aeroallergen Sensitization**	Yes	1.68 (0.78, 3.63)
		No	2.15 (1.06, 4.36)
Ever AR		Yes	1.26 (0.90, 1.78)
		No	1.33 (0.95, 1.85)

[A] P-values are Bonferroni-corrected, and 97.5% confidence intervals are reported to correspond to this correction.

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