

Atopic phenotypes identified with latent class analyses at age 2 years

Suzanne Havstad, MA,^a Christine Cole Johnson, PhD,^a Haejin Kim, MD,^b Albert M. Levin, PhD,^a Edward M. Zoratti, MD,^b Christine L. M. Joseph, PhD,^a Dennis R. Ownby, MD,^c and Ganesa Wegienka, PhD^a *Detroit, Mich, and Augusta, Ga*

Background: Atopic sensitization (ie, atopy) is the most commonly reported risk factor for asthma. Recent studies have begun to suggest that atopy, as conventionally defined, might be an umbrella term that obscures more specific allergic disease types.

Objective: We sought to determine whether distinct and meaningful atopic phenotypes exist within a racially diverse birth cohort using 10 allergen-specific serum IgE (sIgE) measurements from children aged 2 years.

Methods: Using the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort (62% black), we analyzed sIgE data on 10 allergens (*Dermatophagoides farinae*, dog, cat, timothy grass, ragweed, *Alternaria alternata*, egg, peanut, milk, and German cockroach) obtained from 594 children at age 2 years. Conventional atopy was defined as at least 1 sIgE level of 0.35 IU/mL or greater.

Results: A 4-class solution (latent class model) was the best fit. Class types were labeled “low to no sensitization” (76.9% of sample), “highly sensitized” (2.7%), “milk and egg dominated” (15.3%), and “peanut and inhalant(s)” (5.1%). Almost one third (32.2%) of the low to no sensitization group met the criteria for conventional atopy. The highly sensitized group was significantly associated with a doctor’s diagnosis of asthma after age 4 years (odds ratio [OR], 5.3; 95% CI, 1.6-17.4), whereas the milk and egg dominated and peanut and inhalant(s) groups were not (ORs of 1.6 [95% CI, 0.8-3.0] and 1.8 [95% CI, 0.6-4.9], respectively). Children of black race were more likely to be in the 3 multisensitized groups ($P = .04$).

Conclusion: Classification by sIgE patterns defined groups whose membership is more strongly associated with atopic dermatitis, wheeze, and asthma compared with conventional atopy. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: Atopy, phenotype, latent class analysis, birth cohort

Abbreviations used

AD:	Atopic dermatitis
GM:	Geometric mean
LCA:	Latent class analysis
OR:	Odds ratio
sIgE:	Allergen-specific serum IgE
WHEALS:	Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

Atopic sensitization (ie, atopy), which is commonly defined as having at least 1 positive allergen-specific serum IgE (sIgE) test result, is often reported as a risk factor for asthma.¹ However the definition of atopy has been inconsistent, with studies often differing on the number, type, or both (eg, inhalant, food, or animal) of allergens used for testing. Although this variability is often present for understandable reasons, such as financial constraints, regional variations in allergen prevalence, or both, this imprecision can corrupt potential associations between atopy and allergic disease outcomes. Furthermore, several recent publications hypothesize that atopy, as typically defined, might lack specificity and that nuances in the pattern, measurement timing, or both of specific allergen sensitization might also be important in allergic disease development.¹⁻⁴ Custovic et al² state that atopy encompasses a number of different endotypes (“distinct disease entities”) that differ in their association with asthma. Simpson et al¹ demonstrated that atopy in their birth cohort of children represented separate phenotypes with a marked variation in their associations with disease.

The approach of using atopic phenotypes in analyses, if consistently applied and proved insightful, represents a paradigm shift in allergic disease research. We sought to explore whether distinct and meaningful atopic phenotypes exist within our racially diverse general risk birth cohort using the results of 10 allergen-specific IgE measurements at age 2 years. Using an unsupervised statistical tool that ignores outcomes and only considers individual sensitization patterns to suggest groupings (latent class mixture models), we identified patterns of classes of allergen sensitization based on sIgE measurements at age 2 years. We then examined whether numerous risk factors varied across the classes. Finally, rates of allergic diseases (atopic dermatitis [AD], wheeze, and doctor’s diagnosis of asthma) were compared between these classes to determine whether any class carried a different risk for any of these clinical outcomes.

METHODS

Study population

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) is a birth cohort from southeastern Michigan that has

From ^athe Department of Public Health Sciences and ^bthe Department of Internal Medicine, Division of Allergy, Henry Ford Hospital, Detroit, and ^cthe Department of Pediatrics, Georgia Regents University, Augusta.

Supported by National Institutes of Health grants R01 AI051598 and P01 AI089473.

Disclosure of potential conflict of interest: S. Havstad, A. M. Levin, D. R. Ownby, and G. Wegienka have received research support from the National Institutes of Health (NIH). C. C. Johnson has received research support from the NIH, has consulted for Sucampo Expert Panel Meeting and McNeil Expert Panel Meeting, and has received payment for lectures from the Aspen Allergy Conference. H. Kim and E. M. Zoratti have received research support from the National Institute of Allergy and Infectious Diseases (NIAID). C. L. M. Joseph has received research support and travel support from the NIAID.

Received for publication July 2, 2013; revised January 16, 2014; accepted for publication January 22, 2014.

Corresponding author: Suzanne Havstad, MA, 1 Ford Place, 3E, Detroit, MI 48202.

E-mail: shavsta1@hfhs.org.

0091-6749/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2014.01.022>

previously been described.^{5,6} Briefly, women were eligible for inclusion in the study if they were in their second or third trimester of pregnancy, were between 21 and 49 years of age, and lived in a predefined cluster of ZIP codes in Detroit and its surrounding suburbs. Recruitment was completed between August 2003 and November 2007. There have been 5 follow-up contacts to date at 1, 6, 12, 24, and 48 months after the child's birth. This research was approved by the Henry Ford Hospital Institutional Review Board.

Total and specific IgE

Blood was collected at the 2-year clinic visit to determine levels of total IgE and sIgE to 10 allergens: *Dermatophagoides farinae*, dog, cat, timothy grass, ragweed, *Alternaria alternata*, egg, peanut, milk, and German cockroach. Total IgE and sIgE levels were measured with the Pharmacia UniCAP system (ThermoFisher Scientific, Kalamazoo, Mich). Conventional atopic sensitization (ie, atopy) was defined as at least 1 positive test result (sIgE ≥ 0.35 IU/mL) to any of the 10 allergens.

Asthma

During the interview at age 4 years, parents were asked to report whether the child had ever received a doctor's diagnosis of asthma.

AD

At a physical examination of the child at the 2-year clinic visit, physicians recorded whether they concluded the child currently had AD, had a history of AD without presently having it, or had no history of AD.

Wheeze

Parents reported whether their children had at least 1 episode of "wheezing or whistling in the chest" in the past 12 months during the interview at age 2 years.

Parental allergic history

Parental allergic history was defined as positive if there was a report of ever having a doctor's diagnosis of hay fever or allergic rhinitis. For 19% (234/1258) of the families, father's self-report of history was used; otherwise, the mother's report of the father's history was substituted. Parental history of asthma was defined similarly.

Maternal atopy

Maternal blood was collected during pregnancy or at 1 month after delivery. Atopy was defined as having at least 1 sIgE level of 0.35 IU/mL or greater for any of the following 8 allergens: *D farinae*, dog, cat, timothy grass, ragweed, *A alternata*, egg, and German cockroach. We have previously shown that there is little change in sensitization during pregnancy compared with 1 month postpartum.⁷

Obstetric history

During the prenatal interview, women were asked to report the timing, duration, and outcome of all prior pregnancies. The child's delivery type (vaginal or cesarean section) was collected from the mother's medical record.

Endotoxin and allergen levels in dust samples

Dust samples were collected from the children's bedroom floors at the 1-month home visit. Samples were analyzed for cat allergen (Fel d 1), dog allergen (Can f 1), dust mite allergen (Der f 1), cockroach allergen (Bla g 2), and endotoxin using methods we have previously published.⁸

Statistical analysis

Latent class analysis (LCA) is an unsupervised statistical method that simultaneously considers a number of variables to identify homogeneous

mutually exclusive groups (or classes) that exist within a heterogeneous population. The latent class groupings are not known in advance but are inferred from the data.⁹ LCA was used to determine whether children could be grouped together based on their specific pattern of sensitization to the 10 allergens measured. The conventional definition of atopy (having levels of ≥ 1 sIgE ≥ 0.35 IU/mL) classifies children into 2 groups: atopic (sensitized) and nonatopic (ie, levels of all measured sIgEs < 0.35 IU/mL). This approach typically does not take into consideration the types of allergen to which they are sensitized (eg, food allergen vs aeroallergen) or, for children with more than 1 positive sensitization, the particular combination of allergens to which they are sensitized.

Using Mplus version 7.2,¹⁰ the latent class model was fit by using full-information maximum likelihood under the missing at random assumption. By using full-information maximum likelihood, subjects with partially missing data were not excluded from the analysis. Because of insufficient blood quantity, the percentage of missing measurements for each of the 10 sIgEs ranged from 0.8% ($n = 5$) to 4.4% ($n = 26$). The appropriate number of classes was determined by using an iterative process in which the model was fit with an increasing number of classes, and the model with the best representation of data was selected. We used the likelihood ratio test to determine the number of classes along with the Bayesian Information Criterion to determine the best fit (see Table E1 in this article's Online Repository at www.jacionline.org).¹¹

By using the final LCA model, the posterior probability of latent class membership for each subject was derived, and each subject was assigned to the class for which he or she had the maximum posterior probability. The assignment process ensures that subjects within a class are more homogeneous than those between classes. The average posterior probability (also called entropy) for our final model was high at 0.92 (1 represents perfect classification, and 0 represents perfect misclassification). Given the high entropy of the final model, we used the straightforward "classify-analyze" approach¹² as the primary analysis. Where possible, we repeated the analyses incorporating the posterior probability through weighting, and as expected, results were very consistent.

Odds ratios (ORs) and 95% CIs were calculated by using multinomial logistic regression. Multinomial logistic regression models were used to assess the relationship between risk factors and phenotype (class).

RESULTS

Cohort characteristics

Of the 1258 women originally enrolled in WHEALS, 594 (47%) of their children had blood drawn and at least 1 specific IgE value measured at a 2-year clinic visit (average age, 2.3 years). The 594 children included in this analysis are comparable with the 664 excluded children (Table I) in terms of mother's age at birth (mean, 29.8 [SD, 5.2] vs 29.4 [SD, 5.3] years, respectively; $P = .14$) and racial distribution (60.6% vs 63.7% black, $P = .26$). Family size at birth and maternal allergic history were also similar. However, the included children were slightly more likely to have a mother with more than a high school education (79.6% vs 72.7%, $P = .004$).

Latent classes characterized

Using our latent class model, we characterized the following classes: (1) low to no sensitization; (2) highly sensitized; (3) milk- and egg-dominated sensitization; and (4) peanut and/or inhalant allergen/no milk sensitization. Fig 1 shows the rate of sensitization to each of the 10 allergens among the 4 latent classes. Descriptions of each class follow.

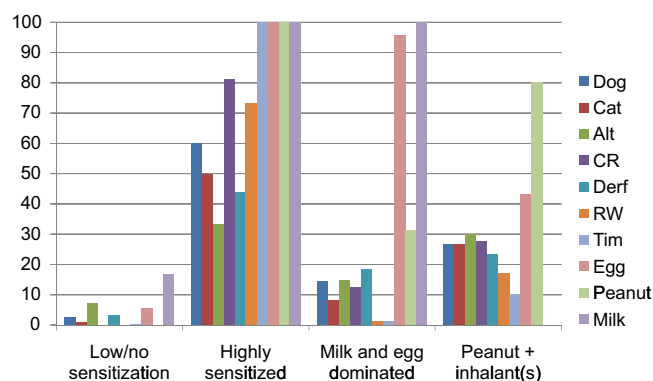
Class 1 ($n = 457$): Low to no sensitization. The majority (67.8% [$n = 310$]) assigned to this class had no sensitization (no sIgE ≥ 0.35 IU/mL), which is the traditional

TABLE I. Participants' characteristics by inclusion in analysis (n = 1258)

	Included (n = 594)	Excluded (n = 664)	P value
Maternal age at birth (y), mean (SD)	29.8 (5.2)	29.4 (5.3)	.14
Black race, no. (%)	360 (60.6)	423 (63.7)	.26
Maternal allergic history,* no. (%)	178 (30.5)	207 (31.6)	.67
High school education or less, no. (%)	121 (20.4)	181 (27.3)	.004
Children (age <18 y) in household at birth, mean (SD)	1.0 (1.2)	1.1 (1.3)	
Family size at birth, mean (SD)†	3.8 (1.3)	3.9 (1.4)	.17

*Nineteen with missing information.

†Count includes newborn, mother, spouse, or significant other and sibling or siblings.

**FIG 1.** Prevalence of sensitization (allergen sIgE ≥ 0.35) to individually tested allergens within each latent class. Alt, *Alternaria alternata*; CR, cockroach; Derf, *Dermatophagoides farinae*; RW, ragweed; Tim, timothy grass.

criterion used to define someone as nonatopic or nonsensitized. Of the remaining 147 subjects in this class, nearly all (91% [n = 134]) were monosensitized (only 1 sIgE ≥ 0.35 IU/mL) to the following: 17.2% (n = 23) to egg, 16.4% (n = 22) to *Alternaria* species, 7.5% (n = 10) to *D farinae*, 4.5% (n = 6) to dog, 1.5% (n = 2) to cat, and 0.8% (n = 1) to timothy grass. This class is used as the reference group for OR calculations involving the latent class groupings.

Class 2 (n = 16): Highly sensitized. All 16 children in this group were sensitized to at least 4 of the same allergens: milk, egg, peanut, and timothy grass. The median number of allergens to which a child in this class was sensitized was 7, and 18.7% (n = 3) were sensitized to all 10 allergens. The rate of sensitization was lowest for *Alternaria* species (31.2% [n = 5]) and *D farinae* (43.7% [n = 7]); all other allergens had a rate greater than 50%.

Class 3 (n = 91): Milk and egg dominated. Nearly all (94.5% [n = 86]) of the 91 children in this group were sensitized to both milk and egg, and a quarter of those (27.9% [n = 24]) were sensitized to, at a minimum, all 3 food allergens tested. Sensitization to 2 (n = 39) or 3 (n = 30) allergens was present in 75.8% of this group, with 36 of the 39 with 2 sensitizations being sensitized to milk plus egg. The milk and egg combination also dominated the remaining group with 3 or more total allergen sensitizations (n = 50; all but 2 had milk and egg). Peanut was the most common coallergen at 48.0% (n = 24). The remaining 26 children were sensitized to milk plus egg (no peanut) plus at least 1 inhalant allergen (no single inhalant dominated).

Class 4 (n = 30): Peanut and inhalant(s)/no milk. Peanut was the most common single allergen identified in this

class (80% [n = 24]), with the remaining 20% (n = 6) sensitized to 2 or more aeroallergens. A total of 24 (80%) were sensitized to at least 1 aeroallergen. Egg sensitization occurred 43.3% (n = 13) of the time and always in co-occurrence with peanut. There were no milk-sensitized children in this class. The majority were sensitized to a total of 2 (n = 12) or 3 (n = 8) allergens. There was no dominant aeroallergen sensitization (n = 9 to *Alternaria* species; n = 8 to each of dog, cat, and cockroach; n = 7 to *D farinae*; n = 5 to ragweed; and n = 3 to timothy grass).

Latent class membership and AD, wheeze, and doctor's diagnosis of asthma

Being atopic, as defined by the traditional definition, was associated with having AD (OR, 1.8; 95% CI, 1.1-2.8; Table II). Table II shows that the odds of the clinical outcomes of AD and doctor's diagnosis of asthma (interview at age 4 years) are highest when comparing class 2 (highly sensitized), class 3 (milk and egg), and class 4 (peanut and inhalant(s)/no milk) with class 1 (low/no sensitization); however, the greatest odds were among those in class 2 (highly sensitized; OR, 5.2, 95% CI, 1.8-14.7). Results of analyses with the outcome of current AD are similar (see Table E2 in this article's Online Repository at www.jacionline.org).

Traditional atopy was not associated with either wheeze (OR, 1.4; 95% CI, 0.8-2.4) or a doctor's diagnosis of asthma (OR, 1.1; 95% CI, 0.8-1.6; Table II). Only those who were in class 4 (peanut and inhalant[s]/no milk) were more likely to have wheezed (OR, 2.9; 95% CI, 1.4-6.1) than those in class 1 (low/no sensitization). Class 2 (highly sensitized) was the only group to have increased odds of having a doctor's diagnosis of asthma (OR, 5.3; 95% CI, 1.6-17.4).

Risk factors and latent class membership

Table III shows the extensive list of possible risk factors that were tested for association with latent class membership. These are factors we have previously used in our WHEALS analyses.^{6,13,14} Although there was variability in the distribution of most of the risk factors across the classes for many variables considered (eg, smoking, delivery type, and pet exposure), only a few reached statistical significance. Maternal atopy was positively associated with the higher-risk classes (classes 2-4). Cord blood total IgE levels were statistically significantly higher (both $P < .01$) in both class 2 (highly sensitized) and class 3 (milk and egg dominated) but not class 4 (peanut and inhalant[s]) compared with class 1 ($P = .25$). As expected, black race was associated with the higher-risk classes, but the associations reached statistical significance for class 3 compared with class 1 (OR, 1.8; 95% CI, 1.1-2.9).

DISCUSSION

These data suggest that class membership defined by allergen-specific IgE patterns might identify groups whose membership is more strongly associated with important allergic manifestations, such as AD and having a doctor's diagnosis of asthma, compared with using the conventional atopy grouping defined by having at least 1 increased sIgE level. The data suggest that the children who are highly sensitized (class 2) are the most likely to have ever had AD and are more likely than those who have minimal

TABLE II. ORs (95% CIs) for AD, doctor's diagnosis of asthma, and wheeze

	Conventional atopy (any sensitization vs no sensitization)	Class 2 (highly sensitized) vs class 1 (no/low sensitization)	Class 3 (milk and egg) vs class 1 (no/low sensitization)	Class 4 (peanut and inhalant[s]) vs class 1 (no/low sensitization)
Ever had AD	1.8 (1.1-2.8)	5.2 (1.8-14.7)	2.4 (1.4-4.0)	2.8 (1.2-6.5)
Any wheeze in last 12 mo	1.4 (0.8-2.4)	2.0 (0.7-5.4)	0.9 (0.5-1.4)	2.9 (1.4-6.1)
Parental report of child's doctor's diagnosis of asthma	1.1 (0.8-1.6)	5.3 (1.6-17.4)	1.6 (0.8-3.0)	1.8 (0.6-4.9)

TABLE III. Cohort characteristics by atopic phenotype

	Class 1 (low to no sensitization)	Class 2 (highly sensitized)	Class 3 (milk and egg dominated)	Class 4 (peanut plus inhalant[s])	P value
No.	457	16	91	30	
No. of positive sIgE test results, mean (SD)	0.4 (0.6); median = 0	7.2 (1.9); median = 7	2.9 (1.1); median = 3	2.8 (1.1); median = 3	<.001
Cord blood IgE, GM (95% CI)	0.25 (0.22-0.29)	0.68 (0.32-1.43)	0.64 (0.48-0.86)	0.33 (0.19-0.55)	<.001
Maternal total IgE, GM (95% CI)	32.7 (27.9-38.4)	81.3 (30.9-214)	57.3 (40.5-81.2)	67.7 (36.6-125)	<.001
Atopic mother (%)	53.9	75.0	65.6	78.6	.008
Black race (%)	57.3	68.8	70.3	73.3	.044
Household smoke exposure (%)	23.8	31.2	30.8	20.0	.44
Cesarean section (%)	35.4	31.3	36.7	44.8	.75
Child's BMI ≥85th percentile (%)	18.5	20.0	15.0	25.9	.65
Firstborn (%)	36.1	50.0	35.2	40.0	.68
Predelivery pet (%)	41.1	43.8	31.9	43.3	.39
Breast-fed ever (%)	77.0	87.5	83.5	80.0	.43
Breast-fed <6 mo (%)	73.4	62.5	74.4	75.9	.77
Introduction to solid food before 4 mo of age (%)	39.2	25.0	44.0	40.0	.53
Mother smoked during pregnancy (%)	9.4	6.2	12.1	10.0	.84
Married (%)	65.4	81.2	61.5	66.7	.49
Parental history of asthma (%)	29.3	35.7	36.9	34.5	.53
Maternal history of allergy (%)	30.2	25.0	28.6	33.3	.93
Maternal current asthma (%)	10.5	18.7	7.7	10.0	.58
Parental history of allergy (%)	39.6	38.5	40.5	35.7	.98
Male (%)	50.8	56.3	53.9	66.7	.38
Unemployed (%)	18.7	18.8	14.4	16.7	.81
Post-high school degree (%)	32.0	43.7	33.0	36.7	.75
At least 1 alcoholic drink in year before pregnancy (%)	59.3	75.0	63.7	70.0	.36
Household income ≥\$80,000 (%)	29.7	37.5	38.0	52.0	.069
HAP insurance	43.2	62.5	55.0	40.0	.091
Detectable Der f 1 (%)	18.3	6.3	13.8	14.8	.47
Detectable Fel d 1 (%)	47.0	50.0	39.5	40.7	.59
Detectable Can f 1 (%)	30.8	50.0	22.5	40.7	.085
Living room floor endotoxin level, GM (95% CI)	18.8 (16.5-21.4)	16.4 (8.2-32.9)	15.0 (11.0-20.6)	14.9 (9.7-21.4)	.35
Maternal age (y), mean (SD)	29.7 (5.3)	31.4 (5.8)	30.4 (5.1)	28.9 (4.4)	.28
Gestational age (wk), mean (SD)	38.8 (1.7)	38.9 (1.2)	38.7 (1.8)	38.7 (2.1)	.83
Birth weight (g), mean (SD)	3358 (596)	3384 (348)	3309 (575)	3199 (743)	.54
At least 1 antibiotic prescription given before 6 mo of age (%)	19.2	13.3	14.5	26.1	.55

BMI, Body mass index; GM, geometric mean.

sensitization (class 1) to wheeze and to have a doctor's diagnosis of asthma. The identified associations are stronger than the association that compared children who had any sensitization with those who had none. Interestingly, the associations between class and asthma diagnosis were similar in class 3 and class 4, suggesting that food allergens were not as strongly associated with asthma as being highly sensitized.

Although some of our OR estimates were not extremely precise, the observed associations suggest that risks for allergic disease outcomes do vary by sensitization patterns and that patterns should be considered in allergic disease analyses. Similarly, although only a few statistically significant associations between risk factors and classes were identified, there were also notable variations in the distributions of risk factors across

classes that likely did not reach statistical significance because of the small sample size. This work, which uses a racially diverse cohort in the United States, supports recent discussions and study results that have been urging researchers to refine the way in which we think about patterns of allergic sensitization in relation to allergic diseases. A logical next step is for various cohorts to apply this approach, both alone and in combination with other cohorts to increase sample size. This approach would provide more precise estimates and allow the identification of groups at highest risk of AD and asthma, as well as associated risk factors, because it appears that use of the traditional definition of atopy might obscure varying levels of risk in subgroups defined by their sensitization patterns.

The number and type of classes characterized here is not intended to be an exhaustive list because the analytic approach used needs to be replicated and compared in other cohorts. For example, classes might vary by population (age, sex, and race) or region. Our study uniquely extends the work of others by examining a more recently born, younger, and racially mixed cohort. We additionally introduce some potentially interesting cosensitization patterns from our cross-sectional analyses, with peanut sensitization as equally likely to be paired with at least 1 inhalant sensitization as with the 2 other foods. Milk and egg cosensitization was the most common pairing, perhaps because of the age of this cohort and relatively common exposure, but this pairing was also consistently associated with the lowest rate of allergic disease outcomes among the 3 higher-risk groups.

Other researchers have applied latent class/cluster analytic methods in a similar way, primarily to explore asthma or wheeze phenotypes.¹⁵⁻²⁵ The few publications that report analyses exploring atopic phenotypes are from racially homogeneous populations and older birth cohorts with sensitization measured at several time points involving 2 European birth cohorts (Manchester Asthma and Allergy Study¹ and Isle of Wight²⁶). Our results are difficult to directly compare with these other published results, partly because we have sIgE levels measured only once (at age 2 years). For example, Simpson et al¹ identified 5 classes when considering measures at 1, 3, 5, and 8 years of age (multiple early, multiple late, dust mite, non-dust mite, and no latent vulnerability) and concluded only multiple early atopy was associated with asthma. Our results are consistent in that the highly sensitized class (at least 4 increased sIgE levels) was significantly associated with asthma diagnosis. In contrast, we do not show any dust mite-dominated group. This also suggests that there might be geographic differences in key allergens related to allergic diseases, perhaps related to differences in the average concentrations of inhalant allergens.

Both of these populations are largely white, and the cohorts were begun in 1989 (Manchester Asthma and Allergy Study) and 1990 (Isle of Wight), respectively.^{1,4,26} Our birth cohort began enrollment in 2003 and is racially diverse, with 62% black race. Although examination of longitudinal patterns is a strength for those cohorts, in clinical practice serial determination of sensitization (by sIgE measurement or skin prick test) is not commonly available.

In the Australian Childhood Asthma Prevention Study,³ 3 classes were identified among 509 children enrolled in a randomized controlled trial of an intervention of dust mite avoidance and omega-3 fatty acid supplementation: (1) late mixed inhalant sensitization, (2) mixed food and inhalant sensitization, (3) dust mite monosensitized, and (4) no atopy. The latent classes were

derived from skin prick tests administered at 1.5, 3, 5, and 8 years of age, and members of the classes with sensitization were more likely to have had eczema, rhinitis, asthma, airway hyperresponsiveness, poor asthma control, and airflow obstruction compared with the children without atopy. Although our study differs because of the use of sIgE levels rather than skin prick test responses and the lack of multiple time points, we also characterized a mixed food and inhalant group but not a dust mite-monosensitized group. This might be due to geographic or socioeconomic variations, as well as the earlier age (2 years) of our cohort. They also looked at a limited number of common risk factors in relation to the groupings and found no differences except for an inverse association of maternal smoking that we did not duplicate.

Limitations of our study include the relatively small sample size of our higher-risk groupings, affecting the precision of estimated associations (eg, CIs) between some of the classes and the allergic diseases and risk factors. In particular, larger studies, perhaps even through the combination of multiple birth cohorts, are needed to obtain adequate power to fully explore which potentially modifiable risk factors might be driving the “allergic march.” Furthermore, although asthma, which is difficult to diagnose in young children, was based on a doctor’s diagnosis as reported in the interview at age 4 years, asthma in this study might have been better classified with LCAs if we had additional information on lung function, cytokines, and eosinophils to combine with sIgE results to examine potential risk factors.^{19,23,25,27} We also acknowledge that the outcome of parental report of wheeze can be nonspecific; however, it is only one outcome we examined, and parental report of wheeze has been used in numerous important allergic disease studies.^{22,28,29}

We want to emphasize that the classes were determined by using sensitization to the 10 allergens alone, and no outcome data were involved in the calculations to perform the groupings. Therefore the different risks associated with different classes observed in our study population provide evidence of the hypothesis that distinct endotypes are present in our study population. Also, because we further hypothesized that using these alternative groups in analyses might serve as more specifically defined endotypes, we also compared how the new classes relate to allergic outcome compared with that of the traditionally used risk factor of atopy (any sIgE ≥ 0.35 IU/mL).

There is a need for examination of sensitization patterns in young children from a racially mixed population. There were few differences in common risk factors across the classes, with race being a notable exception. The racial difference observed could play a role in the racial disparities seen in asthma if early-life food allergen sensitization is more strongly associated with asthma than other types of sensitization. This insight could lead to understanding ways to reduce racial disparities in asthma incidence and exacerbation.

In conclusion, we agree with Simpson et al¹ and others who suggest “viewing atopic sensitization as a dichotomous trait in its relationship to asthma may be an oversimplification.” A notable finding of our analysis is that 32% of the lowest risk group would be considered atopic by the conventional definition. If these 32% are truly at low to no risk for subsequent development of allergic diseases, then using the conventional definition of atopy would incorrectly force risk estimates closer to the null and thus perhaps lead to false-negative findings. If these phenotypes do represent different diseases, then surveillance, risk

factor, and prognostic studies; clinical trials; and genome-wide genetic association studies that have used the crude definitions might be misleading, have missed true associations, or have even created false ones. Larger studies are needed to fully explore this possibility, offering hope that this new conceptualization of defining distinct endotypes in analyses will yield tangible evidence to inform prevention and treatment strategies.

Key messages

- Evidence that allergic sensitization (or atopy) as defined by at least 1 allergen-specific IgE level of 0.35 IU/mL or greater is a nonspecific classification system to assess the risk of subsequent allergic disease is mounting. This report adds to that evidence by identifying 4 distinct classes within a racially mixed, recently born birth cohort of 2-year-old children.
- Failure to consider distinct patterns of cosensitization might limit the clinician's or researcher's ability to accurately identify associations that will help inform prevention and treatment strategies.

REFERENCES

1. Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181:1200-6.
2. Custovic A, Lazic N, Simpson A. Pediatric asthma and development of atopy. *Curr Opin Allergy Clin Immunol* 2013;13:173-80.
3. Garden FL, Simpson JM, Marks GB. Atopy phenotypes in the Childhood Asthma Prevention Study (CAPS) cohort and the relationship with allergic disease: clinical mechanisms in allergic disease. *Clin Exp Allergy* 2013;43:633-41.
4. Lazic N, Roberts G, Custovic A, Belgrave D, Bishop CM, Winn J, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy* 2013;68:764-70.
5. Havstad S, Wegienka G, Zoratti EM, Lynch SV, Boushey HA, Nicholas C, et al. Effect of prenatal indoor pet exposure on the trajectory of total IgE levels in early childhood. *J Allergy Clin Immunol* 2011;128:880-5.e4.
6. Wegienka G, Havstad S, Joseph CL, Zoratti E, Ownby D, Woodcroft K, et al. Racial disparities in allergic outcomes in African Americans emerge as early as age 2 years. *Clin Exp Allergy* 2012;42:909-17.
7. Perry LM, Ownby DR, Wegienka GR, Peterson EL, Woodcroft KJ, Joseph CL, et al. Differences in total and allergen specific IgE during pregnancy compared with 1 month and 1 year post partum. *Ann Allergy Asthma Immunol* 2009;103:342-7.
8. Ownby DR, Peterson EL, Williams LK, Zoratti EM, Wegienka GR, Woodcroft KJ, et al. Variation of dust endotoxin concentrations by location and time within homes of young children. *Pediatr Allergy Immunol* 2010;21:533-40.
9. McLachlan G, Peel D. Finite mixture models. 1st ed. New York: Wiley-Interscience; 2000.
10. Muthen LK, Muthen BO. Mplus user's guide. Los Angeles: Muthen & Muthen; 1998-2013.
11. Nylund KL, Asparouhov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. *Struct Equation Model* 2007;14:535-69.
12. Clogg CC. Handbook of statistical modeling for the social and behavioral sciences. In: Arminger G, Clogg CC, Sobel ME, editors. . New York: Plenum Press; 1995.
13. Wegienka G, Johnson CC, Havstad S, Ownby DR, Nicholas C, Zoratti EM. Life-time dog and cat exposure and dog- and cat-specific sensitization at age 18 years. *Clin Exp Allergy* 2011;41:979-86.
14. Joseph CL, Ownby DR, Havstad SL, Woodcroft KJ, Wegienka G, MacKechnie H, et al. Early complementary feeding and risk of food sensitization in a birth cohort. *J Allergy Clin Immunol* 2011;127:1203-10.e5.
15. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180:388-95.
16. Halder P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
17. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405-13.
18. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
19. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382-9, e1-13.
20. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J* 2012;40:55-60.
21. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31:974-81.
22. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011;127:1505-12.e14.
23. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974-80.
24. Weinmayr G, Keller F, Kleiner A, du Prel JB, Garcia-Marcos L, Battles-Garrido J, et al. Asthma phenotypes identified by latent class analysis in the ISAAC phase II Spain study. *Clin Exp Allergy* 2013;43:223-32.
25. Smith JA, Drake R, Simpson A, Woodcock A, Pickles A, Custovic A. Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008;177:1358-63.
26. Roberts G, Zhang H, Karmaus W, Raza A, Scott M, Matthews S, et al. Trends in cutaneous sensitization in the first 18 years of life: results from the 1989 Isle of Wight birth cohort study. *Clin Exp Allergy* 2012;42:1501-9.
27. Fitzpatrick AM, Baena-Cagnani CE, Bacharier LB. Severe asthma in childhood: recent advances in phenotyping and pathogenesis. *Curr Opin Allergy Clin Immunol* 2012;12:193-201.
28. Yao W, Barbe-Tuana FM, Llapur CJ, Jones MH, Tiller C, Kimmel R, et al. Evaluation of airway reactivity and immune characteristics as risk factors for wheezing early in life. *J Allergy Clin Immunol* 2010;126:483-8.e1.
29. Behbod B, Sordillo JE, Hoffman EB, Datta S, Muilenberg ML, Scott JA, et al. Wheeze in infancy: protection associated with yeasts in house dust contrasts with increased risk associated with yeasts in indoor air and other fungal taxa. *Allergy* 2013;68:410-8.

TABLE E1. LCA model fit statistics

No. of classes	Degrees of freedom	Log likelihood	BIC	LMR <i>P</i> value
1	1013	−1780.6	3625.1	
2	1002	−1513.8	3161.6	<.001
3	991	−1459.3	3146.3	.19
4	980	−1435.9	3123.1	.003
5	969	−1417.2	3179.2	.25

BIC, Bayesian Information Criterion (lower value implies better fit);

LMR, Lo-Mendell-Rubin likelihood ratio test.

TABLE E2. Rates of allergic outcomes by atopic phenotype class

	Class 1 (low to no sensitization)	Class 2 (highly sensitized)	Class 3 (milk and egg dominated)	Class 4 (peanut plus inhalant[s])	P value
No.	457	16	91	30	
Current AD (doctor's diagnosis [%])	10.5	40.0	25.9	30.8	<.001
Ever AD (doctor's diagnosis [%])	18.2	53.3	34.6	38.5	<.001
Doctor's diagnosis of asthma (%)	11.8	41.7	17.5	19.2	.014
At least 1 wheeze attack in past 12 mo (%)	28.2	43.7	25.3	53.3	.012