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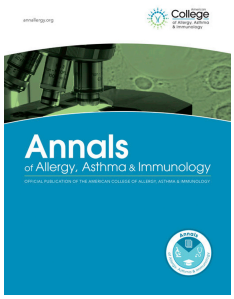

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Exploring Latent Classes to Identify Prenatal and Early-life Sources of Racial Disparities in Allergic Disease

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We previously reported that racial differences in rates of allergic disease outcomes emerge as early as age 2 years, but could not explain the differences by examining a series of individual factors.(1, 2) Hypothesizing that racial differences are not entirely due to genetic factors, this challenge called for the application of an analytical approach that would simultaneously address the interrelatedness of the factors given power constraints. Latent class (LC) analysis uses underlying relationships between selected variables to group individuals. The goal of this work was to determine whether prenatal and early life factors traditionally related to the subsequent development of allergic disease could identify LCs in the WHEALS birth cohort and assess if the distinguishing factors of the LCs were the same for Black and White children. Finally, classes were examined for differential risk of allergic outcomes at age 2 years including eczema, serum-specific allergen sensitization, multisensitization, positive skin prick tests (SPT) and asthma at age 3-7 years.

"WHEALS" is a birth cohort that enrolled predominantly Black and White pregnant women ages 21-49 in the Detroit, Michigan area; enrollment did not depend on maternal allergic disease history.(3)(4) Details of pregnancy and delivery were collected from maternal medical records. A subset of children volunteered to undergo a study-specific clinic visit at age 2 years to assess the following outcomes: SPT, sensitization defined by allergen-specific IgE (sIgE), and evaluation of eczema/atopic dermatitis (AD). Doctor diagnosis of asthma by age 3-7 years was subsequently collected by interview.

The LC model was fit using full information maximum likelihood under the missing at random assumption, allowing for partially missing data. Bayesian Information Criteria was used to

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select the number of classes. Logistic regression was used to investigate binary outcomes (≥1 positive SPT, ≥1 positive sIgE, ≥2 positive sIgE (multisensitization), eczema, asthma).

The LC model was developed using the following traditionally examined risk factors, some of which needed to be collapsed for modeling purposes: mother sensitized to common allergens by (sIgE), race (Black or White), firstborn, prenatal vitamin D (25(OH)D≥15ng/ml), child ever breastfed, delivery mode, dog in the home, marital status, maternal obesity prior to pregnancy (BMI≥30), maternal education, prenatal systemic antibiotic or vaginal antifungal medication use (5), any prenatal environmental tobacco smoke (ETS) exposure, child born in autumn/winter, child gender, and household income (≥$80,000).

In the subcohort of 1,087 Black or White children, 2 classes were identified; however, the model parameters differed by race ($p<0.001$), indicating these underlying constructs depend on race and that race-specific classes, rather than classes combined for White and Black children, were needed. Among White children, the class we will label “high socioeconomic status (SES)” was more common (63%) than the “low SES” class; among Black children, the “low SES” class was more common (60%). The probability of each characteristic by class and race are shown in Supplemental Figure 1. In both races, “high SES” mothers were more likely to have higher income and education, be married, and breastfed their children, compared to mothers in the “low “SES” classes. In both races, “low SES” was more likely to have ETS exposure than “high SES”. However, among White children only, “high SES” mothers were more likely to be atopic, while “low SES” mothers were more likely to have C-section births and be obese. Among Black

children, “low SES” mothers were more likely to have prenatal vitamin D deficiency and antibiotic usage.

Figure 1 and Supplemental Table 1 show associations between race-specific classes and allergy-related outcomes. The odds of allergic outcomes by class only differed significantly for multisensitization among Black children, where those in the “high SES” Class had higher odds of multisensitization compared to those in the “low SES” Class (odds ratio=OR=2.03, 95% CI 1.29, 3.19). Compared to White children in the “high SES” Class, Black children in the “high SES” Class had higher odds of sensitization (OR=2.08, 95% CI 1.25, 3.45), multisensitization (OR=5.41, 95% CI 2.69, 10.90), SPT positivity (OR=1.94, 95% CI 1.10, 3.41), and eczema (OR=3.15, 95% CI 1.66, 5.97); however, these differences between race groups were not statistically significant for “low SES” Classes. Additionally, Black children in the “low SES” Class had higher odds of SPT positivity (OR=1.90, 95% CI 1.08, 3.32) and eczema (OR=3.08, 95% CI 1.63, 5.80) than White children in the “high SES” Class. Further, “low SES” White children had rates of the outcomes that were intermediate between the Black children (both classes) and the “high SES” Class White children; notably, odds of multisensitization was significantly higher in “high SES” Black children, compared to White “low SES” Class children (OR=2.87, 95% CI 1.19, 6.89).

This LCA revealed two underlying subgroups which were differentiated by factors usually associated with SES. These classes were further distinguished by clinical and biological factors separately within each race, indicating that the construct of SES may have different levels of impact for White and Black children. In other words, the exposures and lifestyles that cluster

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together appear to be somewhat different by race and this makes a difference when relating these variables to allergic outcomes. Further, being "high SES" versus "low SES" was more "beneficial" for White children than Black children. Among "high SES" children only, Black children still had significantly higher odds of allergic outcomes. These concepts align with the "Minorities' Diminished Return" hypothesis, which states that "SES generates less health for Blacks than Whites."(6)

While the evidence examining SES factors and asthma control/management is growing, the literature on the role of SES factors affecting allergic disease development is sparse.(7-9) These analyses are in line with recent analyses of the National Survey of Children's Health.(10) Among children living above the poverty line versus those living below the poverty line, White children, but not Black children, were less likely to have reported a doctor diagnosis of asthma. These and the present data suggest that "societal and structural barriers" exist and underlie these racial disparities.(10) Future work in disease causation must assess the role of these elusive barriers in order to yield breakthroughs in allergic disease prevention that will benefit all individuals.

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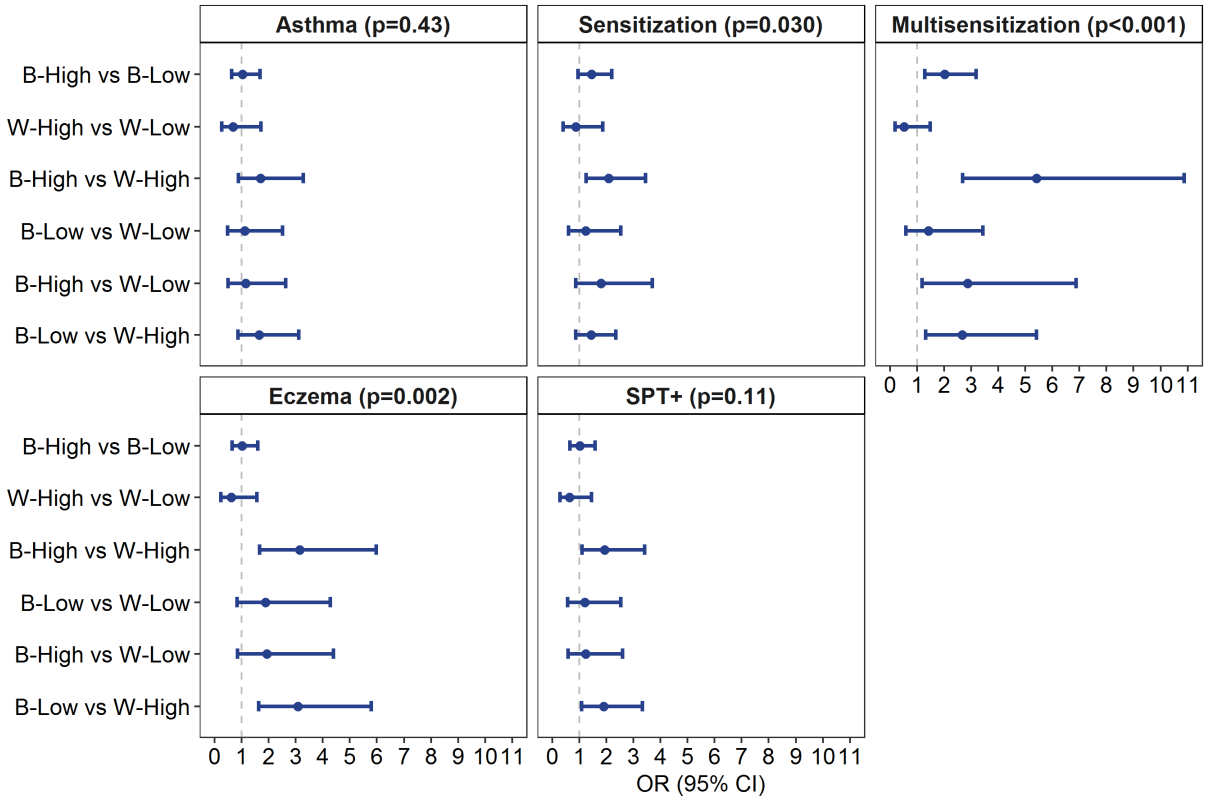

Figure 1. Association between Race-Specific Classes and Allergy-Related Outcomes. *High*="High SES" classes; *Low*="Low SES" classes; B=Black child, W=White child. Multisensitization is defined as ≥2 positive sIgEs.

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