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Increased risk of asthma at age 10 years for children sensitized to multiple allergens

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ABSTRACT

Background: Childhood sensitization patterns have been previously found to be related to variable risk of early life allergic disease in several birth cohorts.
Objective: To determine whether these risks persist into later childhood.
Methods: In the birth cohort of the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study, previous latent class analysis based on sensitization to 10 allergens found the following 4 early life sensitization patterns at age 2 years: "highly sensitized," "milk/egg dominated," "peanut and inhalant(s)," and "low to no sensitization." At an age 10 study-specific visit, children were evaluated by an allergist for current asthma and atopic dermatitis through a physical examination and interviews with the child and parent or guardian. Total and specific immunoglobulin E (IgE), spirometry, and methacholine challenge were also completed.
Results: Compared with children sensitized to none or 1 allergen, children sensitized to 4 or more food and inhalant allergens at age 2 had the highest risk of current asthma (relative risk [RR], 4.42; 95% confidence interval [CI], 2.58-7.59; $P < .001$) and bronchial hyperresponsiveness (RR, 1.77; 95% CI, 1.29-2.42; $P < .001$). In addition, they had the highest levels of total IgE (geometric mean, 800 IU/mL; 95% CI, 416-1536) among the 4 groups. Risk of current atopic dermatitis did not depend on pattern of sensitization but remained increased for children with any sensitization (RR, 2.23; 95% CI, 1.40-3.55; $P < .001$). No differences in spirometry (forced expiratory volume in 1 second, forced expiratory flow between 25% and 75%, and forced expiratory volume in 1 second/forced vital capacity) were identified.
Conclusion: The previously reported importance of a specific pattern of sensitization in early life (sensitization to ≥4 inhalant and food allergens) continues to be associated with an increased risk of asthma, bronchial hyperresponsiveness, and high total IgE at age 10 years.

Introduction

Growing evidence considers pregnancy to age 2 years to be critical to a child's health and development and to set them on an initial trajectory for future health or disease (ie, Developmental Origins of Health and Disease).[1,2] In the birth cohort of the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS), we previously revealed that rather than treating "sensitization" as a dichotomous indicator (sensitized to any allergen-specific immunoglobulin E [sIgE] vs none), patterns of sensitization to specific allergens identified with latent class analysis could more precisely identify subgroups of children with varying risks of asthma. We reported that children sensitized to 4 or more food and inhalant allergens ("highly sensitized") by age 2 years were at greater risk of reporting a doctor diagnosis of asthma by age 4 to 7 years compared with children who were sensitized to no more than 1 allergen (odds ratio, 5.3; 95% confidence interval [CI], 1.6-17.4).[3]

Using the well-characterized and racially diverse WHEALS birth cohort, 10-year study-specific clinic visits were completed. The visits included collection of detailed health histories with spirometry, IgE measurements, methacholine challenge, and a physical examination and assessment by an allergist.[4] The present analyses evaluated whether the elevated asthma-related risk for those in the "highly sensitized" group identified at 2 years persisted to age 10 years.

Methods

In 2003 to 2007, WHEALS enrolled predominantly Black and White pregnant women aged 21 to 49 years residing in the

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southeastern Michigan area, including residents of Detroit and its suburbs. Enrollment was not dependent on a woman's allergic disease history.[3] Their children were re-contacted and completed a study-specific clinic visit at approximately age 10 years as detailed previously.[4] All aspects of this study were approved by the Henry Ford Health System Institutional Review Board. Written informed consent and assent were obtained.

Atopic Sensitization at 2-Year Study Visit

During a study clinic visit when the children were approximately 2 years of age, sIgEs for 7 inhalant allergens (dog, cat, Timothy grass [*Phleum pratense*], ragweed [*Ambrosia artemisiifolia*], mold [*Alternaria alternata*], dust mite [*Dermatophagoides farinae*], and German cockroach [*Blattella germanica*]) and 3 foods (hen's egg, peanut, milk) were measured in serum samples from the children (Pharmacia UniCAP, Thermo Fisher Scientific, Kalamazoo, Michigan).[3] A positive test result was defined as sIgE greater than or equal to 0.35 IU/mL, and the child was classified as sensitized to that allergen. Previous latent class analysis based on sensitization to the 10 sIgEs identified the following 4 distinct early life sensitization patterns (ELSPs): "highly sensitized," "milk/egg dominated," "peanut and inhalant(s)," and "low/no sensitization."[3] Each participant was placed in the group with the highest posterior probability.

Ten-Year Study Visit

Briefly, WHEALS children were invited to participate in a 10-year study-based clinic visit, in which an allergist evaluated the child for asthma and atopic dermatitis (AD) through a physical examination and interviews with the child and parent or guardian. Questions covered previous and current health, environmental exposures, and demographics. Diagnosis of current asthma and AD was based on allergist assessment as previously reported[4] but, briefly, included the results from the clinic visit, with a focus on symptom and medication use in the previous 12 months. The same panel of sIgEs and total IgE measured at age 2 years was measured in serum samples collected at the study visit at age 10 years. Spirometry and methacholine challenge were performed in accordance with the American Thoracic Society criteria and have been previously described.[4,5] Abnormal bronchial hyperresponsiveness (BHR) was defined standardly, from the provocation concentration causing a 20% fall in forced expiratory volume in 1 second (FEV1), as 0 to 16 mg/mL vs greater than 16 mg/mL for normal BHR.

Statistical Analysis

Differences in categorical variables between ELSP groups were tested using a χ^2 or Fisher's exact test. Approximately normally distributed variables, such as age and body mass index (BMI) percentiles, were compared with analysis of variance, whereas nonnormally distributed variables (eg, total IgE) were evaluated with Kruskal-Wallis tests. Total IgE has a skewed distribution which approximates normality upon log transformation, and therefore geometric means (GM) are reported to represent central tendency for this variable only. To account for possible bias caused by loss to follow-up, stabilized inverse probability weights (IPWs) were used based on methods we have previously described.[4] All IPW-adjusted standardized differences were under 5%, indicating balance of the covariates.[6]

Relative risks (RRs) with 95% CIs are presented by ELSP groups, with "low/no sensitization" as the referent. Conventional sensitization, defined as greater than or equal to 1 positive sIgE result vs no sensitization, is provided for comparison. All RRs were calculated using a log-link binomial generalized linear model, weighting by IPW.[7]

Results

Of the 594 children who completed a clinic visit at age 2 years, 218 children were either not located (n = 109) or declined to participate in the clinic visit (n = 109). There were 376 WHEALS participants who completed both a clinic visit at age 2 years and 10 years and were previously classified into 1 of 4 ELSP groups based on their sensitization pattern at age 2 years: "highly sensitized" (3.7% of sample), "milk/egg dominated" (15.7%), "peanut and inhalant" (5.1%), and "low/no sensitization" (75.5% of sample). WHEALS participants included in these analyses vs those not included differed by race and maternal age but not maternal education, marital status at delivery, maternal history of asthma, sex of infant, delivery mode, and birth order (Table 1). All these variables were included in the IPW.

There were no differences among the 4 ELSP groups with respect to sex, race, and BMI (Table 2). There were age differences in that the children from the "peanut and inhalant" group were slightly younger (mean, 9.8; SD, 0.7) than the 3 other groups (P = .03). Because age of the child at the 10-year visit was found to be statistically significantly associated (P = .03) with early childhood atopy phenotype group, all analyses were repeated with adjustment for age, and the results did not change meaningfully (results not revealed). In addition, contemporaneous use of allergy/asthma medications differed significantly among the 4 groups, with those in the low/no sensitization group having the lowest rate of use (18.9%).

Not all ELSP groups had elevated risks for each of the outcomes (Table 3). The "highly sensitized" ELSP group had the highest risk of "current asthma" (RR, 4.42; 95% CI, 2.58-7.59; $P < .001$) and BHR (RR, 1.77; 95% CI, 1.29-2.42; $P < .001$) at the 10-year clinic visit (Table 2). Children in this group tended to have the highest levels of total IgE of any group (GM = 800 IU/mL, 95% CI, 416-1536), with the next closest group, "peanut and inhalant," still being statistically significantly lower with a geometric mean of 236 IU/mL (95% CI, 144-385) (Fig 1). The "milk/egg dominated" group did not differ from the "peanut and inhalant" group (GM = 186 IU/mL [95% CI, 134-257] and

Table 1
Retained vs Lost to Follow-Up (N = 594)

Characteristic	Included(N = 376)	Excluded(N = 218)	*P* value
Maternal age (y) at birth, mean (SD)	30.1 (5.3)	29.2 (4.9)	.03
Black race, n (%)	256 (68.1)	126 (57.8)	.01
Female (birth report) sex, n (%)	179 (47.6)	106 (48.6)	.81
Mom attended at least some college at predelivery, n (%)	306 (81.4)	167 (76.6)	.16
Mom married at predelivery, n (%)	243 (64.6)	145 (66.5)	.64
C-section delivery, n (%)[a]	129 (34.4)	87 (39.9)	.17
Firstborn, n (%)	144 (38.3)	73 (33.5)	.24
ETS at predelivery, n (%)	96 (25.5)	52 (23.9)	.64
Maternal history of asthma at predelivery, n (%)	74 (19.7)	39 (17.9)	.59

Abbreviation: ETS, environmental tobacco smoke.
[a]Missing delivery information on n = 1.

Table 2
Cohort Characteristics at Age 10 Years by ELSP

Characteristic	ELSP				*P* value[a]
	Highly sensitized(N = 14)	Milk/egg dominated(N = 59)	Peanut and inhalants(N = 19)	Low/no sensitization(N = 284)	
Female, n (%)	7 (50.0)	25 (42.4)	5 (26.3)	142 (50.0)	.18
Black race, n (%)	9 (64.3)	44 (74.6)	17 (89.5)	186 (65.5)	.10
Age (y), mean (SD)	10.5 (1.3)	10.4 (1.0)	9.8 (0.7)	10.3 (0.8)	.03
BMI-for-age percentile, mean (SD)	62.5 (32.3)	64.1 (32.7)	55.8 (34.6)	56.1 (36.4)	.45
Abnormal bronchial hyperresponsiveness					.02
Yes	9 (81.8)	29 (63.0)	9 (50.0)	5.6)	
No	2 (18.2)	17 (37.0)	9 (50.0)	143 (54.4)	
BHR categories					.04
BHR normal (>16)	2 (18.2)	17 (37.0)	9 (50.0)	143 (54.4)	
BHR borderline (4-16)	3 (27.3)	14 (30.4)	3 (16.6)	61 (23.2)	
BHR mild (1-<4)	3 (27.3)	11 (23.9)	5 (27.8)	46 (17.5)	
BHR moderate/severe (<1)	3 (27.3)	4 (8.7)	1 (5.6)	13 (4.9)	
Asthma					<.001
Yes	8 (66.7)	13 (24.5)	7 (38.9)	39 (14.6)	
No	4 (33.3)	40 (75.5)	11 (61.1)	228 (85.4)	
Atopic dermatitis					.002
Yes	4 (33.3)	19 (33.9)	7 (36.8)	42 (15.5)	
No	8 (66.7)	37 (66.1)	12 (63.2)	229 (84.5)	
sIgE positive[b]					
Dog, n (%)	9 (69.2)	27 (47.4)	11 (57.9)	34 (12.3)	<.001
Cat, n (%)	10 (71.4)	20 (35.1)	9 (47.4)	40 (14.5)	<.001
Timothy grass, n (%)	11 (78.6)	22 (38.6)	8 (42.1)	58 (21.0)	<.001
Ragweed, n (%)	11 (78.6)	17 (29.8)	7 (36.8)	32 (11.6)	<.001
Mold mixture, n (%)	10 (71.4)	25 (43.9)	12 (63.2)	66 (23.9)	<.001
Dust mite, n (%)	10 (71.4)	23 (40.4)	11 (57.9)	48 (17.4)	<.001
German cockroach, n (%)	10 (71.4)	19 (33.3)	6 (31.6)	17 (6.2)	<.001
Hen's egg, n (%)	10 (76.9)	12 (21.0)	2 (10.5)	6 (2.2)	<.001
Milk, n (%)	9 (64.3)	19 (33.3)	4 (21.0)	27 (9.8)	<.001
Peanut, n (%)	13 (92.9)	15 (26.3)	9 (47.4)	25 (9.1)	<.001
≥4 positive sIgE[b]	12 (85.7)	27 (47.4)	12 (63.2)	41 (14.9)	<.001
0 or 1 positive sIgE[b]	2 (14.3)	15 (26.3)	4 (21.0)	181 (65.6)	<.001
Allergy/asthma medication(s), n (%)					
Allergy	6 (42.9)	27 (46.6)	11 (57.9)	115 (40.9)	.47
Controller	2 (14.3)	11 (19.0)	6 (31.6)	25 (8.9)	.006
Rapid-acting (bronchodilator)	7 (50.0)	16 (27.6)	9 (47.4)	52 (18.5)	.001
Oral steroid	0 (0)	3 (5.2)	2 (10.5)	12 (4.3)	.42
Any asthma medication	7 (50.0)	19 (32.8)	9 (47.4)	53 (18.9)	.001

Abbreviations: BHR, bronchial hyperresponsiveness; BMI, body mass index; ELSP, early life sensitization pattern; sIgE, specific immunoglobulin E.
[a] χ^2 test for categorical variables; analysis of variance for age and BMI.
[b] Positive result defined as sIgE greater than or equal to 0.35 IU/mL.

Table 3
Age 10 Outcomes by ELSP and Conventional Atopy (Relative Risk After Inverse Probability Weighting[a])

Outcome	Highly sensitized vs low/no sensitization		Milk/egg dominated vs l ow/no sensitization		Peanut and inhalant(s) vs low/no sensitization		Any sensitization (conventional atopy) vs no sensitization	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Asthma	4.42 (2.58-7.59)	<.001	1.81 (1.04-3.12)	.03	2.92 (1.57-5.43)	.001	1.70 (1.08-2.67)	.02
Abnormal BHR	1.77 (1.29-2.42)	<.001	1.26 (0.95-1.66)	.10	1.06 (0.64-1.73)	.82	1.26 (1.01-1.57)	.04
Atopic dermatitis	2.10 (0.82-5.41)	.12	2.61 (1.71-3.98)	<.001	2.25 (1.14-4.47)	.02	2.23 (1.40-3.55)	.001

Abbreviations: BHR, bronchial hyperresponsiveness; CI, confidence interval; ELSP, early life sensitization pattern; IPW, inverse probability weights; RR, relative risk.
[a] Variables included in IPW: race, maternal age, maternal education, marital status at delivery, maternal history of asthma, sex of infant, delivery mode, and birth order.

GM = 236 IU/mL [95% CI, 144-385], respectively). The "low/no sensitization" group had the lowest levels (GM = 43 IU/mL [95% CI, 36-51]). Risk of having AD at age 10 years (Table 3) was not different among the ELSP groups. No statistically significant differences were found among the 10-year visit spirometry measures of FEV1, forced expiratory flow between 25% and 75%, and FEV1/forced vital capacity between the ELSP groups (eFig 1, eFig 2, eFig 3).

Children who had "any sensitization" (conventional definition) were more likely to have an increased risk of asthma, BHR, and AD compared with children who were not sensitized (Table 3). The RRs tended to be smaller than the largest RRs for the ELSP groups because the associations found with "any sensitization" are a mixture of associations in the ELSP groups.

Discussion

The highly sensitized ELSP group identified at age 2 years also had the highest risks of having asthma, BHR, and AD and had the highest total IgE levels at 10 years of age. No effect was found for spirometry measures. Risk of AD was elevated for all 3 ELSP groups compared with the "low/no sensitization" group, but the risk did not differ among the 3 groups. This indicates that no specific allergen patterns were clearly discriminatory for having AD at age 10 years, but those who had at least one sensitization at age 2 years had more than double the risk of AD at age 10 years. We also found that the conventional definition of sensitization did not identify the subgroup of children at highest risk of the outcomes as was done with the latent classes.

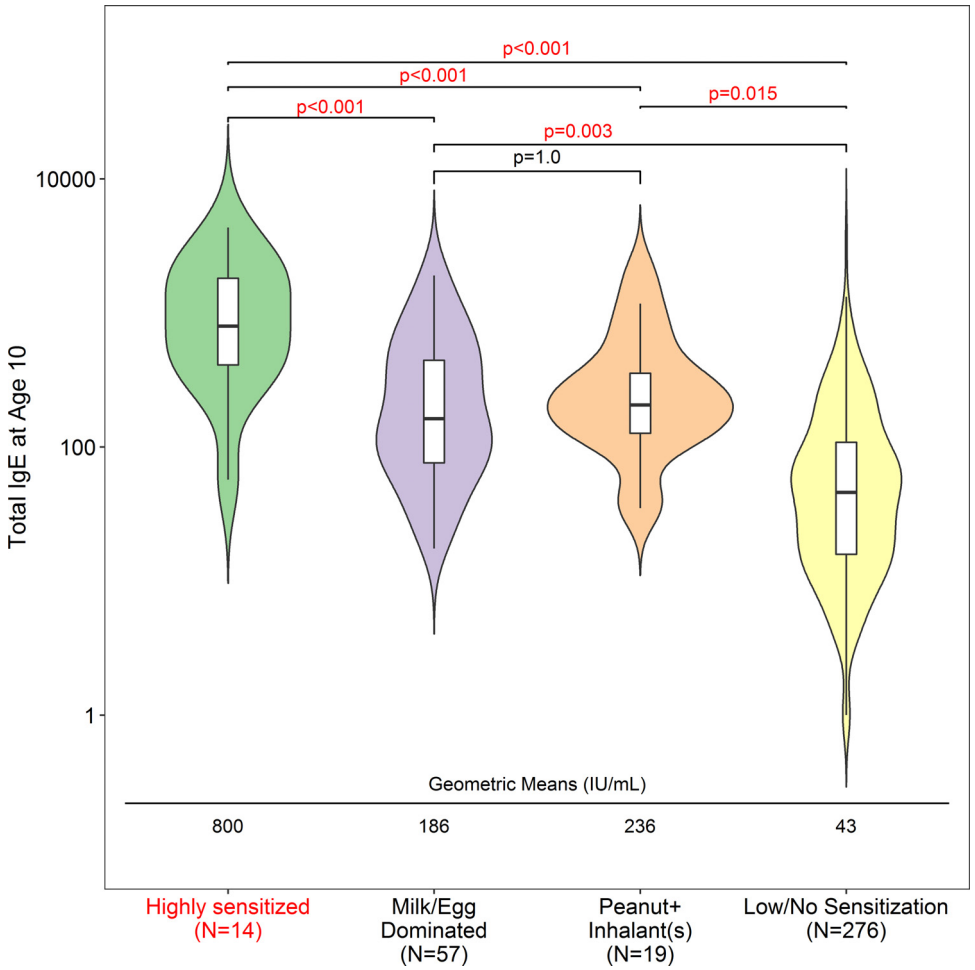

Figure 1. Total IgE at age 10 study visit by ELSP. Violin plot: the x-axis is the ELSP. The y-axis is the total IgE on $\log_{10}$ scale. The geometric mean is listed for each class. The white boxes represent the typical box plot with middle bar representing the median. The straight lines on the top and bottom of the boxes represent the interquartile range. The colored areas are rotated density plots. ELSP, early life sensitization pattern; IgE, immunoglobulin E.

Other studies in the United States and Canada have evaluated the longitudinal patterns of sensitization and allergic diseases from early life throughout adolescence; however, in contrast with these studies, our study specifically evaluates the very early life pattern of sensitization at age 2 years and later risk of asthma.[8–12] The mean IgE of 800 IU/mL in this "highly sensitized" ELSP group is commensurate with a severe asthma phenotype found in inner-city children—a subgroup represented in our study population.[13] These publications and our work seem to confirm the existence of a subset of children at extraordinarily high risk for current asthma that, importantly, based on these results, could be readily identifiable from a blood sample before the age of 2 years.

Limitations of this study include the inevitable loss to follow-up in the intervening 8-year period between scheduled study clinic visits; however, our analytical approach abates some of this concern through use of IPW. In addition, population characteristics among the ELSP groups, which were not significantly different in the year 2 data, were not found to be different in the year 10 data. This study was not powered to look at racial differences among the ELSP groups; however, we believe that, given previous findings by us and others,[4,14–17] this would be important to pursue in a larger cohort. Asthma severity was not systematically measured in this cohort. Finally, we did not conduct oral food challenges and are thus unable to distinguish whether children are simply "sensitized" or have actual food allergies.

This work further supports the idea that prevention of asthma should focus on the very early life. We posit that some children on a trajectory to subsequently develop asthma can be identified by age 2 years. We do not mean to imply that all children who go on to develop asthma can be identified at age 2 years; however, some children may be identifiable at this early age—or even potentially earlier. Importantly, not only do children at highest risk for developing asthma need to be identified as early as possible, but also the goal should be to mitigate the risk of these children toward asthma.

Affordable mass screening is needed to identify, as early in life as possible, children at highest risk of developing asthma and those children that need intervention to prevent future asthma. Future studies should evaluate whether routine screening for allergic sensitization in early life—such as screening done for lead levels—and then intervention for these children would reduce risk for later asthma. In addition, intervention strategies are needed for these young children. Introducing immunotherapy as early as possible to symptomatic children should also be investigated for reducing asthma risk. Furthermore, we need to understand how existing and future biological therapies, such as anti-IgE or anti-interleukin 4, 5, and 13 therapies, may interrupt the progression of developing the T_H2 immune responses that fuel allergic asthma. There may also be future interventions directed toward promoting healthy gut microbiota development that potentially could also lessen progression of allergic asthma. Techniques to measure panels of sIgEs in low blood volumes

for minimal cost are also needed. Primary care physicians must be involved in the development and performance of screening protocols.

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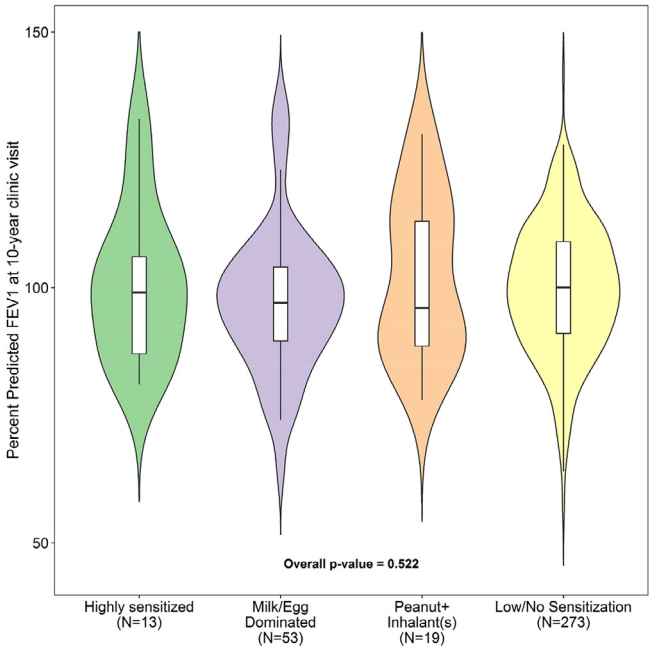
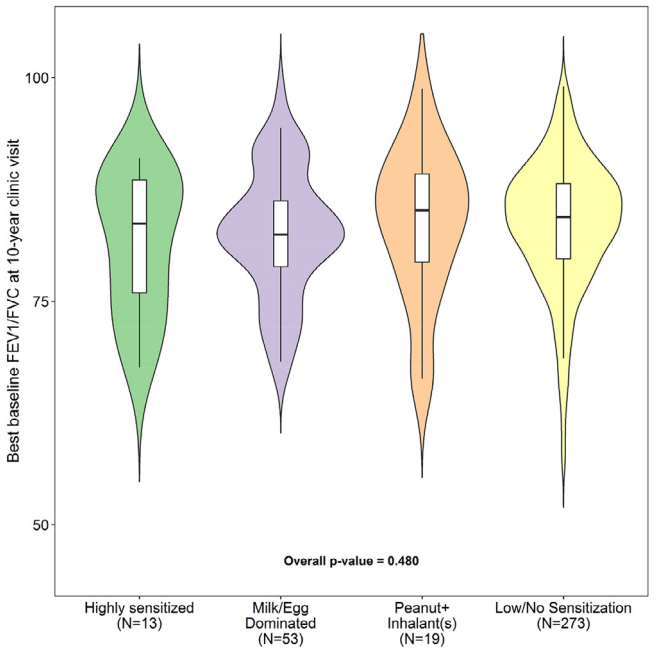
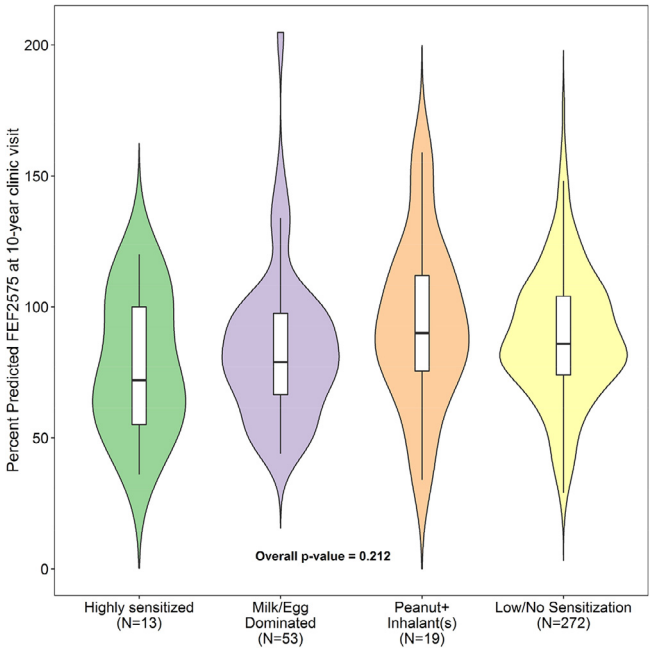


eFigure 1. Percent-predicted FEV1 at 10-year clinic visit by atopic classes. FEV1, forced expiratory volume in 1 second.



eFigure 2. Best baseline FEV1/FVC at 10-year clinic visit by atopic classes. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.



eFigure 3. Percent-predicted FEF25%-75% at 10-year clinic visit by atopic classes. FEF25%-75%, forced expiratory flow between 25% and 75%.