

Exploring the Utility of Noninvasive Type 2 Inflammatory Markers for Prediction of Severe Asthma Exacerbations in Children and Adolescents



Samar P. Shah, MD^{a,b}, Jocelyn Grunwell, MD, PhD^{a,b}, Jennifer Shih, MD^{a,b}, Susan Stephenson, PhD^a, and Anne M. Fitzpatrick, PhD^{a,b} Atlanta, Ga

What is already known about this topic? Studies have demonstrated associations between elevated blood eosinophils, poor symptom control, and exacerbations in adults with asthma. The utility of blood eosinophils in the prediction of asthma exacerbations in children is unclear.

What does this article add to our knowledge? Elevated blood eosinophils were associated with acute visits for asthma, but optimal blood eosinophil cut-points differed by age group. The addition of a second type 2 inflammatory biomarker improved prediction of an acute visit only in adolescents.

How does this study impact current management guidelines? Blood eosinophils and other noninvasive markers of type 2 inflammation may be useful in the clinical assessment of children and adolescents with asthma, but features of type 2 inflammation vary by age.

BACKGROUND: Noninvasive markers of type 2 inflammation are needed to identify children and adolescents who might benefit from personalized biologic therapy.

OBJECTIVE: We hypothesized that blood eosinophil counts would predict 1 or more acute visits for asthma and that prediction could be improved with the addition of a second, noninvasive type 2 inflammatory biomarker.

METHODS: Children and adolescents 5 to 21 years (N = 589) with an asthma exacerbation necessitating systemic corticosteroid treatment in the previous year completed a characterization visit and telephone calls at 6 and 12 months. The primary outcome was an acute visit for asthma with receipt of systemic corticosteroids. Acute visits were verified by medical record review. Exploratory outcomes included time to first acute visit and hospitalization.

RESULTS: Acute visits occurred in 106 (35.5%) children and 72 (24.8%) adolescents. Elevated blood eosinophils were associated

with increased odds and shorter time to first acute visit, but optimal cut-points differed by age (≥ 150 vs ≥ 300 cells/ μ L for children vs adolescents, respectively). The addition of a second marker of type 2 inflammation did not improve prediction in children, but increased the odds and hazard of an acute visit up to 16.2% and 11.9%, respectively, in adolescents. Similar trends were noted for hospitalizations.

CONCLUSIONS: Blood eosinophils and other noninvasive markers of type 2 inflammation may be useful in the clinical assessment of children and adolescents with asthma. However, features of type 2 inflammation vary by age. Whether children and adolescents also respond differently to management of type 2 inflammation is unclear and warrants further evaluation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2624-33)

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^aDepartment of Pediatrics, Emory University, Atlanta, Ga

^bCenter for Cystic Fibrosis and Airways Disease Research, Children's Healthcare of Atlanta, Atlanta, Ga

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Corresponding author: Anne M. Fitzpatrick, PhD, Department of Pediatrics, Emory University, 2015 Uppergate Drive, Atlanta, GA 30322. E-mail: anne.fitzpatrick@emory.edu.

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Asthma symptom control is suboptimal in the majority of children worldwide.¹ Even in developed nations with widespread availability of asthma controller medications such as inhaled corticosteroids (ICS) and standardized treatment guidelines,² more than 50% of children with asthma experience an exacerbation each year.³ Although the factors responsible for asthma exacerbations in children are complex and include limited access to care,⁴ poor adherence to ICS,^{5,6} and exposures to environmental allergens and irritants such as tobacco smoke,⁷⁻⁹ it is also recognized that children with exacerbation-prone asthma are a heterogeneous group¹⁰ with differing biological mechanisms or "endotypes" that contribute to varied clinical outcomes and longitudinal disease trajectories.¹¹ However, the precise biological mechanisms that contribute to exacerbations in children are not well understood.

Abbreviations used

CI- Confidence interval

FEV₁- Forced expiratory volume in 1 second

ICS- Inhaled corticosteroid

OR- Odds ratio

Type 2 inflammation, which is driven by IL-4, IL-5, and IL-13 and characterized by high IgE antibody titers and eosinophilia,¹² is thought to be a pivotal risk factor for persistent and severe wheezing and airflow obstruction in children with asthma¹³⁻¹⁶ that may be amenable to treatment with personalized biologic therapy. However, studies of type 2 inflammation in children are quite limited. Whereas the majority of studies of type 2 inflammation in adults have focused on gene expression in invasive airway samples obtained for research purposes,^{17,18} bronchoscopy for research purposes is typically not performed in patients with pediatric asthma, particularly in children without severe uncontrolled asthma.¹⁹ Furthermore, although other studies of type 2 inflammation in adults have used induced sputum samples,^{20,21} the induced sputum procedure is not feasible in younger children and has a relatively poor success rate (ie, sample yield) in preadolescents.^{22,23} Noninvasive markers of type 2 inflammation are therefore needed in children with exacerbation-prone asthma to identify those patients who might benefit from personalized biologic therapy.

We therefore analyzed 12-month longitudinal data from a cohort of children and adolescents with exacerbation-prone asthma participating in asthma research studies in Atlanta, Georgia. We hypothesized that blood eosinophil counts would predict 1 or more acute visits for asthma at 6 or 12 months after measurement, defined as an emergency department visit or unscheduled health care visit with receipt of systemic corticosteroids, and that prediction of acute events could be improved with the addition of a second, noninvasive type 2 inflammatory biomarker.

METHODS

This study was a secondary analysis of children and adolescents with exacerbation-prone asthma participating in asthma research studies at Emory University in Atlanta, Georgia, between January 2007 and December 2016. Children and adolescents 5 to 21 years of age were eligible for inclusion if they had a physician diagnosis of asthma, an exacerbation necessitating systemic corticosteroid treatment in the previous year, and either $\geq 12\%$ reversibility in the forced expiratory volume in 1 second (FEV₁) after bronchodilator administration or airway hyperresponsiveness to methacholine evidenced by a provocative concentration of methacholine causing a 20% decline in FEV₁ of 16 mg/mL or less. Exclusion criteria included premature birth before 35 weeks of gestation, current smoking, or other airway disorders mimicking asthma such as pulmonary aspiration or vocal cord dysfunction. Permission to proceed with this study was granted by the Emory University Institutional Review Board. Informed written consent and assent were obtained.

Study design and procedures

Participants completed a baseline study visit that was postponed if acute illness or an asthma exacerbation treated with systemic corticosteroids was reported within the preceding 4 weeks. At the study visit, participants completed questionnaires pertaining to

demographics, medical history, and symptoms. Neighborhood characteristics were obtained from the 2010-2014 American Community Survey.²⁴ Spirometry (KoKo PDS; Ferraris, Louisville, Colo) was performed as previously described following a bronchodilator withhold.²⁵ The best of 3 forced vital capacity maneuvers was interpreted according to population reference equations²⁶ before and after 4 inhalations of albuterol sulfate (90 μ g/actuation) delivered through a metered dose inhaler. Airway hyperresponsiveness to methacholine was also measured in a subset of participants with $<12\%$ FEV₁ reversibility to ensure study eligibility as described previously.²⁷ Exhaled nitric oxide concentrations were measured with a commercial device (NIOX MINO; Circassia Pharmaceuticals, Chicago, Ill).²⁸ Aeroallergen sensitization was assessed by specific IgE testing (Children's Healthcare of Atlanta, Atlanta, Ga) or skin prick testing with the following extracts: tree mix (*Quercus alba*, *Ulmus americana*, *Platanus acerifolia*, *Salix caprea*, *Populus deltoides*), grass mix (*Cynodon dactylon*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Sorghum halepense*, *Paspalum notatum*), weed mix (*Artemisia vulgaris*, *Chrysanthemum leucanthemum*, *Taraxacum vulgare*, *Solidago virgaurea*), common ragweed (*Ambrosia artemisiifolia*), *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, dog dander, cat dander, German cockroach (*Blattella germanica*), *Dermatophagoides farinae*, and *Dermatophagoides pteromyssinus* (Greer Laboratories, Lenoir, NC). Venipuncture was also performed for quantification of blood eosinophils and total IgE (Children's Healthcare of Atlanta). Participants were also telephoned at 6 and 12 months after the study visit and questioned about asthma-related health care utilization.

Outcome measures

The primary outcome measure was 1 or more acute visits for asthma (defined as an emergency department visit or unscheduled health care visit) with receipt of systemic corticosteroids at 6 or 12 months after measurement.²⁹ Exploratory outcomes included time to first acute visit and hospitalization. Acute visits and hospitalizations were verified by a review of medical records.

Statistical analyses

Data were analyzed with SPSS Statistics (Version 24; IBM, Armonk, NY) with stratification by age group (5-11 vs 12-21 years). Complete demographic data, asthma medical history data, lung function data, and outcome data were available for all participants (N = 589). However, blood eosinophil counts, serum IgE, exhaled nitric oxide, and aeroallergen sensitization were missing in 35 (5.9%), 55 (9.3%), 30 (5.1%), and 50 (8.5%) of participants and were subjected to multiple imputation to retain variables in the models. Little's χ^2 tests were performed on the expectation-maximum covariance matrix of key study variables (age, sex, race, household education, asthma controller medications, FEV₁ % predicted value, blood eosinophil counts, serum IgE, exhaled nitric oxide, and aeroallergen sensitization) to confirm that values were missing completely at random. Multiple imputation was performed using a fully conditional specification (Markov Chain Monte Carlo algorithm) with 5 iterations. Data presented are pooled estimates.

Multivariate logistic regression was performed to obtain odds ratios (ORs) for acute visits within 12 months. Cox proportional hazards regression was used to determine time to first acute visit. Predictors included blood eosinophils (≥ 150 , ≥ 200 , ≥ 250 , and ≥ 300 cells/ μ L), exhaled nitric oxide (≥ 35 ppb for children aged 5-11 years and ≥ 50 ppb for adolescents aged 12-21 years),²⁸ serum IgE concentration (≥ 100 , ≥ 200 , and ≥ 300 kU/L),³⁰ and

aeroallergen sensitization (any sensitization and multiple sensitization). Models were adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use.

RESULTS

Five hundred eighty-nine children ($N = 299$) and adolescents ($N = 290$) with an asthma exacerbation in the previous year were enrolled. Demographic features of the participants are shown in Table I.

Noninvasive type 2 inflammatory markers

Blood eosinophil counts were 344.1 ± 274.5 cells/ μ L in children and 296.5 ± 265.2 cells/ μ L in adolescents. The distribution of blood eosinophil counts, exhaled nitric oxide, serum IgE, and the percentage of positive aeroallergens is shown in Figure 1, A-D. In children and adolescents, patterns of sensitization were as follows: mold sensitization, 47.8% and 47.9%; pollen sensitization, 62.5% and 59.3%; cat sensitization, 32.2% and 39.5%; dog sensitization, 28.7% and 33.5%; dust mite sensitization, 63.9% and 60.7%; and cockroach sensitization, 25.3% and 30.4%, respectively. Associations between blood eosinophils, exhaled nitric oxide, serum IgE, and the percentage of positive allergens are shown in Figure 1, E-G.

Acute visits

The primary outcome of interest, an acute visit for an asthma exacerbation with receipt of systemic corticosteroids, occurred in 106 (35.5%) children and 72 (24.8%) adolescents. Among participants with an acute visit, the time to first acute visit was 140.5 ± 120.7 days in children and 122.3 ± 103.2 days in adolescents. Hospitalizations occurred in 22 (20.8%) children and 19 (26.4%) adolescents.

Single biomarker prediction of acute events

Crude and adjusted associations between acute visits and noninvasive type 2 inflammatory markers are shown in Table II. In children, blood eosinophil counts (≥ 150 , ≥ 200 , and ≥ 250 cells/ μ L) and sensitization were significant predictors of acute visit after covariate adjustment, although blood eosinophils ≥ 150 cells/ μ L were most strongly associated with acute visit. Frequency of daytime symptoms was also associated with acute visits, but associations were of a lesser magnitude than those observed for the type 2 inflammatory markers (adjusted OR: 1.23, 95% confidence interval (CI): 1.02, 1.47).

In adolescents, blood eosinophil counts (≥ 150 , ≥ 200 , ≥ 250 , and ≥ 350 cells/ μ L), serum IgE ≥ 100 kU/L, and sensitization were significant predictors of acute visit after covariate adjustment. However, in contrast to children, blood eosinophils ≥ 300 cells/ μ L were most strongly associated with the odds of having an acute visit for asthma. The frequency of daytime symptoms was also associated with acute visits, but associations were again of a lesser magnitude than those observed for the type 2 inflammatory markers (adjusted OR: 1.85, 95% CI: 1.47, 2.33). However, for each of the type 2 inflammatory predictors irrespective of age group, specificity remained poor (Table II).

Time to first acute visit analyses for children and adolescents also showed similar trends (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Multiple biomarker prediction of acute events

To determine whether blood eosinophils plus a second noninvasive marker of type 2 inflammation provided better

detection of acute visits for asthma over 12 months, blood eosinophils, serum IgE, and sensitization were modeled as interaction terms. The results are provided in Table III. In children, the interaction of blood eosinophils with serum IgE ≥ 100 kU/L and sensitization was associated with increased odds of acute visit by 12 months, but the corresponding ORs were not increased compared with blood eosinophils as a single predictor. In subset analysis of children with symptoms more than twice weekly, similar results were noted and there was again no additional benefit of a second noninvasive marker of type 2 inflammation compared with blood eosinophils alone (Table III).

In contrast, in adolescents, the interaction of blood eosinophils with sensitization increased the odds of acute visit for asthma by up to 16.2% compared with blood eosinophils alone (Table III). In subset analysis of adolescents with symptoms more than twice weekly, sensitization also provided some additive effects (Table III).

Time to first acute visit analyses showed similar trends in children and adolescents (Table E2, available in this article's Online Repository at www.jaci-inpractice.org), with a significantly shorter time to first acute visit in adolescents with elevated blood eosinophils (≥ 300 cells/ μ L) and sensitization (Figure 2). In subset analysis of adolescents with symptoms more than twice weekly, a significant interaction between blood eosinophils ≥ 300 cells/ μ L and any sensitization was again noted, and this association was stronger than that noted for blood eosinophils as a single predictor (Table E2).

Hospitalization

In children, blood eosinophils ≥ 150 cells/ μ L were associated with increased odds of hospitalization (adjusted OR: 2.50, 95% CI: 1.23, 5.07). The interaction of blood eosinophils with sensitization did not reach the level of significance (eosinophils ≥ 150 cells/ μ L plus any sensitization, adjusted OR: 1.42, 95% CI: 0.37, 5.42; eosinophils ≥ 150 cells/ μ L plus multiple sensitization, adjusted OR: 1.38, 95% CI: 0.42, 4.51). In adolescents, blood eosinophils ≥ 300 cells/ μ L were similarly associated with increased odds of hospitalization (adjusted OR: 4.79, 95% CI: 1.28, 17.93). The interaction of blood eosinophils with sensitization was also associated with increased odds of hospitalization in adolescents (eosinophils ≥ 300 cells/ μ L plus any sensitization, adjusted OR: 4.79, 95% CI: 1.28, 17.93; eosinophils ≥ 300 cells/ μ L plus multiple sensitization, adjusted OR: 5.10, 95% CI: 1.36, 19.08), although lack of precision in the point estimates was noted.

DISCUSSION

In this cohort of children and adolescents with exacerbation-prone asthma in Atlanta, Georgia, elevated blood eosinophils were associated with acute visits for asthma exacerbations over 12 months of follow-up in both univariate and adjusted analyses. However, optimal cut-points for blood eosinophils differed by age and were lower for children 5 to 11 years (≥ 150 cells/ μ L) than for adolescents (≥ 300 cells/ μ L). Furthermore, the addition of a second noninvasive marker of type 2 inflammation (ie, sensitization) was not useful in children but improved prediction of acute events in adolescents. These observations suggest that single measures of blood eosinophils and other noninvasive markers of type 2 inflammation can aid clinical assessment of children and adolescents with asthma. However, these data also suggest that features of type 2 inflammation vary by age.

TABLE I. Features of the participants

	All participants (N = 589)	Children aged 5-11 y (N = 299)	Adolescents aged 12-21 y (N = 290)
Age (y)	12.6 ± 4.4	9.1 ± 1.8	16.2 ± 3.2
Asthma duration (y)	9.0 ± 4.3	6.6 ± 2.8	11.8 ± 4.2
Males	334 (56.7)	178 (59.5)	156 (53.8)
Race			
White	196 (33.3)	77 (25.8)	119 (41.0)
Black	332 (56.4)	196 (65.6)	136 (46.9)
More than 1 race	55 (9.3)	24 (8.6)	31 (10.7)
Other	6 (1.0)	2 (0.7)	4 (1.4)
Hispanic ethnicity	43 (7.3)	21 (7.0)	22 (7.6)
Household education level			
Refused	117 (19.9)	52 (17.4)	65 (22.4)
Did not complete high school	20 (3.4)	9 (3.0)	11 (3.8)
High school diploma	74 (12.6)	42 (14.0)	32 (11.0)
Some college or technical training	175 (29.7)	84 (28.1)	91 (31.4)
College degree	203 (34.5)	112 (37.5)	91 (31.4)
Family history			
Father with asthma	127 (21.6)	73 (24.4)	54 (18.6)
Mother with asthma	205 (34.8)	114 (38.1)	91 (31.4)
Other medical conditions			
Obesity	150 (25.5)	79 (26.5)	71 (24.5)
Pneumonia (ever)	254 (43.1)	127 (42.5)	127 (43.8)
Recurrent sinusitis	155 (26.3)	66 (22.1)	89 (30.7)
Eczema	322 (54.7)	191 (63.9)	131 (45.2)
Allergic rhinitis	463 (78.6)	242 (80.9)	221 (76.2)
Nasal polyps	32 (5.4)	10 (3.3)	22 (7.6)
Gastroesophageal reflux	123 (20.9)	49 (16.4)	74 (25.5)
Asthma controller medications			
Inhaled corticosteroid	451 (76.6)	258 (86.3)	193 (66.6)
Long-acting β -agonist	328 (55.7)	157 (52.5)	171 (59.0)
Montelukast	347 (58.9)	195 (65.2)	152 (52.4)
Omalizumab	19 (3.2)	7 (2.3)	12 (2.3)
Indoor exposures			
Cat	79 (13.4)	32 (10.7)	47 (16.2)
Dog	199 (33.8)	97 (32.4)	102 (35.2)
Tobacco smoke	92 (15.6)	33 (11.0)	59 (20.3)
ZIP code features			
Population (in thousands)	34.4 ± 16.6	34.8 ± 17.1	33.8 ± 16.0
Unemployment (% of adults)	12.6 ± 5.8	12.6 ± 5.6	12.6 ± 6.1
Bachelor's degree (% of adults)	31.9 ± 16.5	30.7 ± 15.5	33.4 ± 17.5
Below poverty threshold (% of families)	20.2 ± 11.5	19.8 ± 10.7	20.5 ± 12.4
Asthma health care utilization			
Emergency department (past year)	276 (46.9)	170 (56.9)	106 (36.6)
Hospitalization (past year)	151 (25.6)	84 (28.1)	67 (23.1)
Intubation for asthma (ever)	78 (13.2)	37 (12.4)	41 (14.1)
Symptoms (past 4 wk)			
Nighttime symptoms >twice weekly	112 (19.1)	61 (20.5)	51 (17.7)
Dyspnea >twice weekly	142 (24.3)	70 (23.6)	72 (25.0)
Wheeze >twice weekly	125 (21.4)	60 (20.3)	65 (22.6)
Lung function (% predicted value)			
Baseline FVC	100.6 ± 15.4	102.7 ± 14.5	98.5 ± 16.1
Baseline FEV ₁	90.3 ± 17.8	93.6 ± 16.3	86.9 ± 18.6
Postbronchodilator FVC	107.1 ± 15.4	110.3 ± 14.6	103.7 ± 15.6
Postbronchodilator FEV ₁	103.1 ± 16.4	107.2 ± 16.0	99.0 ± 15.7

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.

Data represent the mean ± standard deviation or the number of participants (%).

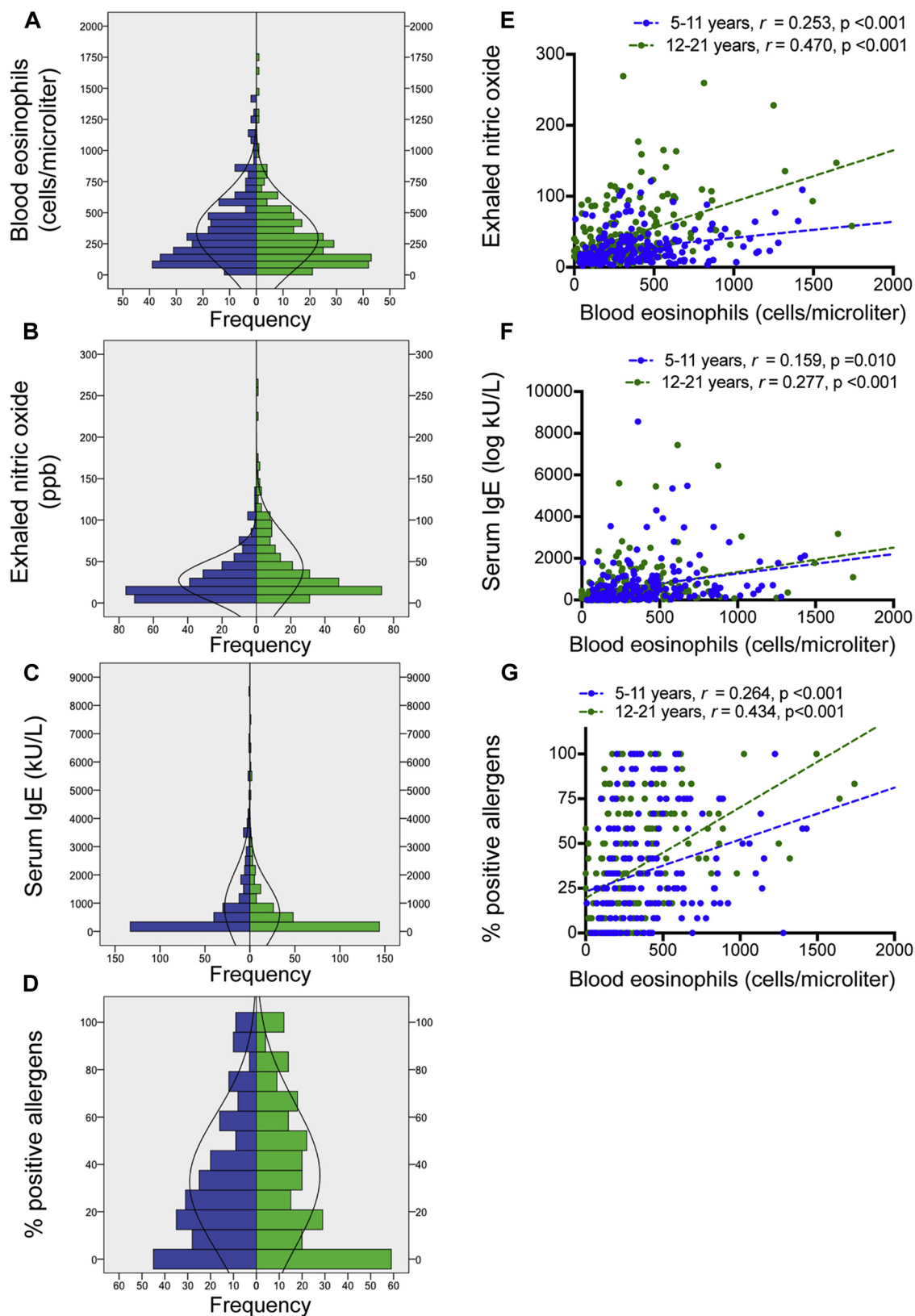


FIGURE 1. Distribution of **A**, blood eosinophils; **B**, exhaled nitric oxide; **C**, serum IgE; and **D**, percentage of positive allergens and associations between blood eosinophils and **E**, exhaled nitric oxide; **F**, serum IgE; and **G**, percentage of positive allergens in children 5-11 years (blue) and adolescents 12-21 years (green).

TABLE II. Associations between single noninvasive type 2 inflammatory markers and an acute visit for asthma by 12 months (primary outcome)

Age group	Predictor	Percentage with outcome	Crude OR (95% CI)	Adjusted OR† (95% CI)	Sensitivity	Specificity
Children 5-11 y	Elevated blood eosinophils					
	≥150 cells/μL	40.4	2.68 (2.07, 3.46)*	2.39 (1.83, 3.13)*	0.848	0.312
	≥200 cells/μL	40.4	1.81 (1.47, 2.22)*	1.66 (1.33, 2.06)*	0.707	0.437
	≥250 cells/μL	41.1	1.74 (1.43, 2.12)*	1.51 (1.23, 1.87)*	0.627	0.509
	≥300 cells/μL	39.8	1.42 (1.17, 1.73)*	1.19 (0.97, 1.46)	0.510	0.578
	Elevated exhaled nitric oxide‡	35.2	0.99 (0.80, 1.22)	0.97 (0.78, 1.22)	0.293	0.708
	Elevated serum IgE					
	≥100 kU/L	35.7	1.06 (0.84, 1.35)	0.99 (0.77, 1.28)	0.777	0.246
	≥200 kU/L	35.5	1.00 (0.82, 1.23)	0.86 (0.69, 1.08)	0.648	0.360
	≥300 kU/L	35.8	1.04 (0.85, 1.26)	0.92 (0.75, 1.14)	0.547	0.465
Adolescents 12-21 y	Aeroallergen sensitization					
	Any sensitization	37.4	1.84 (1.37, 2.47)*	1.65 (1.21, 2.25)*	0.893	0.188
	Multiple sensitization	38.2	1.64 (1.30, 2.08)*	1.49 (1.17, 1.91)*	0.694	0.426
	Elevated blood eosinophils					
	≥150 cells/μL	28.7	1.98 (1.54, 2.55)*	1.50 (1.13, 1.98)*	0.772	0.392
	≥200 cells/μL	31.5	2.46 (1.93, 3.12)*	1.82 (1.40, 2.36)*	0.727	0.492
	≥250 cells/μL	32.5	2.24 (1.79, 2.80)*	1.61 (1.26, 2.07)*	0.621	0.586
	≥300 cells/μL	35.7	2.53 (2.03, 3.16)*	2.04 (1.60, 2.60)*	0.555	0.687
	Elevated exhaled nitric oxide‡	31.3	1.59 (1.26, 2.00)*	1.24 (0.95, 1.61)	0.354	0.757
	Elevated serum IgE					
	≥100 kU/L	28.3	2.00 (1.54, 2.61)*	1.43 (1.06, 1.92)*	0.769	0.361
	≥200 kU/L	27.7	1.47 (1.17, 1.85)*	1.04 (0.81, 1.35)	0.628	0.461
	≥300 kU/L	28.0	1.44 (1.16, 1.80)*	1.07 (0.84, 1.37)	0.555	0.535
	Aeroallergen sensitization					
	Any sensitization	29.3	4.69 (3.17, 6.93)*	2.39 (1.54, 3.71)*	0.928	0.263
	Multiple sensitization	30.8	4.06 (2.95, 5.58)*	2.31 (1.63, 3.28)*	0.730	0.438

CI, Confidence interval; ICS, inhaled corticosteroid; OR, odds ratio.

* $P < .05$.

†Adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use.

‡Defined as ≥35 ppb for children 5-11 years and ≥50 ppb for adolescents 12-21 years.

In adults, numerous studies have shown associations between elevated blood eosinophils, poorer asthma control, and asthma exacerbations in general asthma populations,³¹⁻³³ which are a primary driver of asthma-related health care utilization and cost.³⁴ For example, adults with elevated blood eosinophils (ie, ≥350 or ≥400 cells/μL) have a greater risk of hospital admission^{35,36} and hospital readmission within the next year,³⁷ as well as nearly 2-fold increased health care costs.³⁸ Our findings are similar to these studies and others that have noted an increased frequency of exacerbation or increased prevalence of severe asthma exacerbation in children and adolescents with higher blood eosinophil counts.^{39,40} However, to our knowledge, our observation of age-related differences in noninvasive type 2 inflammatory markers between preadolescent children and adolescents has not been previously reported.

Although a few other studies have also examined multiple versus single noninvasive type 2 biomarkers in pediatric populations, there are important methodological differences worth mentioning. For example, whereas Konradsen et al⁴¹ noted improved discrimination of exacerbations in children with “high” exhaled nitric oxide and “high” blood eosinophils based on median split of the sample, this analysis was cross-sectional in nature and did not address potential sources of variable confounding.⁴¹ A similar analysis of National Health and Nutrition

Examination Survey results³³ likewise noted higher odds of asthma exacerbations and emergency department visits in participants with exhaled nitric oxide concentrations ≥50 ppb and blood eosinophils ≥500 cells/μL, but this analysis spanned a broad age range (6-80 years) and used biomarker cut-points that are more suitable for adults than children²⁸ and therefore have unclear sensitivity and specificity for outcome detection in pediatric populations. In an unrelated study, Malinovschi et al⁴² also noted an increased prevalence of uncontrolled asthma and frequent asthma exacerbations in patients with simultaneous increases in exhaled nitric oxide concentrations (≥20 ppb) and blood eosinophil counts (≥300 cells/μL) after covariate adjustment, but this study again spanned a wide age range (10-35 years) and was cross-sectional in nature.

Strengths of the present study include the detailed clinical characterization and follow-up of enrolled participants with verification of outcomes (ie, acute events) through medical records review. The larger nature of the sample also permitted stratification by age group and adjustment for key covariates (sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use) that are known to be associated with the primary outcome of interest (acute visits for asthma).⁴³ The inclusion criterion of an exacerbation treated with systemic corticosteroids in the previous year also ensured a study population

TABLE III. Associations between multiple noninvasive type 2 inflammatory markers* and an acute visit for asthma by 12 months

Group	Model	Adjusted OR† (95% CI)	Change in OR relative to blood eosinophils
<i>Children 5-11 y</i>			
All patients (N = 299)	Blood eosinophils ≥ 150 cells/ μ L	2.39 (1.83, 3.13)	—
	Blood eosinophils ≥ 150 + IgE > 100 kU/L	1.51 (1.22, 1.88)	−36.8%
	Blood eosinophils ≥ 150 + any sensitization	2.07 (1.64, 2.62)	−13.4%
	Blood eosinophils ≥ 150 + multiple sensitization	1.85 (1.48, 2.30)	−22.6%
Symptoms > twice weekly (N = 70)	Blood eosinophils ≥ 150 cells/ μ L	4.34 (2.36, 7.98)	—
	Blood eosinophils ≥ 150 + IgE > 100 kU/L	1.82 (1.09, 3.03)	−58.1%
	Blood eosinophils ≥ 150 + any sensitization	2.32 (1.42, 3.79)	−46.5%
	Blood eosinophils ≥ 150 + multiple sensitization	1.65 (1.07, 2.54)	−62.0%
<i>Adolescents 12-21 y</i>			
All patients (N = 290)	Blood eosinophils ≥ 300 cells/ μ L	2.04 (1.60, 2.60)	—
	Blood eosinophils ≥ 300 + IgE > 100 kU/L	1.68 (1.31, 2.14)	−17.6%
	Blood eosinophils ≥ 300 + any sensitization	2.27 (1.78, 2.91)	11.3%
	Blood eosinophils ≥ 300 + multiple sensitization	2.37 (1.86, 3.02)	16.2%
Symptoms > twice weekly (N = 72)	Blood eosinophils ≥ 300 cells/ μ L	2.44 (1.70, 3.51)	—
	Blood eosinophils ≥ 300 + IgE > 100 kU/L	2.43 (1.60, 3.69)	−0.4%
	Blood eosinophils ≥ 300 + any sensitization	2.72 (1.88, 3.94)	11.5%
	Blood eosinophils ≥ 300 + multiple sensitization	2.54 (1.69, 3.82)	4.1%

CI, Confidence interval; ICS, inhaled corticosteroid; OR, odds ratio.

Bold indicates statistical significance ($P < .05$).

*Modeled as interaction terms.

†Adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use.

with sufficient disease burden at greatest risk for the primary outcome, because several prior studies in children have identified a recent exacerbation treated with systemic corticosteroids as the strongest risk factor for subsequent exacerbations regardless of disease severity or use of controller medications.^{40,44-47} This may explain why other investigators have found no associations between noninvasive type 2 inflammatory markers and clinical outcomes in milder, general asthma populations irrespective of prior exacerbation history.⁴⁸ Indeed, the prevalence of acute visits in our study was similar to that observed in other studies of children and adolescents with difficult-to-treat asthma.^{49,50}

Nonetheless, this study does have limitations. Recognizing that biomarker cut-points are ideal for practicing clinicians, we elected not to analyze blood eosinophil counts as a continuous measure (converted to the log scale). However, the optimal cut-point of blood eosinophils for clinical detection of type 2 inflammation is still not clear. One retrospective study of children 5 to 11 years in a large medical care organization compared blood eosinophil cutoff points of 150, 200, 300, and 400 cells/ μ L and their associations with the rate and risk of future exacerbation.⁵¹ That analysis identified an ideal cut-point of 300 cells/ μ L, which was associated with a 52% increase in asthma exacerbation rate and a 40% increase in the frequency of any exacerbation.⁵¹ It is unclear why the 300 cells/ μ L cut-point was not significant in our study, although this finding could be due to differences in sociodemographics between the study populations. Our observation of a higher optimal blood eosinophil cut-point (≥ 300 cells/ μ L) in adolescents is in keeping with other studies of older populations. For example, one study of patients ≥ 12 years with severe uncontrolled asthma found that a blood eosinophils ≥ 400 cells/ μ L was a significant risk factor for 2 or more asthma exacerbations and any emergency department visit

or hospitalization in the outcome year after covariate adjustment.⁵² Similarly, in adults 18 to 64 years with persistent asthma, a blood eosinophil cut-point of 400 cells/ μ L also predicted the annualized rate of subsequent exacerbations and short-acting β -agonist pharmacy dispenses.⁵³ Nonetheless, other studies have argued for differing cut-points of blood eosinophils for the initiation of biologic therapy. Secondary analyses of adults treated with mepolizumab (ie, anti-IL-5) have shown a reduction of exacerbation rates by 52% in patients with baseline blood eosinophil counts of at least 150 cells/ μ L.⁵⁴ In that same study, exacerbation rates were reduced by 70% in patients with baseline blood eosinophil counts ≥ 500 cells/ μ L.⁵⁴ However, in other biologic studies, adults with blood eosinophil counts ≥ 300 cells/ μ L treated with either dupilumab (ie, anti-IL-4 receptor α) or benralizumab (ie, anti-IL-5 receptor α) had the greatest reduction in the risk of severe asthma exacerbations.^{55,56}

Other important limitations of the study include the measurement of type 2 biomarkers at a single time point, which may not be optimal for the assessment of type 2 inflammation. For example, one analysis of adults with severe asthma found that “same day” measurements of blood eosinophils and IgE identified only half of the eosinophilic group.³⁶ A separate study of adults with mild asthma also noted marked within-subject variability in blood eosinophil counts measured on 4 different occasions that were not solely due to seasonal fluctuations or asthma medication use.⁵⁷ However, other studies have shown that multiple measures of blood eosinophils only marginally increase the sensitivity of the biomarker.⁵⁸ It is also possible that blood eosinophils may not adequately reflect the degree of type 2 inflammation in the airways. However, unlike blood eosinophils, airway eosinophils have not been associated with responsiveness to mepolizumab therapy in adults.^{58,59}

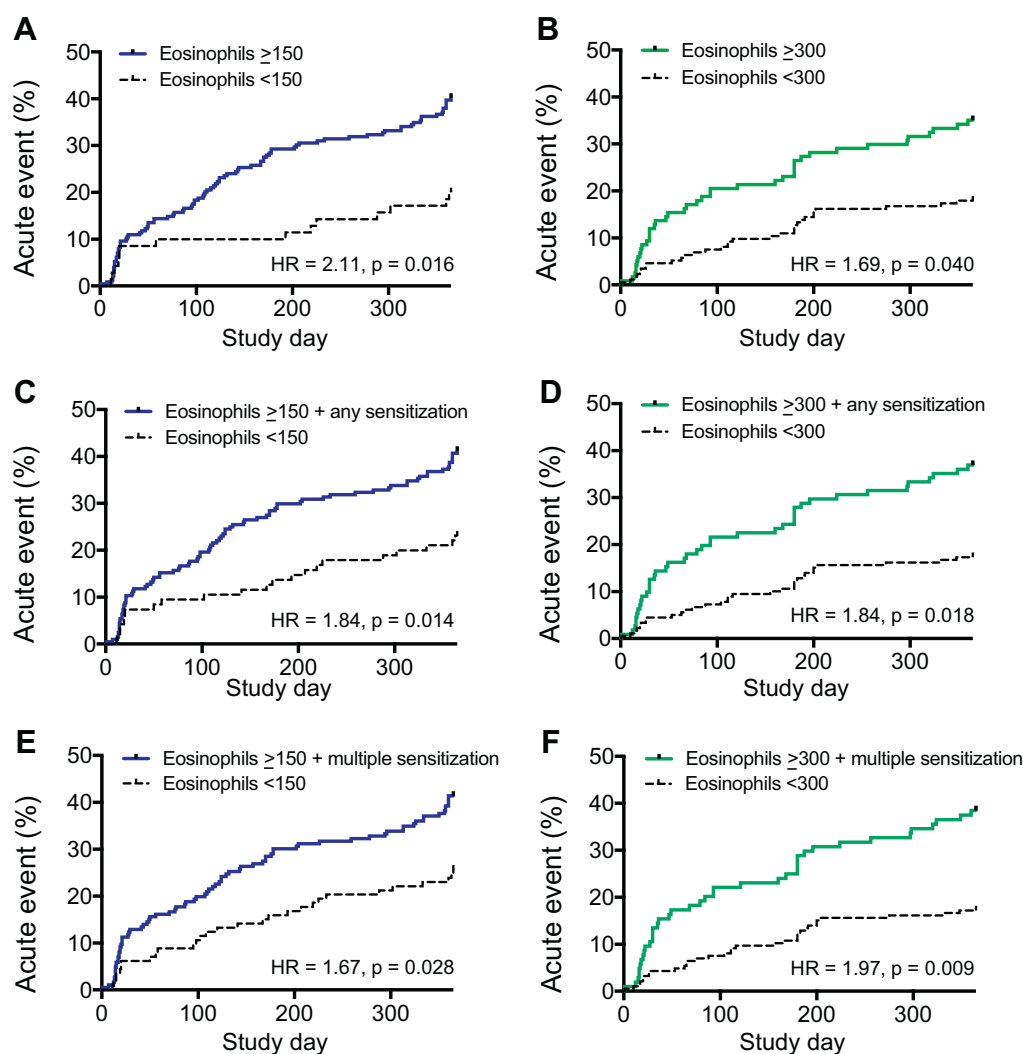


FIGURE 2. Time to first acute visit in children aged 5-11 years (left panels, blue) and adolescents (right panels, green) based on elevated blood eosinophils alone (**A**, **B**), elevated blood eosinophils plus any sensitization (**C**, **D**), and elevated blood eosinophils plus multiple sensitization (**E**, **F**). Models were adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and inhaled corticosteroid use.

Blood eosinophils have been shown to predict sputum eosinophilia⁶⁰ and offer several advantages over airway eosinophil measurement, which is invasive and difficult to perform in general populations of children. Furthermore, although periostin has been shown to correlate with blood and airway eosinophils and exhaled nitric oxide concentrations in adults with asthma,^{61,62} periostin concentrations were not available in the present study for comparison. Studies of periostin are also very limited in children with asthma, with little conclusive data,⁶³ because periostin levels are typically higher in children than in adults due to osteoblast stimulation during linear growth.⁶⁴ Finally, the observed associations between blood eosinophils and acute visits in the present study may potentially be due to unmeasured confounding, despite adjustment of models for known cofounders such as demographic features, household education level, tobacco smoke exposure, and ICS use. For example, the frequency of systemic corticosteroid use before

study enrollment was not adequately documented and could potentially impact blood eosinophil counts. Other factors such as lung function, which are also associated with exacerbations, were also not accounted for by the model and could have also contributed to our observations.

In summary, elevated blood eosinophils were associated with increased odds and shorter time to first acute visit for asthma in children and adolescents, particularly in patients with frequent symptoms, but optimal cut-points for blood eosinophils differed by age. The addition of a second marker of type 2 inflammation improved prediction of acute events, but only in adolescents. Similar trends were noted for asthma hospitalizations. Blood eosinophils and other noninvasive markers of type 2 inflammation may therefore be useful in the clinical assessment of children and adolescents with asthma. Whether children and adolescents also respond differently to management strategies for type 2 inflammation is unclear and warrants further evaluation.

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TABLE E1. Time to acute event for asthma by 12 months, according to single noninvasive type 2 inflammatory markers

Age group	Predictor	Adjusted HR* (95% CI)	P value
Children 5-11 y	Elevated blood eosinophils		
	≥150 cells/μL	2.03 (1.62, 2.56)	<.001
	≥200 cells/μL	1.40 (1.40, 1.17)	<.001
	≥250 cells/μL	1.28 (1.08, 1.52)	.004
	≥300 cells/μL	1.06 (0.89, 1.25)	—
	Elevated exhaled nitric oxide†	0.96 (0.81, 1.14)	—
	Elevated serum IgE		
	≥100 kU/L	1.01 (0.82, 1.24)	—
	≥200 kU/L	0.86 (0.72, 1.02)	—
	≥300 kU/L	0.93 (0.77, 1.09)	—
	Aeroallergen sensitization		
	Any sensitization	1.42 (1.09, 1.84)	.009
	Multiple sensitization	1.37 (1.12, 1.67)	.002
Adolescents 12-21 y	Elevated blood eosinophils		
	≥150 cells/μL	1.37 (1.08, 1.72)	.008
	≥200 cells/μL	1.63 (1.30, 2.03)	<.001
	≥250 cells/μL	1.49 (1.21, 1.83)	<.001
	≥300 cells/μL	1.77 (1.45, 2.15)	<.001
	Elevated exhaled nitric oxide†	1.11 (0.89, 1.37)	—
	Elevated serum IgE		
	≥100 kU/L	1.38 (1.08, 1.78)	.011
	≥200 kU/L	1.07 (0.87, 1.32)	—
	≥300 kU/L	1.07 (0.88, 1.31)	—
	Aeroallergen sensitization		
	Any sensitization	2.32 (1.55, 3.45)	<.001
	Multiple sensitization	2.17 (1.58, 2.99)	<.001

CI, Confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid.

*Adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use.

†Defined as ≥35 ppb for children 5-11 years and ≥50 ppb for adolescents 12-21 years.

TABLE E2. Time to acute event for asthma by 12 months for multiple noninvasive type 2 inflammatory markers*

Group	Model	Adjusted HR [†] (95% CI)	Change in HR relative to blood eosinophils
<i>Children 5-11 y</i>			
All participants (N = 299)	Blood eosinophils ≥ 150 cells/ μ L	2.03 (1.62, 2.56)	—
	Blood eosinophils ≥ 150 + IgE > 100 kU/L	1.40 (1.17, 1.67)	−31.0%
	Blood eosinophils ≥ 150 + any sensitization	1.78 (1.46, 2.16)	−12.3%
	Blood eosinophils ≥ 150 + multiple sensitization	1.61 (1.35, 1.93)	−20.7%
Symptoms >twice weekly (N = 70)	Blood eosinophils ≥ 150 cells/ μ L	4.54 (1.34, 15.46)	—
	Blood eosinophils ≥ 150 + IgE > 100 kU/L	2.70 (1.09, 6.70)	−40.5%
	Blood eosinophils ≥ 150 + any sensitization	2.27 (0.97, 5.32)	−50.0%
	Blood eosinophils ≥ 150 + multiple sensitization	1.80 (0.83, 3.90)	−60.4%
<i>Adolescents 12-21 y</i>			
All participants (N = 290)	Blood eosinophils ≥ 300 cells/ μ L	1.77 (1.45, 2.15)	—
	Blood eosinophils ≥ 300 + IgE > 100 kU/L	1.48 (1.22, 1.81)	−16.4%
	Blood eosinophils ≥ 300 + any sensitization	1.93 (1.58, 2.35)	9.0%
	Blood eosinophils ≥ 300 + multiple sensitization	1.98 (1.62, 2.41)	11.9%
Symptoms >twice weekly (N = 72)	Blood eosinophils ≥ 300 cells/ μ L	2.11 (1.06, 4.21)	—
	Blood eosinophils ≥ 300 + IgE > 100 kU/L	2.04 (1.01, 4.14)	−3.3%
	Blood eosinophils ≥ 300 + any sensitization	2.23 (1.11, 4.50)	5.7%
	Blood eosinophils ≥ 300 + multiple sensitization	2.02 (1.01, 4.06)	−4.3%

CI, Confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid.

Bold indicates statistical significance ($P < .05$).

*Modeled as interaction terms.

†Adjusted for sex, ethnicity, race, household education level, tobacco smoke exposure, and ICS use.