Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

function decline. Given the close relationship between exacerbations and airway inflammation, interventions targeted at reducing exacerbations might also reduce airway inflammation.

Limitations include the lack of biological specimens to confirm airway remodeling. A direct measure of medication compliance was also unavailable. Exacerbation data were collected semiannually by using patient recall for the prior 3 months and thus did not include the entire year or 6-month period from the data collection point. However, this might cause a potential underestimation of asthma exacerbation counts, thus biasing results toward the null hypothesis of no association between exacerbations and lung function decline.

In summary, longitudinal data from the TENOR study suggest that asthma exacerbations accelerate lung function decline. The extent of possible structural changes in the airways caused by exacerbations and the subsequent risk of airway remodeling require further study. These findings emphasize the importance of preventing exacerbations to preserve lung function, particularly in younger populations.

We thank David R. Mink of ICON Clinical Research (South San Francisco, Calif) for statistical programming support.

William J. Calhoun, MD[a]
Tmirah Haselkorn, PhD[b]
Dave P. Miller, MS[c]
Theodore A. Omachi, MD, MBA[b]

From [a]University of Texas Medical Branch, Galveston, Tex; [b]Genentech, Inc, South San Francisco, Calif; and [c]ICON Clinical Research, San Francisco, Calif. E-mail: wjcalhou@utmb.edu.

TENOR was funded by Genentech, Inc (South San Francisco, Calif) and Novartis Pharmaceuticals (East Hanover, NJ).

Disclosure of potential conflict of interest: W. J. Calhoun has consultant arrangements with Genentech, Inc. T. Haselkorn has consultant arrangements with Genentech, Inc. D. P. Miller has received consultant fees and fees for participation in review activities from Genentech, Inc and is employed by ICON Clinical Research. T. A. Omachi has received travel support from and is employed by Genentech, Inc and has stock/stock options with Roche.

REFERENCES

1. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J 2007;30:452-6.
2. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 2009;179:19-24.
3. Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 1999;14:892-6.
4. Rennard SI, Farmer SG. Exacerbations and progression of disease in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:88-92.
5. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847-52.
6. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. Design and baseline characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32-9.
7. Saetta M, Finkelstein R, Cosio MG. Morphological and cellular basis for airflow limitation in smokers. Eur Respir J 1994;7:1505-15.
8. US Department of Health and Human Services, National Institute of Health. Expert panel report 3: guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. Washington (DC): National Heart Lung and Blood Institute; 2007.
9. Davies DE. The bronchial epithelium in chronic and severe asthma. Curr Allergy Asthma Rep 2001;1:127-33.

Available online June 20, 2015.
http://dx.doi.org/10.1016/j.jaci.2015.05.014

Comparison of risk factors for viral and nonviral asthma exacerbations

To the Editor:

Asthma exacerbations secondary to viral illnesses are an important cause of morbidity among children with asthma, and allergy is a risk factor for virus-induced exacerbations. Although less frequent, some exacerbations of asthma occur independently of viral illnesses. The patterns and cause of asthma exacerbations have been investigated in cross-sectional studies,[1] but longitudinal data are lacking.

We sought to determine whether there are separate groups of children who have asthma exacerbations with viruses and children who have asthma exacerbations without viruses. In addition, we tested the hypothesis that there are distinct risk factors for virus-induced exacerbations and exacerbations not associated with viral infection.

The Childhood Origins of Asthma (COAST) study followed 259 children prospectively from birth to age 6 years, and 217 were followed until age 11 years. Of those, 102 children met the criteria for asthma at 6, 8, and/or 11 years of age (Table I). This subset of COAST children was predominantly male (63%). Forty-nine percent had a family history of maternal asthma, and 34% had a history of paternal asthma. Forty-seven percent had aeroallergen sensitization at the age of 6 years and 52% at the age of 11 years. The majority (94%) lived in a home without smoke exposure. At year 6, 15% of children were taking a daily controller either seasonally or perennially compared with 35% of children by year 12.

An asthma exacerbation was defined as an illness in which a child required a step-up plan of care, use of oral corticosteroids, or both. A severe asthma exacerbation was defined by the use of oral corticosteroids.

Nasal samples were collected during asthma exacerbations and analyzed for respiratory tract viruses. Respiratory tract viruses were identified by using multiplex PCR.[2] Allergen-specific IgE levels were measured by using ImmunoCAP (Phadia, Portage, Mich) performed at age 6 and 11 years, and positive results were defined as 0.35 kU/L or greater.[3]

Of the 102 COAST children with asthma, 60% had at least 1 exacerbation between ages 6 and 11 years, and 38% had more than 1 exacerbation. When grouped by exacerbation cause, 40 (40%) children had no exacerbations, 23 (22%) had only viral exacerbations, 13 (13%) had only nonviral exacerbations, and 19 (19%) had a mixture of both viral and nonviral exacerbations. There were 7 (6%) children who each had 1 exacerbation but no nasal sample. Children who had only viral or only nonviral exacerbations had fewer exacerbations on average (mean, 2.4 [95% CI, 1.3-4.4] and 1.5 [95% CI, 0.6-3.4], respectively) than children who experienced both viral and nonviral exacerbations (mean, 6.9 [95% CI, 4.7-10.1]). Children with at least 2 exacerbations had the highest prevalence of allergic sensitization and total IgE levels at age 11 years (see Table E1 in this article's Online Repository at www.jacionline.org).

There were a total of 217 exacerbations, of which 192 included nasal samples obtained for viral analysis. Viruses were identified in 69% of exacerbations, and rhinovirus was most commonly identified (34% of exacerbations, see Fig E1 in this article's Online Repository at www.jacionline.org). The total number of exacerbations was positively associated with total IgE levels at age 6 years ($P = .009$; incidence rate ratio (IRR) with respect to a

TABLE I. Factors associated with asthma exacerbations between ages 6 and 11 years in the COAST cohort (n = 102)

		All exacerbations		Viral exacerbations		Nonviral exacerbations	
	No.	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
Overall no. of exacerbations		2.1 ± 3.3		1.3 ± 2.4		0.6 ± 1.2	
Sex							
Female	39	2.3 ± 3.9	.61	1.4 ± 2.9	.64	0.6 ± 1.4	.91
Male	63	2.0 ± 2.9		1.2 ± 2.0		0.6 ± 1.0	
Year 6 aeroallergen sensitization							
No	35	1.7 ± 2.3	.10	1.1 ± 1.8	.27	0.4 ± 0.8	.14
Yes	47	2.9 ± 4.1		1.8 ± 3.1		0.8 ± 1.4	
Year 11 aeroallergen sensitization							
No	23	1.3 ± 1.2	.008	0.8 ± 1.1	.03	0.4 ± 0.6	.11
Yes	52	3.2 ± 4.1		1.9 ± 3.0		0.9 ± 1.5	
Maternal asthma							
No	53	1.7 ± 2.4	.17	1.0 ± 1.8	.21	0.5 ± 0.9	.37
Yes	49	2.7 ± 4.0		1.6 ± 2.9		0.7 ± 1.4	
Paternal asthma							
No	66	2.0 ± 2.9	.41	1.2 ± 2.1	.65	0.5 ± 1.0	.17
Yes	34	2.5 ± 4.0		1.5 ± 3.0		0.8 ± 1.5	
Smoke in home (year 6)							
No	94	2.2 ± 3.4	.49	1.4 ± 2.5	.16	0.6 ± 1.2	.62
Yes	6	1.3 ± 1.5		0.3 ± 0.5		0.3 ± 0.5	
Dog in home (year 6)							
No	64	2.1 ± 3.2	.79	1.3 ± 2.2	.80	0.6 ± 1.3	.69
Yes	36	2.3 ± 3.5		1.4 ± 2.9		0.7 ± 1.0	
Cat in home (year 6)							
No	75	2.5 ± 3.6	.03	1.5 ± 2.7	.11	0.7 ± 1.3	.10
Yes	25	1.2 ± 1.9		0.8 ± 1.4		0.3 ± 0.7	

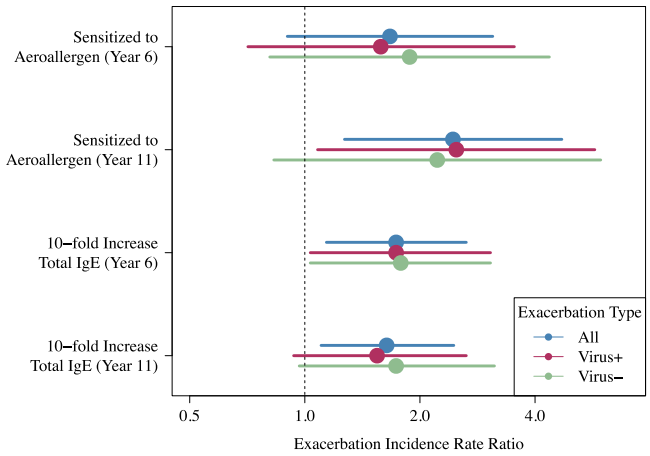

FIG 1. Aeroallergen sensitization and higher total IgE levels were associated with greater numbers of exacerbations. Aeroallergen sensitization and total IgE levels are also associated with the number of both viral and nonviral exacerbations.

1-unit increase in $\log_{10}$ IgE, 1.74 [95% CI, 1.15-2.64]) and 11 years ($P = .02$; IRR, 1.64 [95% CI, 1.10-2.46]), and with aeroallergen sensitization at age 11 years ($P = .008$; IRR, 2.44 [95% CI, 1.27-4.70]; Fig 1). Having a cat in the home at year 6 was associated with a reduced number of exacerbations (IRR, 0.47 [95% CI, 0.24-0.91]; $P = .03$).

Risk factors for viral and nonviral exacerbations were similar. For example, viral exacerbations were positively associated with total IgE levels at age 6 years ($P = .04$; IRR, 1.76 [95% CI, 1.02-3.02]) and aeroallergen sensitization at age 11 years ($P = .03$; IRR, 2.49 [95% CI, 1.08 5.73]), and nonviral exacerbations were positively associated with total IgE levels at age 6 years ($P = .04$; IRR, 1.77 [95% CI, 1.02-3.08]) and aeroallergen sensitization at age 11 years (trend: $P = .11$; IRR, 2.22 [95% CI, 0.83-5.94]; Fig 1).

Finally, we compared the severity of viral versus nonviral exacerbations. Twenty-three percent (14/60) of nonviral exacerbations and 17% (23/132) of viral exacerbations were severe ($P = .34$). Of the 37 severe exacerbations, 14 (38%) were nonviral, 14 (38%) were associated with rhinovirus infection, and 9 (24%) were associated with other viruses. The greatest number of severe exacerbations, regardless of cause, occurred during the fall (October and November) and spring (March, see Figs E2 and E3 in this article's Online Repository at www.jacionline.org).

This study provides new data about patterns of asthma exacerbation over a 6-year span in a cohort of suburban children. Notably, children who experienced multiple episodes had at least 1 viral exacerbation. Risk factors for having viral or nonviral asthma exacerbations were similar and consisted of indicators of atopy (ie, total IgE and aeroallergen sensitivity).

Previous studies have established that atopy is a risk factor for virus-induced wheezing and exacerbations of asthma. For example, wheezing illnesses in children older than 2 years are most common in children who have rhinovirus infections together with allergic sensitization, nasal eosinophilia, or increased nasal eosinophil cationic protein levels.[4] Additional studies have identified increased expression of the FcεRI receptor on monocytes and dendritic cells during acute asthma exacerbations.[5] One potential mechanism by which IgE could affect viral exacerbations relates to effects of the FcεRI on interferon responses. *In vitro* experiments demonstrated that increased FcεRI expression on plasmacytoid dendritic cells and IgE cross-linking strongly inhibited

rhinovirus-induced interferon production in cells from children with allergic asthma.[6]

Strengths of the current study include the longitudinal analysis of exacerbations over a 6-year period. Much of the current literature evaluates the cause of asthma exacerbations from a cross-sectional perspective and not prospectively over multiple years. The study is limited by the relatively small numbers of children in each group, particularly the groups with only viral and only nonviral exacerbations, and the fact that most of the children with asthma in this cohort study have relatively mild disease.

In conclusion, our findings demonstrate that atopy is an important risk factor for both viral and nonviral exacerbations. These data are consistent with a clinical study of omalizumab, in which blocking IgE-mediated inflammation prevented both viral and nonviral exacerbations in children with moderate-to-severe asthma.[7] One implication of these findings is that treatment aimed at reducing levels of IgE or perhaps other effectors of allergic inflammation could represent a common strategy to reduce morbidity caused by viral and nonviral asthma exacerbations.

Amaziah T. Coleman, MD[a]
Daniel J. Jackson, MD[a]
Ronald E. Gangnon, PhD[b]
Michael D. Evans, MS[b]
Robert F. Lemanske, Jr, MD, FAAAAI[a]
James E. Gern, MD, FAAAAI[a]

From [a]the Departments of Pediatrics and Medicine and [b]the Department of Bioinformatics, University of Wisconsin School of Medicine and Public Health, Madison, Wis. E-mail: acoleman@medicine.wisc.edu.

Supported by the National Institutes of Health (grant nos. P01 HL70831 and UL1TR000427).

Disclosure of potential conflict of interest: D. J. Jackson has received research support from the National Heart, Lung, and Blood Institute (NHLBI) and has received consultancy fees from GlaxoSmithKline and Genentech. R. E. Gangnon has received research support from the NHLBI. M. D. Evans has received research support from the National Institutes of Health (NIH). R. F. Lemanske, Jr, reports grants from the University of Wisconsin during the conduct of the study; other from board membership and personal fees from the University of Wisconsin; grants from the NHBLI; personal fees from Merck, Sepracor, SA Boney and Associates, GlaxoSmithKline, the American Institute of Research, Genentech, Double Helix Development, and Boehringer Ingelheim, Michigan Public Health, Allegheny General Hospital, the AAP, West Allegheny Health, California Chapter 4, the Colorado Allergy Society, the Pennsylvania Allergy Society, Howard Pilgrim Health, the California Society of Allergy, the NYC Allergy Society, the World Allergy Organization, APAPARI, Elsevier, UpToDate, the Kuwait Allergy Society, Lurie Children's Hospital, Boston Children's Hospital, Health Star Communications, LA Children's Hospital, and Northwestern University, and the Western Society of Allergy, Asthma, and Immunology, the American Academy of Allergy, Asthma & Immunology outside the submitted work; and grants from Pharmaxis outside the submitted work. J. E. Gern has received research support from the NIH, GlaxoSmithKline, and Merck and has received consultancy fees from GlaxoSmithKline, Johnson & Johnson, Merck, MedImmune, Boehringer Ingelheim, Gilead, and Genentech. A. T. Coleman declares no relevant conflicts of interest.

REFERENCES

1. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 1995;310:1225-9.
2. Lee WM, Grindle K, Pappas T, Marshall DJ, Moser MJ, Beaty EL, et al. High-throughput, sensitive, and accurate multiplex PCR-microsphere flow cytometry system for large-scale comprehensive detection of respiratory viruses. J Clin Microbiol 2007;45:2626-34.
3. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667-72.
4. Rakes GP, Arruda E, Ingram JM, Hoover GE, Zambrano JC, Hayden FG, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. Am J Respir Crit Care Med 1999;159:785-90.
5. Holt PG, Strickland DH, Sly PD. Virus infection and allergy in the development of asthma: what is the connection? Curr Opin Allergy Clin Immunol 2012;12:151-7.
6. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol 2012;130:489-95.
7. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364:1005-15.

Available online July 17, 2015.
http://dx.doi.org/10.1016/j.jaci.2015.05.038

Does azithromycin modify viral load during severe respiratory syncytial virus bronchiolitis?

To the Editor:

Early life respiratory syncytial virus (RSV) bronchiolitis is a major risk factor for subsequent recurrent wheezing and asthma.[1,2] The highest asthma risk occurs in infants with severe bronchiolitis requiring hospitalization[3]: up to 75% of hospitalized infants experience at least 3 additional wheezing episodes and almost 50% are diagnosed with asthma by the age of 7 years.[1]

We recently reported the results of a proof-of-concept trial, "Azithromycin for the Prevention of recurrent Wheezing following RSV bronchiolitis (APW-RSV)," in which azithromycin (AZM) treatment of infants hospitalized with RSV bronchiolitis resulted in a lower likelihood of subsequent recurrent wheezing.[4] Anti-inflammatory effects of AZM were detected in that study: relative to placebo, AZM treatment resulted in a greater decline in nasal lavage IL-8 levels by day 15 ($P = .03$).[4] However, other mechanisms through which AZM may exert this protective effect remain uncertain. Previous laboratory investigations have suggested that macrolides have *in vitro* antiviral activity because pretreatment of *ex vivo* human respiratory epithelial cells with AZM[5] or clarithromycin[6] reduced replication and release of RSV[6] and rhinovirus.[5] In addition, AZM pretreatment reduces rhinovirus replication in cystic fibrosis bronchial epithelial cells.[7] However, potential *in vivo* antiviral effects of macrolides have not been investigated in humans infected with respiratory viruses. Therefore, we hypothesized that our finding of AZM's reduction in post-RSV recurrent wheeze[4] was mediated, at least in part, by antiviral activity.

In this present study, we aimed to address 2 research questions. Does AZM have antiviral activity as demonstrated by lower RSV loads in serial nasal lavage samples obtained during RSV bronchiolitis? Does this potential antiviral activity mediate the reduction in recurrent wheeze detected in our proof-of-concept trial?

A detailed description of the APW-RSV study has been reported elsewhere.[4] Briefly, this was a randomized, double-masked, placebo-controlled, proof-of-concept trial involving 40 infants with RSV bronchiolitis. Eligible infants were aged 1 to 18 months, otherwise healthy, and hospitalized for the first episode of bronchiolitis with confirmed RSV infection. Infants with a history of prematurity were excluded. Study treatments were either AZM oral suspension 10 mg/kg once daily for 7 days, followed by 5 mg/kg once daily for 7 additional days, or an oral placebo suspension. AZM therapy was well tolerated as mild gastrointestinal adverse events (diarrhea, vomiting, or abdominal pain) during the active treatment phase were recorded in 15 children (7 azithromycin, 8 placebo); none warranted discontinuation of study medication.[4] The study protocol was

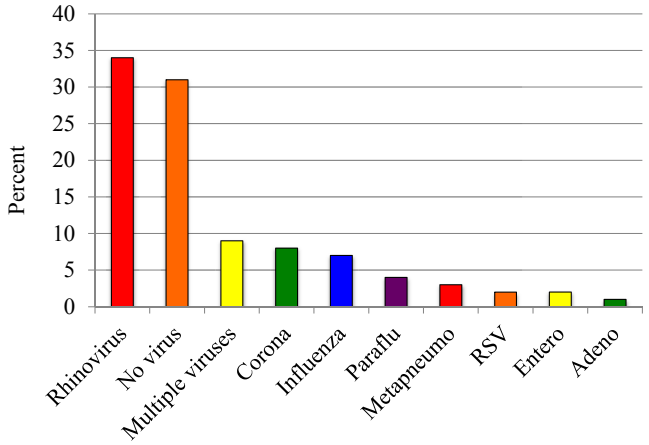

FIG E1. Virology of exacerbations. *RSV*, Respiratory syncytial virus.

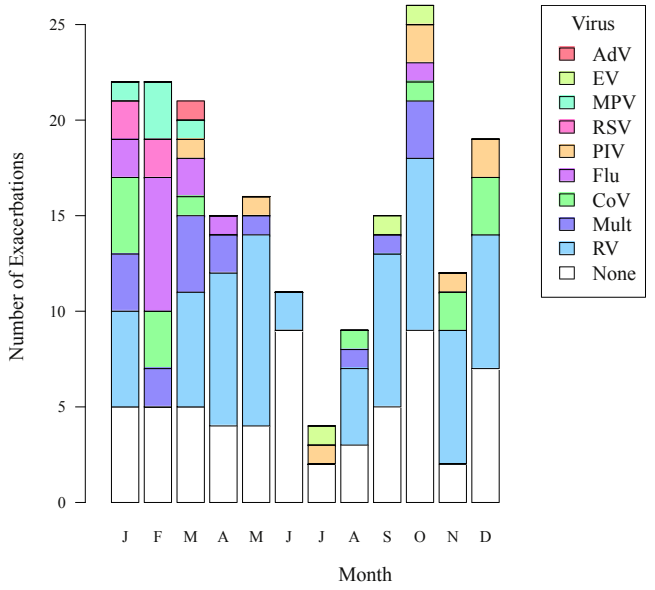

FIG E2. Virology of exacerbations by month. *AdV*, Adenovirus; *CoV*, coronavirus; *EV*, enterovirus; *MPV*, metapneumovirus; *Mult*, multiple viruses; *PIV*, parainfluenza virus; *RSV*, respiratory syncytial virus; *RV*, rhinovirus.

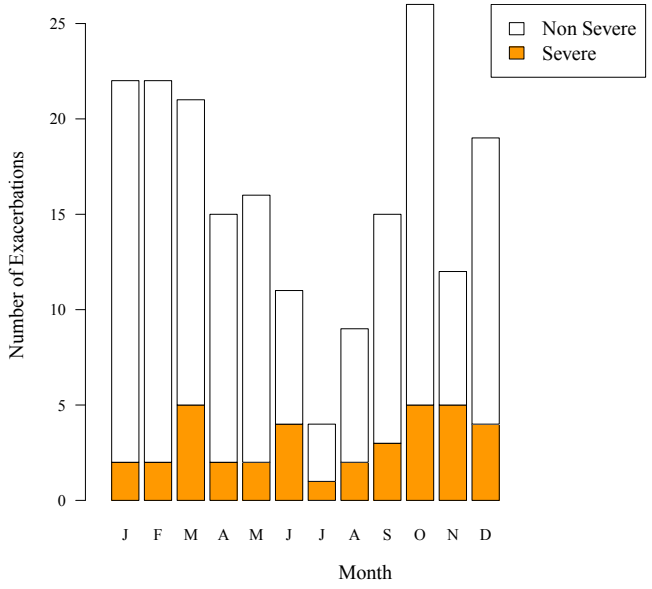

FIG E3. Severity of exacerbations by month.

TABLE E1. Characteristics of children with 0, 1, or 2 or more exacerbations

	No. of exacerbations			*P* value	
	0	1	≥2	0 vs ≥2	1 vs ≥2
No. of children	40	23	39		
Sex	17 F, 23 M	7 F, 16 M	15 F, 24 M	.71	.52
Maternal asthma	50%	39%	51%	.91	.35
Paternal asthma	33%	36%	33%	1.00	.81
Maternal allergy	90%	83%	84%	.44	.87
Paternal allergy	84%	75%	86%	.78	.30
Aeroallergen sensitization (sIgE), year 6 (kU/L)	60%	41%	63%	.81	.14
Aeroallergen sensitization (sIgE), year 11 (kU/L)	74%	44%	78%	.73	.02
Total IgE, year 6 (kU/L)	51 (25-126)	46 (9-129)	96 (25-280)	.62	.09
Total IgE, year 11 (kU/L)	49 (26-460)	59 (18-228)	119 (44-472)	.53	.04
Positive skin test response, year 9	56%	47%	62%	.60	.29
FENO, year 6 (ppb)	9.1 (7.2-11.1)	5.9 (4.7-11.0)	7.9 (6.1-18.3)	.74	.14
FENO, year 8 (ppb)	8.1 (7.0-10.1)	8.9 (5.2-20.0)	10.6 (7.6-28.7)	.14	.28
FENO, year 11 (ppb)	15.0 (9.4-24.5)	10.6 (8.8-24.6)	15.7 (8.7-32.4)	.76	.61
Blood eosinophils (%), year 6	3.0 (1.0-5.0)	2.5 (1.0-4.0)	3.0 (1.0-5.2)	.71	.96
Blood eosinophils (%), year 8	4.0 (2.0-5.0)	2.5 (1.0-5.0)	4.0 (2.5-5.5)	.45	.04
Blood eosinophils (%), year 11	5.0 (2.0-6.0)	4.0 (1.0-5.2)	4.0 (2.0-6.0)	.69	.18

F, Female; *FENO*, fraction of exhaled nitric oxide; *M*, male; *ppb*, parts per billion.