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Available online January 10, 2012.
doi:10.1016/j.jaci.2011.11.045

Recurrent severe exacerbations in early life and reduced lung function at school age

To the Editor:

Asthma exacerbations have been linked to progressive loss of lung function in school-age children and adults.[1] Previous longitudinal studies have suggested that lung function deficits in children with persistent wheezing are established by school age, and these deficits can persist into adulthood.[2-4] Because the first several years of life are a critical time in lung growth and development, we hypothesized that recurrent severe wheezing exacerbations during early life could lead to airway remodeling and be associated with reductions in lung function at school age.

Children at high risk for asthma and allergic disease based on parental histories of asthma, allergies, or both were enrolled in the Childhood Origins of Asthma study from birth, and the timing, cause, and severity of respiratory illnesses were followed prospectively, as previously described.[5] Severe exacerbations were defined, per the American Thoracic Society criteria, as an episode requiring systemic corticosteroids.[6] Prebronchodilator (5-8 years of age) and postbronchodilator (6-8 years of age) spirometry was performed at scheduled annual visits. Acceptability of spirometry was determined based on criteria published by Eigen et al.[7] A total of 225 children completed acceptable spirometry between 5 and 8 years of age and were included in this analysis.

The cohort was divided into 4 groups based on wheezing history during the first 3 years of life: no wheezing illness (n = 111), mild-to-moderate wheezing only (n = 69), 1 severe wheezing episode requiring oral corticosteroids (OCSs; n = 23), and recurrent (>1) severe wheezing episodes requiring OCSs (n = 22). Mixed-effect linear regression models were used to assess the effect of group on lung function between ages 5 and 8 years. These models included child as a random effect and group, age, and the interaction between group and age as fixed effects, with asthma, sex, height, weight, race, smoke exposure, and aeroallergen sensitization as control variables. In the absence of significant interactions between age and group, lung function differences by group are presented as least-squares means or the marginal mean for a balanced population across age and the other covariates. The Fisher protected least significant difference method was used to account for multiple comparisons among the 4 groups.

The characteristics of children in each of the 4 groups defined by wheezing and exacerbation histories are shown in Table I. Children with 2 or more severe exacerbations had a higher rate of asthma at school age compared with the rest of the cohort. Early aeroallergen sensitization within the first 2 years of life was additionally noted to be associated with higher rates of severe exacerbations. There were no differences among groups for height, weight, sex, race, or smoke exposure.

Children with a history of recurrent severe wheezing exacerbations during the first 3 years of life had significantly reduced prebronchodilator FEV_1 at school age (1.26 L; 95% CI, 1.19-1.34 L) when compared with children with no wheezing (1.37 L; 95% CI, 1.32-1.41 L; $P = .01$), mild-to-moderate wheezing only (1.34 L; 95% CI, 1.30-1.39 L; $P = .05$), and only 1 severe episode requiring OCSs (1.38 L; 95% CI, 1.31-1.45 L; $P = .02$). Similar differences in forced expiratory volume in 0.5 seconds ($FEV_{0.5}$) at school age were seen among these groups (Fig 1, *A*). In contrast, there were no significant differences in $FEV_{0.5}$ or FEV_1 values among children with no wheezing, mild-to-moderate wheezing only, or only 1 severe episode requiring OCSs (Fig 1, *A*). Postbronchodilator differences in $FEV_{0.5}$ and FEV_1 values between children with histories of recurrent severe wheezing exacerbations and the other 3 groups of children were not statistically significant (Fig 1, *B*).

In this study we used requirement for systemic steroids as a marker for illness severity to demonstrate that children with recurrent severe wheezing exacerbations during the first 3 years of life had lower lung function at school age when compared with children with a single severe exacerbation, mild-to-moderate wheezing only, or no wheezing history. These findings have important potential implications because prior studies have shown that abnormalities in lung function present at school age persist at least into early adulthood.[2,3]

The reductions in lung function present in this high-risk cohort are consistent with the effects of severe exacerbations on lung function in older children and adults with asthma reported by O'Byrne et al.[1] However, in our study these reductions in lung function were at least partially reversible with a bronchodilator, whereas O'Byrne et al reported postbronchodilator differences in patients with severe exacerbations, particularly those patients not taking an inhaled corticosteroid. The observational nature of the Childhood Origins of Asthma study and the numbers of children in each group in our study do not allow us to determine whether treatment affected our findings.

The results of our study suggest that severe episodes of wheezing during this critical time in lung growth and development, which were associated with a greater likelihood of asthma at school age, might have deleterious effects on the airways. We hypothesize that these events, typically associated with viral respiratory tract infections, lead to airway damage and remodeling, and plausible mechanisms by which this can occur have been described.[8] Furthermore, it is possible that these more severe episodes lead to enhanced damage and perhaps a more prolonged remodeling process. When this occurs recurrently, it is particularly

TABLE I. Characteristics of children in each comparison group

	No wheezing (n = 111)	Mild-to-moderate wheezing (n = 69)	1 Severe exacerbation (n = 23)	≥2 Severe exacerbations (n = 22)	*P* value
Height (year 8)	129 ± 5	129 ± 5	130 ± 5	128 ± 7	.48
Weight (year 8)	62 ± 11	62 ± 11	63 ± 11	70 ± 21	.59
Asthma diagnosis, year 6 or 8	16%	49%	65%	77%	<.0001
Male sex	54%	59%	74%	59%	.37
Smoke exposure	25%	22%	22%	41%	.33
White race	89%	90%	87%	77%	.42
Aeroallergen sensitization					.007
Never	55%	48%	56%	32%	
First sensitized at years 1-2	15%	22%	35%	50%	
First sensitized at years 3-6	30%	30%	9%	18%	

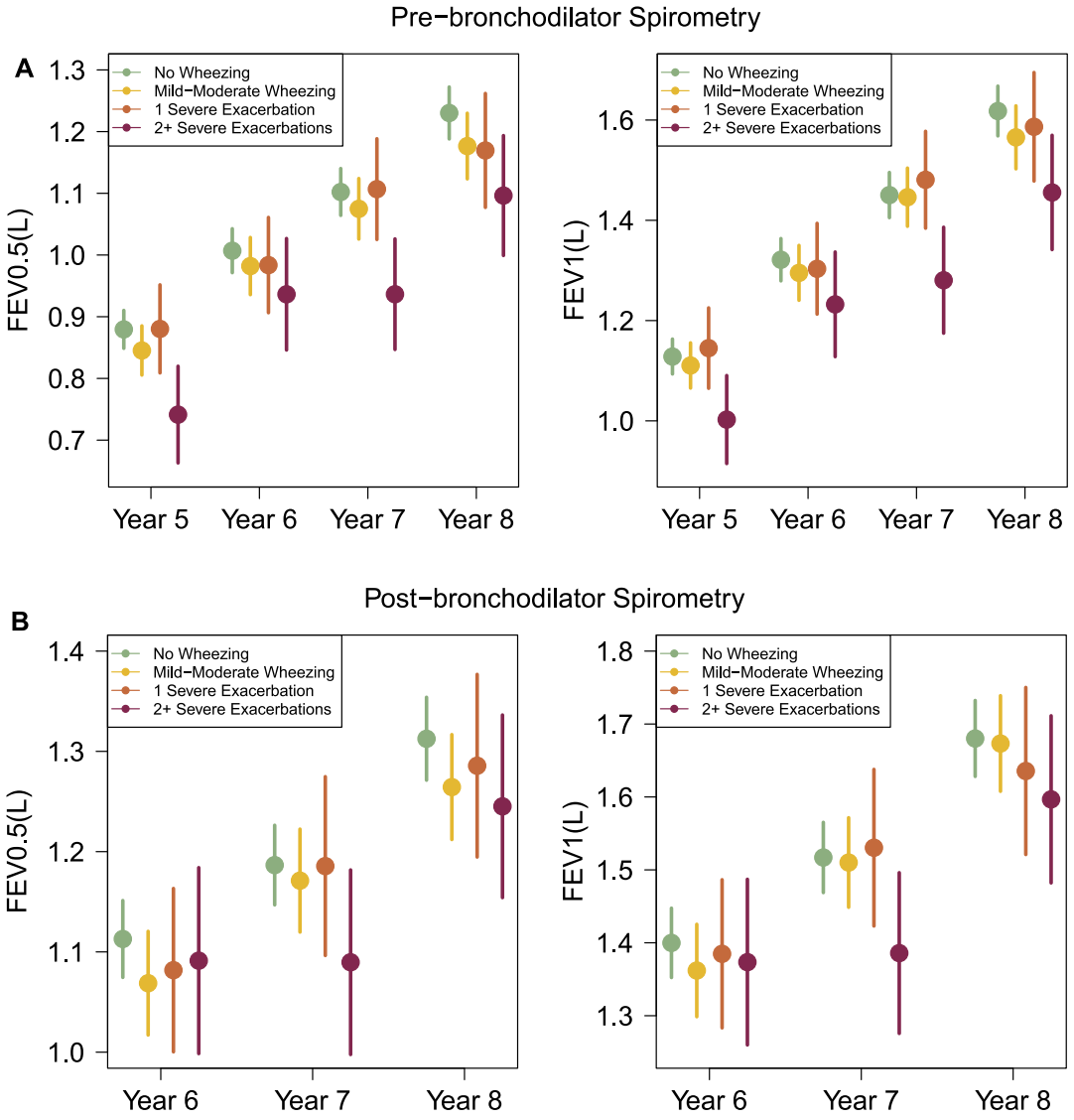

FIG 1. A, Prebronchodilator $FEV_{0.5}$ and FEV_1 values assessed longitudinally between 5 and 8 years of age were significantly decreased in children with histories of recurrent (≥2) wheezing exacerbations treated with OCSs when compared with those seen in children with no wheezing, mild-to-moderate wheezing, or 1 severe wheezing exacerbation requiring OCSs. This figure demonstrates that these between-group differences were stable over time. **B,** Postbronchodilator $FEV_{0.5}$ and FEV_1 values assessed longitudinally between 6 and 8 years of age were not significantly different between children with histories of recurrent (≥2) severe wheezing exacerbations treated with OCSs and those children with no wheezing, mild-to-moderate wheezing, or 1 severe exacerbation requiring OCSs.

problematic for the developing young child. Importantly, remodeling and airway changes typical of asthma can occur in children between 1 and 3 years of age.[9] The partial postbronchodilator reversibility seen in the recurrent exacerbation group in our study suggests that these children might not yet have fixed obstruction; however, it will be interesting to longitudinally assess for progressive loss of lung function in these children with early recurrent exacerbations.

A limitation of this study is the lack of baseline lung function measurements from the first several years of life, preventing us from definitively determining whether these severe wheezing episodes caused progressive loss of lung function, were due to an initial low baseline lung function, or both. However, data from the Tucson Children's Respiratory Study suggest that abnormalities in lung function might not be present during the first year of life but develop during early childhood in children with persistent wheezing.[3]

Our findings highlight the importance of close follow-up for children with histories of severe exacerbations during early life and suggest that preventing additional severe wheezing episodes could affect subsequent morbidity caused by loss of lung function. Thus novel strategies for the prevention of wheezing exacerbations, particularly in preschool children, are sorely needed.

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Supported by National Institutes of Health grants R01 HL61879, P01 HL70831, M01 RR03186, and 1UL1RR025011 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources (NCRR).

Disclosure of potential conflict of interest: R. F. Lemanske, Jr, is a speaker for Merck, AstraZeneca, Doembecher Children's Hospital, Washington University, the Medicus Group, Park Nicolet Institute, the American College of Allergy, Asthma & Immunology, the Los Angeles Allergy Society, the Michigan Allergy/Asthma Society, the Medical College of Wisconsin, the Fund for Medical Research and Education (Detroit), Children's Hospital of Minnesota, the Toronto Allergy Society, the American Academy of Allergy, Asthma & Immunology, Beaumont Hospital (Detroit), University of Illinois, the Canadian Society of Allergy and Clinical Immunology, New York Presbyterian, the Med Media Educational Group, Onpointe Medical Communications, the Medical University of South Carolina, Health Matters Communication, Bishop McCann, Donohue, Purohit, Miller, the Center for Health Care Education, University of California—San Francisco, the American Thoracic Society, the University of Iowa, Indiana University, the American Lung Association of the Upper Midwest, Vanderbilt University, Rochester Children's Hospital, the Colorado Allergy Society, the Pennsylvania Allergy Society, Howard Pilgrim Health Care, and the California Allergy Society; has consultant arrangements with AstraZeneca, Map Pharmaceuticals, Gray Consulting, Smith Research, the Merck Childhood Asthma Network, Novartis, Quintiles/Innovex, RC Horowitz & Co, International Meetings and Science, Scienomics, Scientific Therapeutics, Cognidmed, SA Boney and Associates, GlaxoSmithKline, and Double Helix Development; is an author for Up-to-Date; is a textbook editor for Elsevier; and receives royalties from Elsevier. J. E. Gern is on the scientific advisory board for and has stock options with 3V Biosciences; has consultant arrangements with Centocor, Boehringer Ingelheim, GlaxoSmithKline, Biota, MedImmune, and Theraclone; and receives research support from AstraZeneca and GlaxoSmithKline. D. J. Jackson receives research support from Pharmaxis, the National Institutes of Health, and the American Academy of Allergy, Asthma & Immunology/GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online January 10, 2012.
doi:10.1016/j.jaci.2011.11.046

Obesity is not linked to increased whole-body mast cell burden in children

To the Editor:

Obesity is clearly associated with insulin resistance and chronic low-grade inflammation.[1,2] Macrophages appear to be especially important in this relationship because they infiltrate adipose tissue and produce a variety of inflammatory cytokines.[1] Exploring the contribution of other immune cells to the development of obesity, Liu et al[3] described a role for mast cells in the development of obesity and diabetes in mice. Using genetically modified mice and pharmacologic stabilizers of mast cells, they demonstrated that mast cells and mast cell–mediated protease expression can promote the growth of white adipose tissue. Importantly, the idea that mast cells might function in a similar manner in human obesity was suggested by the finding of increased numbers of mast cells in human white adipose tissue from obese compared with lean subjects in their study. Furthermore, mean serum tryptase levels were higher in obese (13.1 ng/mL) than lean (7.7 ng/mL) subjects, as determined by using an in-house tryptase assay. We attempted to replicate these data by comparing serum tryptase levels in obese, overweight, and lean subjects from a pediatric population.

Because the serum total tryptase level, which is comprised primarily of α and β protryptases, seems to correlate with the whole-body burden of mast cells,[4] we measured levels of this protein in subjects 8 to 18 years old recruited through newspaper advertisement for research participation. The cohort contained a diverse group of children and adolescents with and without obesity, impaired glucose tolerance, and/or diabetes mellitus (Fig 1, *A*, and see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). Because the body mass index (BMI) is age and sex specific in children and teens,[5] we divided the subjects based on the BMI percentiles by age and sex into those who were of healthy weight (BMI ≥5th to <85th percentile), overweight (BMI ≥85th to <95th percentile), and obese (BMI ≥95th percentile). Comparisons were made by using the nonparametric Kruskal-Wallis test because the data were not normally distributed after standardization to percentiles. No statistical difference in the