

Letter to the Editor

Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma

To the Editor:

Some patients with asthma are at increased risk for irreversible airflow obstruction after structural airway changes.¹⁻³ Asthma exacerbations can adversely affect the natural history of asthma by contributing to increased rates of lung function decline, systemic effects, and premature mortality.⁴ The effect of airway inflammation associated with asthma exacerbations might be a risk factor for airway remodeling.^{1,2} In patients with chronic obstructive pulmonary disease (COPD), a link between the frequency of exacerbations and more rapid decline in FEV₁ has been well established.⁵ However, there is limited evidence of this effect in patients with asthma, with available studies relying on relatively small cohorts, including adults only, being retrospective in nature, or being conducted within the controlled setting of a randomized trial.^{1,2}

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study represents the largest observational prospective cohort of patients with severe or difficult-to-treat asthma studied to date.⁶ The TENOR study provides a unique opportunity to prospectively examine the association between asthma exacerbations and lung function in a real-world setting, with subanalyses by age. The objective of this analysis was to determine whether annual lung function changes were associated with the presence or absence of exacerbations in that year for children, adolescents, and adults.

Patients in the TENOR study were followed for 3 years. Postbronchodilator percent predicted FEV₁ (ppFEV₁) was collected annually, and asthma exacerbations (overnight hospitalization, emergency department visit, or steroid burst in the prior 3 months) were collected semiannually. Annual change in ppFEV₁ was modeled by using repeated measures as a function of exacerbations during that year, baseline ppFEV₁, age, sex, race/ethnicity, and body mass index (BMI). Patients with COPD and current smokers were excluded. All data analyses were generated with SAS software, version 9.3, of the SAS System for Windows (SAS Institute, Cary, NC).

Of the 4756 patients enrolled in the TENOR study, 2429 patients (children [6-11 years], n = 317; adolescents [12-17 years], n = 309; and adults [≥18 years], n = 1803) were included in the analysis (Fig 1), contributing 4477 patient-years of follow-up. Baseline demographics and clinical characteristics by age group are shown in Tables E1 and E2 in this article's Online Repository at www.jacionline.org, respectively. In all patients the 12-month change in ppFEV₁ was lower among those with any asthma exacerbation compared with those with no asthma exacerbation (-1.27 ± 0.26 vs 0.70 ± 0.22 , net difference = 1.97 ± 0.36 , $P < .001$) after adjustment for baseline ppFEV₁, age, sex, race/ethnicity, and BMI (Fig 2). The association between exacerbation history and 12-month change in ppFEV₁ was highly statistically significant in adults (-1.14 ± 0.30 vs 0.68 ± 0.25 , net difference = 1.82 ± 0.41 , $P < .001$). In adolescents the 12-month change in ppFEV₁ was -1.60 ± 0.87 versus 0.54 ± 0.65 (net difference = 2.14 ± 1.13 , $P = .063$). In children

the 12-month change in ppFEV₁ by exacerbation history was -2.23 ± 0.70 versus 0.90 ± 0.67 (net difference = 3.13 ± 1.01 , $P < .003$). A sensitivity analysis was conducted to determine the effect of including follow-up data only at year 1. The results were consistent with the findings of the main analysis; however, the net difference in adults was larger (see Table E3 in this article's Online Repository at www.jacionline.org).

These results demonstrate that asthma exacerbations were statistically significantly associated with annual change in lung function after adjusting for baseline lung function and other potential confounding variables. This suggests that exacerbations contribute to progressive loss of lung function. The largest net difference in ppFEV₁ was observed in children, followed by adolescents. Although the data were underpowered for statistical tests of interaction by age group, these results suggest the potential for larger lung function decline associated with asthma exacerbations in younger populations who have not yet achieved peak FEV₁.

Our findings extend limited available research on this topic. In a cohort of 93 adult nonsmokers with moderate-to-severe asthma, one severe exacerbation was associated with a 30.2-mL greater annual decline in FEV₁.¹ In a *post hoc* analysis of 190 placebo-treated patients in the START (inhaled steroid treatment as regular therapy in early asthma) trial,² decrease in ppFEV₁ was significantly greater in children and adults who experienced a severe exacerbation than in patients who did not (eg, in adults the mean annual decline was 66 and 34 mL, respectively), which is in line with findings of borderline statistical significance in adolescents in the current analysis. However, the association between asthma exacerbations and FEV₁ decline was not observed in patients who were randomized to daily budesonide. In the current analysis, which was conducted within an observational real-world setting, decreases in ppFEV₁ associated with asthma exacerbations were observed despite nearly all patients across age groups being treated with inhaled corticosteroids.

In patients with COPD, exacerbations contribute to airflow limitation, but such limitation results from both direct airway effects, such as bronchoconstriction, and diffuse pulmonary parenchymal destruction, leading to loss of elastic recoil and reduced radial airway traction.⁷ In patients with asthma direct airway effects are the primary mechanism of decline in FEV₁.⁸ Damage to airway epithelium that is characteristic of asthma and particularly active during exacerbations can initiate repair responses, leading to peribronchiolar fibrosis and compromised lung function.⁹ Thus, although mean changes in ppFEV₁ were small in our analysis, a larger difference resulting from the cumulative long-term effect of exacerbations is expected.

It is difficult to distinguish whether an asthma exacerbation itself or airway inflammation might be contributing to exacerbation risk. Patients with exacerbations were more likely to have 3 or more control problems compared with those without exacerbations (41% vs 19%) and less likely to have no control problems (11% vs 22%). Because of the close relationship between these measures, it is possible that exacerbations are a marker for poor control rather than the primary cause of lung function decline. Given the close relationship between exacerbations and airway inflammation, interventions targeted at reducing exacerbations might also reduce airway inflammation.

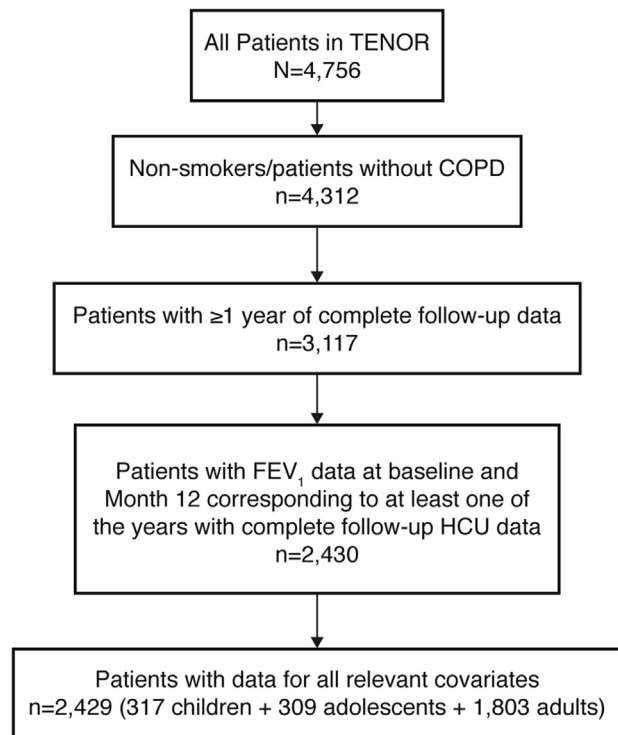


FIG 1. Flow diagram for the full analysis cohort (n = 2429). HCU, Health care use.

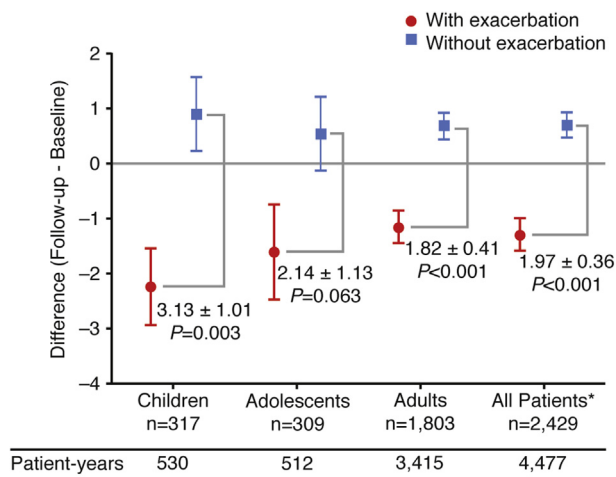


FIG 2. Twelve-month change in ppFEV₁ by asthma exacerbation status. Error bars represent SEs. *Full analysis cohort.

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.

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METHODS

Study design and patients

The TENOR study design and methodology have been published previously.^{E1} In brief, the TENOR study was a multicenter, prospective, observational cohort study conducted over 3 years (2001–2004) at 283 sites across the United States, including community physicians, managed care organizations, academic centers, and group practices. A total of 4756 patients aged 6 years or older with severe or difficult-to-treat asthma who were receiving care from an allergist or pulmonologist were enrolled. The design and protocol of the TENOR study were approved by a central institutional review board and, when necessary, by the institutional review board at each site.

Patients were selected for the TENOR study if they (1) received care from their asthma specialist (allergist or pulmonologist) for at least 1 year; (2) had high health care system use (≥ 2 unscheduled asthma care visits or ≥ 2 oral corticosteroid bursts) in the past 12 months or high medication use at the time of enrollment (requiring ≥ 3 asthma controller medications, daily high doses of inhaled corticosteroids, or ≥ 5 mg/d oral prednisone); and (3) were able to read and understand English. All patients or their guardians provided written informed consent.

Data collection

Demographic data, clinical data, and medication use were collected by study coordinator interview and evaluated at baseline and every 6 months. Health care use in the previous 3 months was self-reported at baseline and at each 6-month visit. Prebronchodilator and postbronchodilator FEV₁ were measured at baseline and annually in accordance with the American Thoracic Society guidelines.^{E2} Asthma control was assessed by using the Asthma Therapy Assessment Questionnaire (ATAQ). The ATAQ control index ranges from 0 to 4 problems and has been validated in adult populations.^{E3}

Asthma exacerbations

Asthma exacerbations were defined as a hospitalization, emergency department visit, or oral corticosteroid burst in the 3 months before each study visit. Each year, patients had 2 follow-up examinations: 1 at month 6 and 1 at month 12. The presence or absence of exacerbations represented the presence or absence of exacerbations during the 3 months from the data collection point.

Analytic cohort

Patients with at least 1 year of complete follow-up data were included. The complete year could have been the first, second, or third year of follow-up, with a complete year consisting of 1 semiannual and 1 annual record in that year. Patients with FEV₁ data at baseline and month 12, corresponding to at least 1 of the years with complete follow-up health care use data and with data for all relevant covariates, were included. Patients with COPD and current smokers were excluded.

Statistical analysis

Demographic and clinical characteristics at baseline by age group (children aged 6–11 years, adolescents aged 12–17 years, and adults aged ≥ 18 years) were assessed by using descriptive statistics. Annual change in postbronchodilator ppFEV₁ was tabulated by study year. A repeated-measures ANOVA model estimated ppFEV₁ at 1-year intervals as a function of ppFEV₁ in the

preceding year and asthma exacerbations in the same year the change was measured. Age, sex, race/ethnicity, and BMI were included as additional covariates. Individual patients could contribute 1, 2, or 3 years of data to the analysis. A compound symmetry covariance structure was used to account for within-patient correlation because multiple observations per patient were used. A model was fit for all patients, and 3 additional models were fit and stratified by age group.

RESULTS

Baseline demographics and clinical characteristics

Patients included in the analysis were older (40.0 ± 20.9 vs 34.9 ± 20.6 , $P < .0001$), were more likely to be white (78.0% vs 69.0%, $P < .0001$), and had a higher mean BMI (28.3 ± 8.2 vs 27.7 ± 8.3 , $P = .02$) at baseline compared with patients not included in the analysis. The majority of adult patients were female (70.4%), whereas the majority of children and adolescents were male (69.4% and 58.6%, respectively). Most patients had private insurance (73.1%). The rate of skin test positivity was highest in adults (82.7%) compared with children (59.2%) and adolescents (67.0%, Table E1).

Patients' clinical characteristics at baseline are shown in Table E2. Rates of allergic rhinitis were highest in adult patients compared with those in children and adolescents, whereas rates of atopic dermatitis were highest in children compared with those in adolescents and adults. IgE levels were highest in adolescents (195.2 ± 4.7 IU/mL) compared with those in children (170.1 ± 6.2 IU/mL) and adults (81.1 ± 5.1 IU/mL). Regardless of age, patients were more likely to report either 2 or 3 or more asthma control problems, as reported by the ATAQ, than 0 or 1 problem. Across age groups, the majority of patients were using 3 or more long-term controller medications at baseline, with nearly all patients in each age group (95.0% to 96.4%) using an inhaled corticosteroid and 71.0% to 81.6% using a long-acting β_2 -agonist. Among patients receiving 3 or more controllers, 88% were receiving a leukotriene modifier, 22% were receiving methylxanthines, and 10% were receiving cromolyn sodium or nedocromil.

Sensitivity analysis

Results of the sensitivity analysis with restriction of the model to follow-up data only at year 1 were consistent with the findings from the main set of analyses; however, the net difference in adults was larger (Table E3).

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TABLE E1. Patients' baseline demographics

	Children (n = 317)	Adolescents (n = 309)	Adults (n = 1803)	All patients* (n = 2429)
Mean $\pm$ SD age (y)	9.1 (1.7)	13.9 (1.6)	49.9 (14.3)	40.0 (20.9)
Sex, no. (%)				
Male	220 (69.4)	181 (58.6)	533 (29.6)	934 (38.5)
Female	97 (30.6)	128 (41.4)	1270 (70.4)	1495 (61.5)
Race/ethnicity, no. (%)				
White	210 (66.2)	204 (66.0)	1481 (82.1)	1895 (78.0)
Black	62 (19.6)	78 (25.2)	194 (10.8)	334 (13.8)
Hispanic	27 (8.5)	17 (5.5)	88 (4.9)	132 (5.4)
Asian/Pacific Islander	3 (1.0)	2 (0.6)	28 (1.6)	33 (1.4)
Other	15 (4.7)	8 (2.6)	12 (0.7)	35 (1.4)
BMI (kg/m ²), mean (SD)	19.9 (5.0)	24.4 (7.2)	30.5 (7.6)	28.3 (8.2)
Insurance status, no. (%)				
Commercial/PPO	152 (47.9)	152 (49.2)	812 (45.0)	1116 (45.9)
HMO	82 (25.9)	74 (23.9)	504 (28.0)	660 (27.2)
Medicaid/Medicare	66 (20.8)	66 (21.4)	376 (20.9)	508 (20.9)
Other†	17 (5.4)	17 (5.5)	111 (6.2)	145 (6.0)

HMO, Health maintenance organization; PPO, preferred provider organization.

*Full analysis cohort.

†“Other” includes military/veteran, self-pay, and other.

TABLE E2. Patients' clinical characteristics at baseline*

	Children (n = 317)	Adolescents (n = 309)	Adults (n = 1803)	All patients† (n = 2429)
Asthma duration (y), mean (SD)	6.0 (2.5)	9.7 (3.7)	24.5 (16.9)	20.2 (16.4)
Skin test, no. (%)				
No	105 (33.1)	82 (26.5)	208 (11.5)	395 (16.3)
Yes, positive	187 (59.0)	205 (66.3)	1483 (82.3)	1875 (77.2)
Yes, negative	24 (7.6)	19 (6.1)	103 (5.7)	146 (6.0)
Allergic rhinitis, no. (%)	198 (62.5)	207 (67.0)	1305 (72.4)	1710 (70.4)
Atopic dermatitis, no. (%)	65 (20.5)	45 (14.6)	248 (13.8)	358 (14.7)
IgE level (IU/mL), (geometric mean)	170.1 (6.2)	195.2 (4.7)	81.1 (5.1)	99.7 (5.4)
ATAQ control problems, no. (%)				
0	25 (10.5)	31 (11.9)	331 (18.6)	387 (17.0)
1	40 (16.7)	42 (16.1)	350 (19.7)	432 (19.0)
2	109 (45.6)	125 (47.9)	563 (31.7)	797 (35.0)
≥3	65 (27.2)	63 (24.1)	532 (30.0)	660 (29.0)
No. of long-term controllers, no. (%)				
0-1	21 (6.6)	14 (4.5)	118 (6.5)	153 (6.3)
2	102 (32.2)	86 (27.8)	637 (35.3)	825 (34.0)
≥3	194 (61.2)	208 (67.3)	1046 (58.0)	1448 (59.6)
Inhaled corticosteroid use, no. (%)	301 (95.0)	298 (96.8)	1736 (96.4)	2335 (96.3)
Long-acting β_2 -agonist use, no. (%)	225 (71.0)	248 (80.5)	1469 (81.6)	1942 (80.1)
Postbronchodilator ppFEV ₁ , mean (SD)	95.8 (18.4)	91.9 (18.9)	80.0 (22.2)	83.6 (22.2)

*Percentages are based on nonmissing data. There were 13 missing skin test results, 1 missing allergic rhinitis value, 1 missing atopic dermatitis value, 153 missing ATAQ values, 3 missing long-term controller values, 32 missing IgE level values, and 12 missing asthma duration values.

†Full analysis cohort.

TABLE E3. Results of sensitivity analysis

	Children (6-11 y)	Adolescents (12-17 y)	Adults (≥18 y)	Overall
Original analysis				
Patient-years	550	512	3415	4477
Difference ± SE	3.13 ± 1.01	2.14 ± 1.13	1.82 ± 0.41	1.97 ± 0.36
<i>P</i> value	.0003	.063	<.001	<.001
Sensitivity analysis*				
Patients	293	293	1660	2246
Difference ± SE	3.05 ± 1.48	1.97 ± 1.52	2.86 ± 0.78	2.72 ± 0.64
<i>P</i> value	.041	.20	<.001	<.001

*Sensitivity analysis restricted the model to follow-up data only at year 1. Years 2 and 3 were ignored.