

Original Article

Asthma Exacerbations and Triggers in Children in TENOR: Impact on Quality of Life

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What is already known about this topic? The association between asthma triggers and asthma exacerbations in children has been established, but their impact on pediatric asthma-related quality of life has not been reported.

What does this article add to our knowledge? This article assesses the impact of asthma exacerbations and asthma triggers on asthma-specific quality of life in children aged 6 to 12 years, including severity and number of exacerbations.

How does this study impact current management guidelines? These results highlight the need for asthma trigger identification and patient education on trigger avoidance in the pediatric population, as well as the importance of assessing pediatric asthma-related quality of life.

BACKGROUND: Data examining associations between asthma exacerbations, triggers, and asthma-related quality of life (QOL) in children with severe/difficult-to-treat asthma are unavailable.

OBJECTIVE: To evaluate real-world data on relationships between asthma exacerbations, triggers, and QOL in

children using data from TENOR (The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens), a 3-year observational study of patients with severe/difficult-to-treat asthma, including those aged 6 to 12 years. **METHODS:** QOL was examined using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and defined exacerbations hierarchically (descending order of severity): hospitalization, emergency department visit, steroid burst, no exacerbation, using the highest value from months 6 and 12. One-way ANOVA was used to test for differences in PAQLQ domain scores at month 12 across exacerbation severity, total number of asthma exacerbations, and number of baseline asthma triggers. Mantel-Haenszel chi-square test was used to test the association between the number of triggers and exacerbation hierarchy.

RESULTS: Greater severity of asthma exacerbations was associated with significantly ($P < .001$) lower mean PAQLQ domain scores, indicating poorer QOL. A higher number of asthma exacerbations was associated with significantly ($P < .001$) lower mean PAQLQ domain scores. PAQLQ scores were significantly lower with higher numbers of baseline triggers. Higher baseline number of asthma triggers was associated with greater severity ($P = .05$) and number of asthma exacerbations ($P < .001$).

CONCLUSIONS: A higher number of asthma triggers at baseline was associated with greater asthma severity and number of asthma exacerbations and lower QOL in children with severe/difficult-to-treat asthma. © 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Asthma-related quality of life; Asthma triggers; Difficult-to-treat asthma; Pediatric asthma; Severe asthma; Severe exacerbations

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Abbreviations used

ATAQ- Asthma Therapy Assessment Questionnaire

ED- emergency department

HCU- health care resource utilization

LSM- least-squares mean

OR- odds ratio

PAQLQ- Pediatric Asthma Quality of Life Questionnaire

QOL- quality of life

TENOR- The Epidemiology and Natural History of Asthma:
Outcomes and Treatment Regimens

Asthma affects 6.3 million children in the United States (8.6% of the population <18 years of age) and is associated with a substantial social and economic burden.¹ In children, a higher economic burden of asthma is noted when asthma severity worsens.² Fifty-two percent of children with asthma in 2011 had 1 or more exacerbations that put them at risk for adverse outcomes, including emergency department (ED) visits, hospitalizations, and missed school days.³ In the same year, asthma was the primary diagnosis listed for 215,000 ED visits in children younger than 15 years.⁴ On the basis of 2013 data, almost half (49%) of children aged 5 to 17 years with self-reported asthma missed 1 or more days of school, representing 13.8 million school days missed.⁵ For children with asthma, the impact of poorly controlled or severe asthma often extends to caregivers who report missing work or other activities because of the child's asthma.⁶

Asthma is a heterogeneous disease with defined phenotypes that may impact the course and management of the disease.^{7,8} Recognizing characteristics of asthma that may correlate with disease severity and negatively impact a child's asthma-related quality of life (QOL) is important. Most (~80%) children with asthma have an allergic component to their disease.⁹ Children with asthma and 1 or more parent-reported allergic conditions were more likely to have used oral corticosteroids or visited the ED in the past year than children without an allergic condition.⁹ In a conceptual model constructed using data from inner-city children, asthma severity was related to a defined allergy pathway that linked allergen sensitization, allergy inflammation, pulmonary physiology, and rhinitis.¹⁰ Asthma triggers, occurrences or elements that lead to initiation or worsening of asthma symptoms, have also been associated with severe asthma exacerbations in children.¹¹

Using data from the 3-year, prospective, observational study, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR),^{12,13} Luskin et al¹⁴ previously demonstrated a strong association between both asthma exacerbation frequency and severity and the number of triggers with asthma-related QOL in adolescents and adults aged 13 years and older with severe or difficult-to-treat asthma. We sought to conduct a similar analysis in children aged 6 to 12 years.

METHODS

Study design

TENOR was a prospective observational cohort study conducted at 283 sites in the United States between 2001 and 2004. The details of study design and methodology, as well as baseline cohort characteristics, have been previously published.^{12,15} Briefly, TENOR enrollment included patients aged 6 years and older from

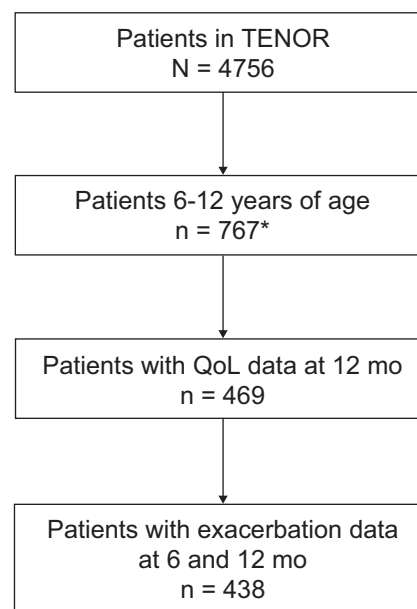


FIGURE 1. Patient disposition. *Number excludes 3 children who were aged 5 years at baseline.

diverse geographic areas with severe or difficult-to-treat asthma receiving care from an allergist or pulmonologist. Difficult-to-treat asthma was defined as 1 or more of the following: (1) a need for multiple asthma medications, (2) severe or frequent exacerbations, (3) an inability to avoid triggers, and (4) complex medication regimen. Enrollment consideration was given to children with mild-to-moderate asthma if their asthma was considered difficult to treat by the evaluating physician and inclusion criteria were met (for additional inclusion/exclusion criteria, see Table E1 in this article's Online Repository at www.jaci-inpractice.org).¹² Patients were recruited from typical patient care settings, including managed care organizations, community physicians/practices, and academic centers. TENOR did not include an experimental intervention; patients continued to receive treatment as recommended by their allergist or pulmonologist. TENOR was approved by a central institutional review board and, when necessary, by the institutional review board at each site.

Data collection

Patients had follow-up visits at 6-month intervals after enrollment. At baseline and each subsequent visit, various clinical, demographic, laboratory, and patient-reported outcome assessments were completed. For participants younger than 12 years, the child's parent or guardian was present to help answer interview questions and complete the questionnaires.

Health care resource utilization and asthma exacerbations. Health care resource utilization (HCU) data, defined as self-reported hospitalizations, ED visits, and oral corticosteroid bursts in the 3 months before study visit, were collected semi-annually. HCU data were used to determine the total number and severity of asthma exacerbations. For each patient, an asthma exacerbation was defined by the most severe exacerbation that occurred in the 3 months before the month 6 and 12 visits. Asthma exacerbation severity was defined in descending order of severity:

TABLE I. Demographic and clinical characteristics by exacerbation severity type

Characteristic	No exacerbation	Steroid burst	ED visit	Hospitalization	All patients	P value*
Patients, n	220	123	66	29	438	
Male, n (%)	150 (68.2)	83 (67.5)	42 (63.6)	22 (75.9)	297 (67.8)	.70
White, n (%)	164 (74.5)	77 (62.6)	32 (48.5)	11 (37.9)	284 (64.8)	<.001
Age at baseline (y), mean $\pm$ SD	9.3 $\pm$ 1.8	9.4 $\pm$ 1.8	9.1 $\pm$ 1.7	9.2 $\pm$ 1.6	9.3 $\pm$ 1.8	.67
Treatment setting, n (%)†						.22
Pulmonologist	128 (60.4)	69 (58.5)	39 (60.0)	23 (79.3)	259 (61.1)	
Allergist	84 (39.6)	49 (41.5)	26 (40.0)	6 (20.7)	165 (38.9)	
Asthma duration (y), mean $\pm$ SD	6.0 $\pm$ 2.7	6.8 $\pm$ 2.5	6.1 $\pm$ 2.6	6.8 $\pm$ 2.4	6.3 $\pm$ 2.6	.03
Atopic dermatitis, n (%)	44 (20.0)	20 (16.3)	12 (18.2)	10 (34.5)	86 (19.6)	.19
Allergic rhinitis, n (%)	136 (61.8)	85 (69.1)	48 (72.7)	18 (62.1)	287 (65.5)	.49
BMI percentile, mean $\pm$ SD‡	69.4 $\pm$ 27.4	70.0 $\pm$ 30.7	68.5 $\pm$ 28.6	75.8 $\pm$ 26.5	69.9 $\pm$ 28.4	.69
% predicted prebronchodilator FEV1, mean $\pm$ SD	91.4 $\pm$ 19.6	86.0 $\pm$ 17.4	87.0 $\pm$ 22.3	83.0 $\pm$ 21.8	88.8 $\pm$ 19.6	.05
% predicted postbronchodilator FEV1, mean $\pm$ SD	98.1 $\pm$ 18.8	92.8 $\pm$ 16.4	94.8 $\pm$ 18.2	91.5 $\pm$ 20.5	95.8 $\pm$ 18.3	.07
Geometric mean (95% CI) baseline serum IgE level (IU/mL)	181.7 (142.9-231.1)	166.5 (118.3-234.1)	177.5 (115.8-272.1)	238.0 (125.6-451.1)	180.0 (151.6-213.8)	.82
Nights in hospital (baseline + 6 mo), mean $\pm$ SD	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	4.30 $\pm$ 2.84	0.3 $\pm$ 1.3	<.001
ATAQ score, n (%)†						<.001
0	21 (11.8)	5 (5.5)	0 (0)	1 (4.3)	27 (7.9)	
1	31 (17.4)	20 (22.0)	7 (13.7)	2 (8.7)	60 (17.5)	
2	94 (52.8)	36 (39.6)	23 (45.1)	11 (47.8)	164 (47.8)	
3	29 (16.3)	28 (30.8)	17 (33.3)	4 (17.4)	78 (22.7)	
4	3 (1.7)	2 (2.2)	4 (7.8)	5 (21.7)	14 (4.1)	

BMI, Body mass index.

*Assessed by using χ^2 test for categorical variables and 1-way ANOVA for continuous variables for differences across the number of asthma exacerbation severity categories.

†Percentages based on nonmissing data.

‡Calculated using growth charts from the Centers for Disease Control and Prevention.¹⁹

hospitalization, ED visit, steroid burst, and no exacerbation. For each patient, asthma exacerbation severity was defined by the highest value in the hierarchy from both the month 6 and 12 visits. The total number of exacerbations was defined as the sum of hospitalizations, ED visits, and corticosteroid bursts from both the month 6 and 12 visits.

Pediatric asthma-related QOL. Pediatric asthma-related QOL in child participants was assessed annually using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), a validated tool that measures functional problems in children with asthma.¹⁶⁻¹⁸ The questionnaire includes 23 questions in 3 domains (symptom, activity limitation, and emotional function) that are scored on a 7-point Likert scale (1 = extremely bothered to 7 = not bothered at all). The mean of all 23 responses provides the overall PAQLQ score, with a lower score representing a lower QOL. Within each domain, individual domain scores are the mean of the included items. A change in score greater than 0.5 is considered clinically important for an individual patient.¹⁶

Asthma control. Results from patient responses on the Asthma Therapy Assessment Questionnaire (ATAQ), obtained at baseline, were used to provide insight into patient perception of asthma control in the 4 weeks to 12 months before enrollment. The ATAQ assessed asthma control in 4 domains: (1) self-perception of asthma control; (2) missed work, school, or normal daily activities because of asthma; (3) nighttime awakenings due to asthma symptoms; and (4) use of quick-reliever medications. The ATAQ scoring ranges from 0 (no control problems) to 4 (control problems).

Asthma triggers. Information on asthma triggers was obtained at baseline and annually thereafter through self-administered questionnaires. Patients were asked if, in the previous 12 months, they had experienced a cough, wheeze, or other symptom of asthma as a result of exposure to a trigger. Emotional stress and cold and/or sinus infection were categorized as nonallergic triggers. Pollen, animals, mold and/or dampness, and dust were categorized as allergic triggers. Patients were able to select more than 1 possible trigger.

Statistical analyses. The analytic cohort included patients aged 6 to 12 years with nonmissing HCU data at months 6 and 12, and nonmissing PAQLQ data at month 12. Baseline demographic and clinical characteristics were summarized using percentages for categorical variables and mean $\pm$ SD for continuous variables. Differences in demographic and clinical characteristics across asthma exacerbation severity and number of triggers were assessed using the Mantel-Haenszel chi-square test for categorical variables and 1-way ANOVA for continuous variables. One-way ANOVA was used to test for statistically significant differences in PAQLQ domain scores at month 12 across asthma exacerbation severity, total number of asthma exacerbations, and number of asthma triggers. The association between the number of triggers at baseline and asthma exacerbations during follow-up (severity and total number) was assessed, as well as overall differences in asthma exacerbation severity and the total number of asthma exacerbations (categorized as 0, 1-2, 3-4, and ≥ 5) across the number of asthma trigger categories (0-1, 2-3, 4-5, 6) using the Mantel-Haenszel chi-square test.

Multivariable linear regression was used to model the overall PAQLQ score at the month 12 follow-up visit as a function of the 6 common asthma triggers (emotional stress, cold and/or sinus

TABLE II. Demographic and clinical characteristics by number of triggers

Characteristic	No. of triggers				All patients	P value*
	0-1	2-3	4-5	6		
Patients, n	50	156	166	66	438	
Male, n (%)	33 (66.0)	99 (63.5)	118 (71.1)	47 (71.2)	297 (67.8)	.46
White, n (%)	29 (58.0)	102 (65.4)	111 (66.9)	42 (63.6)	284 (64.8)	.71
Age at baseline (y), mean $\pm$ SD	9.4 $\pm$ 1.8	9.2 $\pm$ 1.8	9.3 $\pm$ 1.8	9.6 $\pm$ 1.8	9.3 $\pm$ 1.8	.45
Treatment setting, n (%)†						.02
Pulmonologist	38 (77.6)	98 (64.5)	87 (54.4)	36 (57.1)	259 (61.1)	
Allergist	11 (22.4)	54 (35.5)	73 (45.6)	27 (42.9)	165 (38.9)	
Asthma duration (y), mean $\pm$ SD	6.0 $\pm$ 2.7	6.0 $\pm$ 2.6	6.3 $\pm$ 2.7	7.1 $\pm$ 2.3	6.3 $\pm$ 2.6	.02
Atopic dermatitis, n (%)	5 (10.0)	20 (12.8)	43 (25.9)	18 (27.3)	86 (19.6)	<.001
Allergic rhinitis, n (%)	15 (30.0)	94 (60.3)	120 (72.3)	58 (87.9)	287 (65.5)	<.001
BMI percentile, mean $\pm$ SD‡	73.1 $\pm$ 26.4	68.0 $\pm$ 29.2	69.5 $\pm$ 28.9	72.7 $\pm$ 27.3	69.9 $\pm$ 28.4	.57
% predicted prebronchodilator FEV1, mean $\pm$ SD	87.7 $\pm$ 15.3	88.5 $\pm$ 22.0	89.6 $\pm$ 19.1	88.4 $\pm$ 17.9	88.8 $\pm$ 19.6	.93
% predicted postbronchodilator FEV1, mean $\pm$ SD	93.5 $\pm$ 16.6	96.1 $\pm$ 20.8	95.0 $\pm$ 16.8	98.9 $\pm$ 16.0	95.8 $\pm$ 18.3	.47
Geometric mean (95% CI) baseline serum IgE (IU/mL)	102.1 (51.9-200.9)	163.1 (124.5-213.6)	206.3 (160.9-264.4)	249.5 (155.9-399.1)	180.0 (151.6-213.8)	.04
Nights in hospital (baseline + 6 mo), mean $\pm$ SD	0.08 $\pm$ 0.44	0.18 $\pm$ 1.01	0.30 $\pm$ 1.43	0.68 $\pm$ 1.82	0.3 $\pm$ 1.3	.04
ATAQ score, n (%)†						.002
0	9 (20.5)	10 (8.2)	7 (5.4)	1 (2.1)	27 (7.9)	
1	14 (31.8)	22 (18.0)	21 (16.2)	3 (6.4)	60 (17.5)	
2	12 (27.3)	60 (49.2)	66 (50.8)	26 (55.3)	164 (47.8)	
3	9 (20.5)	26 (21.3)	28 (21.5)	15 (31.9)	78 (22.7)	
4	0 (0.0)	4 (3.3)	8 (6.2)	2 (4.3)	14 (4.1)	

BMI, Body mass index.

*Assessed by using χ^2 test for categorical variables and 1-way ANOVA for continuous variables for differences across the number of asthma triggers categories.

†Percentages based on nonmissing data.

‡Calculated using growth charts from the Centers for Disease Control and Prevention.¹⁹

infection, pollen, animals, mold and/or dampness, and dust) at baseline. For each asthma trigger, the least-squares mean (LSM) for the difference in the PAQLQ score between patients with and without the trigger was generated, along with the SE and *P* value. For asthma exacerbations, a multivariable proportional odds model was generated to predict exacerbation hierarchy across the month 6 and 12 follow-up visits as a function of the 6 common asthma triggers at baseline. Odds ratios (ORs) that denote the likelihood of experiencing a severe asthma exacerbation among children with the asthma trigger were generated along with 95% CIs and *P* values.

RESULTS

Of the 4756 patients enrolled in TENOR, 767 were between the ages of 6 and 12 years at baseline (after exclusion of 3 children who were aged 5 years at baseline). A total of 438 children aged 6 to 12 years had exacerbation data at both 6 and 12 months and were included in the analysis (Figure 1).

Patients' demographic and clinical characteristics by asthma exacerbation severity

Patients' characteristics by asthma exacerbation severity are presented in Table I. There were no significant differences across age, sex, or body mass index percentile (calculated from growth charts¹⁹) between the exacerbation categories. Pediatric patients with greater numbers of severe asthma exacerbations (ED visit or hospitalization) during the first year of follow-up were significantly more likely to be nonwhite and have a longer duration of

asthma than patients with less severe asthma exacerbations. Lower prebronchodilator FEV1 was associated with increased severity of asthma exacerbations (*P* = .05). There was evidence of a trend toward an association between lower prebronchodilator and postbronchodilator FEV1 and increased severity of asthma exacerbations, but the association did not reach statistical significance. The number of asthma control problems, as measured by the ATAQ score, increased with increasing asthma exacerbation severity. These findings were similar when patients were grouped by exacerbation sum (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Patients' demographic and clinical characteristics by the number of asthma triggers

When children were categorized by the number of self-reported asthma triggers, there were no noted differences by age, sex, or race/ethnicity (Table II). Children with a greater number of asthma triggers had a longer duration of asthma, a higher prevalence of atopic dermatitis and allergic rhinitis, and a higher geometric mean total serum IgE level. The number of nights in the hospital was significantly greater with higher numbers of asthma triggers (*P* = .04).

Association between asthma exacerbations and pediatric asthma-related QOL

At 12 months, significantly lower (*P* < .001) PAQLQ scores in each domain were observed with greater severity of asthma exacerbations (no exacerbation, steroid burst, ED visit,

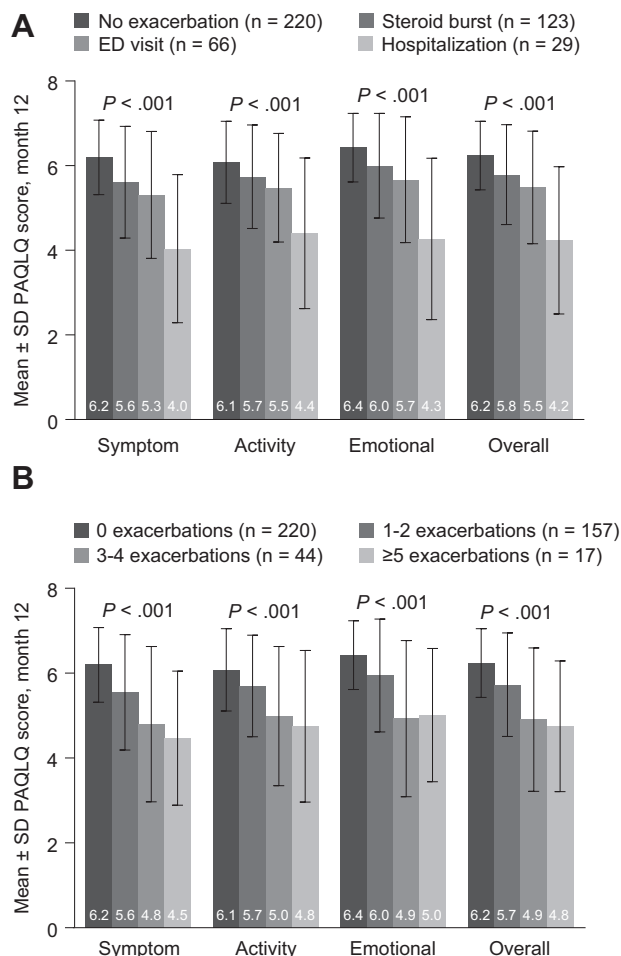


FIGURE 2. Relationship of PAQLQ score at month 12 and (A) severity and (B) number of asthma exacerbations within the first year of follow-up.

hospitalization), indicating poorer QOL: symptom domain score, 6.2 ± 0.9 , 5.6 ± 1.3 , 5.3 ± 1.5 , and 4.0 ± 1.8 , respectively ($P < .001$); activity domain score, 6.1 ± 1.0 , 5.7 ± 1.2 , 5.5 ± 1.3 , and 4.4 ± 1.8 , respectively ($P < .001$); emotional domain score, 6.4 ± 0.8 , 6.0 ± 1.2 , 5.7 ± 1.5 , and 4.3 ± 1.9 , respectively ($P < .001$); and overall score, 6.2 ± 0.8 , 5.8 ± 1.2 , 5.5 ± 1.3 , and 4.2 ± 1.7 , respectively ($P < .001$) (Figure 2, A). A higher total number of asthma exacerbations during the first year of follow-up was also associated with poorer asthma-related QOL at month 12 ($P < .001$; Figure 2, B).

Association between asthma triggers and asthma-related QOL

A higher number of asthma triggers reported at baseline was associated with poorer QOL at month 12 (Figure 3). Mean $\pm$ SD PAQLQ scores in each domain were significantly lower with higher numbers of baseline asthma triggers (0-1, 2-3, 4-5, and 6): symptom domain score, 6.1 ± 1.1 , 5.9 ± 1.3 , 5.7 ± 1.3 , and 5.4 ± 1.5 , respectively ($P = .003$); activity domain score, 6.1 ± 0.9 , 5.9 ± 1.2 , 5.7 ± 1.2 , and 5.4 ± 1.5 , respectively ($P = .008$); emotional domain score, 6.5 ± 0.9 , 6.2 ± 1.3 , 6.0 ± 1.2 , and 5.7 ± 1.5 , respectively ($P = .007$); and overall score, 6.2 ± 0.9 , 6.0 ± 1.2 , 5.8 ± 1.2 , and 5.5 ± 1.4 , respectively ($P = .003$).

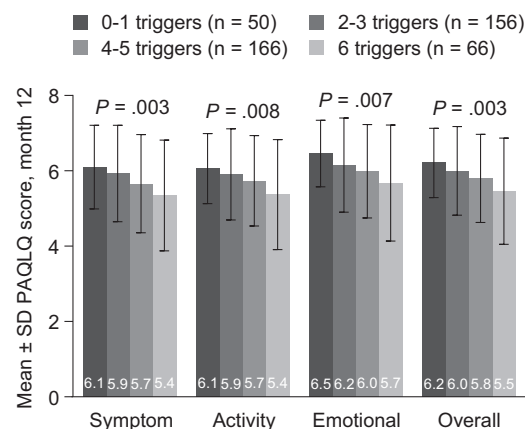


FIGURE 3. Relationship of PAQLQ score at month 12 and number of triggers at baseline.

Association between asthma triggers and asthma exacerbations

During the first year of follow-up, a higher number of asthma triggers was associated with greater severity of asthma exacerbations ($P = .053$; Figure 4, A), and the relationship with a higher number of asthma exacerbations was significant ($P < .001$; Figure 4, B). Statistically significant lower PAQLQ domain scores were observed with higher numbers of allergic triggers at baseline ($P < .01$; Table III). Statistically significant lower PAQLQ overall scores, symptom scores, and emotional domain scores were observed with higher numbers of nonallergic triggers at baseline ($P < .05$; Table IV). Mean PAQLQ activity domain scores were slightly lower when there were 2 nonallergic triggers at baseline (5.7) than with 0 or 1 (5.9), but this difference was not significant.

Multivariable analysis

The relationship among individual asthma triggers and asthma exacerbations and asthma-related QOL was also examined. Individual triggers that were predictive of overall PAQLQ score in univariate analyses included emotional stress (LSM difference, -0.310 ; $P = .008$), animals (LSM difference, -0.362 ; $P = .002$), mold and/or dampness (LSM difference, -0.315 ; $P = .006$), and dust (LSM difference, -0.399 ; $P = .001$). When considering the effects of all 6 triggers in multivariable analyses, only animal triggers was statistically significantly associated with poor QOL (LSM difference, -0.240 ; $P = .05$). For asthma exacerbations, the triggers that were strongly predictive of an asthma exacerbation at the univariable level were emotional stress (OR, 2.02; 95% CI, 1.40-2.91; $P < .001$), mold and/or dampness (OR, 2.00; 95% CI, 1.40-2.85; $P < .001$), and dust (OR, 1.65; 95% CI, 1.13-2.43; $P = .01$). In multivariable analyses, emotional stress (OR, 1.84; 95% CI, 1.24-2.72; $P = .002$) and mold and/or dampness (OR, 1.87; 95% CI, 1.25-2.80; $P = .002$) were strongly predictive of an asthma exacerbation.

DISCUSSION

The findings from the TENOR observational study, with the largest cohort of children with severe or difficult-to-treat asthma, is the first to directly assess the association of asthma exacerbations and asthma triggers with pediatric asthma-related QOL. Our

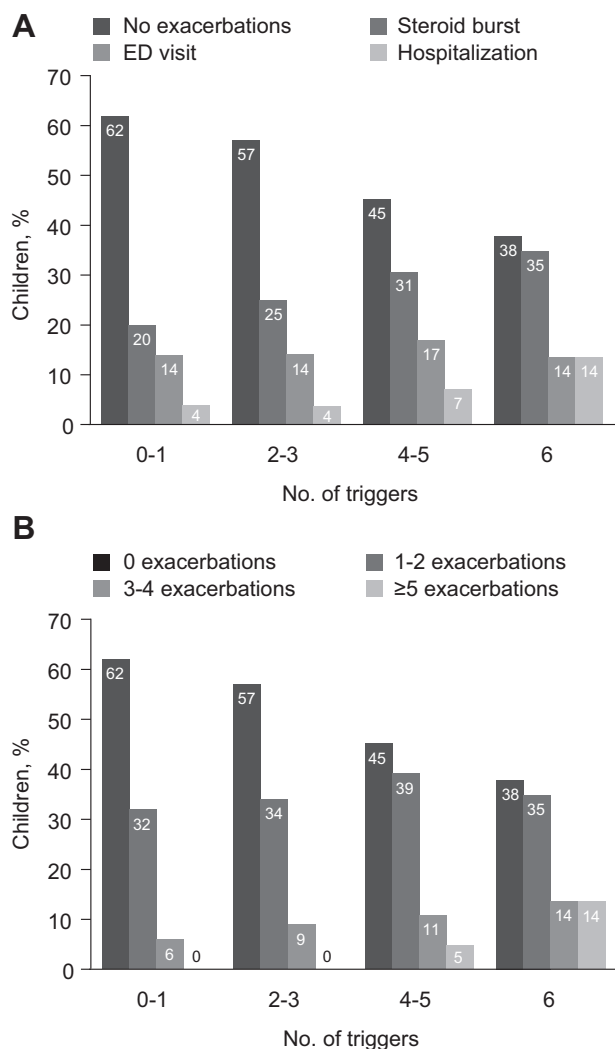


FIGURE 4. Relationship of the number of asthma triggers at baseline with (A) severity and (B) number of asthma exacerbations. $P = .053$ for overall difference in the number of asthma triggers by severity of exacerbation category. $P < .001$ for overall difference in the number of asthma triggers by number of exacerbation category.

analyses indicate that asthma exacerbations of greater severity and higher number in a 12-month follow-up period were associated with poorer asthma-related QOL at month 12 in children aged 6 to 12 years. We also identified a relationship between the number of asthma triggers at baseline in children and the severity and number of asthma exacerbations at 12 months. In addition, our analysis showed a relationship between a higher number of baseline triggers, whether allergic or nonallergic, and poorer asthma-related QOL at month 12. The results of this study highlight the importance of assessing asthma triggers and pediatric asthma-related QOL in children with asthma to more accurately design interventions that specifically target modifiable factors that impact the risk of future exacerbation.

These results extend the findings of Luskin et al¹⁴ to include children as young as 6 years. In the TENOR population that included patients aged 13 years and older, increased severity and

TABLE III. Number of allergic* asthma triggers at baseline and PAQLQ domain scores at month 12

Mean $\pm$ SD score	No. of triggers			All patients (N = 438)	P value†
	0-1 (n = 144)	2-3 (n = 207)	4 (n = 87)		
PAQLQ domain					
Symptom	6.0 $\pm$ 1.2	5.7 $\pm$ 1.3	5.4 $\pm$ 1.4	5.8 $\pm$ 1.3	.002
Activity	6.0 $\pm$ 1.0	5.8 $\pm$ 1.3	5.4 $\pm$ 1.4	5.8 $\pm$ 1.2	.001
Emotional	6.3 $\pm$ 1.1	6.0 $\pm$ 1.3	5.7 $\pm$ 1.5	6.1 $\pm$ 1.3	.008
Overall	6.1 $\pm$ 1.0	5.8 $\pm$ 1.2	5.5 $\pm$ 1.3	5.9 $\pm$ 1.2	.001

*Symptoms as a result of exposure to pollen, animals, mold and/or dampness, or dust.

†Derived from 1-way ANOVA for differences across the number of asthma trigger categories.

TABLE IV. Number of nonallergic* asthma triggers at baseline and PAQLQ domain scores at month 12

Mean $\pm$ SD score	No. of triggers			All patients (N = 438)	P value†
	0 (n = 44)	1 (n = 159)	2 (n = 235)		
PAQLQ domain					
Symptom	5.9 $\pm$ 1.4	6.0 $\pm$ 1.2	5.6 $\pm$ 1.4	5.8 $\pm$ 1.3	.008
Activity	5.9 $\pm$ 1.3	5.9 $\pm$ 1.1	5.7 $\pm$ 1.3	5.8 $\pm$ 1.2	.14
Emotional	6.2 $\pm$ 1.2	6.2 $\pm$ 1.2	5.9 $\pm$ 1.4	6.1 $\pm$ 1.3	.03
Overall	6.0 $\pm$ 1.3	6.0 $\pm$ 1.1	5.7 $\pm$ 1.3	5.9 $\pm$ 1.2	.02

*Symptoms as a result of exposure to emotional stress and cold and/or sinus infection.

†Derived from 1-way ANOVA for continuous variables for differences across the number of asthma trigger categories.

frequency of exacerbations, as well as a higher number of baseline triggers, were significantly associated with a poorer asthma-related QOL at month 12. Interestingly, results of univariate analyses demonstrated that all 6 triggers (emotional stress, cold and/or sinus infection, pollen, animals, mold and/or dampness, dust) were significantly predictive of QOL.¹⁴ However, in the younger population reported here, only emotional stress, animals, and mold and/or dampness were predictive of overall QOL. Multivariable analyses in the adolescent and adult TENOR population showed that emotional stress, dust, mold and/or dampness, and pollen were strongly associated with poor QOL.¹⁴ In the TENOR population of children aged 6 to 12 years, only animal triggers were strongly associated with poor QOL. It is possible that this is related to the ease of recognition of animal triggers by parents. In addition, adult patients might have increased awareness of events/exposures that worsen their asthma control.

Childhood asthma has a high component of allergic disease and is often associated with other allergic conditions, such as allergic rhinitis.²⁰ In TENOR, of the children aged 6 to 12 years, allergic rhinitis was present in 66% of patients and atopic dermatitis was present in approximately 20% of patients. Although the percentage of patients with atopic dermatitis was highest in the patients classified as having the most severe disease, this was not true of patients with allergic rhinitis. Examination of data from a longitudinal study of asthma in inner-city children noted an important relationship between rhinitis in the difficult-to-control asthma phenotype (patients requiring National Heart,

Lung, and Blood Institute Asthma Management Guidelines steps 4, 5, or 6 [≥ 500 $\mu\text{g}/\text{d}$ of fluticasone]).²¹

Some of these associations have been observed in other studies. In a population of 227 children aged 8 to 15 years with asthma, a higher number of asthma triggers was associated with reduced asthma-related QOL.²² QOL, as measured by the PAQLQ, was directly related to asthma control and severity in 100 children and adolescents aged 7 to 17 years with asthma.²³ Children with severe asthma (school-aged, $n = 99$) or severe wheeze (preschoolers, $n = 81$) were compared with school-aged children with mild/moderate asthma ($n = 49$) or preschoolers with mild/moderate wheeze ($n = 53$) in the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cross-sectional study.²⁴ Children in the severe cohorts scored lower on the PAQLQ, indicating more QOL impairment compared with those in the mild/moderate cohorts. The impact of poorly controlled asthma in children from urban areas was assessed in a caregiver survey.²⁵ Children with inadequately controlled asthma had worse health-related QOL than did children whose asthma was controlled.

The association between higher severity and number of exacerbations and number of triggers and poorer pediatric asthma-related QOL in this population of children was evident across all domains (symptom, activity, and emotional). We did observe an impact in the emotional domain, a domain whose impact is sometimes underappreciated. In fact, children with asthma have a higher risk for comorbid depression and anxiety.²⁶ In a population-based study, hospitalized children with a chronic physical illness, including asthma, had a higher likelihood of being discharged from the hospital with a comorbid mood or anxiety disorder than children without a chronic physical illness.²⁷ Nonallergic (psychological) triggers have been associated with low QOL.²⁸ In another study, adolescents with asthma ($n = 3546$) were more likely to have symptoms of depression and anxiety than adolescents without asthma ($n = 24,884$): aggregate prevalence, depression, 0.27 (95% CI, 0.18-0.39) versus 0.13 (95% CI, 0.09-0.19); anxiety, 0.33 (95% CI, 0.19-0.52) versus 0.21 (95% CI, 0.12-0.33).²⁹ These comorbid conditions are associated with a higher asthma symptom burden,³⁰ as well as higher HCU and related costs.³¹ The association between comorbid depression and anxiety and asthma may be related to disease severity; the association of asthma and psychological comorbidity was not seen as often in children and adolescents with well-controlled asthma.³² Alternatively, the existence of a mood disorder in children with asthma may contribute to poor asthma control; it is possible that a common neuroendocrine dysregulation is shared by anxiety/depression and poorly controlled asthma. Additional research is needed to clarify the reasons for the association.

The management of severe asthma in children remains an unmet need.³³ When assessing asthma-related QOL, it is important to use a comprehensive tool that can identify the impact of asthma across all facets of life. We used the PAQLQ in these analyses, which is a validated, comprehensive instrument for evaluating asthma-related QOL in children.³⁴ Pediatric patients with triggers and their caregivers should receive education and assistance regarding avoidance of identified triggers. The high prevalence of allergic comorbidity in children with asthma make allergy testing and identification of triggers an important component of patient care.³⁵ This information allows for instruction on trigger avoidance and management of the allergic

component of asthma. All these components can be used to design interventions that modify the risk of a future exacerbation.

Study limitations

TENOR's large patient population, as well as the many clinical and patient-reported outcomes that were collected permitting quantitative evaluation of relationships in the data, gives strength to the findings. There are limitations that should also be considered in interpreting the study results. First, asthma exacerbations were not continuously assessed for the full first year of TENOR participation; rather, these were included only the 3 months before each study visit per the study protocol, which was designed to enhance accurate recall. Thus, the number of asthma exacerbations was an estimate of those experienced in the first year. Second, it is possible that a single asthma exacerbation was counted more than once (once each in different HCU categories: hospitalizations, ED visits, steroid bursts). Third, triggers and atopic status were self-reported by the parent and, thus, might not have been complete or accurate. Last, the study included only children with severe or difficult-to-treat asthma treated by allergists or pulmonologists and may not be generalizable to other children with asthma of different severity, or those primarily treated by general pediatricians.

CONCLUSIONS

The association between lower pediatric asthma-related QOL and greater severity and number of asthma exacerbations in children with severe or difficult-to-treat asthma in our analyses was compelling and highlights the importance of exacerbation prevention in these patients. We also found that a higher number of triggers was associated with greater severity and number of asthma exacerbations, suggesting that avoidance and management of asthma triggers may reduce the severity and number of asthma exacerbations. This may, in turn, improve asthma-related QOL in this population of children.

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ONLINE REPOSITORY

TABLE E1. Select TENOR inclusion/exclusion criteria

Needed for inclusion	□ Age ≥ 6 y with diagnosis of asthma □ Under care of current provider for ≥ 1 y □ Physician assessed as severe or difficult to treat (more than 1 reason allowed): ○ Multiple drugs required ○ Frequent exacerbations ○ Severe exacerbations ○ Unable to avoid triggers ○ Complex medication regimen □ Able to read/understand English and provide informed consent
Must also have ≥ 1 of the following:	□ ≥ 2 unscheduled care visits for asthma in the past 12 mo □ ≥ 1 oral corticosteroid dose in the past 12 mo □ Require chronic daily high doses of inhaled steroids or ≥ 5 mg of oral prednisone (current) □ Using ≥ 3 medications to control asthma (current)
Reasons for exclusion	□ ≥ 30 pack-years of smoking history □ Cystic fibrosis primary diagnosis □ Severe cardiovascular disease □ Severe psychiatric disorder (excluding anxiety or depression) □ Cancer (excluding nonmelanoma skin cancer or cancer in complete remission for ≥ 5 y) □ Systemic disease that is significant such that patient is not expected to survive the length of the study (2-3 y) □ Known alcohol or drug abuser

TABLE E2. Demographic and clinical characteristics by exacerbation sum

Characteristic	Exacerbation sum				All patients	P value*
	0	1-2	3-4	≥5		
Patients, n	220	157	44	17	438	
Male, n (%)	150 (68.2)	107 (68.2)	29 (65.9)	11 (64.7)	297 (67.8)	.98
White, n (%)	164 (74.5)	88 (56.1)	23 (52.3)	9 (52.9)	284 (64.8)	<.001
Age at baseline (y), mean ± SD	9.3 ± 1.8	9.2 ± 1.7	9.5 ± 1.7	9.3 ± 2.1	9.3 ± 1.8	.88
Treatment setting, n (%)†						.62
Pulmonologist	128 (60.4)	92 (60.5)	26 (60.5)	13 (76.5)	259 (61.1)	
Allergist	84 (39.6)	60 (39.5)	17 (39.5)	4 (23.5)	165 (38.9)	
Asthma duration (y), mean ± SD	6.0 ± 2.7	6.4 ± 2.5	7.1 ± 2.4	7.0 ± 2.4	6.3 ± 2.6	.028
Atopic dermatitis, n (%)	44 (20.0)	30 (19.1)	8 (18.2)	4 (23.5)	86 (19.6)	.59
Allergic rhinitis, n (%)	136 (61.8)	109 (69.4)	30 (68.2)	12 (70.6)	287 (65.5)	.74
BMI (kg/m ²), mean ± SD‡	19.8 ± 4.9	20.3 ± 5.1	20.8 ± 5.8	20.3 ± 5.2	69.9 ± 28.4	.61
% predicted prebronchodilator FEV1, mean ± SD	91.4 ± 19.6	84.7 ± 20.1	87.2 ± 17.5	94.7 ± 16.6	88.8 ± 19.6	.017
% predicted postbronchodilator FEV1, mean ± SD	98.1 ± 18.8	91.8 ± 17.4	95.3 ± 16.6	102.8 ± 17.4	95.8 ± 18.3	.011
Geometric mean (95% CI) baseline serum IgE (IU/mL)	181.7 (142.9-231.1)	173.6 (129.2-233.2)	187.0 (105.5-331.4)	201.6 (110.0-369.4)	180.0 (151.6-213.8)	.99
Nights in hospital, (baseline + 6 mo)	0.00 ± 0.00	0.27 ± 1.19	0.77 ± 1.68	2.94 ± 3.93	0.3 ± 1.3	<.001
ATAQ score, n (%)†						<.001
0	21 (11.8)	5 (4.2)	1 (2.7)	0 (0.0)	27 (7.9)	
1	31 (17.4)	24 (20.3)	5 (13.5)	0 (0.0)	60 (17.5)	
2	94 (52.8)	49 (41.5)	16 (43.2)	5 (50.0)	164 (47.8)	
3	29 (16.3)	34 (28.8)	13 (35.1)	2 (20.0)	78 (22.7)	
4	3 (1.7)	6 (5.1)	2 (5.4)	3 (30.0)	14 (4.1)	

*Assessed by using χ^2 test for categorical variables and 1-way ANOVA for continuous variables for differences across the exacerbation sum categories.

†Percentages based on nonmissing data.

‡Calculated using growth charts from the Centers for Disease Control and Prevention.¹⁹