

Impact of Asthma Exacerbations and Asthma Triggers on Asthma-related Quality of Life in Patients with Severe or Difficult-to-Treat Asthma

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What is already known about this topic? Although the association between asthma triggers and asthma exacerbations is well established, few studies have quantified the impact of these variables on asthma-related quality-of-life (QoL) or the impact of asthma exacerbation severity on QoL.

What does this article add to our knowledge? The greater severity and numbers of asthma exacerbations were significantly associated with decreases in asthma-related QoL. Poorer QoL and greater asthma exacerbation severity and frequency were significantly associated with higher numbers of asthma triggers at baseline.

How does this study impact current management guidelines? Avoidance of asthma triggers may be an effective treatment strategy to reduce exacerbation rates and improve asthma-related QoL in patients with severe or difficult-to-treat asthma, although formal interventional trials would be required to confirm this.

BACKGROUND: Few data are available that evaluate the relationship among asthma exacerbations, asthma triggers, and asthma-related quality of life (QoL).

OBJECTIVE: To evaluate the impact of asthma exacerbations and asthma triggers on QoL.

METHODS: Patients with severe or difficult-to-treat asthma, ages ≥ 13 years ($n = 2679$) from the TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens)

3-year observational study were included. Exacerbations were defined hierarchically in descending order of severity (hospitalization, emergency department [ED] visit, steroid burst, no exacerbation) by using data from months 6 and 12. The total number (frequency) of exacerbations was assessed. Asthma-related QoL was measured at month 12 by using the Mini-Asthma QoL Questionnaire (Mini-AQLQ); self-reported asthma triggers were collected at baseline and annually. We used 1-way ANOVA to test for differences in Mini-AQLQ domain scores across asthma exacerbation severity, the total number of asthma exacerbations, and the number of asthma triggers. **RESULTS:** A significant decrease ($P < .001$) in Mini-AQLQ domain scores was seen with increasing severity of asthma exacerbation (no exacerbation, steroid burst, ED visit, and hospitalization); symptom (5.5, 4.8, 4.3, and 4.2), activity (5.8, 5.2, 4.6, and 4.4), emotional (5.6, 5.0, 4.4, and 4.2), exposure (5.0, 4.5, 4.0, and 3.9); and overall (5.5, 4.9, 4.3, and 4.1). Increasing exacerbation frequency and the number of baseline asthma triggers also were associated with significant decreases in Mini-AQLQ domain scores. An increasing number of asthma triggers were associated with an increase in severity and frequency of exacerbations.

CONCLUSION: Avoidance of asthma triggers may reduce exacerbation rates and improve asthma-related QoL in patients with severe or difficult-to-treat asthma. Interventional studies are warranted to further explore these outcomes. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:544-52)

Key words: Severe asthma; Difficult-to-treat asthma; Allergic triggers; Quality-of-life

Asthma exacerbations are responsible for a large disease burden, including hospitalization, decline in lung function, and death.¹ It has been shown that asthma costs are directly related to patients' levels of asthma control, with the highest costs incurred in patients with severe

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Abbreviations used

BMI- Body mass index

ED- Emergency department

HCU- Health care utilization

FEV₁- Forced expiratory volume in 1 second

LSM- Least squares mean

Mini-AQLQ- Mini-Asthma Quality of Life Questionnaire

NA- Not applicable

NS- Not significant

OR- Odds ratio

QoL- Quality of life

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

uncontrolled asthma.²⁻⁴ Despite the widespread dissemination of asthma guidelines, many patients have inadequately controlled disease,⁵⁻⁷ and experience frequent exacerbations of asthma.⁸⁻¹⁰ It is estimated that, during a 12-month period, approximately 40% of patients with severe asthma will require an emergency department (ED) visit compared with 20% of patients with moderate asthma and 15% of those with mild asthma.¹¹

Increases in the prevalence of asthma in the United States¹² have been accompanied by a rise in reports of allergen sensitivity.¹³ Although the association between asthma triggers and asthma exacerbations is well established, few studies have directly examined the individual impact of these highly interconnected variables on asthma-related quality of life (QoL) or have quantified the impact of the severity of the asthma exacerbation on QoL. In a 4-week study of 112 patients with moderate-to-severe asthma, patients who had exacerbations during the study period reported poorer QoL than those patients who did not have exacerbations.¹⁴ A further decrease in QoL was observed in patients who had been hospitalized as a result of an exacerbation. In a study of 296 patients with moderate-to-severe asthma who presented to a US ED with an asthma exacerbation, those who reported more asthma triggers had worse overall QoL scores and more frequent exacerbations, and were more likely to have been previously hospitalized for asthma and oral corticosteroids than patients who reported fewer asthma triggers.¹⁵

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study was a large, prospective, observational cohort study of patients with severe or difficult-to-treat asthma that was initiated in 2001.¹⁶ The study assessed a broad range of clinical and patient-reported outcomes over a 3-year period. We analyzed the population of patients ages ≥ 13 years enrolled in the TENOR study to (1) assess the association between the severity of asthma exacerbations and asthma-related QoL, (2) evaluate the impact of asthma triggers on asthma-related QoL, and (3) assess the association between asthma triggers and the severity of asthma exacerbations (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

METHODS

Patients

Patients ages ≥ 6 years with physician-assessed severe or difficult-to-treat asthma were included in the TENOR study. Asthma was considered difficult to treat based on a number of prespecified parameters, including a need for multiple asthma medications, severe exacerbations, frequent exacerbations, an

inability to avoid triggers, and complex medication regimen (multiple reasons were allowed).¹⁶ Patients with mild or moderate asthma were eligible for enrollment if their asthma was considered difficult to treat by the evaluating physician and they met the additional inclusion criteria. TENOR study enrollment criteria are shown in Figure E2 (in this article's Online Repository at www.jaci-inpractice.org).

Study design

The study design and methodology of TENOR have been published previously.¹⁶ In brief, the TENOR study was a multicenter, observational cohort study conducted over a 3-year period (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 with severe or difficult-to-treat asthma who were receiving care from an allergist or pulmonologist were enrolled. TENOR study was approved by a central institutional review board and, when necessary, by the institutional review board at each site.

Data collection

After enrollment, the patients attended follow-up visits every 6 months. A range of clinical, demographic, standard laboratory, and patient-reported assessments were completed at baseline and over the 3-year follow-up period. Health care utilization (HCU) data were collected every 6 months and were based on self-reported hospitalizations, ED visits, and oral corticosteroid bursts during the 3 months before each study visit. Asthma-related QoL data were collected annually by using the validated Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ),¹⁷ with lower scores indicating poorer asthma-related QoL. Data on asthma triggers were collected at baseline and annually by using a self-administered questionnaire. The 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 any of the following common asthma triggers: emotional stress, cold and/or sinus infection, pollen, animals, mold and/or dampness, or dust. The patients could check "all that apply" for this question.

Asthma exacerbations

The severity of asthma exacerbations and the total number of asthma exacerbations were evaluated for each patient by using HCU data from the month-6 and month-12 study visits (which assessed HCU during the 3 months before each visit). Asthma exacerbation severity was defined in descending order of severity: hospitalization, ED visit, steroid burst, and no exacerbation. For each patient, an asthma exacerbation was defined as the "highest" value in the hierarchy from both the month-6 and month-12 visits. The total number of exacerbations was defined as the sum of hospitalizations, ED visits, and steroid bursts from both the month-6 and month-12 visits.

Analytic cohort

Patients ages ≥ 13 years with nonmissing HCU data at month 6 and month 12, and nonmissing QoL data at month 12 were included in the analyses.

Statistical analyses

Baseline demographic and clinical characteristics were summarized by using percentages for categorical variables and mean $\pm$ SD for continuous variables. Differences in

TABLE I. Baseline demographic and clinical characteristics: categorized by asthma exacerbation severity type*

	No exacerbation	Steroid burst	ED visit	Hospitalization	P value†
No. of patients	1382	913	226	158	NA
Age (y), mean ± SD	46.6 ± 18.2	47.6 ± 16.6	42.1 ± 15.7	39.3 ± 18.6	<.001
Women, no. (%)	905 (65.5)	640 (70.1)	178 (78.8)	115 (72.8)	<.001
Race, no. (%)					<.001
White	1148 (83.1)	766 (83.9)	140 (61.9)	98 (62.0)	
Nonwhite	234 (16.9)	147 (16.1)	86 (38.1)	60 (38.0)	
Treatment setting, no. (%)					<.001
Pulmonologist	368 (27.2)	262 (29.5)	87 (40.8)	79 (52.0)	
Allergist	985 (72.8)	626 (70.5)	126 (59.2)	73 (48.0)	
BMI (kg/m ²), mean ± SD	29.3 ± 7.4	30.1 ± 7.8	33.0 ± 9.6	30.8 ± 8.1	<.001
Allergic rhinitis, no. (%)	989 (71.6)	667 (73.1)	160 (70.8)	107 (67.7)	NS
Allergic dermatitis, no. (%)	195 (14.1)	122 (13.4)	34 (15.0)	20 (12.7)	NS
% Predicted prebronchodilator FEV ₁ , mean ± SD	78.0 ± 22.0	71.9 ± 23.2	71.5 ± 26.2	65.1 ± 21.7	<.001
% Predicted postbronchodilator FEV ₁ , mean ± SD	83.0 ± 21.9	76.8 ± 22.8	76.3 ± 23.1	72.3 ± 21.5	<.001

BMI, Body mass index; NA, not applicable; NS, not significant.

*Asthma exacerbation severity was based on HCU data collected at month 6 and month 12; 15 patients were excluded due to missing HCU data at month 12; therefore, 2679 were included in this analysis.

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

TABLE II. Baseline demographic and clinical characteristics: categorized by number of asthma triggers*

	No. of asthma triggers				P value†
	0-1	2-3	4-5	6	
No. of patients	204	713	1144	633	NA
Age (y), mean ± SD	49.5 ± 21.4	48.8 ± 17.9	45.6 ± 17.4	43.1 ± 15.8	<.001
Women, no. (%)	100 (49.0)	431 (60.4)	808 (70.6)	513 (81.0)	<.001
Race, no. (%)					NS
White	164 (80.4)	586 (82.2)	927 (81.0)	488 (77.1)	
Nonwhite	40 (19.6)	127 (17.8)	217 (19.0)	145 (22.9)	
Treatment setting, no. (%)					.02
Pulmonologist	79 (39.3)	215 (31.1)	342 (30.7)	168 (27.4)	
Allergist	122 (60.7)	476 (68.9)	773 (69.3)	446 (72.6)	
BMI (kg/m ²), mean ± SD	28.2 ± 6.6	29.8 ± 7.7	29.9 ± 7.6	30.6 ± 8.5	.002
Allergic rhinitis, no. (%)	93 (45.6)	424 (59.5)	873 (76.3)	545 (86.1)	<.001
Allergic dermatitis, no. (%)	16 (7.8)	60 (8.4)	174 (15.2)	125 (19.7)	<.001
% Predicted prebronchodilator FEV ₁ , mean ± SD	72.1 ± 22.5	73.7 ± 23.8	75.6 ± 23.6	74.8 ± 21.4	NS
% Predicted postbronchodilator FEV ₁ , mean ± SD	76.8 ± 22.2	78.3 ± 22.8	80.7 ± 23.2	80.4 ± 21.0	.04

BMI, Body mass index; NA, not applicable; NS, not significant.

*Asthma exacerbation severity was based on HCU data collected at month 6 and month 12; 15 patients were excluded due to missing HCU data at month 12; therefore, 2679 were included in this analysis.

†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.

demographic and clinical characteristics across asthma exacerbation severity and the number of asthma triggers categories were assessed by using χ^2 test for categorical variables and 1-way ANOVA for continuous variables. One-way ANOVA was used to test for statistically significant differences in Mini-AQLQ domain scores at month 12 across asthma exacerbation severity, total number of asthma exacerbations, and number of asthma triggers. The association between asthma triggers at baseline and asthma exacerbations during the first year of follow-up (severity and total number) also was assessed; 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) were assessed by using χ^2 tests.

Multivariable linear regression was used to model the overall Mini-AQLQ score at the month-12 follow-up visit as a function of the 6 common asthma triggers (emotional stress, cold and/or sinus 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 Mini-AQLQ 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 month-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 more-severe exacerbation among patients with the asthma trigger were generated along with 95% CIs and *P* values.

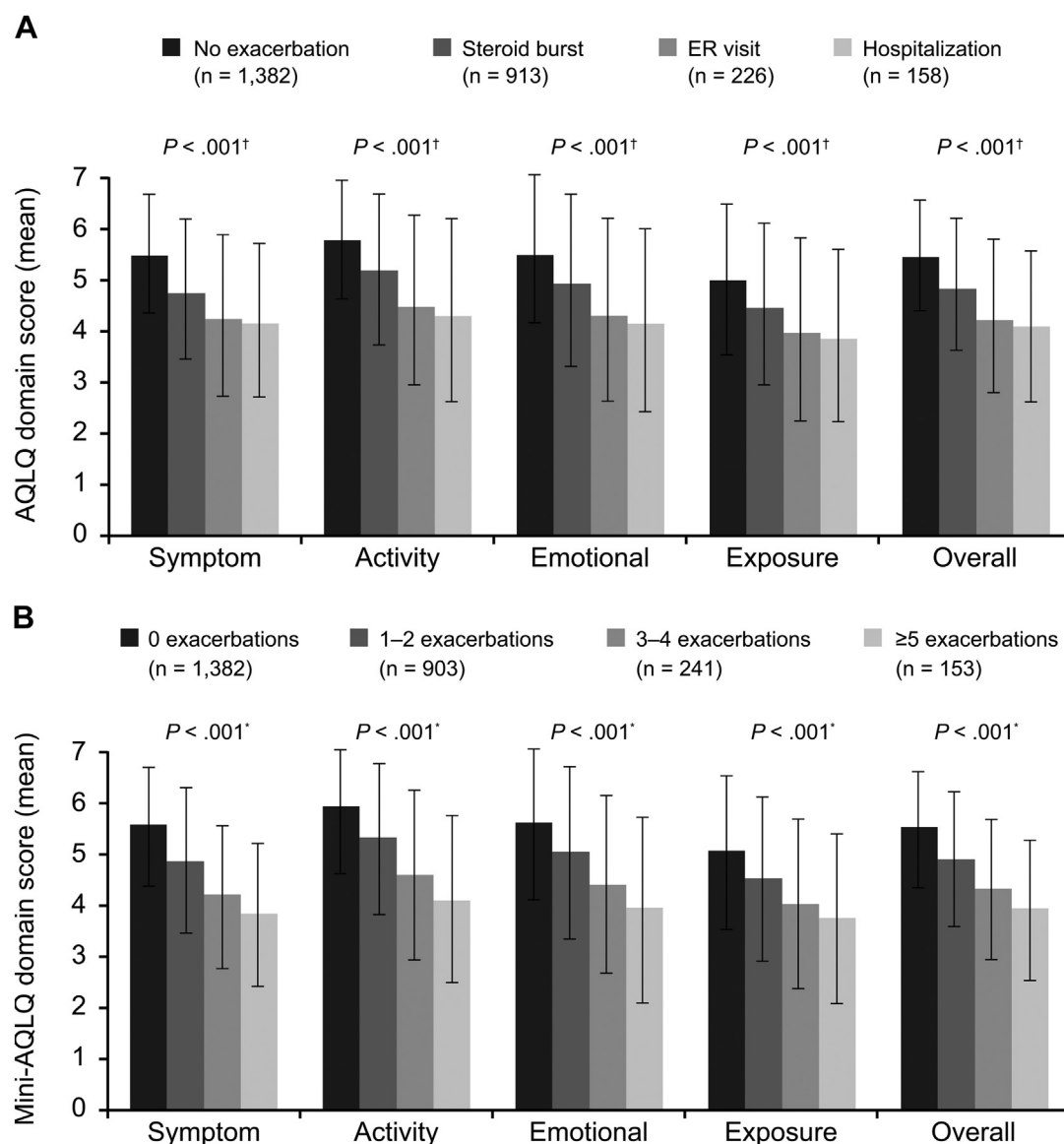


FIGURE 1. Increases in asthma exacerbation severity (A) and the number of exacerbations within the first year of follow-up (B) were associated with lower Mini-AQLQ domain scores at month 12. The total number of asthma exacerbations was based on HCU data collected at month 6 and month 12; 15 patients were excluded due to missing HCU data at month 12, with the remaining 2679 being included in the analysis. P values derived from 1-way ANOVA for differences in QoL scores within each Mini-AQLQ domain † (A) across asthma exacerbation severity categories or * (B) across the total number of asthma exacerbation.

RESULTS

Patient demographic and clinical characteristics

The disposition of patients from the TENOR study included in the current analyses is shown in Figure E3 (in this article's Online Repository at www.jaci-inpractice.org). Of 4756 patients enrolled in the TENOR study, 3985 (83.8%) were ages ≥ 13 years; data from 2679 of these were available for analysis (67.2% of the population ages ≥ 13 years). Patients included in the analysis were slightly more likely to be white (80.3% vs 72.1%; $P < .001$), to have lower lung function (mean $\pm$ SD percentage predicted prebronchodilator FEV₁, 74.6 $\pm$ 23.0 vs 76.7 $\pm$ 24.0; $P = .014$), and to have a higher mean $\pm$ SD body mass index (BMI) (29.9 $\pm$ 7.8 vs 29.4 $\pm$ 7.9; $P = .036$) at baseline versus those patients not included in the analysis. Patient demographics

and clinical characteristics for the analytic cohort categorized by asthma exacerbation severity and number of asthma triggers are shown in Tables I and II.

Patients with more severe asthma exacerbations (ED visits or hospitalizations) during the first year of follow-up were significantly more likely to be younger, female, nonwhite, under the care of a pulmonologist, have a higher BMI, and have poorer lung function (based on the percentage predicted pre- and postbronchodilator FEV₁) compared with those patients who had no exacerbations or required only steroid bursts (Table I). Patients with more asthma triggers at baseline (4–5 or 6 triggers) were significantly more likely to be younger, female, under the care of an allergist, have a higher BMI, have associated allergic rhinitis and atopic dermatitis, and have poorer lung function

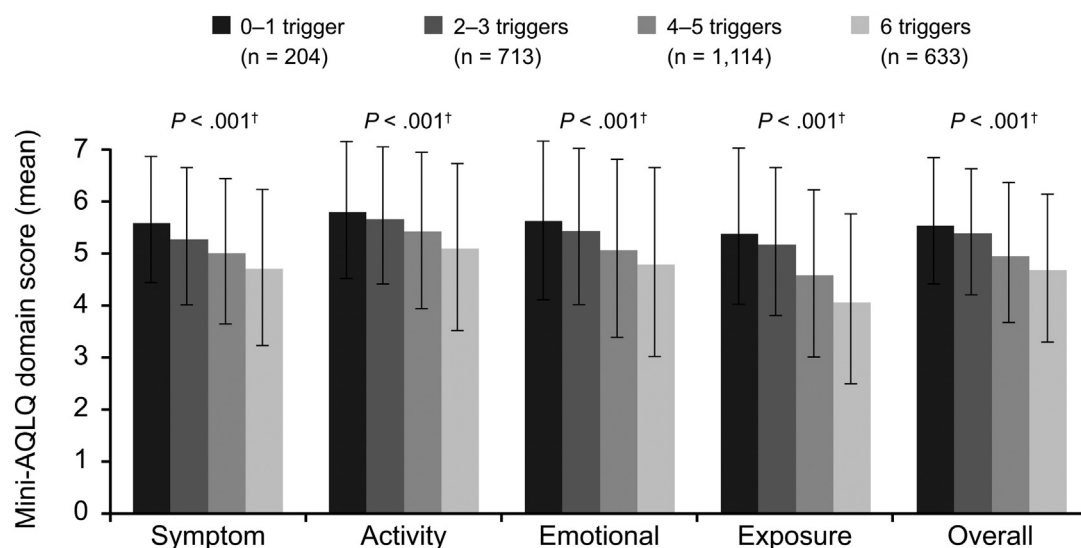


FIGURE 2. Association between baseline number of asthma triggers (symptoms from exposure to emotional stress, cold and/or sinus infection, pollen, animals, mold and/or dampness, or dust) and Mini-AQLQ domain scores at month 12. †Derived from 1-way ANOVA for differences in QoL scores within each Mini-AQLQ domain across the number of asthma triggers categories.

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

	Mini-AQLQ domain scores, mean $\pm$ SD			<i>P</i> value†
	0-1 (n = 552)	2-3 (n = 1269)	4 (n = 873)	
Symptom	5.4 $\pm$ 1.3	5.1 $\pm$ 1.4	4.8 $\pm$ 1.4	<.001
Activity	5.7 $\pm$ 1.3	5.5 $\pm$ 1.4	5.2 $\pm$ 1.6	<.001
Emotional	5.6 $\pm$ 1.5	5.2 $\pm$ 1.7	4.9 $\pm$ 1.7	<.001
Exposure	5.3 $\pm$ 1.4	4.8 $\pm$ 1.6	4.2 $\pm$ 1.6	<.001
Overall	5.5 $\pm$ 1.2	5.1 $\pm$ 1.3	4.8 $\pm$ 1.4	<.001

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

†Derived from 1-way ANOVA.

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

	Mini-AQLQ domain scores, mean $\pm$ SD			<i>P</i> value†
	0 (n = 259)	1 (n = 964)	2 (n = 1471)	
Symptom	5.6 $\pm$ 1.2	5.3 $\pm$ 1.3	4.8 $\pm$ 1.5	<.001
Activity	5.8 $\pm$ 1.2	5.7 $\pm$ 1.4	5.2 $\pm$ 1.5	<.001
Emotional	5.6 $\pm$ 1.4	5.4 $\pm$ 1.6	5.0 $\pm$ 1.7	<.001
Exposure	5.3 $\pm$ 1.4	4.9 $\pm$ 1.6	4.5 $\pm$ 1.6	<.001
Overall	5.6 $\pm$ 1.1	5.3 $\pm$ 1.2	4.9 $\pm$ 1.4	<.001

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

†Derived from 1-way ANOVA.

(based on the percentage predicted postbronchodilator FEV₁) compared with those patients who had fewer asthma triggers (0-1 or 2-3 triggers) (Table II).

Association between asthma exacerbations and asthma-related QoL

Poorer asthma-related QoL at month 12 with increasing asthma exacerbation severity was observed within the first 6 months of follow-up (Figure 1, A). A statistically significant decrease ($P < .001$) in mean $\pm$ SD Mini-AQLQ domain scores (which indicates worse asthma-related QoL) was seen with increasing severity of asthma exacerbation (no exacerbation, steroid burst, ED visit, and hospitalization): symptom domain score, 5.5 $\pm$ 1.2, 4.8 $\pm$ 1.4, 4.3 $\pm$ 1.6, and 4.2 $\pm$ 1.5, respectively; activity domain score, 5.8 $\pm$ 1.2, 5.2 $\pm$ 1.5, 4.6 $\pm$ 1.7, and 4.4 $\pm$ 1.8, respectively; emotional domain score, 5.6 $\pm$ 1.5, 5.0 $\pm$ 1.7, 4.4 $\pm$ 1.8, and 4.2 $\pm$ 1.8, respectively; exposure domain score, 5.0 $\pm$ 1.5, 4.5 $\pm$ 1.6, 4.0 $\pm$ 1.8, and 3.9 $\pm$ 1.7, respectively; and overall score, 5.5 $\pm$ 1.1, 4.9 $\pm$ 1.3, 4.3 $\pm$ 1.5, and 4.1 $\pm$ 1.5, respectively. Similarly, asthma-related QoL at

month 12 worsened with an increasing total number of asthma exacerbations during the first year of follow-up ($P < .001$) (Figure 1, B).

Association between asthma triggers and QoL

Poorer asthma-related QoL at month 12 was observed with increasing numbers of asthma triggers at baseline (Figure 2). Mean $\pm$ SD Mini-AQLQ scores in each domain significantly decreased ($P < .001$) with increasing numbers of asthma triggers (0-1, 2-3, 4-5, and 6 triggers): symptom domain score, 5.6 $\pm$ 1.2, 5.3 $\pm$ 1.3, 5.0 $\pm$ 1.4, and 4.7 $\pm$ 1.5, respectively; activity domain score, 5.8 $\pm$ 1.3, 5.7 $\pm$ 1.3, 5.4 $\pm$ 1.5, and 5.1 $\pm$ 1.6, respectively; emotional domain score, 5.6 $\pm$ 1.5, 5.5 $\pm$ 1.5, 5.1 $\pm$ 1.7, and 4.8 $\pm$ 1.8, respectively; exposure domain score, 5.5 $\pm$ 1.5, 5.2 $\pm$ 1.4, 4.6 $\pm$ 1.6, and 4.1 $\pm$ 1.6, respectively; and overall score, 5.6 $\pm$ 1.2, 5.4 $\pm$ 1.2, 5.0 $\pm$ 1.3, and 4.7 $\pm$ 1.4, respectively. Statistically significant decreases in Mini-AQLQ domain scores were seen with increasing numbers of both allergic and nonallergic asthma triggers at baseline ($P < .001$) (Tables III and IV).

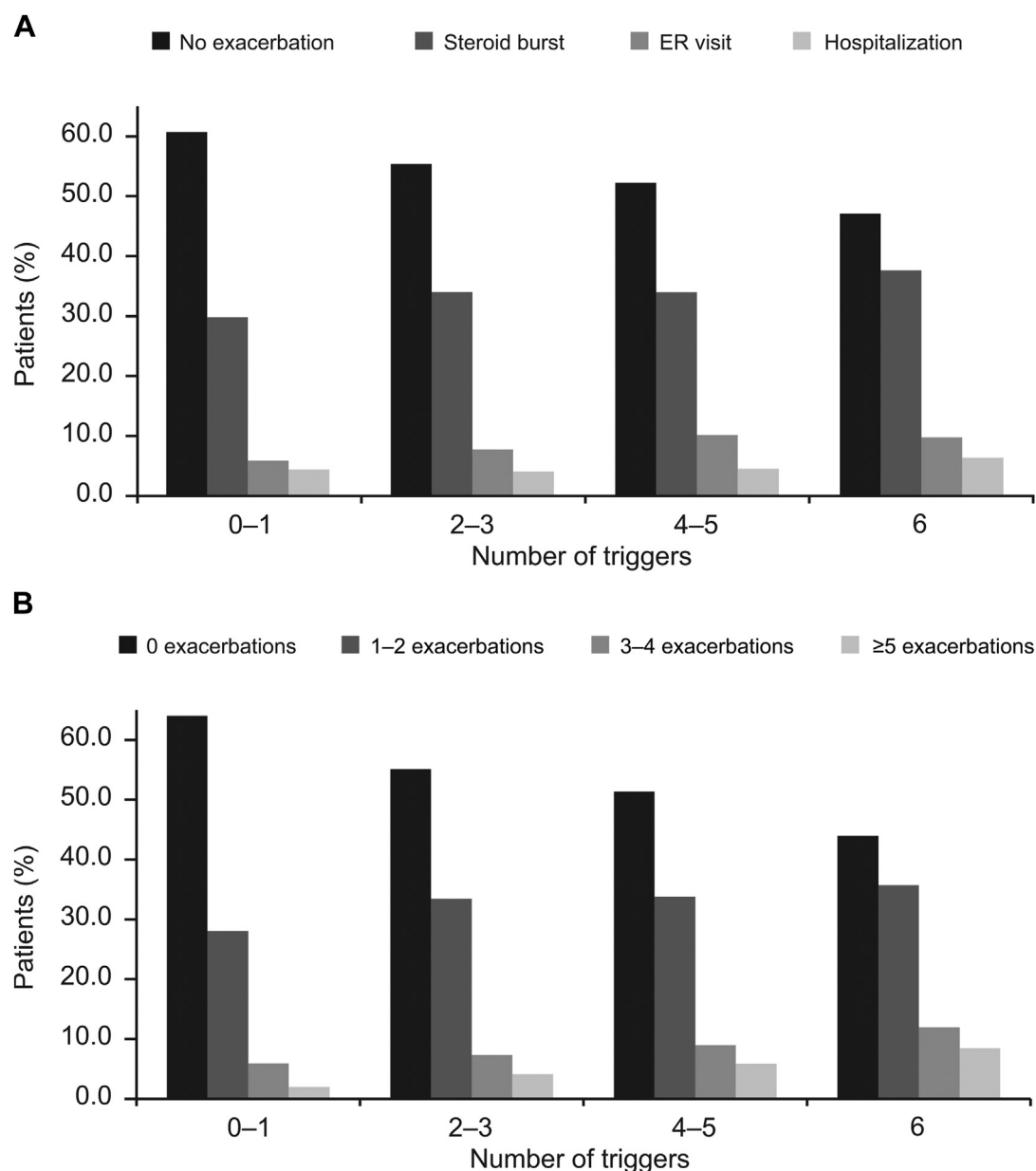


FIGURE 3. Asthma exacerbation severity (A) and the number of exacerbations within the first year of follow-up (B) were associated with baseline number of asthma triggers (symptoms from exposure to emotional stress, cold and/or sinus infection, pollen, animals, mold and/or dampness, or dust). Asthma exacerbation severity and total number of asthma exacerbations were based on HCU data collected at month 6 and month 12; 15 patients were excluded due to missing HCU data at month 12; therefore, 2679 patients were included in this analysis. $P < .001$ for overall difference in the number of asthma triggers by asthma exacerbation severity or the total number of asthma exacerbations categories.

Association between asthma triggers and asthma exacerbations

Within the first year of follow-up, the frequency of each asthma exacerbation type increased significantly with an increasing number of asthma triggers at baseline ($P < .01$) (Figure 3, A). The percentage of patients with no exacerbations decreased as the number of triggers increased. Similar findings were observed for the total number of exacerbations, which increased as the number of asthma triggers at baseline increased (Figure 3, B).

Multivariable analysis

Additional analyses were performed to examine the relationship among each individual asthma trigger and asthma exacerbations and asthma-related QoL. All 6 individual triggers were significantly predictive of overall QoL in a univariate analysis. In multivariable analyses, the effects of the 6 triggers, when adjusting for one another, indicated that emotional stress was most strongly associated with poor QoL (LSM difference, -0.412 ; $P < .001$), followed by dust (LSM difference, -0.324 ; $P < .001$), mold and/or dampness (LSM difference, -0.188 ; $P < .001$), and pollen

(LSM difference, -0.192 ; $P = .001$). The association with cold and/or sinus infection was marginally significant (LSM difference, -0.128 ; $P = .06$) and was nonsignificant for animals (LSM difference, 0.034 ; $P = .52$). For asthma exacerbations, all the triggers were significantly predictive at the univariable level, except for pollen and animals. In multivariable analyses, cold and/or sinus infection were most strongly predictive of an asthma exacerbation (OR 1.55 [95% CI, 1.26-1.91]; $P < .001$), followed by emotional stress (OR 1.42 [95% CI, 1.21-1.66]; $P < .001$), and mold and/or dampness (OR 1.21 [95% CI, 1.02-1.43]; $P = .03$). The associations for pollen, animals, and dust were nonsignificant.

DISCUSSION

This analysis from the TENOR observational study, to our knowledge, is the first to directly assess the impact of asthma exacerbations and asthma triggers on asthma-related QoL in a large cohort of patients with severe or difficult-to-treat asthma. Our results showed that greater severity and numbers of asthma exacerbations within the first year of follow-up were significantly associated with decreases in asthma-related QoL at month 12. A poorer QoL and greater severity and frequency of asthma exacerbations during the first year of follow-up were significantly associated with a higher number of asthma triggers at baseline. Analysis of our results suggests that it is possible to identify a subset of patients with difficult-to-control asthma who are at increased risk for adverse outcomes, including exacerbations, severe exacerbations, and decreased QoL, and in whom intensive interventions may be appropriate. Specifically, these interventions may include (1) asthma management and treatment that prevent asthma exacerbations, and (2) close monitoring and management of asthma triggers, including behavioral modification.

The results obtained support previous investigations of the impact of asthma exacerbations and asthma triggers on asthma-related QoL.^{14,15} For example, 1 study of 296 patients who presented to the ED for an asthma exacerbation demonstrated that patients with a greater number of trigger factors had poorer asthma outcomes,¹⁵ whereas another study showed that, over a 4-week study period, patients who experienced an exacerbation had significantly poorer QoL.¹⁴ However, in contrast to these earlier studies, which were shorter and based on smaller populations of patients, the present study was a 1-year prospective analysis in a large sample of 2679 patients and, in addition, was able to quantify the degree of impact on QoL by using a variety of asthma triggers and definitions for asthma exacerbations.

Previous analyses of data from the TENOR study, as well as other studies, have shown that a recent severe asthma exacerbation is the strongest predictor of a future exacerbation.^{8,18-21} Likewise, consistently poorly controlled asthma increases the risk of future severe exacerbations.⁷ Asthma treatment guidelines recommend a stepwise approach by using the minimum effective pharmacologic intervention to achieve asthma control,^{22,23} with more intensive steps by using novel, personalized treatments that reduce the exacerbation incidence in specific populations.²²⁻²⁶ Optimal asthma management should include patient education on self-management, which incorporates a personalized written action plan that documented daily management and ways to recognize and handle worsening asthma.^{22,23,27} A systematic review of 17 randomized controlled trials showed that, compared with usual care (which did not include an action plan), adding a written asthma

self-management action plan reduced the risk of hospitalizations by $>40\%$ and ED visits by $>20\%$ in adults.²⁸

Asthma triggers are consistently reported as contributors to poor asthma control,²⁹ and poor asthma control increases the risk of a future exacerbation.⁷ Interestingly, our analysis showed that, of all 6 asthma triggers included, a nonallergic trigger, emotional stress, was the strongest predictor of poor QoL and one of the strongest predictors of an asthma exacerbation. Results of research have demonstrated the influence of psychological factors on pulmonary function and airway immunology.³⁰⁻³² More recently, a systematic review found that acute stress, anxiety, and negative affects were repeatedly linked with higher fractional exhaled nitric oxide levels.³² Anxiety sensitivity (specifically, physical concerns) significantly predicted asthma control and all domains of asthma-related QoL in a recent survey of 368 patients with asthma from a community allergy asthma office.³³ Analysis of these findings suggests that targeting emotional stresses associated with asthma may be a novel way to improve asthma control and QoL. Another nonallergic trigger, cold and/or sinus infection, was not strongly associated with QoL, which may be due to its temporary nature but was strongly predictive of an asthma exacerbation, a finding that has been well documented in the literature.³⁴ It can be speculated that the association between pollen and poor QoL is present because patients with this asthma trigger have to avoid the outdoors; the lack of an association with exacerbations may be because these patients actually avoid the outdoors.

In addition to considering the type of asthma trigger, this analysis demonstrated that the number of asthma triggers, irrespective of whether they are of allergic or nonallergic origin, directly correlates with QoL, which suggests that a dedicated effort to avoid triggers as an essential component of asthma care is vital in all patients, particularly for those with heightened sensitivity to a range of asthma triggers. Although a recent systematic review of asthma triggers concluded that scientific evaluation of optimal trigger management has been inconsistent and sparse,²⁹ current asthma guidelines state that reducing patients' exposure to some categories of triggers (risk factors) improves asthma control and reduces medication needs,^{22,23} and most clinicians recommend allergen avoidance as an essential part of the management of allergic disease in patients once asthma is established. Similarly, avoidance of nonallergic triggers also would need to be recommended.

Coordinated, multifaceted interventions that encompass environmental assessment and control, as well as patient education, have been systematically reviewed and found to be effective in improving QoL in children and adolescents with asthma; however, further evaluation is needed in adults before conclusions can be drawn regarding this population.³⁵ Recent findings from a study of data from the National Health and Nutrition Examination Study in the United States showed that a high proportion of adults with asthma are sensitized to ≥ 1 allergen (75.4% of younger and 65.2% of older adult patients with asthma) and that all patients ages ≥ 55 years who had >1 ED or urgent care visit were atopic.¹³ In the current study, severity and frequency of asthma exacerbations were significantly associated with a greater number of asthma triggers at baseline. Taken together, analysis of these results suggests that avoidance of asthma triggers, both allergic and nonallergic, is essential for patients of all ages, and that physicians should advise patients on asthma trigger avoidance strategies.

The large size of the TENOR cohort, the prospective nature of the study, and the wide range of clinical and patient-reported outcomes collected allow for robust and clinically meaningful analyses. Furthermore, the novel, hierarchical approach to assessing asthma exacerbation severity (in descending order: hospitalization, ED visit, steroid burst, and no exacerbation) used in this analysis correlated well with other outcomes, including QoL and the number of triggers. Limitations of the study include potential misclassification of patients' self-reported asthma triggers and the lack of continuous assessment over the first year of follow-up. In addition, the generalizability of our findings is limited to patients with severe or difficult-to-treat asthma, as defined by TENOR inclusion criteria as well as patients treated at specialty allergist and pulmonologist sites. HCU data were collected semiannually with recall for the prior 3 months. It is possible, therefore, that, for the "total number of exacerbations" variable, a single exacerbation may have been counted up to 3 times (steroid burst, ED visit, hospitalization). It is important to note that our research did not investigate whether triggers could have additional predictive value above and beyond a recent history of exacerbations. Finally, the components of the Mini-AQLQ relate to susceptibility to environmental stimuli, which could partially explain the associations found in this analysis between asthma triggers and asthma-related QoL.

In summary, we showed that asthma exacerbations frequency and severity and the number of triggers at baseline were strongly associated with patients' asthma-related QoL. We also identified specific asthma triggers that were strongly associated with QoL and a risk of a future exacerbation. Analysis of these results suggests that physicians should emphasize asthma trigger avoidance with patients, in conjunction with rigorous management of severe or difficult-to-treat asthma according to treatment guidelines to control asthma and prevent exacerbations, thus improving patient QoL. To avoid confounding factors, our analysis included only patients ages ≥ 13 years. We plan to conduct similar analyses in pediatric patients from the TENOR cohort. Additional research, particularly via interventional trials, is merited to prospectively evaluate the impact of rigorous asthma trigger control on patient QoL and asthma exacerbations.

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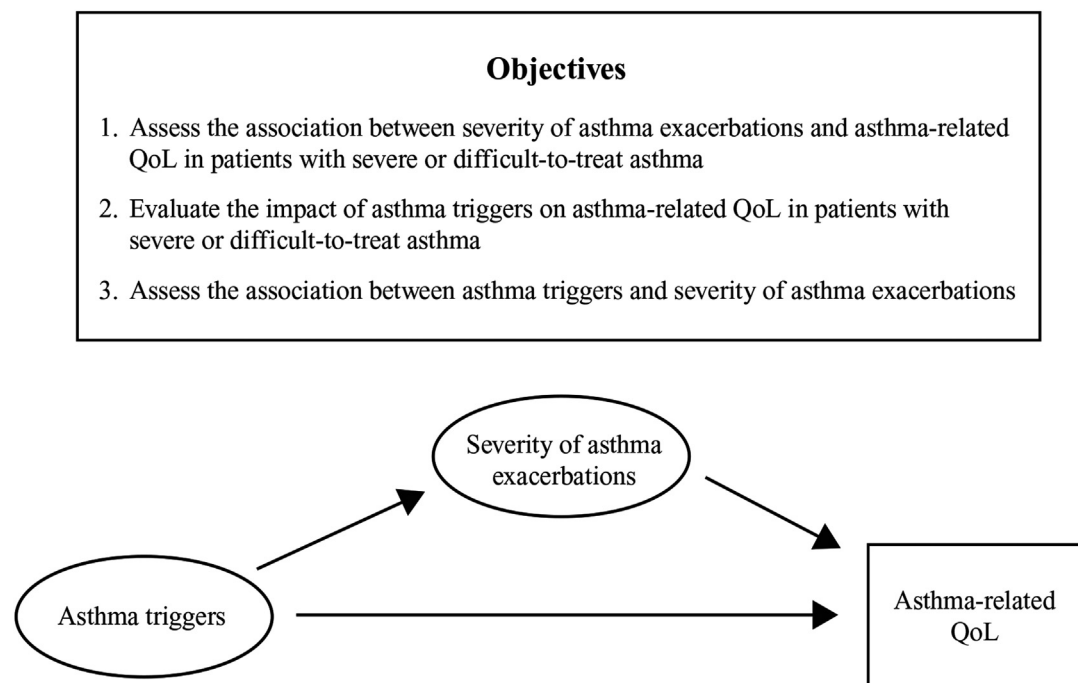


FIGURE E1. Current analysis objectives.

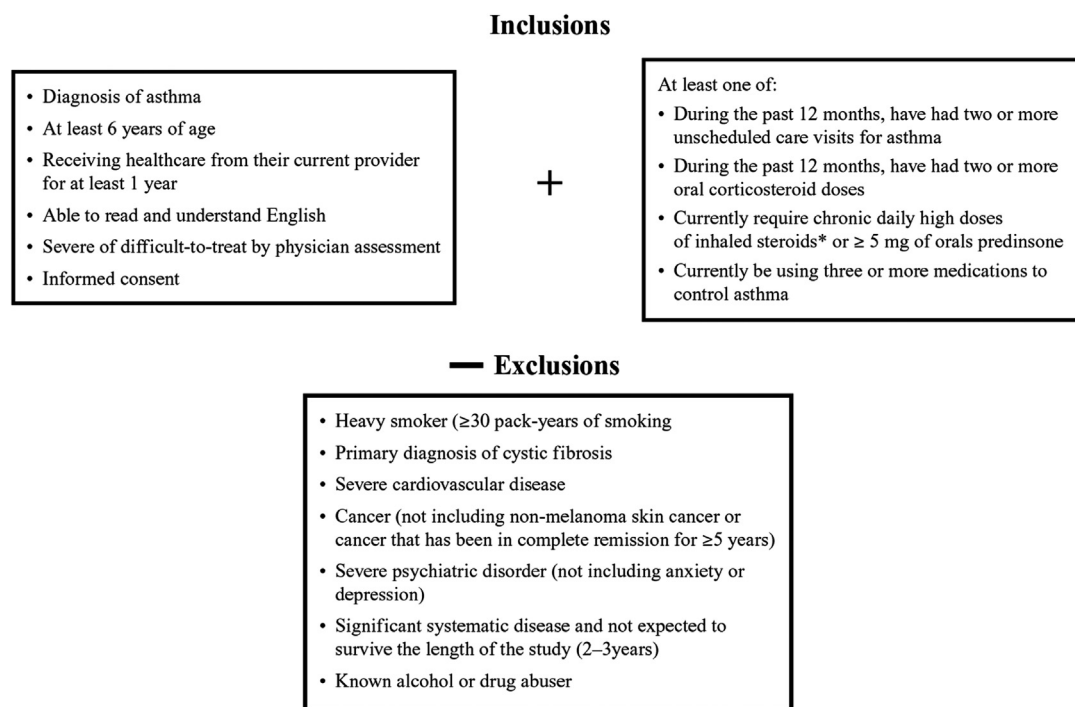


FIGURE E2. TENOR study enrollment criteria. *Daily high doses of inhaled steroids were defined by the American Thoracic Society Refractory Asthma Guidelines for Adults and by the National Heart Lung and Blood Institute guidelines for children. Adapted from Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, et al. (Reference 21)

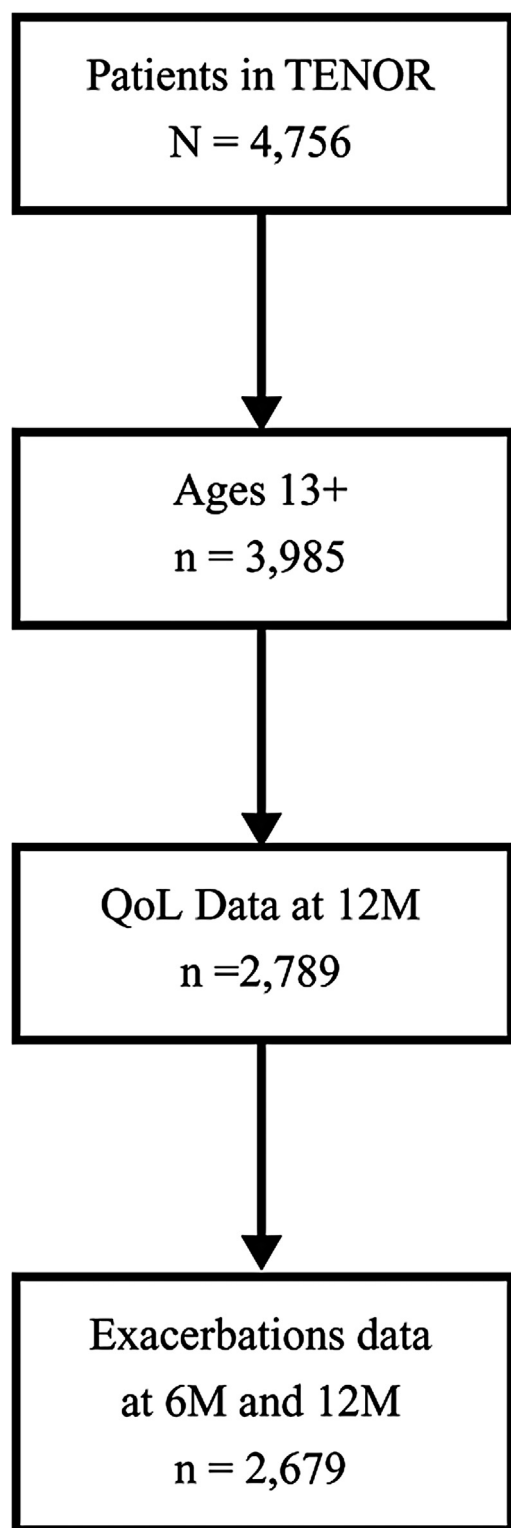
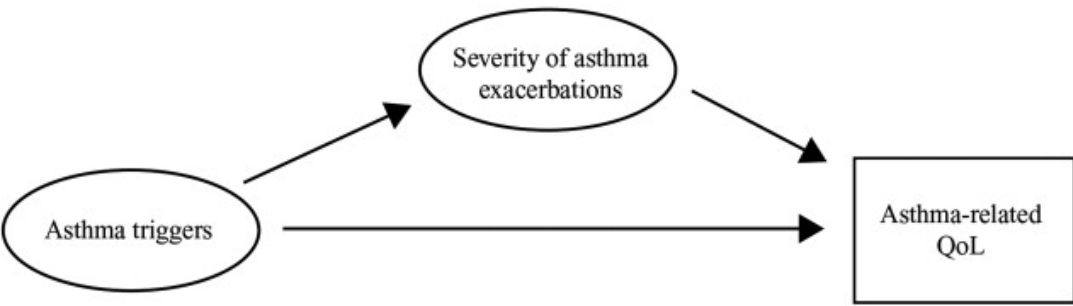


FIGURE E3. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement diagram for patient disposition. When analyzing the association between asthma severity and asthma-related QoL, baseline and month 6 HCU data were used, with 2694 patients included in the analysis. When analyzing the association between the total number of asthma exacerbations and asthma-related QoL, HCU data at month 6 and month 12 were used, with 2679 patients included in the analysis (15 patients had missing HCU data at month 12).

Objectives

1. Assess the association between severity of asthma exacerbations and asthma-related QoL in patients with severe or difficult-to-treat asthma
2. Evaluate the impact of asthma triggers on asthma-related QoL in patients with severe or difficult-to-treat asthma
3. Assess the association between asthma triggers and severity of asthma exacerbations



Inclusions

- Diagnosis of asthma
- At least 6 years of age
- Receiving healthcare from their current provider for at least 1 year
- Able to read and understand English
- Severe or difficult-to-treat by physician assessment
- Informed consent

+

At least one of:

- During the past 12 months, have had two or more unscheduled care visits for asthma
- During the past 12 months, have had two or more oral corticosteroid doses
- Currently require chronic daily high doses of inhaled steroids* or ≥ 5 mg of orals prednisone
- Currently be using three or more medications to control asthma

— Exclusions

- Heavy smoker (≥ 30 pack-years of smoking)
- Primary diagnosis of cystic fibrosis
- Severe cardiovascular disease
- Cancer (not including non-melanoma skin cancer or cancer that has been in complete remission for ≥ 5 years)
- Severe psychiatric disorder (not including anxiety or depression)
- Significant systematic disease and not expected to survive the length of the study (2–3 years)
- Known alcohol or drug abuser

Patients in TENOR

N = 4,756



Ages 13+

n = 3,985



QoL Data at 12M

n = 2,789



Exacerbations data
at 6M and 12M

n = 2,679