Risk Factors Associated With Persistent Airflow Limitation in Severe or Difficult-to-Treat Asthma*

Insights From the TENOR Study

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Background: **The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study is among the largest to assess persistent airflow limitation and the first to evaluate a wide range of potential risk factors in high-risk patients with severe or difficult-to-treat asthma. A better understanding is needed regarding factors associated with persistent airway obstruction; this study was performed to determine demographic and clinical characteristics associated with persistent airflow limitation.**

Methods: **Data from adult patients (≥ 18 years old) with severe or difficult-to-treat asthma were evaluated. Patients with COPD, obesity with a restrictive respiratory pattern, or a ≥ 30 pack-year history of smoking were excluded. Patients with persistent airflow limitation (postbronchodilator FEV_1/FVC ratio ≤ 70% at two annual consecutive visits) and normal postbronchodilator FEV_1/FVC ratio (75 to 85%) were compared. Multivariate analysis identified factors independently associated with persistent airflow limitation.**

Results: **Of 1,017 patients, 612 patients (60%) showed evidence of persistent airflow limitation. Risk factors were as follows: older age (odds ratio [OR] per 10 years, 1.4; 95% confidence interval [CI], 1.3 to 1.6); male gender (OR, 4.5; 95% CI, 2.3 to 8.5); black ethnicity (OR, 2.2; 95% CI, 1.3 to 3.8); current or past smoking (OR, 3.9; 95% CI, 1.8 to 8.6; and OR, 1.6; 95% CI, 1.2 to 2.3, respectively); aspirin sensitivity (OR, 1.5; 95% CI, 1.0 to 2.4); and longer asthma duration (OR per 10 years, 1.6; 95% CI, 1.4 to 1.8). Protective factors were Hispanic ethnicity, higher education, family history of atopic dermatitis, pet(s) in the home, and dust sensitivity.**

Conclusions: **Persistent airflow limitation is prevalent in patients with severe or difficult-to-treat asthma and is associated with identifiable clinical and demographic characteristics.**

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Key words: airway remodeling; difficult-to-treat asthma; irreversible airway obstruction; persistent airflow limitation; severe asthma

Abbreviations: ATAQ = Asthma Therapy Assessment Questionnaire; CI = confidence interval; HCU = health-care utilization; NPAFL = no persistent airflow limitation; OR = odds ratio; PAFL = persistent airflow limitation; TENOR = The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

Asthma is a chronic inflammatory disease of the airways characterized by reversible airflow obstruction.[1] For many asthma patients, however, airway obstruction fails to completely reverse following treatment. Numerous airway structural changes have been identified in both the central and peripheral airways (*eg*, increased airway smooth-muscle mass, mucous gland and goblet-cell hyperplasia, and thickening of the reticular basement membrane) and are also associated with asthma.[2] However, the relationship between airway physical changes and the degree of airway obstruction has yet to be determined.

Chronic, persistent airflow limitation (PAFL) is reported to occur in patients with asthma as a function of severity and/or duration of disease.[3–5] Quantitative techniques (*ie*, high-resolution CT)[6–8] and qualitative

techniques (*ie*, endobronchial biopsy)[9] show modest correlations between bronchial abnormalities, decreased lung function, and more severe disease. The concept of airway remodeling has emerged from these and other early studies[2,10] that associate clinical manifestations of persistent and irreversible airflow limitation with structural changes. The variability in the clinical course of asthma from patient to patient, however, suggests that specific factors might accelerate or delay this progressive decline in lung function. Studies[3–5,11,12] suggest that there may be a subset of patients who are at risk for PAFL. As it is not clear which patients will develop PAFL, the determination of specific associated factors could add insight into the clinical management of those at risk.

Few studies delineate the characteristics that may predispose patients toward PAFL. We analyzed demographic and clinical data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, a large-scale observational study[13] of nearly 5,000 patients with severe or difficult-to-treat asthma. The primary objective of the TENOR study was to better understand the natural history of asthma in the understudied severe asthma population. Using multiple observations over time for postbronchodilator FEV_1/FVC ratio, we defined PAFL (FEV_1/FVC ratio $\leq$ 70%) and analyzed an array of questionnaire data from the adult TENOR study population to identify factors associated with PAFL. This study is one of the largest to assess PAFL, and the first to evaluate factors associated with PAFL in patients with severe or difficult-to-treat asthma.

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Materials and Methods

Study Design and Participants

The TENOR study was a prospective, observational, 3-year study of patients with severe or difficult-to-treat asthma in the United States. Study sites (both allergists and pulmonologists) were selected from diverse geographic areas to represent typical settings where patients receive care, including managed-care organizations, community physicians or group practices, and academic centers. Patients continued to receive usual asthma treatment during the study, as indicated by their asthma specialist.

Detailed study characteristics for the TENOR study have been described previously.[13] Briefly, the study population comprised patients aged $\geq$ 6 years with severe or difficult-to-treat asthma by physician assessment; patients with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult to treat and they met the additional inclusion/exclusion criteria, described in detail in the online repository.[13] Patients had to be receiving care from their physician/provider for at least 1 year, and have evidence of either high use of the health-care system, medications, or both. Patients were excluded if they had a $\geq$ 30 pack-year smoking history or had a diagnosis of cystic fibrosis. The TENOR study design and protocol were approved by a central Institutional Review Board and, when necessary, by the Institutional Review Board at each site.[13]

This analysis was restricted to adults $\geq$ 18 years old at baseline (n = 3,489). Patients with COPD or emphysema (n = 298), possible abnormal lung function due to obesity (defined as body mass index $\geq$ 30 kg/m^2, FVC $<$ 80% of predicted, and FEV_1/FVC ratio $>$ 75%; n = 198) and patients with missing (n = 1,043), out-of-range (n = 296) or inconsistent spirometry data (n = 637) at baseline and/or first available follow-up over the 3-year study were excluded. The remaining 1,017 patients were categorized into PAFL and no PAFL (NPAFL) groups and included in the analysis. Figure 1 summarizes these exclusion criteria.

Demographic and Clinical Assessments

Demographic and clinical data were collected by study coordinator interview and evaluation. Historical data on skin testing, comorbid conditions, and family history of allergic conditions were also collected. Asthma triggers were self-reported at baseline and annually. Asthma-related health-care utilization (HCU) [*eg*, emergency department visits, overnight hospitalizations, corticosteroid bursts, and unscheduled office visits/physician contacts during the 3 months prior to each of the study visits] was also collected.

Spirometry

Spirometry measurements (according to American Thoracic Society guidelines[14]) were collected at baseline and annually. All study sites were required to have a certified device calibrated daily for performing flow spirometry. PAFL was defined as a postbronchodilator FEV_1/FVC ratio $\leq$ 70% at both baseline and first available follow-up assessment for which there were non-

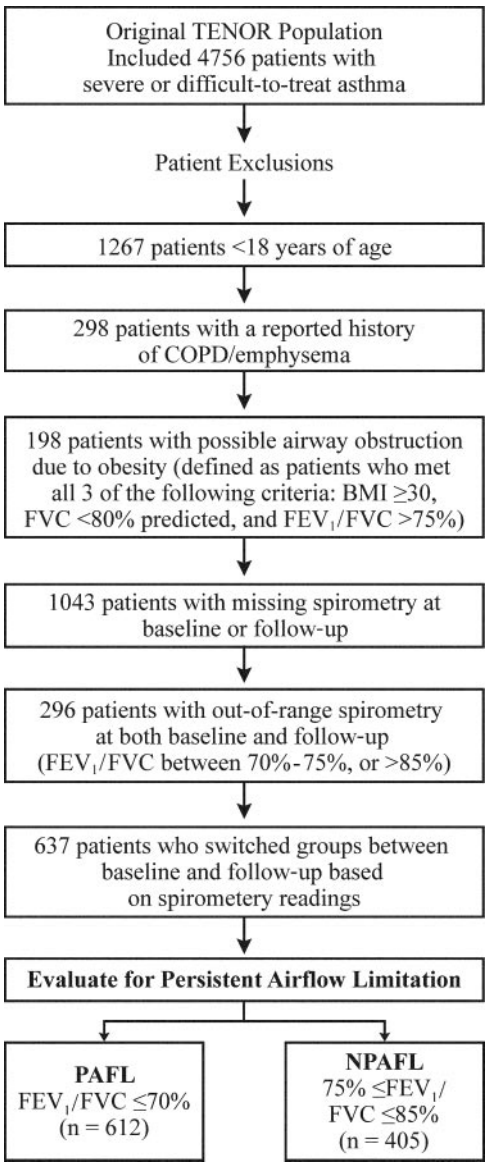

FIGURE 1. Selection of final analysis: PAFL and NPAFL subgroups. BMI = body mass index.

missing data. For some patients, the first available follow-up was at month 12; for others, it was month 24. NPAFL was defined as a postbronchodilator FEV_1/FVC ratio between 75% and 85%, inclusive, at both baseline and first annual follow-up assessment. This approach ensured that patients with an FEV_1/FVC ratio between 70% and 75%, FEV_1/FVC ratio > 85%, or intermittent bronchodilator-resistant obstruction were excluded; only patients with consistently normal or abnormal lung function were evaluated.

Patient Self-Reported Assessments

Patients completed the validated, self-administered Asthma Therapy Assessment Questionnaire (ATAQ) at baseline and semiannually to evaluate asthma symptoms and level of asthma control.[15] Seven items of the ATAQ were used to calculate the baseline control index (range, 0 to 4; where 0 = no control problems, to 4 = four control problems), reflecting the level of control in the past 4 weeks to 12 months. Higher scores indicate poorer asthma control.

Statistical Methods

Descriptive statistics were generated comparing patients with PAFL and NPAFL. Significance testing was performed using χ^2 tests for categorical variables and Student t test for continuous variables. All significant covariates at the univariable level were considered in a stepwise multivariable logistic regression model using an α level of 0.05 for entering and remaining in the model. For N-level categorical variables, the univariate test of significance was based on a single N-1° of freedom test for that variable. Interactions between gender and significant variables from the multivariable model were tested using the Breslow-Day test. Interaction terms that remained significant were included in the final model.

RESULTS

There were 4,756 patients with severe or difficult-to-treat asthma enrolled in the TENOR study; of these, 3,489 were adults.[13] After applying the previously described exclusion criteria, 1,017 adult patients who met the criteria for PAFL or NPAFL were included in this analysis: 612 PAFL patients (60%) and 405 NPAFL patients (40%) [Fig 1].

Baseline characteristics for the two groups are presented in Table 1. PAFL patients were older and more likely male, black, and previous smokers compared with NPAFL patients. PAFL was associated with earlier onset (≤ 12 years old) and longer duration (31 ± 17 years) [mean ± SD] of asthma. Total mean IgE was higher in PAFL than NPAFL patients (101.0 IU/mL vs 74.9 IU/mL, respectively; $p = 0.0045$), and PAFL patients had more severe asthma (as determined by physician assessment and a history of intubation). No other HCU measures were significantly different between the two groups (data not shown).

Baseline descriptions of allergic comorbidities and asthma triggers (Table 2) were generally more common in the NPAFL group than the PAFL group: history of a positive skin test result (96% vs 92%, $p = 0.0179$), allergic rhinitis (79% vs 68%, $p = 0.0001$), family history of allergic comorbidities, and allergic triggers (mold in the home, pet(s) in the home, breathing dust). Conversely, aspirin sensitivity affected a higher proportion of PAFL patients (16%) than NPAFL patients (11%, $p = 0.0221$). NPAFL patients reported significantly more problems controlling their asthma compared with PAFL patients ($p < 0.05$) [Fig 2].

Univariate analysis (Fig 3, *top*, *A*) and multivariate analysis (*bottom*, *B*) were performed to identify factors associated with PAFL. Multivariate analysis identified several independent factors for PAFL, including older age (odds ratio [OR] per 10 years, 1.4: 95% confidence interval [CI], 1.3 to 1.6). Black patients were 2.2 times

Table 1—*Characteristics of the Study Cohort at Baseline by Persistent Airflow Limitation Status

Characteristics	PAFL	NPAFL	p Value
All patients (n = 1,017)	612 (60)	405 (40)	
Age, yr†	54 ± 15	45 ± 13	< 0.0001
Gender			< 0.0001
Female	365 (60)	323 (85)	
Male†	247 (40)	82 (20)	
Race/ethnicity			0.0017
White	507 (83)	347 (86)	
Black†	74 (12)	25 (6)	
Hispanic†	18 (3)	27 (7)	
Other	13 (2)	6 (2)	
Smoking history			< 0.0001
Never smoked	350 (57)	291 (72)	
Past smoker†	238 (39)	100 (25)	
Current smoker†	24 (4)	14 (4)	
Early-onset asthma (≤ 12 yr old)	245 (40)	129 (32)	0.0069
Duration of asthma, yr†	31 ± 17	20 ± 14	< 0.0001
Diabetes	51 (8)	18 (5)	0.0159
Education			< 0.0001
College graduate†	215 (35)	184 (45)	
Employment status			< 0.0001
Working full time	248 (41)	227 (56)	
Total IgE, IU/mL	100.1 (88.6–114.6)	74.9 (63.9–87.8)	0.0045
Physician-assessed severity			< 0.0001
Severe	405 (66)	149 (37)	
Moderate	203 (33)	246 (61)	
Mild	4 (1)	10 (3)	
History of intubation	113 (19)	25 (6)	< 0.0001

*Data are presented as No. (%), mean ± SD, or geometric mean (95% CI).
†Significant factor in multivariate analysis.

more likely than white patients (95% CI, 1.3 to 3.8) and men were 4.5 times more likely than women (95% CI, 2.3 to 8.5) to have PAFL. There was a significant interaction between gender and duration of asthma; disease duration contributed more to PAFL in women than men (OR per 10 years in women, 1.6; 95% CI 1.4 to 1.8; OR per 10 years in men, 1.3; 95% CI, 1.1 to 1.5). Past smoking, but not present smoking, was significantly associated with PAFL at the univariate level; however, present smokers were on average approximately 20 years younger than past smokers. After controlling for age and other covariates in the multivar-

Table 2—*Distribution of Allergic Comorbidities and Asthma Triggers by Persistent Airflow Limitation Status

Characteristics	PAFL	NPAFL	p Value
Positive skin test results (among patients who were tested)	475 (92)	348 (96)	0.0179
History of allergic rhinitis	418 (68)	321 (79)	0.0001
Family history of allergic rhinitis	218 (36)	195 (48)	< 0.0001
Family history of atopic dermatitis†	78 (13)	96 (24)	< 0.0001
Family history of allergy	334 (55)	249 (62)	0.0314
Mold in home	85 (14)	79 (20)	0.0199
Pets in home†‡	266 (44)	245 (61)	< 0.0001
Breathing dust, trigger†	466 (76)	337 (83)	0.0089
Taking aspirin, trigger†	99 (16)	45 (11)	0.0221

*Data are presented as No. (%).
†Significant factor in multivariate analysis.
‡Cats at home, dogs at home, and multiple pets at home each occurred significantly more frequently in NPAFL group ($p < 0.05$).

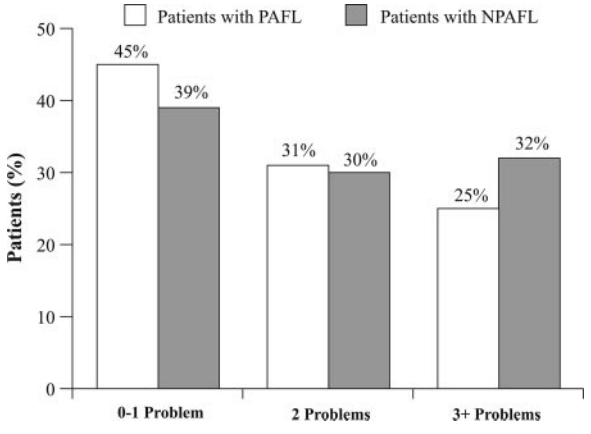

FIGURE 2. ATAQ questionnaire results: self-reported number of problems with asthma control by airflow limitation status. *$p < 0.05$ for overall comparison of control problems by airflow limitation status.

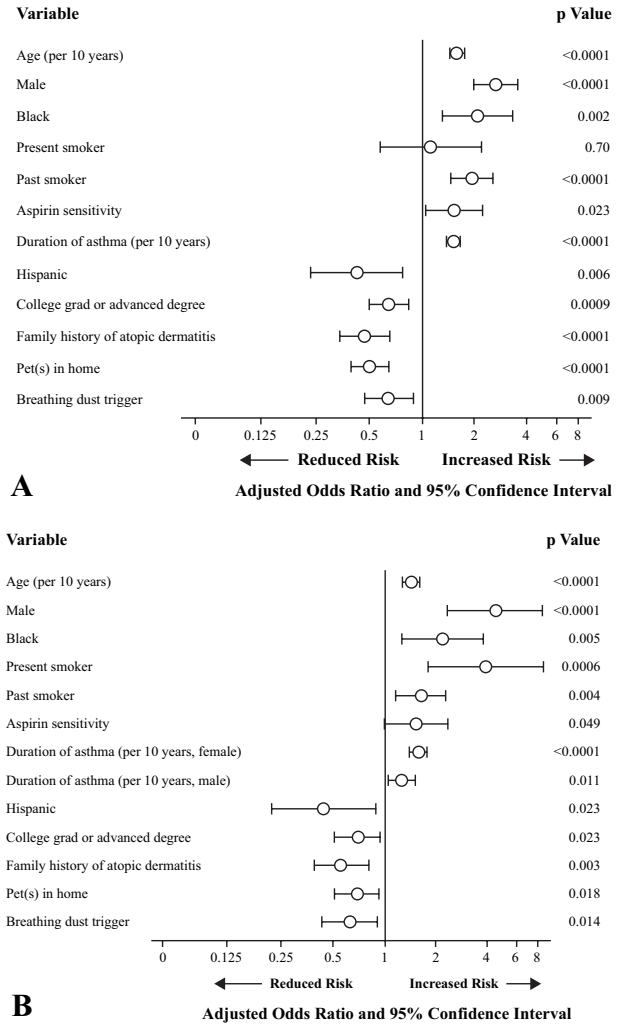

FIGURE 3. Factors independently associated with PAFL based on univariate analysis (*top*, *A*) and multivariate analysis (*bottom*, *B*) The stepwise model included all variables (age, gender, race, total serum IgE, onset of asthma, smoking history, and targeted allergies and comorbidities) that were statistically significant at the 0.05 level, adjusting for the other variables in the model. grad = graduate.

iate model, active smoking was significantly associated with a higher risk of PAFL, with present smokers demonstrating an approximate fourfold increased risk of PAFL (95% CI, 1.8 to 8.6) and past smokers demonstrating a 1.6-fold increased risk of PAFL (95% CI, 1.2 to 2.3). Aspirin sensitivity was independently associated with PAFL (OR, 1.5; 95% CI, 1.0 to 2.4). Protective factors for PAFL included Hispanic ethnicity (OR, 0.44; 95% CI, 0.22 to 0.89), a college education or advanced degree (OR, 0.70; 95% CI, 0.51 to 0.95), a family history of atopic dermatitis (OR, 0.56; 95% CI, 0.39 to 0.82), pet(s) in the home (OR, 0.69; 95% CI, 0.51 to 0.94), and dust sensitivity (OR, 0.63; 95% CI, 0.43 to 0.91).

DISCUSSION

The TENOR study is the first to evaluate characteristics associated with PAFL in a large cohort of patients with severe or difficult-to-treat asthma. In this analysis, 60% of 1,017 adults with two consistent spirometric measures showed PAFL as measured by a postbronchodilator FEV_1/FVC ratio $\leq 70\%$ at two consecutive study visits. Patients with PAFL were more likely to be older, black, and male, and have aspirin sensitivity, a longer duration of disease, a history of intubation, and severe asthma; however, rates of urgent HCU were similar between PAFL and NPAFL groups. Compared with patients who never smoked, active smokers had a higher risk of PAFL than previous smokers. Patients with NPAFL were more likely to be Hispanic, well educated, have a family history of atopic dermatitis, have pet(s) in the home, and report dust as an asthma trigger. These patients demonstrated substantial symptoms and control problems but were generally assessed as having mild or moderate asthma.

Approximately 71% of the original adult TENOR study population (≥ 18 years old) were excluded from this analysis. Many patients (n = 1,043) could not be analyzed due to missing spirometry measurements at baseline or follow-up visits. Excluding patients with comorbidities that could contribute to airflow obstruction (*ie*, 298 patients with a history of COPD or emphysema and 198 obese patients with preserved FEV_1/FVC ratios) limited the number of patients falling into the PAFL category. In addition, patients with intermittent bronchodilator-resistant obstruction demonstrated by variable spirometry readings at baseline and first follow-up (637 patients) were excluded, as well as 296 patients with out-of-range spirometry measures. Thus, our definitions of PAFL and NPAFL included patients at extreme ends of the airflow spectrum. Exclusion of patients with an FEV_1/FVC ratio between 70% and 75% allowed for a conservative gap between patients with PAFL and NPAFL. We realize this approach may have excluded some individuals with borderline or less developed PAFL; however, this facilitated the identification of factors associated with PAFL. This is consistent with an analysis[16] demonstrating that patients with an FEV_1/FVC ratio $< 70\%$ are universally classified as having significant airway obstruction.

The significant demographic and clinical differences between the PAFL and NPAFL groups suggest the presence of at least two distinct patterns of disease progression in patients with severe or difficult-to-treat asthma. The idea that asthma is clinically and pathophysiologically heterogeneous has been previously proposed, and distinct asthma

phenotypes have been defined based on age at asthma onset or predominant airway inflammatory infiltrate.[17–19] Consistent with other studies,[3–5] PAFL was associated with more severe asthma, longer disease duration, and aspirin sensitivity. An independent TENOR study analysis[4] also showed that adults with aspirin-sensitive asthma have more severe disease and airway obstruction than aspirin-insensitive asthma patients. It may be possible that for patients in whom disease duration and severity are risk factors for PAFL, chronic inflammation of the airways may contribute to PAFL development.

With regard to NPAFL associations, a similar "allergic" phenotype in patients with early onset asthma was observed by Miranda and colleagues.[19] These patients had a positive family history of allergic comorbidities and increased airway reactivity to allergic triggers, but better lung function.[19] The allergic factors that appear to prevent PAFL are in stark contrast to the "nonallergic" factors that define PAFL. The mechanism(s) by which allergy averts PAFL are unclear but may be due to a unique protection derived from the effects of inherently "twitchy" airways on airway structure, mechanical force, or inflammatory and related repair.

In this analysis, men were 4.5 times more likely than women to have PAFL, consistent with previous studies.[3,5] These data, in association with general epidemiologic data demonstrating greater prevalence and severity of asthma in women,[13,20,21] highlight previous findings that show that women appear to have a higher level of asthma severity than men despite better lung function. This observation was also reported in a previous TENOR study analysis[22] and suggests that asthma and PAFL may have gender-specific driving factors. In fact, this analysis demonstrated that 10 years of asthma duration was a stronger factor in the development of PAFL in women than men. Therefore, duration and severity of asthma may be more important in the development of PAFL in women; while in men, PAFL may be characterized by particular or distinct risk factors from PAFL in women. Earlier onset and greater incidence of childhood asthma observed in male patients[23] while airways are still developing and growing may result in changes that predispose the airways toward remodeling during adulthood.

Black patients were 2.2 times more likely and Hispanics almost 50% less likely than white patients to have PAFL. Asthma susceptibility genes vary in different races and may, in part, account for different outcomes in asthma.[24,25] In support of this concept, studies[26–29] have shown that black patients are more likely than the general population to carry polymorphisms associated with poor response to β-agonists and corticosteroids. Additionally, other studies[25,30] have shown polymorphisms in the genes for T-helper type 2 cytokine pathways that vary in blacks and other racial/ethnic groups. Together, the increased risk for PAFL and poor response to asthma medications may contribute to the disproportionally high asthma morbidity and mortality observed in black patients.[20] The mechanism behind the protection by Hispanic ethnicity against PAFL may be difficult to establish because the Hispanic population in the United States is diverse in terms of racial geography, culture, education, and socioeconomic factors.[31] Analyses to address subgroup-specific contributions to PAFL and NPAFL could not be performed because data on Hispanic origin were not collected in the TENOR study.

Active smokers had a higher risk of PAFL, suggesting that smoking may act synergistically with asthma to promote PAFL. These data are supported by previous studies showing the additive effects of smoking and asthma on the rate of decline of FEV_1 in adults,[32] and the poorer response of smokers with asthma to inhaled corticosteroids.[33,34] Data show progression of PAFL is augmented by smoking (hindered by concomitant presence of allergies, as evidenced by the "more allergic" NPAFL profile), which supports the Dutch hypothesis that obstructive lung disease is driven by inflammation but can be altered by environmental factors such as smoking and allergen exposure.[35,36] Alteration of PAFL development by environmental factors, however, is not absolute. Although current smoking correlated strongly with PAFL, this analysis showed that a significant number of nonsmokers and past smokers exhibited PAFL. Since smoking does not appear to be necessary to cause PAFL, and other factors (*ie*, gender and race) can independently contribute to PAFL, development may be driven by multiple factors that vary depending on patient demographic and clinical characteristics. Still, these data suggest that current smokers have some degree of acute effect of smoking on lung function. Further, at least among these asthmatics with a minimal cumulative smoke exposure (and not diagnosed with COPD or emphysema), quitting smoking might permit some restoration of airflow limitation.

A potential limitation of this study is that patients were not given a trial course of oral corticosteroids for several weeks followed by evaluation of pulmonary function tests to evaluate for irreversible obstructive lung disease.[37] However, our assessment of lung function (FEV_1/FVC ratio) at two different visits to include only those patients who fall within the well-accepted physiologic range of airflow obstruction increases our clinical confidence that the appropriate subset of patients was analyzed. In addition, longitudinal studies using FEV_1[11,38,39] or FEV_1/FVC[5] to measure persistent

airway obstruction have been reported in the literature, corroborating this assessment method.

Previous studies of PAFL or airway remodeling in adults are few and generally population based; those that focus on severe asthma are small in size and cross-sectional in nature. The TENOR study data allowed for multivariate and subgroup analyses, including a wide range of asthma-related risk factors. The exclusion of heavy smokers, individuals with COPD, and obese patients with preserved FEV_1/FVC ratios, together with the use of longitudinal lung function measures to define PAFL, allowed for a well-defined and robust analysis. The results are representative of patients with severe or difficult-to-treat asthma; however, the large number of study sites in the TENOR study were from diverse geographic areas and represented typical settings where asthma patients receive care. Our findings help define which patients are at risk for PAFL, and the factors that may prevent or reduce progression into a predominantly irreversible form.

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