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ORIGINAL ARTICLE

Evidence for Exacerbation-Prone Asthma and Predictive Biomarkers of Exacerbation Frequency

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Abstract

Rationale: Cross-sectional studies suggest an exacerbation-prone asthma (EPA) phenotype and the utility of blood eosinophils and plasma IL-6 as predictive biomarkers.

Objectives: To prospectively test for EPA phenotype and utility of baseline blood measures of eosinophils and IL-6 as predictive biomarkers.

Methods: Three-year asthma exacerbation data were analyzed in 406 adults in the Severe Asthma Research Program-3. Transition models were used to assess uninformed and informed probabilities of exacerbation in year 3. Binomial regression models were used to assess eosinophils and IL-6 as predictive biomarkers.

Measurements and Main Results: Eighty-three participants (21%) had ⩾1 exacerbation in each year (EPA) and 168 participants (41%) had no exacerbation in any year (exacerbation-resistant asthma). The uninformed probability of an exacerbation in Year 3 was 40%, but the informed probability increased to 63% with an exacerbation in Year 2 and 82% with an exacerbation in Years 1 and 2. The probability of a Year 3 exacerbation with no Year 1 or 2 exacerbations was 13%. Compared with exacerbation-resistant asthma, EPA was characterized by lower FEV_1 and a higher prevalence of obesity, hypertension, and diabetes. High-plasma IL-6 occurred in EPA, and the incident rate ratio for exacerbation increased 10% for each 1-pg/μl increase in baseline IL-6 level. Although high blood eosinophils did not occur in EPA, the incident rate ratio for exacerbations increased 9% for each 100-cell/μl increase in baseline eosinophil number.

Conclusions: Longitudinal analysis confirms an EPA phenotype characterized by features of metabolic dysfunction. Blood measures of IL-6, but not eosinophils, were significantly associated with EPA, and IL-6 and eosinophils predicted exacerbations in the sample as a whole.

Keywords: obesity; IL-6; metabolic dysfunction; exacerbation-prone asthma; type-2 inflammation

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the Subject: Cross-sectional studies in asthma suggest that some patients suffer recurrent exacerbations, whereas others rarely, if ever, suffer exacerbations, yet prospective studies confirming the stability of the exacerbation-prone asthma (EPA) phenotype are limited. Blood measures of eosinophils or IL-6 levels are higher in patients with a history of frequent exacerbations, but the performance characteristics of these biomarkers to predict future exacerbations is poorly understood. Here, we assess the stability of EPA and exacerbation-resistance asthma phenotypes in the Severe Asthma Research Program-3, a 3-year cohort study in asthma. We determine the clinical and immunologic features of EPA and test the performance of blood eosinophil cell counts and plasma IL-6 measures as predictors for asthma exacerbation risk.

What This Study Adds to the Field: Forty-one percent of patients with severe asthma remained exacerbation free during the 3-year cohort study. Conversely, 21% of subjects were exacerbation prone and suffered at least one exacerbation during each year of follow-up. Subjects with EPA accounted for 61% of the exacerbations in the cohort during the 3 years of follow-up, and this subgroup was characterized by increased body mass index, high rates of hypertension and diabetes, higher blood IL-6 measures, but no difference in blood eosinophil cell counts. Baseline blood eosinophil cell counts and plasma IL-6 levels each independently predicted the development of exacerbations. These findings confirm that elevations in blood eosinophils predict exacerbations in some patients and extend understanding of asthma exacerbation risk to include systemic IL-6 inflammation as a significant risk factor that could be modified.

One of the defining features of severe asthma is the persistent incidence of asthma exacerbations despite treatment (1, 2) with inhaled corticosteroids (ICS) (3, 4). Cross-sectional studies in asthma suggest that some patients suffer recurrent exacerbations whereas others rarely if ever suffer exacerbations (5). Yet, prospective studies confirming the frequency of asthma exacerbation rates over multiple years of prospective follow-up are limited (1, 2). Viral infections in the upper airway trigger the majority of asthma exacerbations (6), but lower airway susceptibility to the consequences of upper respiratory tract viral infections is variable among patients. The reasons for why some patients with asthma are prone to exacerbations when exposed to upper respiratory tract infections whereas others are resistant are not well understood.

Increased airway type-2 inflammation is known to increase exacerbation susceptibility (7–9) and treatments that inhibit type-2 inflammation prevent exacerbations in patients with type-2 high asthma (10–13). But many patients are type-2 low (7, 10, 14, 15), and these patients have a significant unmet medical need, including a need for treatments that prevent exacerbations. Recent cross-sectional studies in asthma have demonstrated that patients with high levels of plasma IL-6 or other features of metabolic dysfunction are characterized by frequent exacerbations (16, 17). These findings suggest that elevations in blood measures of IL-6 may identify patients with an increased susceptibility to develop asthma exacerbations.

Here, we assess the stability of exacerbation-resistant and exacerbation-prone phenotypes in the Severe Asthma Research Program-3, a 3-year cohort study in asthma. We analyzed the clinical and immunologic variables that distinguish exacerbation-prone asthma (EPA) from exacerbation-resistant asthma (ERA) and using an *a priori* analysis plan tested the performance of blood eosinophil cell counts and blood IL-6 levels as predictors of asthma exacerbations.

Some of the results of these studies have been previously reported in the form of an abstract (18).

Methods

Subjects

Data were analyzed from the NHLBI SARP-3 (Severe Asthma Research Program-3) cohort trial of 528 adult (age ⩾18 yr) patients with asthma. Four hundred six of the adult patients completed the 3-year study and were included in the final data analysis (Table E1 in the online supplement). Details of the SARP-3 protocol have previously been described in detail (5, 16, 19, 20). Additional details of subject characterization, biospecimen collection, and biomarker analysis are provided in the online supplement. All participants signed an informed consent adherent to the Declaration of Helsinki and approved by the institutional review boards of each center and the NHLBI Data and Safety Monitoring Board.

Definition of Asthma Exacerbations

An asthma exacerbation was defined as a burst of systemic corticosteroids lasting ⩾3 days for the treatment of worsening asthma control (21). This definition was agreed upon by the SARP investigators at the start of the study and described in detail previously (5). Asthma exacerbation events were collected using standardized questionnaires administered at 6-month intervals. Questionnaire administration alternated between phone interviews and in-person visits, and exacerbation events were recorded for a total duration of 3 years of study follow-up (Figure 1A). At each year, subjects were categorized into annual exacerbation frequency categories of zero asthma exacerbations, one or two exacerbations, or three or more exacerbations, based upon the number of exacerbations in the preceding year. We then categorized subjects into longitudinal asthma phenotypes based upon the pattern of annual exacerbation frequencies. Subjects with zero exacerbations over the 3 years of longitudinal follow-up were categorized as ERA, subjects with 1 year of zero exacerbations and at least 1 year with an exacerbation were categorized as exacerbation-intermittent asthma (EIA), and subjects with at least 1 exacerbation at each year were categorized as EPA.

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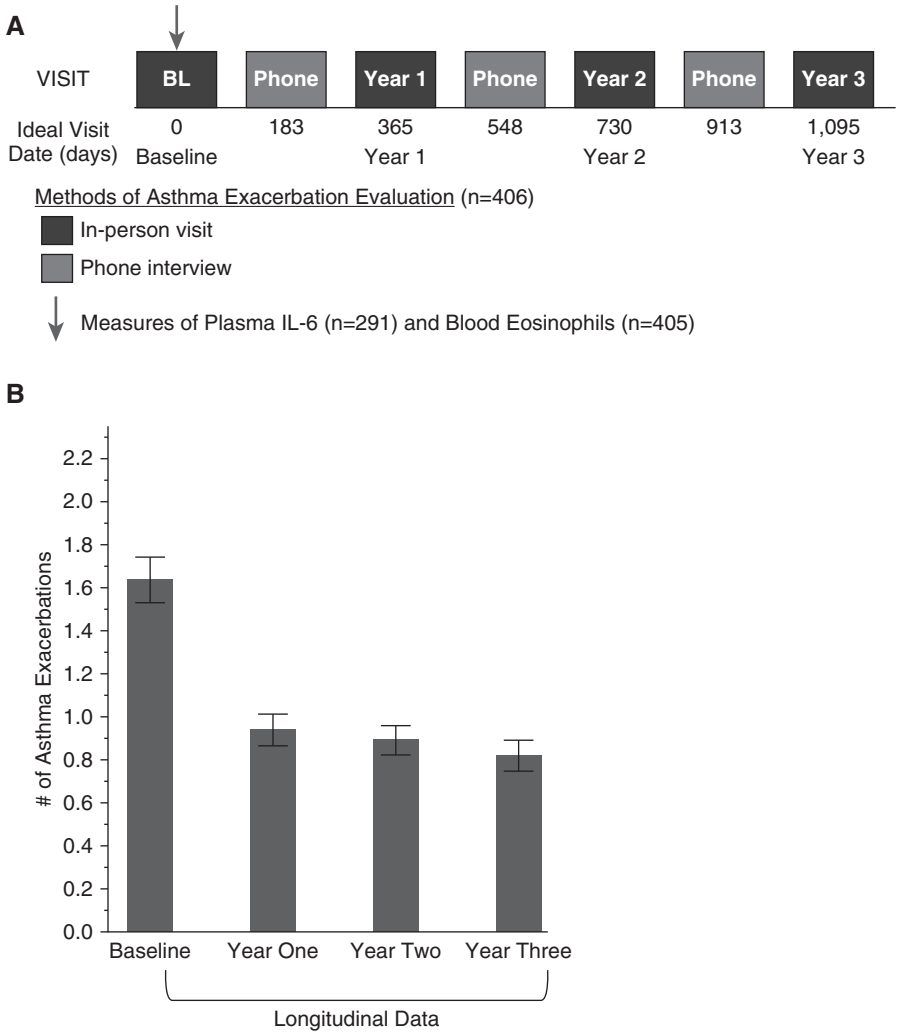

Figure 1. (*A*) Schematic of the SARP (Severe Asthma Research Program) clinical protocol. Asthma exacerbations were assessed at 6-month intervals using alternating phone interviews (gray boxes) and in-person visits (black boxes). Plasma IL-6 measurements and blood eosinophil cell counts were made at a baseline visit (arrow). (*B*) Number of asthma exacerbations that occurred over the SARP 3-year protocol. Baseline asthma exacerbations were recorded based upon subject recall for the year preceding the baseline visit. BL = baseline.

Statistical Methods

Statistical analyses were performed with the JMP 12 software package (SAS Institute), Stata 15.0 (StataCorp), and R statistical package. Comparison of clinical traits across longitudinal asthma phenotypes was made using nonparametric tests of trend. Sankey diagrams (Sankeymatic.com) were used to visually assess the movement of subjects across asthma exacerbation categories annually over the 3 years of follow-up. We used generalized estimating equations to fit second-order transition models to predict the probability of at least one exacerbation occurring during any given year, conditional on exacerbation history in prior years. In these models, differing states of knowledge about exacerbation history in the first 2 years of the study (e.g., uninformed or no prior knowledge, 1 yr of prior knowledge, or 2 yr of prior knowledge) informed the probability of developing an exacerbation at year 3. Negative binomial regression modeling was used to determine the impact of baseline blood eosinophil cell counts and baseline plasma IL-6 levels on the development of asthma exacerbations prospectively. Because prior evidence linked blood eosinophil cells count and plasma IL-6 levels to a history of asthma exacerbations (5, 7, 16), we developed an *a priori* analysis plan focused on blood eosinophils and plasma IL-6 levels as primary predictors of asthma exacerbations. This analysis plan was developed through the use of directed acryclic graphs using the R statistical package daggity (22). Our directed acryclic graph analysis informed our regression models and identified a need to control for age, body mass index, and depression as the minimal sufficient adjustment covariates for estimating the total effect of eosinophils and IL-6 on exacerbation rates. Sensitivity analysis for these binomial regression models were performed to assessed the stability of the relationship between plasma IL-6 levels and blood eosinophil cell counts on the primary outcome of asthma exacerbations. In all analyses, *P* values of less than 0.05 were taken as statistically significant.

Results

Exacerbation Rates and Phenotypes in the SARP-3 Cohort

Three hundred seventy asthma exacerbation events occurred in 406 adult subjects with asthma during Year 1—an event rate of 0.91 events per subject. This event rate was relatively stable in Year 2 and Year 3—0.87 events per subject per year during Year 2 and 0.82 events per subject per year during Year 3 (Figure 1B). This prospective exacerbation rate was significantly lower than the retrospective event rate of 1.6 events per subject per year calculated from recall of asthma exacerbations for the year prior to study enrollment (Figure 1B). Of the 406 subjects with asthma, 244 (60%) did not have an asthma exacerbation during the first year of follow-up, whereas 114 (28%) had one or two exacerbations and 49 (12%) had three or more exacerbations.

A Sankey diagram was used to graphically present the change in annual exacerbation frequency categories over 3 years of longitudinal follow-up (Figure 2A). These plots provide visual representations of both the number of subjects at each annual exacerbation frequency category and the longitudinal flow of these subjects over the course of the study. Subjects who remained exacerbation free at each year of follow-up were classified as ERA, whereas subjects who suffered at least one exacerbation each year were classified as EPA (Figure 2A). The remaining subjects who were exacerbation free one year but

had one exacerbation during one of the other follow-up years were classified as EIA (Figure 2A). Among the 243 subjects who did not have an exacerbation during the first year of follow-up, 168 (69%) remained exacerbation free during the second and third years of follow-up (Figure 2A). Among the 49 subjects who experienced more than two exacerbations during the first year of follow-up, 34 (69%) had at least one exacerbation during the second and third years of follow-up (Figure 2A). Overall, 21% of subjects were exacerbation prone and 41% were exacerbation resistant (Figure 2B). Of the remaining 38% of subjects with EIA, most fluctuated between zero exacerbations and 1–2 exacerbations per year. Annual fluctuations between zero exacerbations per year and more than two exacerbation per year were rare (Figures 2A and E1).

Exacerbation Burden

Although the EPA subgroup was only 21% of the SARP-3 cohort (Figure 2B), 226 of the 370 exacerbations (61%) in the 3 years of longitudinal follow-up occurred in this subgroup. EPA subjects averaged 7.9 exacerbations over the 3 years of follow-up, compared with 2.6 exacerbations per 3 years in the EIA subgroup and zero exacerbations (by definition) in the ERA subgroup (Figure 2C). In addition, EPA subjects averaged 1.0 hospitalization over the 3 years compared with 0.1 hospitalizations per 3 years in the EIA subgroup and 0.02 in the ERA subgroup (Figure 2C) (three hospitalizations occurred in subjects with ERA, but no treatment with

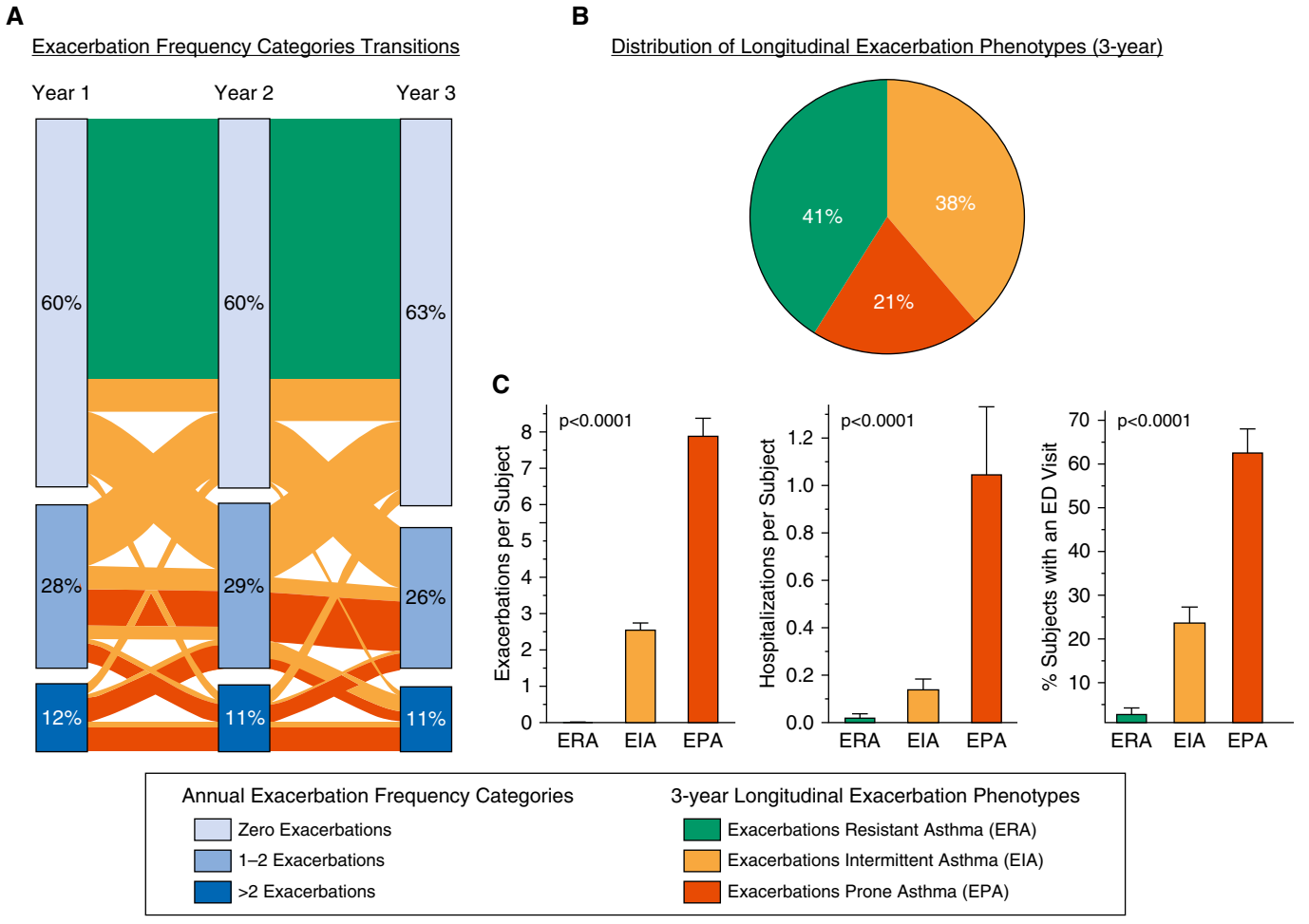

Figure 2. (*A*) Longitudinal change of annual exacerbation frequency categories over time using a Sankey diagram: each blue rectangular node represents the number of subjects in each annual exacerbation frequency category. Subjects with zero exacerbations are represented in light blue, subjects with one or two exacerbations in blue, and subjects with three or more exacerbations in dark blue. The size of the rectangular nodes represents the percentage of subjects at each annual exacerbation frequency category at each year of the study. Horizontal bar lines connect the nodes and depict the number of subjects that transition to and from each node the subsequent year. These horizontal bar lines are color coded based on the longitudinal exacerbation phenotype the subjects fall into over the 3 years of follow-up. The size of the horizontal bar lines represents the number of subjects at each transition: green = exacerbation-resistant asthma (ERA), orange = exacerbation-intermittent asthma, and red = exacerbation-prone asthma (EPA). (*B*) Percentage of subjects in each exacerbation phenotype. ERA was the most common phenotype (41%), whereas the smallest number of subjects demonstrated EPA (21%). (*C*) Exacerbation burden by exacerbation phenotype. The overall exacerbation burden was highly skewed, and EPA subjects experienced a significantly higher number of asthma exacerbations and asthma-related hospitalizations per subject over 3 years of follow-up. EPA subjects were more likely to experience an emergency department visit for asthma over 3 years of follow-up. Error bars denote SEs. ED = emergency department; EIA = exacerbation-intermittent asthma.

systemic corticosteroids was reported). Finally, 62% of the EPA subjects had at least one emergency department visit for asthma during the 3-year study compared with 24% of the EIA subjects and 3% of the ERA subjects (Figure 2C).

Transition Modeling to Analyze Asthma Exacerbation Rates

As a complementary approach to our Sankey diagram analysis, we used transitional modeling to assess the stability of the annual exacerbation categories over time. In this modeling, we assessed the probability of developing an exacerbation during the third year of the study based on differing states of knowledge about exacerbation history in the first 2 years of the study. For example, the probability of having an exacerbation during Year 3 with no prior knowledge of exacerbation (uninformed) history was 0.4 (Figure 3). We observed that under this model, a prior history of exacerbations significantly increased this probability. Specifically, with 1 year of additional knowledge, we found that subjects with one or more exacerbations in the prior year had a 0.63 probability of experiencing an exacerbation during Year 3, whereas subjects with no exacerbation in the prior year had a 0.23 probability of experiencing an exacerbation during Year 3 (Figure 3). Two years of prior exacerbation history further improved the probability estimates. For example, subjects with an exacerbation in each of the first 2 years had a 0.82 probability of having an exacerbation in the third year. In contrast, subjects with no exacerbations in each of the first 2 years had a 0.13 probability of having an exacerbation in the third year (Figure 3). Subjects with intermittent exacerbations in the prior 2 years (1 yr with an exacerbation and 1 yr without) had an intermediate probability of having an exacerbation in the third year at 0.33. Overall, the odds of at least one exacerbation in the future year were 2.7 times higher (95% confidence interval [95% CI], 2.2–3.3) in subjects with an exacerbation in the prior year when compared with subjects with no exacerbations in the prior year. Furthermore, in subjects with at least one exacerbation in each of the prior 2 years, the odds of at least one exacerbation in the future year were 6.3 times higher (95% CI, 4.7–8.5) than if there were no exacerbations in either of the prior 2 years.

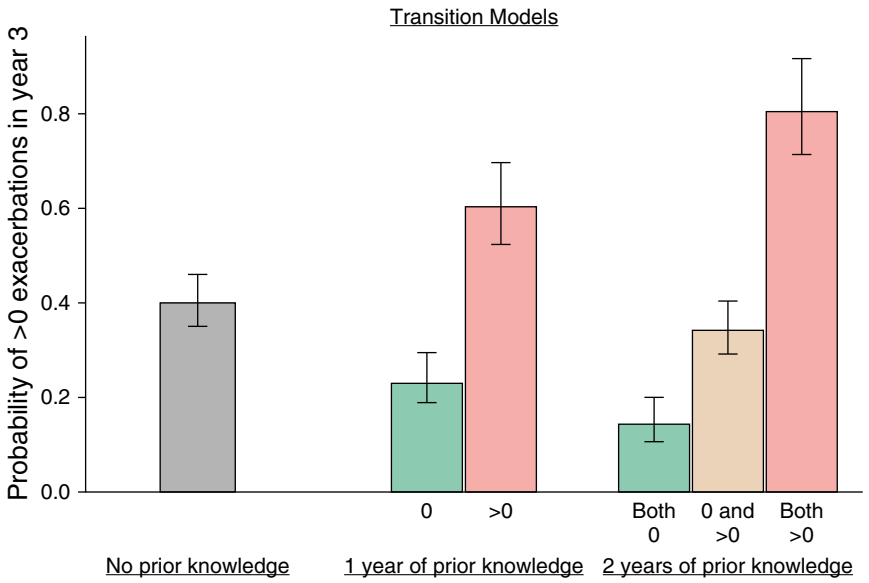

Figure 3. Second order transition modeling; shown are the probabilities of at least one exacerbation occurring in the third year of follow-up, corresponding to different states of knowledge about exacerbation frequency in the prior years. No prior knowledge reflects the observed probability of having an exacerbation at Year 3 (40%). One year of prior knowledge reflects the probability of having an exacerbation at Year 3 with 1 year prior knowledge of exacerbation frequency (0 exacerbation or >0 exacerbations); 2 years of prior knowledge reflects the probability of having an exacerbation at Year 3 with 2 years of prior knowledge of exacerbation history (both years 0, 1 yr of 0 and 1 yr >0, both years >0). Error bars denote 95% confidence intervals.

Clinical Features of Exacerbation Phenotypes

EPA and ERA phenotypes differed with respect to numerous clinical and laboratory features, as shown in Table 1. The EPA phenotype was characterized by older age, a higher proportion of females, increased body mass index, lower measures of lung function, worse asthma symptoms, and a higher frequency of comorbid conditions, including gastroesophageal reflux and nasal polyposis (Table 1). These traits were more common in EIA patients as well (Table 1). The ERA phenotype was also characterized by higher levels of metabolic dysfunction indicators, including blood neutrophil numbers, blood IL-6 levels, history of diabetes mellitus, and history of hypertension (Table 1 and Figure E2). Measures of airway type-2 inflammation, including total blood eosinophil cell counts, sputum eosinophil cell percentages, and fractional exhaled nitric oxide levels, did not differ significantly across the phenotypes (Table 1 and Figure E2).

Plasma IL-6 Measures and Blood Eosinophil Cell Counts as Predictive Biomarkers of Asthma Exacerbations

Plasma IL-6 levels are associated with asthma exacerbations in cross-sectional studies (16). To determine if baseline plasma IL-6 levels predict asthma exacerbations prospectively, we used negative binomial regression modeling to determine if plasma IL-6 levels at baseline predict the development of asthma exacerbations during 3 years of follow-up. For this analysis, we controlled for body mass index, age, and history of depression as the minimal sufficient adjustment covariates for estimating the total effect of IL-6 on exacerbation rates (16, 19, 23) (Figure 4A). We found that each 1-pg/μl increase in baseline plasma IL-6 levels increased the incident rate ratio (IRR) of asthma exacerbations by 10% over 3 years of study follow-up (Table 2 and Figure 4B). We also used the same approach to examine if blood eosinophils predict asthma exacerbation because blood eosinophil counts are associated with asthma exacerbations in cross-sectional studies (5). We found that each 100-cell/μl increase in blood eosinophil counts increased the IRR of asthma exacerbations by 9% over the 3 years of study follow-up (Table 2 and Figure 4C). To compare the relative effects of plasma IL-6 and blood eosinophils on the incident rate of developing an asthma exacerbation, we

Table 1. Clinical Characteristics of Longitudinal Exacerbation Phenotypes

Characteristic	ERA (*n* = 168)	EIA (*n* = 155)	EPA (*n* = 83)	*P* Value*
Age, yr	46.3 (14.4)	49.8 (13.6)	49.3 (13.2)	0.04
Sex, F, *n* (%)	109 (65)	112 (72)	63 (76)	0.06
Asthma exacerbations (3-yr), median (IQR)	0 (0)	2 (1–3)	7 (5–10)	<0.001
BMI at BL, kg/m^2	31.4 (8.4)	32.8 (8.6)	33.7 (7.6)	0.006
BMI ⩾ 30, *n* (%)	75 (45)	91 (59)	52 (63)	0.003
Spirometry data (BL)				
FEV_1, % predicted	76.8 (19.2)	72.7 (18.9)	62.9 (20.6)	<0.001
FVC, % predicted	88.9 (18.0)	83.4 (15.7)	77.5 (17.6)	<0.001
Severe asthma†, *n* (%)	62 (37)	99 (64)	71 (86)	<0.001
High-dose ICS, *n* (%)	72 (43)	101 (65)	71 (86)	<0.001
Daily oral corticosteroids Year 1, *n* (%)	4 (2)	22 (14)	24 (29)	<0.001
Daily oral corticosteroids Year 2, *n* (%)	4 (2)	23 (15)	26 (31)	<0.001
ACT score BL, median (IQR)	20 (16–22)	18 (14–21)	14 (11–17)	<0.001
History of nasal polyps, *n* (%)	21 (13)	35 (23)	32 (40)	<0.001
History of GERD, *n* (%)	48 (29)	80 (53)	54 (67)	<0.001
History of hypertension, *n* (%)	51 (30)	59 (38)	40 (49)	0.004
History of diabetes, *n* (%)	7 (4)	16 (10)	10 (12)	0.02
History of depression, *n* (%)	32 (19)	33 (21)	21 (26)	0.23
Blood cell counts at BL, $\times 10^6$/L				
Total white blood cells	6,748 (2,123)	7,623 (2,469)	8,455 (3,489)	<0.001
Neutrophils	3,934 (1,774)	4,568 (2,192)	5,214 (2,943)	<0.001
Eosinophils	260 (220)	312 (307)	342 (370)	0.32
Blood eosinophils >300 cells/μl, *n* (%)	52 (31)	61 (39)	34 (41)	0.07
Serum IgE, IU/L	399 (688)	326 (445)	264 (470)	0.02
Sputum cell counts at BL, %				
Eosinophils, median (IQR)	0.6 (0.2–1.9)	0.9 (0.1–4.3)	0.8 (0.2–3.9)	0.14
Neutrophils, median (IQR)	52 (32–68)	56 (39–77)	52 (32–78)	0.37
F_{ENO} at BL, ppm	29 (23)	30 (23)	36 (42)	0.49
Plasma IL-6 at BL‡, pg/ml	1.9 (1.8)	2.8 (2.3)	3.3 (2.9)	<0.001

Definition of abbreviations: ACT = asthma control test; BL = baseline visit; BMI = body mass index; EIA = exacerbation-intermittent asthma; EPA = exacerbation-prone asthma; ERA = exacerbation-resistant asthma; F_{ENO} = fractional exhaled nitric oxide; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids; IQR = interquartile range.
Data reported as mean (SD) unless otherwise indicated.
**P* values for association are nonparametric test for trend across ordered groups.
†American Thoracic Society/European Thoracic Society criteria for severe asthma.
‡291 subjects had plasma IL-6 measurements.

transformed the predictor variables of plasma IL-6 and blood eosinophil cell counts into standardized variables. Converting the predictor variables into standardized units (mean of 0 with an SD equal to 1) allows the relative effect sizes to be compared. In this way, we found that the effect size for a 1-SD increase in plasma IL-6 levels was 1.2 and for a 1-SD increase in blood eosinophils was 1.3 (Table 2). Some subjects in our cohort were started on anti–type-2 biologic medications during the study period ($n = 42$). To assess if treatment with anti–type-2 biologic medications influenced our findings, we repeated the binomial regression models excluding these subjects ($n = 42$). This analysis did not significantly alter our results (online supplement). As an additional sensitivity analysis, we repeated our models including all covariates that differed between ERA, EIA, and EPA subgroups in Table 1. This analysis also did not significantly alter the associations between plasma IL-6 or blood eosinophil cell counts on the risk of developing an asthma exacerbation (Table E3).

Association between Systemic IL-6 Inflammation and Asthma Exacerbations Is Not Secondary to Corticosteroids

Systemic exposure to glucocorticoids can cause metabolic dysfunction and could

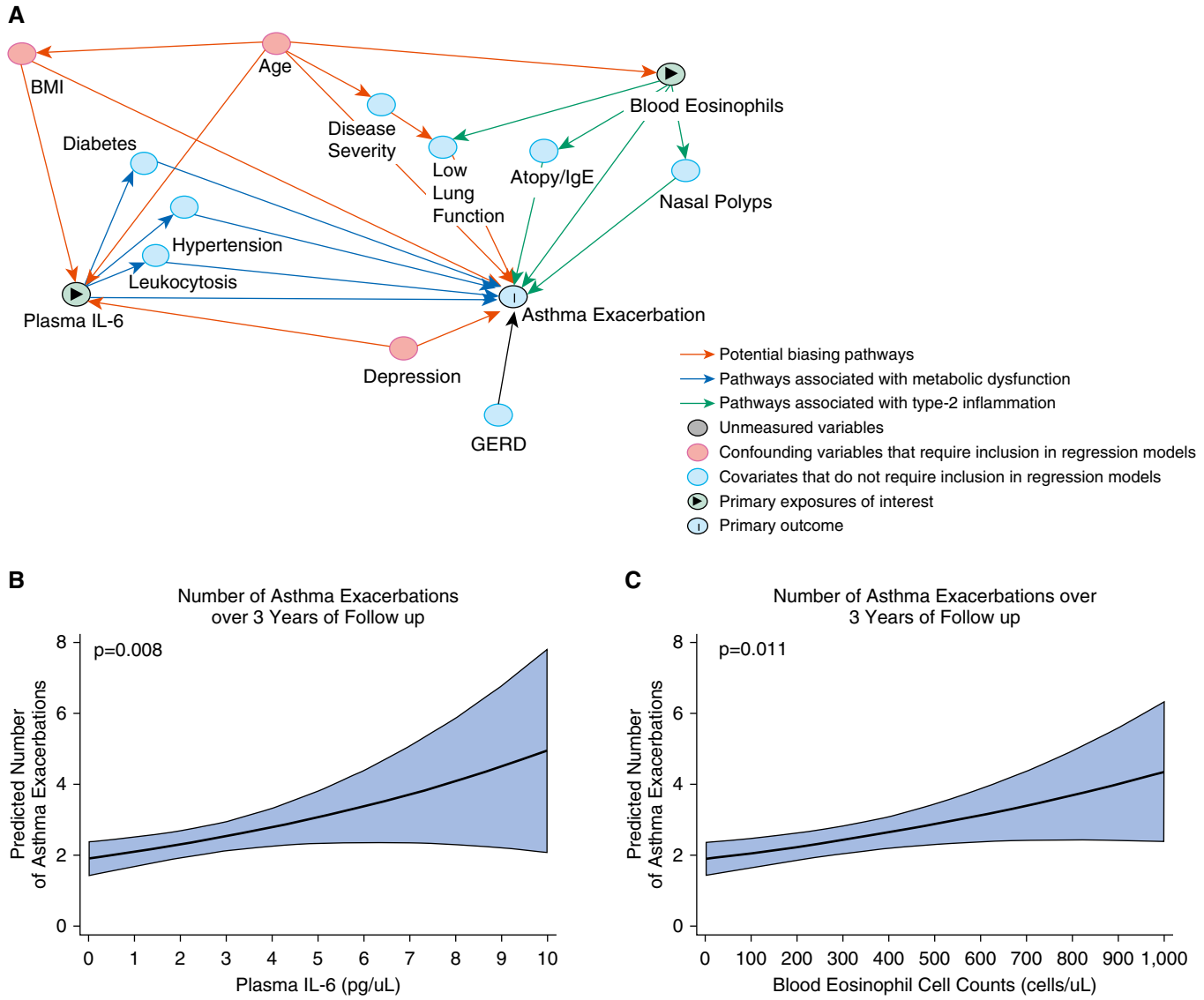

Figure 4. Negative binomial regression models predicting the development of asthma exacerbations over 3 years of follow-up. (*A*) Directed acyclic graph demonstrating the hypothesized relationship between plasma IL-6 and blood eosinophil cell counts on the outcome variable of asthma exacerbations. Body mass index (BMI), age, and depression are the minimal sufficient adjustment set of covariates for estimating the total effect of eosinophils and IL-6 on the primary outcome of exacerbations. Marginal effect of primary predictor variables of (*B*) plasma IL-6 and (*C*) blood eosinophil cell counts are controlled for BMI, age, and history of depression. Marginal effect of plasma IL-6 and blood eosinophils are also controlled for each other. GERD = gastroesophageal reflux disease.

theoretically increase plasma IL-6 measures. To address the possibility that oral corticosteroid use was confounding the association between plasma IL-6 and higher asthma exacerbation rates, we restricted our analysis to subjects with no systemic corticosteroid exposure in the year prior to the baseline plasma IL-6 measurement. These subjects did not suffer any asthma exacerbations requiring >3 days of systemic corticosteroids in the prior year, and they were not taking any oral or systemic corticosteroids as baseline therapy at the time of study enrollment. This approach was designed to eliminate the possibility that elevations in IL-6 were secondary to systemic corticosteroid use. This restriction left us with 142 subjects. Using negative binomial regression models controlling for age, body mass index, depression, and blood eosinophil cell counts, we found a similar and strong association between higher blood plasma IL-6 measures (per 1 unit pg/μl) and an increased incidence of asthma exacerbations over 3 years of longitudinal follow-up (IRR, 1.17; 95% CI, 1.01–1.36; $P = 0.037$; Table E4).

Discussion

Asthma exacerbations do not impact all individuals with severe asthma equally. Some individuals with severe asthma rarely develop exacerbations, whereas others are exacerbation prone and suffer recurrent exacerbations (5). Yet an understanding for what causes this heterogeneity in

Table 2. IRR of Asthma Exacerbations Predicted by Plasma IL-6 and Blood Eosinophil Cell Counts ($n = 291$)*

	IRR (95% CI)	*P* Value
Models using untransformed data (unstandardized)		
Plasma IL-6 pg/μl†	1.11 (1.03–1.19)	0.008
Blood eosinophil cells/μl‡	1.08 (1.02–1.15)	0.011
Models using standardized predictor variables		
Plasma IL-6§	1.3 (1.1–1.5)	0.008
Blood eosinophil cell count‖	1.3 (1.1–1.5)	0.01

Definition of abbreviations: CI = confidence interval; IRR = incident rate ratio.
*Models control for effect of body mass index, age, and depression. Effect of plasma IL-6 is controlled for blood eosinophilia, and effect of blood eosinophila is controlled for plasma IL-6.
†Per 1-pg/μl increase in plasma IL-6.
‡Per 100-cells/μl increase in blood eosinophil cell counts.
§Per 1-SD increase in plasma IL-6.
‖Per 1-SD increase in blood eosinophil cell count.

exacerbation susceptibility remains poorly understood likely because few cohort studies have been conducted in well-characterized patients with severe asthma.

Here, over 3 years of longitudinal follow-up, we quantified the frequency of asthma exacerbations in a large cohort of patients with severe asthma. We confirm that recurrent asthma exacerbations are confined to a relatively small percentage of patients with EPA. Although only 21% of our cohort demonstrated EPA, these subjects suffered 61% of the total number of asthma exacerbations and were responsible for the vast majority of asthma-associated hospitalizations. Furthermore, using transition analysis, we modeled the probability of having a future exacerbation based upon prior exacerbation history. Specifically, the odds of having at least one exacerbation in the current year were 2.7 times higher in patients with an exacerbation in the prior year when compared with exacerbation-free patients, and 6.3 times higher in patients with at least one exacerbation in each of the prior 2 years, when compared with patients with no exacerbations both years. These data reveal that exacerbations in any one year are not random events in the asthma population but rather are events that can be predicted based on past history of exacerbation frequency. To our knowledge, our study is the first to use statistical modeling to longitudinally confirm that patients with EPA tend to persistently develop asthma exacerbations over multiple years of longitudinal follow-up. Interestingly, our findings in asthma contrast with findings in chronic obstructive pulmonary disease in which exacerbation frequencies vary widely from year to year (24). Thus, our work proves the existence of a recurrently exacerbation-prone asthma phenotype.

The historical recall of asthma exacerbation frequency was 77% higher at study initiation when compared with a prospective reporting of asthma exacerbation frequency (Figure 1B). However, exacerbation rates remained relatively stable over the subsequent 3-year follow-up period.

SARP-3 is an observational study, and a likely explanation for this finding is that subjects with asthma overestimate the number of exacerbations that occurred in the year prior to study enrollment. Alternatively, it is also possible that adherence to asthma medications increased during the study period, leading to lower asthma exacerbation rates. Nonetheless, it is clear that historical recall of asthma exacerbation rates overestimated the prospectively observed exacerbation frequencies.

Increases in airway type-2 inflammation are known to increase susceptibility to developing asthma exacerbations (25, 26). Correspondingly, asthma treatment guidelines emphasize treating patients with EPA with escalating doses of corticosteroids and/or other medications that suppress airway type-2 inflammation (4, 27, 28). However, these efforts have not significantly decreased exacerbation rates (29, 30), and we now provide evidence for why such efforts have been disappointing. Surprisingly, although elevations in blood eosinophil cell counts predict the development of asthma exacerbations, blood eosinophils did not differ in EPA compared with ERA or EIA, and 60% of participants with EPA did not demonstrate blood eosinophilia. These findings suggest that the percentage of participants with EPA likely to benefit from treatments directed at type-2 inflammation (13) is significantly less than previously believed. Thus, asthma treatment algorithms that emphasize treating EPA with escalating doses of type-2 inflammation inhibitors (including ICS) are fraught with limitations.

Our results suggest that factors or immunologic processes beyond type-2 inflammation are likely contributing to exacerbation susceptibility. Importantly, we find that the characteristics that distinguish EPA from ERA or EIA are factors associated with metabolic dysfunction. Specifically, we show that subjects with EPA are characterized by high body mass index, old age, and robust increases in systemic inflammatory markers including plasma IL-6 levels and white blood cell counts. Correspondingly, subjects with EPA demonstrate a high frequency of other comorbidities typically associated with metabolic dysfunction, including hypertension and diabetes. These findings suggest a role of metabolic dysfunction as a key risk factor for exacerbation susceptibility (31–33).

Our results build on our prior cross-sectional analyses that found similar associations between high plasma IL-6 levels and retrospective recall of asthma exacerbations (16, 34–36). A limitation of our prior work was the cross-sectional study design, which left open the possibility that treatment with systemic corticosteroids was responsible for the association between plasma IL-6 and high exacerbation rates. Here, we provide evidence to refute this concern and demonstrate that increases in systemic IL-6 inflammation predict the development of exacerbations longitudinally and are not simply reflecting systemic corticosteroid exposure. Together, our findings suggest that systemic IL-6 inflammation is a driver of exacerbation susceptibility.

We have previously shown that obesity and systemic plasma IL-6 levels are associated with impaired natural killer (NK) cell function (37) and lower gene expression signals for $CD8^+$ (cluster of

differentiation 8–positive) cytotoxic T cells (38). Moreover, recent work has demonstrated that obesity and metabolic dysfunction impair the ability of CD8 T cells and NK cells to clear malignant cancer cells (39, 40). Because NK and $CD8^+$ T cells are also responsible for the clearance of infected tissue cells (41), we hypothesize that a similar deficit occurs in these patients with asthma, leading to an increased susceptibility to viral illnesses. In support of this hypothesis, we previously found that self-reported viral illnesses were a more frequent cause of asthma exacerbations in patients with obesity and asthma (42). Furthermore, recent work has demonstrated obesity and metabolic dysfunction as key risk factors for the development of severe viral respiratory disease during the coronavirus disease (COVID-19) pandemic (43, 44). Future studies are needed to understand this link between obesity and increased susceptibility to viral-induced respiratory illness.

As a noninterventional cohort, our study is incapable of proving a causal association between systemic IL-6 inflammation and asthma exacerbations. However, the strengths of our study, including the well-characterized population, the longitudinal follow-up, and the robust measures of systemic inflammation, provide a compelling case for the role of systemic inflammation as a modifier of asthma exacerbation susceptibility. Follow-up mechanistic studies and interventional trials that decrease systemic IL-6 inflammation will need to be done to establish the mechanisms by which systemic IL-6 inflammation alters airway inflammation and to confirm the role of systemic inflammation as a driver of exacerbation susceptibility. Furthermore, up to 40% of the patients in the EPA phenotype demonstrated neither elevations of blood eosinophil cell counts >300 cells/μl nor blood plasma IL-6 levels greater than our prior cutoff of 3.1 pg/μl. Therefore, a significant amount of EPA is not explained by our findings. Additional research is needed to understand why certain patients demonstrate increased susceptibility to developing recurrent exacerbations. Furthermore, participants with EPA were more likely to be taking high doses of ICS or daily oral corticosteroids. Additional work is needed to understand the complex relationship between corticosteroids, airway eosinophilia, and exacerbation susceptibility.

In conclusion, we find that the exacerbation burden in severe asthma is predominately driven by a subgroup of patients with EPA. This subgroup of patients is characterized by features of metabolic dysfunction, including high body mass, increased prevalence of diabetes and hypertension, and increases in systemic IL-6 inflammation. Systemic IL-6 inflammation, but not eosinophils, was significantly associated with EPA, and blood IL-6 and eosinophil cell counts predicted the development of exacerbations in the sample as a whole. Our work provides evidence to consider medications that inhibit systemic IL-6 activity as novel drugs to improve asthma exacerbation rates in patients with EPA (45). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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