

# Relationship of Blood Eosinophil Count to Exacerbations in Chronic Obstructive Pulmonary Disease



Robert S. Zeiger, MD, PhD<sup>a,b</sup>, Trung N. Tran, MD, PhD<sup>c</sup>, Rebecca K. Butler, ScM<sup>a,b</sup>, Michael Schatz, MD, MS<sup>a,b</sup>, Qiaowu Li, MS<sup>a,b</sup>, Deepak B. Khatri, MS, MA, PhD<sup>d</sup>, Ubaldo Martin, MD<sup>e</sup>, Aniket A. Kawatkar, PhD<sup>a,b</sup>, and Wansu Chen, MS, PhD<sup>a,b</sup> San Diego and Pasadena, Calif; and Gaithersburg, Md

**What is already known about this topic?** Chronic obstructive pulmonary disease (COPD) is a major public health problem. Biomarker measurement in sputum and blood during acute COPD exacerbations identify 4 major phenotypic clusters of patients: bacterial (35%), viral (30%), eosinophilic (24%), and paucinflamatory with minimal inflammatory changes (11%).

**What does this article add to our knowledge?** Within a cohort of patients with COPD in a large managed care organization, high blood eosinophil counts were independently associated with future exacerbations.

**How does this study impact current management guidelines?** To improve outcomes for patients with COPD, population care management programs and clinical practice could consider measurement of blood eosinophil count to identify a phenotype with elevated blood eosinophils who might benefit with specific anti-inflammatory and antieosinophilic therapies.

**BACKGROUND:** Eosinophilic airway inflammation characterizes a chronic obstructive pulmonary disease (COPD) phenotype that requires more study.  
**OBJECTIVE:** To investigate the relationship of blood eosinophil count to exacerbations in COPD.

<sup>a</sup>Kaiser Permanente Southern California, San Diego, Calif

<sup>b</sup>Kaiser Permanente Southern California, Pasadena, Calif

<sup>c</sup>Observational Research Center, Gaithersburg, Md

<sup>d</sup>Statistical Sciences, Gaithersburg, Md

<sup>e</sup>Global Medicine Development MedImmune LLC and AstraZeneca, Gaithersburg, Md

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Corresponding author: Robert S. Zeiger, MD, PhD, Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: [robert.s.zeiger@kp.org](mailto:robert.s.zeiger@kp.org).

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**METHODS:** Using administrative pharmacy and health care utilization data from 2009 to 2012, we retrospectively identified patients 40 years or older with a COPD diagnosis, postbronchodilator FEV<sub>1</sub>/forced vital capacity ratio of less than 0.7, and a blood eosinophil count (N = 7,245). COPD exacerbations were defined as hospitalizations or emergency department visits with a primary diagnosis of COPD, or outpatient visits with systemic corticosteroid dispensing within ±14 days associated with an encounter code consistent with a COPD exacerbation. The relationship between the index blood eosinophil count and the rate of COPD exacerbations in the follow-up year was determined by multivariable analyses.

**RESULTS:** Patients with COPD were predominantly male (57.1%), white (71.8%), often current or past smokers (75.4%), and had frequent comorbidities; 19.0% had eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup>, 76.1% were classified as moderate to very severe by lung function, and the COPD exacerbation rate was 0.38 per year (95% CI, 0.37-0.40). After adjustment for potential confounders, COPD exacerbations during 1-year follow-up were significantly greater for patients with blood eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup> (rate ratio [RR], 1.25; 95% CI, 1.10-1.43), greater than or equal to 400 cells/mm<sup>3</sup> (RR, 1.48; 95% CI, 1.26-1.75), and greater than or equal to 500 cells/mm<sup>3</sup> (RR, 1.76; 95% CI, 1.45-2.14), respectively, compared with patients with eosinophils lower than the cutoffs.

**CONCLUSIONS:** In this study, high blood eosinophil counts were an independent risk factor for future exacerbations in patients with COPD, a phenotype that might benefit from therapy directed at eosinophilic-driven disease and inflammation. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:944-54)

**Key words:** COPD; Eosinophils; Exacerbations; GOLD classification; Health care utilization; Managed care

*Abbreviations used*

*COPD*- Chronic obstructive pulmonary disease  
*ED*- Emergency department  
*FVC*- Forced vital capacity  
*GOLD*- Global Initiative for Chronic Obstructive Lung Disease  
*HEDIS*- Healthcare Effectiveness Data and Information Set  
*ICD-9*- International Classification of Diseases, 9th Revision  
*ICS*- Inhaled corticosteroid  
*KPSC*- Kaiser Permanente Southern California  
*LABA*- Long-acting  $\beta_2$ -agonist  
*LAMA*- Long-acting muscarinic antagonist  
*OCS*- Oral corticosteroid  
*RR*- Rate ratio  
*SABA*- Short-acting  $\beta_2$ -agonist

Chronic obstructive pulmonary disease (COPD) is estimated to affect approximately 10% of adults 40 years or older as determined by lung function testing, the best marker of the disease.<sup>1</sup> COPD is a major public health problem leading to high health care utilizations, poor health-related quality of life, substantial cost burden, and many deaths worldwide.<sup>2</sup> The spectrum of COPD defined by Healthcare Effectiveness Data and Information Set (HEDIS) in 2013 included the diagnostic entities COPD, chronic bronchitis, and emphysema.<sup>3</sup> COPD guidelines recommend using specific criteria for COPD diagnosis for patients aged at least 40 years including respiratory symptoms (dyspnea, chronic cough, chronic sputum production) and abnormal lung function (postbronchodilator FEV<sub>1</sub>/forced vital capacity [FVC] ratio of <0.70).<sup>2</sup> In addition, the guidelines stratify abnormal lung function into 4 increasing Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications of airflow limitation on the basis of levels of postbronchodilator FEV<sub>1</sub> % predicted.<sup>4</sup> Specific pharmacologic and nonpharmacologic treatments for COPD are well established.<sup>5</sup>

Exacerbations represent a major and frequent burden for patients with COPD. Many prediction models have been published for COPD exacerbations.<sup>6</sup> The best predictor for frequent exacerbations defined as 2 or more is a previous COPD exacerbation.<sup>7</sup> Compared with patients with no COPD exacerbations, those patients with consistent exacerbations each year during a 3-year follow-up evidenced greater baseline symptom burden, previous exacerbations, more frequent small airway abnormalities, and differences in specific interleukins.<sup>8</sup> Future exacerbations are associated with poorer lung function as represented by increasing GOLD score.<sup>7</sup> In addition, the frequent exacerbation phenotype appears associated with gastroesophageal reflux, poor health-related quality of life, and elevated white blood cell count.<sup>7</sup> Independent predictors for a rehospitalization include a long duration of hospital stay, lower lung function, hypertension, and greater dyspnea score.<sup>9</sup> A study of 2 COPD cohorts using 90 blood biomarkers, but not including blood eosinophil counts, found that although some blood biomarkers were significantly associated with exacerbations, they added minimally to the predictive value of clinical factors.<sup>10</sup>

The burden of COPD in managed care organizations has mainly been reported for patients identified by the *International Classification of Diseases, 9th Revision (ICD-9)* COPD coding by physicians<sup>11,12</sup> and not by obstructive lung function criteria, with the reported misclassification of most patients.<sup>13</sup> In recognition that both symptoms and exacerbations are important

components of COPD, guidelines have added these criteria to better characterize patients with COPD.<sup>4</sup>

Moreover, blood eosinophils may function as a biomarker to identify subgroups of patients with COPD who are more responsive to anti-inflammatory therapies.<sup>14,15</sup> The relationships between blood eosinophil count and COPD burden and exacerbations have only recently received attention. In a large subset of Danish patients with COPD, a blood eosinophil count of greater than or equal to 340 cells/mm<sup>3</sup>, compared with a lower eosinophil count, was associated with a 76% adjusted increased risk for severe and 15% for moderate COPD exacerbations.<sup>16</sup> In that study, COPD was defined using prebronchodilator instead of postbronchodilator determination of a FEV<sub>1</sub>/FVC ratio of less than 0.7.<sup>16</sup>

We examined the relationship between blood eosinophil count at baseline and COPD exacerbation in the follow-up year in a cohort of patients with COPD with both physician and postbronchodilator FEV<sub>1</sub>/FVC diagnoses in a managed care setting. We hypothesized that high blood eosinophil counts at baseline would be an independent risk factor for future exacerbations in COPD.

## METHODS

### Study design

This retrospective cohort study characterized patients with COPD and evaluated the relationship between blood eosinophil counts at baseline and COPD exacerbations in the following 12 months. The study used the Kaiser Permanente Southern California (KPSC) Research Data Warehouse capturing pharmacy and health care utilization data, which allowed identification of adults with COPD (Figure 1, A), as well as the burden of the disease in a large integrated health care system. The study was approved by the KPSC Institutional Review Board with waiver of written consent.

### Patients with COPD

Patients with COPD were defined as adults 40 years or older, identified with HEDIS-defined COPD in the period 2009 to 2012 (*ICD-9* codes 491.x [chronic bronchitis], 492.x [emphysema], 496.x [chronic obstructive lung disease], or 493.2 [chronic obstructive asthma]), and had a postbronchodilator FEV<sub>1</sub>/FVC ratio of less than 0.7 documented on spirometry performed in Southern California Permanente Medical Group pulmonary laboratories that follow American Thoracic Society spirometry guidelines up to 730 days before or up to 180 days after a COPD encounter diagnosis.<sup>17,18</sup> Patients were required to have had a blood eosinophil determination, and continuous KPSC health plan enrollment (no more than 45-day gap per year) and pharmacy coverage for the 1-year baseline period before the index date.<sup>19</sup> The index date was the date of the first blood eosinophil determination up to 1 year after the COPD diagnosis date. The baseline period was the year before the index date, and patients were followed from the day after the index date for 1 year for occurrence of study outcomes and/or death. Exclusions were encounter diagnoses from 2009 to 2012 of asthma (*ICD-9* codes 493.0, 493.1, 493.8, 493.9), cystic fibrosis, bronchiectasis, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and sarcoidosis. The COPD diagnosis date was the first of the *ICD-9* COPD diagnosis dates during the period 2009 to 2012 associated with an abnormal spirometry (Figure 1, B).

### COPD exacerbations

Two definitions for COPD exacerbations based on previous reports<sup>20,21</sup> were examined in this study:

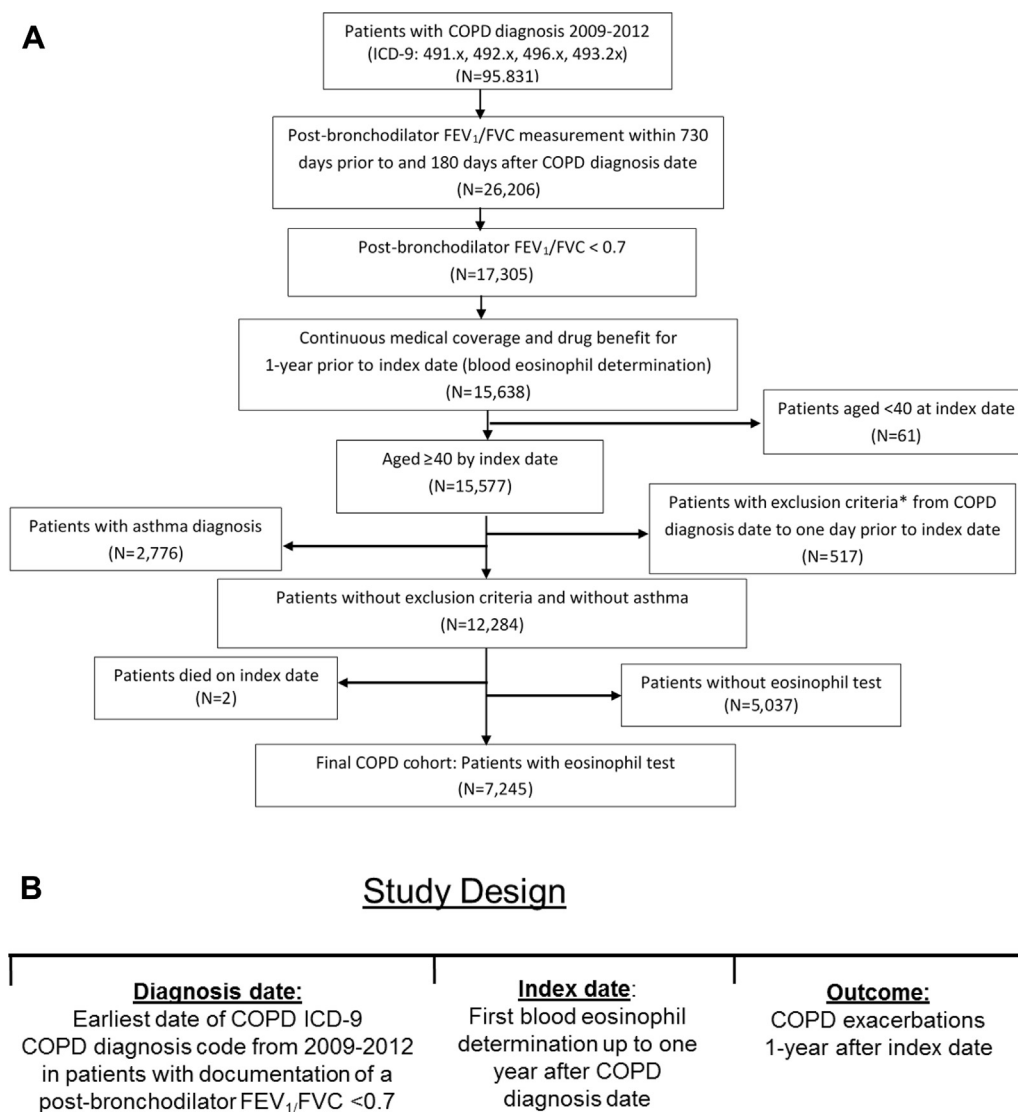


**FIGURE 1.** The Consolidated Standards of Reporting Trials (CONSORT) flowchart for patient identification (**A**) and study design (**B**). **A**, Algorithm for identification of the COPD cohort and number of patients identified with administrative databases. \*Excluded diagnoses from 2009 to 2012 were cystic fibrosis, bronchiectasis, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and sarcoidosis. In addition, patients with asthma (ICD-9 codes 493.0, 493.1, 493.8, and 493.9) were excluded. **B**, Summary of study design.

1. The primary outcome was the composite of a severe COPD exacerbation defined by HEDIS as an acute inpatient or emergency department (ED) visit with a primary discharge diagnosis of COPD<sup>3</sup> or moderate COPD exacerbation defined as a systemic corticosteroid dispensing within  $\pm 14$  days of an outpatient visit<sup>12</sup> with a KPSC encounter code indicating COPD exacerbations due to acute respiratory events (exacerbations, wheezing, pneumonia, and acute bronchitis).
2. The secondary outcome was severe COPD exacerbation defined by HEDIS as an acute inpatient or ED visit with a primary discharge diagnosis of COPD.<sup>3</sup>

A repeat exacerbation for both definitions was determined at more than 14 days<sup>3</sup> from the last inpatient or ED discharge date or from the latter of the last systemic steroid dispensing date and outpatient visit that defined the previous exacerbation.

### Blood cell counts

Total blood leukocytes, eosinophils, neutrophils, and lymphocytes were measured in automated complete blood cell count differentials closest to after the COPD diagnosis date. We used prespecified eosinophil cutoff points at 50 cells/mm<sup>3</sup>, 150 cells/mm<sup>3</sup>, 300 cells/mm<sup>3</sup>, 400 cells/mm<sup>3</sup>, and 500 cells/mm<sup>3</sup> to characterize the study cohort and determine their relationship to future COPD exacerbations.

### Study measures

Education level and household income were determined via address information geocoded to the census block level and linked to census-based group-level information about socioeconomic status.<sup>22</sup> Comorbidities including those reported as risk factors for mortality in COPD<sup>23</sup> were determined. In addition, the Charlson comorbidity index, a composite validated comorbidity scale, was determined.<sup>24</sup>

Long-term medications based on guidelines included long-acting  $\beta_2$ -agonists (LABAs), long-acting muscarinic antagonists (LAMAs), inhaled corticosteroids (ICSs), double therapy (2 of the following: LABA, LAMA, ICS), triple therapy (LABA, LAMA, and ICS), and theophylline (long-acting phosphodiesterase-4 inhibitors were not used at KPSC during the study period). Double and triple therapies were defined as combined medications or separate medications, as long as they were dispensed within a 1-year period of each other. Excess short-acting  $\beta_2$ -agonist (SABA) use was defined as 7 or more SABA canisters dispensed per year, equivalent to 4 or more puffs/d/y.<sup>25</sup> Systemic antibiotic use of the following medication groups was determined: penicillins, cephalosporins, macrolides, tetracycline, fluoroquinolones, sulfonamides, and aminoglycosides. GOLD stratification was determined on the basis of degrees of postbronchodilator FEV<sub>1</sub> % predicted: Gold 1 (mild), 80% or more; GOLD 2 (moderate), 50% to 79%; GOLD 3 (severe), 30% to 49%; and GOLD 4 (very severe), less than 30%.<sup>4</sup> FEV<sub>1</sub> % predicted was not available for 3 patients. Death records derived from the State Death Master files through a linkage process were accessed to determine whether COPD was the primary cause of death.

## Statistical analyses

Demographic and clinical characteristics and comorbidities were compared between patients with high and low blood eosinophil cutoff levels by using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Poisson regression models with a robust error variance were used to estimate the unadjusted and adjusted rate ratios (RRs) and their 95% CIs (for details, see this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).<sup>26</sup> Covariates in the baseline year were included for consideration for adjustments in the multivariable analyses based on their associations with the eosinophil measure and with the COPD exacerbations (for details of modeling, this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Sensitivity analysis was performed with COPD exacerbation also including death caused by COPD (ie, COPD was the underlying cause of death). All analyses were conducted with SAS (version 9.3 for Unix, SAS Institute, Cary, NC). Critical *P* values were set at an alpha value of .05, 2-sided.

## RESULTS

### Baseline characteristics of the COPD cohort

A total of 7245 patients with COPD who had met the study eligibility criteria were included in the study (Figure 1, A). At baseline, patients with COPD were predominantly male (57.1%), white (71.8%), and current or past smokers (75.5%). Comorbidities were frequent with a high Charlson comorbidity index ( $3.6 \pm 2.6$ ), obesity (26.6%), hypertension (75.9%), coronary artery disease (22.7%), congestive heart failure (20.5%), gastroesophageal reflux disease (23.8%), diabetes (22.8%), depression (22.1%), and pneumonia (21.7%) (Table I). The rate of COPD exacerbations during the baseline year was 0.38 (95% CI, 0.37-0.40), with 27% and 7.0% of patients exhibiting 1 or more or 2 or more COPD exacerbations, respectively, and 17.6% having had 1 or more COPD-related ED visit or hospitalization (Table II). Among the patients, 76.1% and 25.4% were at least GOLD 2 and 3, respectively, but only 37.3% had a pulmonologist visit in the baseline year (Table II). Double and triple therapies were used by 19.0% and 12.1%, respectively (Table II).

### Baseline characteristics by blood eosinophil count

The distribution of patients at different blood eosinophil cutoff points was as follows: greater than or equal to 50 cells/mm<sup>3</sup> (80.3%), greater than or equal to 150 cells/mm<sup>3</sup> (47.8%), greater than or equal

to 300 cells/mm<sup>3</sup> (19.0%), greater than or equal to 400 cells/mm<sup>3</sup> (10.2%), and greater than or equal to 500 cells/mm<sup>3</sup> (5.9%) (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Demographic and clinical characteristics and comorbidities of the COPD cohort by the different blood eosinophil cutoff points are presented in Tables E1-E4 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org). The COPD subgroup with blood eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup>, compared with less than 300 cells/mm<sup>3</sup> in the baseline year, had significantly (1) more males and (2) less comorbidities of atrial fibrillation, anxiety, and depression (Table I), (3) greater rates of COPD exacerbation and COPD-related ED visit or hospitalization, (4) more dispensings of short-term rescue medications (SABA and SABA/short-acting muscarinic agent combinations and oral corticosteroids [OCSs]), and (5) greater white blood cell and lymphocyte counts and lower neutrophil count (Table II). Similar findings were observed for other eosinophil cutoff point comparisons at cutoff points of 400 cells/mm<sup>3</sup> and 500 cells/mm<sup>3</sup> for demographic characteristics (Table E1), comorbidities (Table E2), clinical features (Table E3), and medication (Table E4). However, at the lowest cutoff point (50 cells/mm<sup>3</sup>), more blacks (Table E1), greater Charlson comorbidity index score and pneumonia frequency (Table E2), a greater rate of COPD-related ED visits or hospitalizations, greater level of GOLD classification, and greater neutrophil counts (Table E3) were found for patients with low eosinophil count.

### Relationship of baseline blood eosinophil counts and future COPD exacerbations

**Univariate analyses.** Future COPD exacerbations and COPD ED visits or hospitalizations were more frequent for patients with greater blood eosinophil counts at baseline. Lower rates of COPD exacerbations and COPD ED visits or hospitalizations were observed for patients with high versus low eosinophil counts at cutoff point of 50 cells/mm<sup>3</sup>, but the trend reversed with more COPD exacerbations at cutoff points of greater than or equal to 300 cells/mm<sup>3</sup>, greater than or equal to 400 cells/mm<sup>3</sup>, and greater than or equal to 500 cells/mm<sup>3</sup>, and more COPD ED visits or hospitalizations at 400 cells/mm<sup>3</sup> and 500 cells/mm<sup>3</sup> cutoff points (Table III). During the follow-up year, deaths from any causes occurred in 845 (11.7%) and from COPD as the principal cause in 163 (2.2%) members of the cohort at follow-up. Deaths from any cause were less frequent in univariate analyses for patients with greater compared with lesser blood eosinophil counts (Table III).

**Multivariate analyses.** After adjustment for potential confounders, COPD exacerbations during a 1-year follow-up were significantly more frequent for patients with blood eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup> (RR, 1.25; 95% CI, 1.10-1.43), greater than or equal to 400 cells/mm<sup>3</sup> (RR, 1.48; 95% CI, 1.26-1.75), and greater than or equal to 500 cells/mm<sup>3</sup> (RR, 1.76; 95% CI, 1.45-2.14) compared with patients with lower eosinophil counts, respectively (Figure 2, A). COPD ED visits or hospitalizations in the outcome year were also significantly more common for patients with blood eosinophil counts of greater than or equal to 400 cells/mm<sup>3</sup> (RR, 1.44; 95% CI, 1.14-1.80) and greater than or equal to 500 cells/mm<sup>3</sup> (RR, 1.68; 95% CI, 1.28-2.21). After adjustment, no significant associations were seen between blood eosinophil counts and COPD exacerbations or COPD ED visits or hospitalizations at the cutoff point of 50 cells/mm<sup>3</sup> (Figure 2, B). Sensitivity analyses that included deaths with COPD as the primary cause of

**TABLE 1.** Baseline demographic characteristics and comorbidities of the COPD cohort overall and stratified by index blood eosinophil cutoff level (cells/mm<sup>3</sup>)

|                                                  | Index blood eosinophil count   |                                           |                                           |                      |
|--------------------------------------------------|--------------------------------|-------------------------------------------|-------------------------------------------|----------------------|
| Baseline feature                                 | Total (N = 7,245)              | ≥300 cells/mm <sup>3</sup><br>(N = 1,374) | <300 cells/mm <sup>3</sup><br>(N = 5,871) | P value <sup>a</sup> |
| Demographic characteristic                       |                                |                                           |                                           |                      |
| Age (y)                                          | 71.5 ± 9.6                     | 71.3 ± 9.6                                | 71.5 ± 9.6                                | .68                  |
| Sex: male                                        | 4,136 (57.1)                   | 852 (62.0)                                | 3,284 (55.9)                              | <.001                |
| Ethnicity                                        |                                |                                           |                                           |                      |
| White                                            | 5,199 (71.8)                   | 993 (72.3)                                | 4,206 (71.6)                              | .64                  |
| Black                                            | 1,012 (14.0)                   | 157 (11.4)                                | 855 (14.6)                                | .003                 |
| Hispanic                                         | 623 (8.6)                      | 132 (9.6)                                 | 491 (8.4)                                 | .14                  |
| Asian                                            | 248 (3.4)                      | 51 (3.7)                                  | 197 (3.4)                                 | .51                  |
| Others/unknown                                   | 163 (2.2)                      | 41 (3.0)                                  | 122 (2.1)                                 | .041                 |
| Household income through geocoding               | 61,311 ± 26,022<br>(N = 7,233) | 61,301 ± 25,212<br>(N = 1,374)            | 61,313 ± 26,211<br>(N = 5,859)            | .72                  |
| Family education ≤grade 12 (%) through geocoding | 41.0 ± 17.8<br>(N = 7,234)     | 41.0 ± 17.5<br>(N = 1,374)                | 41.0 ± 17.9<br>(N = 5,860)                | .76                  |
| Years of health plan enrollment                  | 21.1 ± 13.0                    | 20.6 ± 13.1                               | 21.2 ± 13.0                               | .089                 |
| Insurance                                        |                                |                                           |                                           |                      |
| Commercial                                       | 2,106 (29.1)                   | 393 (28.6)                                | 1,713 (29.2)                              | .67                  |
| Medicaid                                         | 69 (1.0)                       | 12 (0.9)                                  | 57 (1.0)                                  | .74                  |
| Medicare                                         | 5,094 (70.3)                   | 975 (71.0)                                | 4,119 (70.2)                              | .56                  |
| Smoking status                                   |                                |                                           |                                           | .11                  |
| Current                                          | 620 (8.6)                      | 132 (9.6)                                 | 488 (8.3)                                 |                      |
| Passive                                          | 46 (0.6)                       | 11 (0.8)                                  | 35 (0.6)                                  |                      |
| Quit                                             | 4,840 (66.9)                   | 931 (67.8)                                | 3,909 (66.7)                              |                      |
| Never                                            | 1,724 (23.8)<br>(N = 7,230)    | 299 (21.8)<br>(N = 1,373)                 | 1,425 (24.3)<br>(N = 5,857)               |                      |
| Comorbidities                                    |                                |                                           |                                           |                      |
| Charlson comorbidity index                       | 3.6 ± 2.6                      | 3.5 ± 2.5                                 | 3.6 ± 2.6                                 | .98                  |
| Gastroesophageal reflux                          | 1,724 (23.8)                   | 347 (25.3)                                | 1,377 (23.5)                              | .16                  |
| Obesity                                          | 1,922 (26.6)<br>(N = 7,226)    | 391 (28.5)<br>(N = 1,371)                 | 1,531 (26.1)<br>(N = 5,855)               | .074                 |
| Chronic sinusitis                                | 597 (8.2)                      | 126 (9.2)                                 | 471 (8.0)                                 | .16                  |
| Pneumonia                                        | 1,574 (21.7)                   | 273 (19.9)                                | 1,301 (22.2)                              | .064                 |
| Pulmonary fibrosis                               | 229 (3.2)                      | 43 (3.1)                                  | 186 (3.2)                                 | .94                  |
| Congestive heart failure                         | 1,484 (20.5)                   | 267 (19.4)                                | 1,217 (20.7)                              | .28                  |
| Coronary artery disease                          | 1,646 (22.7)                   | 329 (23.9)                                | 1,317 (22.4)                              | .23                  |
| Atrial fibrillation                              | 1,164 (16.1)                   | 166 (12.1)                                | 998 (17.0)                                | <.001                |
| Hypertension                                     | 5,499 (75.9)                   | 1,056 (76.9)                              | 4,443 (75.7)                              | .36                  |
| Ulcer disease                                    | 146 (2.0)                      | 27 (2.0)                                  | 119 (2.0)                                 | .88                  |
| Peripheral vascular disease                      | 782 (10.8)                     | 157 (11.4)                                | 625 (10.6)                                | .40                  |
| Any diabetes                                     | 1,649 (22.8)                   | 339 (24.7)                                | 1,310 (22.3)                              | .060                 |
| Diabetic kidney disease                          | 820 (11.3)                     | 165 (12.0)                                | 655 (11.2)                                | .37                  |
| Liver cirrhosis                                  | 106 (1.5)                      | 15 (1.1)                                  | 91 (1.5)                                  | .20                  |
| Lung/bronchial/tracheal cancer                   | 467 (6.4)                      | 79 (5.7)                                  | 388 (6.6)                                 | .24                  |
| Breast/pancreatic/esophageal cancer              | 203 (2.8)                      | 40 (2.9)                                  | 163 (2.8)                                 | .78                  |
| Anxiety                                          | 1,032 (14.2)                   | 156 (11.4)                                | 876 (14.9)                                | <.001                |
| Depression                                       | 1,601 (22.1)                   | 261 (19.0)                                | 1,340 (22.8)                              | .002                 |

Data presented as n (%) or mean ± SD. Bold indicates statistical significance ( $P < .05$ ).\*P values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

death in the COPD exacerbation's definition led to similar findings (results not shown).

Other baseline factors associated with an increased rate of COPD exacerbations in the outcome year, in addition to blood eosinophil counts, were greater GOLD classification, more SABA

use, baseline COPD exacerbations, OCS use, pneumonia, anxiety, blacks versus white ethnicity, being female, congestive heart failure, and lower education (Figure 3). Comparable data were noted for the baseline factors associated with an increased rate of future COPD-related ED visits and hospitalizations (Figure 4).

**TABLE II.** Baseline clinical and treatment characteristics of the COPD cohort overall and stratified by index blood eosinophil cutoff level (cells/mm<sup>3</sup>)

|                                              | Index blood eosinophil count |                                        |                                        |          |
|----------------------------------------------|------------------------------|----------------------------------------|----------------------------------------|----------|
| Clinical characteristic                      | Total (N = 7,245)            | ≥300 cells/mm <sup>3</sup> (N = 1,374) | <300 cells/mm <sup>3</sup> (N = 5,871) | P value* |
| COPD exacerbations                           |                              |                                        |                                        |          |
| Incidence, rate/y (95% CI)                   | 0.38 (0.37-0.40)             | 0.45 (0.41-0.50)                       | 0.37 (0.35-0.39)                       | .001     |
| ≥1 exacerbation, n (%)                       | 1,954 (27.0)                 | 409 (29.8)                             | 1,545 (26.3)                           | .009     |
| ≥2 exacerbations, n (%)                      | 507 (7.0)                    | 124 (9.0)                              | 383 (6.5)                              | .001     |
| COPD ED visits or hospitalizations           |                              |                                        |                                        |          |
| ≥1 ED visit, n (%)                           | 1,109 (15.3)                 | 227 (16.5)                             | 882 (15.0)                             | .17      |
| ED visit, rate/y (95% CI)                    | 0.19 (0.10-0.20)             | 0.22 (0.19-0.26)                       | 0.17 (0.17-0.20)                       | .015     |
| ≥1 Hospitalization, n (%)                    | 818 (11.3)                   | 153 (11.1)                             | 665 (11.3)                             | .84      |
| Hospitalization, rate/y (95% CI)             | 0.13 (0.12-0.14)             | 0.14 (0.11-0.16)                       | 0.13 (0.12-0.14)                       | .72      |
| ≥1 ED visit or hospitalization, n (%)        | 1,278 (17.6)                 | 257 (18.7)                             | 1,021 (17.4)                           | .25      |
| ED visit or hospitalization, rate/y (95% CI) | 0.22 (0.21-0.24)             | 0.25 (0.22-0.29)                       | 0.21 (0.20-0.23)                       | .039     |
| Specialist visits, n (%)                     |                              |                                        |                                        |          |
| Pulmonologist visit                          | 2,706 (37.3)                 | 496 (36.1)                             | 2,210 (37.6)                           | .29      |
| Allergist visit                              | 173 (2.4)                    | 39 (2.8)                               | 134 (2.3)                              | .22      |
| Specialist visit                             | 2,790 (38.5)                 | 517 (37.6)                             | 2,273 (38.7)                           | .45      |
| GOLD classification, n (%)                   |                              |                                        |                                        |          |
| 1 (≥80%)                                     | 1,730 (23.9)                 | 331 (24.1)                             | 1,399 (23.8)                           |          |
| 2 (50%-79%)                                  | 3,674 (50.7)                 | 722 (52.5)                             | 2,952 (50.3)                           |          |
| 3 (30%-49%)                                  | 1,535 (21.2)                 | 269 (19.6)                             | 1,266 (21.6)                           |          |
| 4 (<30%)                                     | 303 (4.2)                    | 52 (3.8)                               | 251 (4.3)                              |          |
|                                              | (N = 7,242)                  | (N = 1,374)                            | (N = 5,868)                            |          |
| Blood count/mm <sup>3</sup> , mean ± SD      |                              |                                        |                                        |          |
| White blood cells                            | 8,996 ± 4,231                | 9,483 ± 4,098                          | 8,882 ± 4,253                          | <.001    |
| Eosinophils                                  | 194 ± 231                    | 508 ± 364                              | 120 ± 81                               | <.001    |
| Neutrophils                                  | 6,365 ± 3,503                | 6,077 ± 3,061                          | 6,433 ± 3,596                          | .045     |
| Lymphocytes                                  | 1,696 ± 2,258                | 2,062 ± 1,971                          | 1,611 ± 2,312                          | <.001    |
| Medication dispensed, n (%)                  |                              |                                        |                                        |          |
| Short-acting                                 |                              |                                        |                                        |          |
| SABA singly                                  | 2,482 (34.3)                 | 469 (34.1)                             | 2,003 (34.1)                           | .98      |
| SAMA singly                                  | 183 (2.5)                    | 25 (1.8)                               | 158 (2.7)                              | .064     |
| SABA and SAMA combination                    | 1,532 (21.1)                 | 325 (23.7)                             | 1,207 (20.6)                           | .011     |
| ≥7 SABA                                      | 1,362 (18.8)                 | 298 (21.7)                             | 1,064 (18.1)                           | .002     |
| Long-acting                                  |                              |                                        |                                        |          |
| LABA monotherapy                             | 43 (0.6)                     | 6 (0.4)                                | 37 (0.6)                               | .40      |
| LAMA monotherapy                             | 472 (6.5)                    | 96 (7.0)                               | 376 (6.4)                              | .43      |
| ICS monotherapy                              | 1,447 (20.0)                 | 307 (22.3)                             | 1,140 (19.4)                           | .015     |
| Double therapy                               | 1,374 (19.0)                 | 273 (19.9)                             | 1,101 (18.8)                           | .34      |
| Triple therapy                               | 877 (12.1)                   | 152 (11.1)                             | 725 (12.3)                             | .19      |
| Theophylline                                 | 106 (1.5)                    | 18 (1.3)                               | 88 (1.5)                               | .60      |
| Oral corticosteroid                          | 2,761 (38.1)                 | 559 (40.7)                             | 2,202 (37.5)                           | .029     |
| ≥5 mg/d                                      | 383 (5.3)                    | 71 (5.2)                               | 312 (5.3)                              | .83      |
| Systemic antibiotics                         | 4,213 (58.2)                 | 823 (59.9)                             | 3,390 (57.7)                           | .15      |

SAMA, Short-acting muscarinic antagonist.

Double therapy = 2 of the following 3 medications were dispensed (LABA, LAMA, ICS); Triple therapy = all 3 of the following medications were dispensed (LABA, LAMA, ICS). Bold indicates statistical significance ( $P < .05$ ).

\*P values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis for continuous variables. CIs for rates were determined by robust Poisson regression.

## DISCUSSION

In a US COPD cohort defined by both HEDIS clinical diagnosis and postbronchodilator spirometry criteria, we found that elevated blood eosinophil counts at baseline were independently associated with COPD exacerbations (Figure 2, A) and COPD-related ED visits or hospitalizations in the follow-up year

(Figure 2, B). After adjusting for potential confounders, we found that the rates of future COPD exacerbations were 25%, 48%, and 76% greater for patients with blood eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup>, greater than or equal to 400 cells/mm<sup>3</sup>, and greater than or equal to 500 cells/mm<sup>3</sup>, respectively, compared with those patients with lower blood

**TABLE III.** Univariate analyses of COPD exacerbations, ED visits, hospitalizations, and death during the follow-up year stratified by baseline blood eosinophil counts (cells/mm<sup>3</sup>)

| COPD outcome                                       | Index blood eosinophil count by cutoff point (cells/mm <sup>3</sup> ) |                    |                     |                     |                     |                     |                   |                     |                   |                     | Total<br>(N = 7,245) |
|----------------------------------------------------|-----------------------------------------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|-------------------|---------------------|-------------------|---------------------|----------------------|
|                                                    | ≥50<br>(N = 5,817)                                                    | <50<br>(N = 1,428) | ≥150<br>(N = 3,463) | <150<br>(N = 3,782) | ≥300<br>(N = 1,374) | <300<br>(N = 5,871) | ≥400<br>(N = 740) | <400<br>(N = 6,505) | ≥500<br>(N = 431) | <500<br>(N = 6,814) |                      |
| COPD exacerbations                                 |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| Incidence, rate/y<br>(95% CI)                      | 0.37 (0.34-0.39)‡                                                     | 0.46 (0.41-0.52)   | 0.39 (0.36-0.42)    | 0.38 (0.35-0.41)    | 0.47 (0.41-0.53)‡   | 0.36 (0.34-0.39)    | 0.57 (0.49-0.68)‡ | 0.36 (0.34-0.38)    | 0.70 (0.57-0.85)‡ | 0.36 (0.34-0.39)    | 0.38 (0.36-0.40)     |
| ≥1 exacerbation, n (%)                             | 1,274 (21.9)                                                          | 336 (23.5)         | 781 (22.6)          | 829 (21.9)          | 331 (24.1)          | 1,279 (21.8)        | 197 (26.6)†       | 1,413 (21.7)        | 127 (29.5)‡       | 1,483 (21.8)        | 1,610 (22.2)         |
| ≥2 exacerbations, n<br>(%)                         | 408 (7.0)†                                                            | 130 (9.1)          | 267 (7.7)           | 271 (7.2)           | 129 (9.4)†          | 409 (7.0)           | 91 (12.3)‡        | 447 (6.9)           | 65 (15.1)‡        | 473 (6.9)           | 538 (7.4)            |
| COPD ED visits or hospitalizations                 |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| ≥1 ED visit, n (%)                                 | 596 (10.2)‡                                                           | 202 (14.1)         | 355 (10.3)*         | 443 (11.7)          | 149 (10.8)          | 649 (11.1)          | 99 (13.4)*        | 699 (10.7)          | 65 (15.1)†        | 733 (10.8)          | 798 (11.0)           |
| ED visits, rate/y<br>(95% CI)                      | 0.16 (0.14-0.17)‡                                                     | 0.25 (0.21-0.30)   | 0.16 (0.14-0.19)    | 0.19 (0.17-0.21)    | 0.20 (0.16-0.24)    | 0.17 (0.16-0.19)    | 0.27 (0.21-0.35)‡ | 0.16 (0.15-0.18)    | 0.36 (0.26-0.48)‡ | 0.16 (0.15-0.18)    | 0.18 (0.16-0.19)     |
| ≥1 hospitalization, n<br>(%)                       | 539 (9.3)†                                                            | 171 (12.0)         | 327 (9.4)           | 383 (10.1)          | 148 (10.8)          | 562 (9.6)           | 88 (11.9)*        | 622 (9.6)           | 55 (12.8)*        | 655 (9.6)           | 710 (9.8)            |
| Hospitalizations,<br>rate/y (95% CI)               | 0.13 (0.12-0.14)‡                                                     | 0.20 (0.17-0.24)   | 0.14 (0.12-0.15)    | 0.15 (0.14-0.17)    | 0.17 (0.14-0.20)    | 0.14 (0.13-0.15)    | 0.20 (0.16-0.25)† | 0.14 (0.13-0.15)    | 0.23 (0.17-0.31)† | 0.14 (0.13-0.15)    | 0.14 (0.13-0.16)     |
| ≥1 ED visit or<br>hospitalization,<br>n (%)        | 719 (12.4)‡                                                           | 224 (15.7)         | 425 (12.3)          | 518 (13.7)          | 181 (13.2)          | 762 (13.0)          | 113 (15.3)        | 830 (12.8)          | 70 (16.2)*        | 873 (12.8)          | 943 (13.0)           |
| ED visit or<br>hospitalization,<br>rate/y (95% CI) | 0.19 (0.18-0.21)‡                                                     | 0.29 (0.25-0.34)   | 0.20 (0.18-0.22)    | 0.22 (0.20-0.25)    | 0.24 (0.20-0.29)    | 0.20 (0.19-0.22)    | 0.31 (0.25-0.39)‡ | 0.20 (0.18-0.21)    | 0.38 (0.29-0.51)‡ | 0.20 (0.18-0.22)    | 0.21 (0.19-0.23)     |
| Deaths                                             |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| Any, n (%)                                         | 609 (10.5)‡                                                           | 236 (16.5)         | 315 (9.1)‡          | 530 (14.0)          | 123 (9.0)‡          | 722 (12.3)          | 65 (8.8)*         | 780 (12.0)          | 37 (8.6)*         | 808 (11.9)          | 845 (11.7)           |
| COPD, n (%)                                        | 111 (1.9)‡                                                            | 52 (3.6)           | 51 (1.5)‡           | 112 (3.0)           | 22 (1.6)            | 141 (2.4)           | 15 (2.0)          | 148 (2.3)           | 7 (1.6)           | 156 (2.3)           | 163 (2.2)            |

*P* values determined by  $\chi^2$  test or Fisher exact test and Kruskal-Wallis test for continuous variables. CIs for rates determined by robust Poisson regression.

\**P* < .05.

†*P* < .01.

‡*P* < .001.

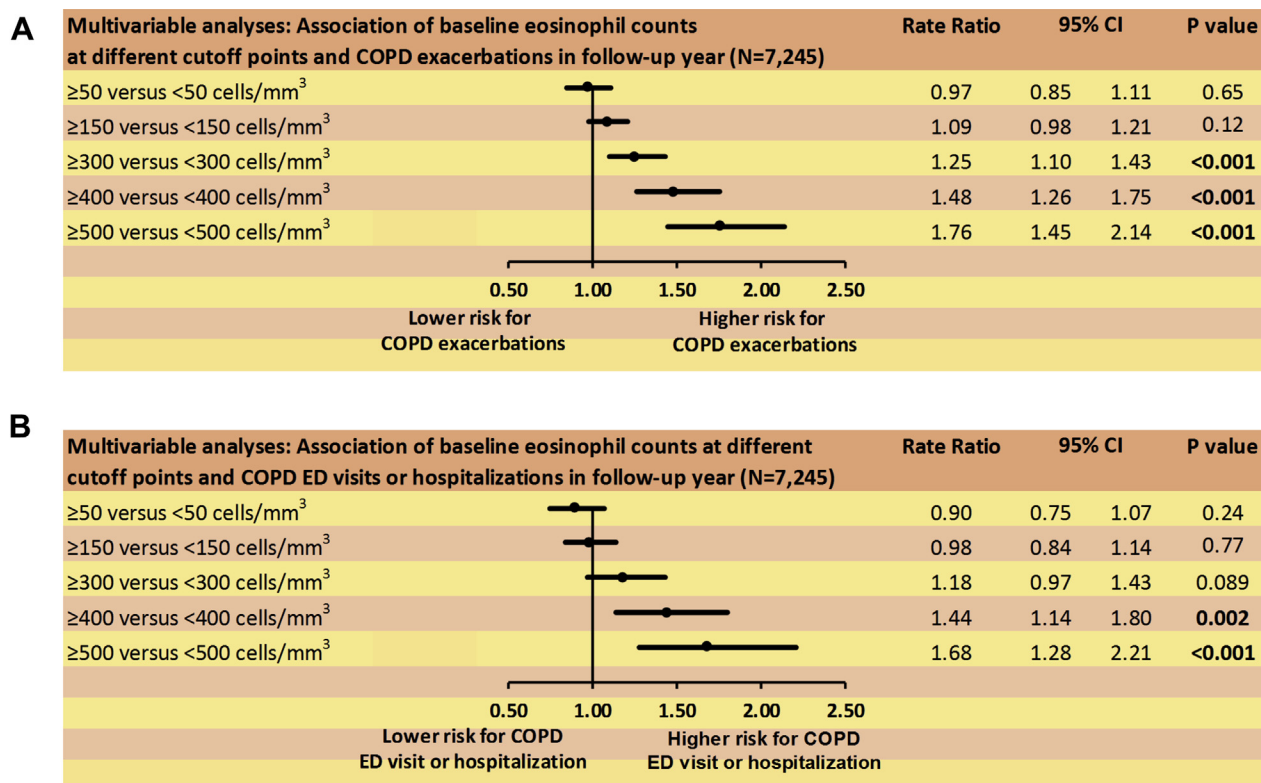


**FIGURE 2.** Adjusted RRs with 95% CIs by Poisson regression models with robust error variance for relationship of blood eosinophil cutoff point at index date in 7245 patients with COPD to COPD exacerbations (A) and COPD ED visits or hospitalizations (B) in the follow-up year.

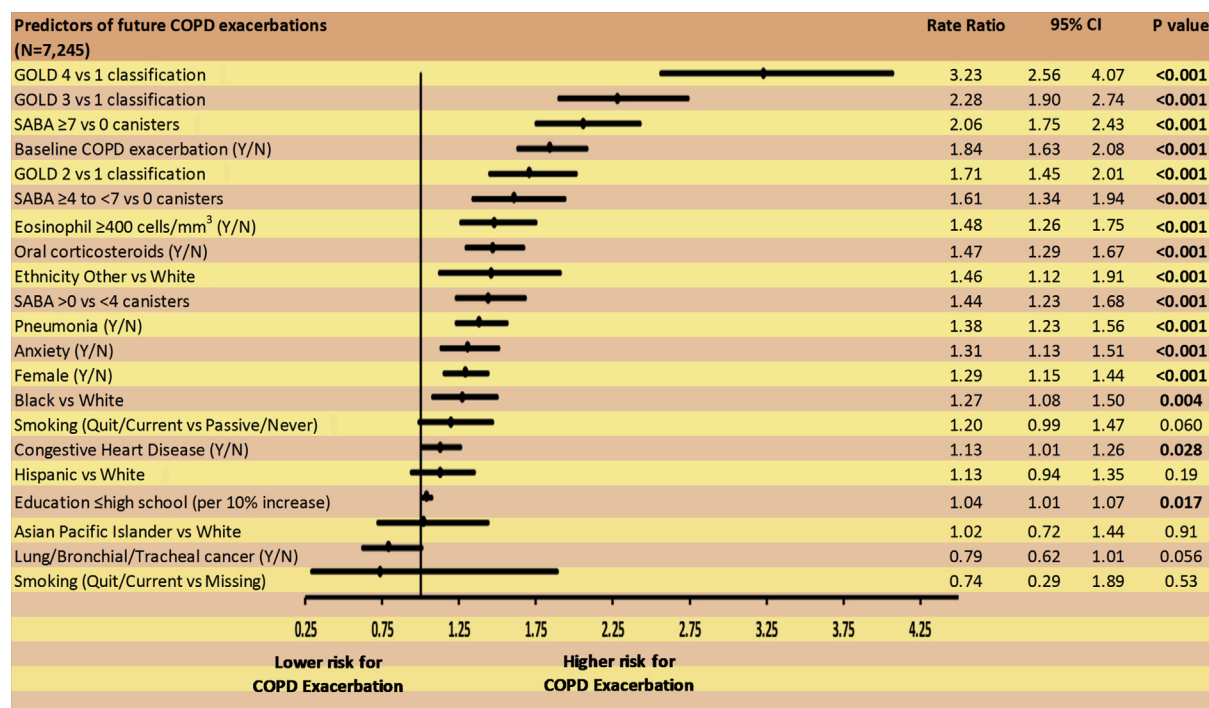


**FIGURE 3.** Adjusted RRs with 95% CIs by Poisson regression models with robust error variance for rate of COPD exacerbations in outcome year for each covariate (predictor) determined in baseline year in 7245 patients with COPD. N, No; Y, yes.

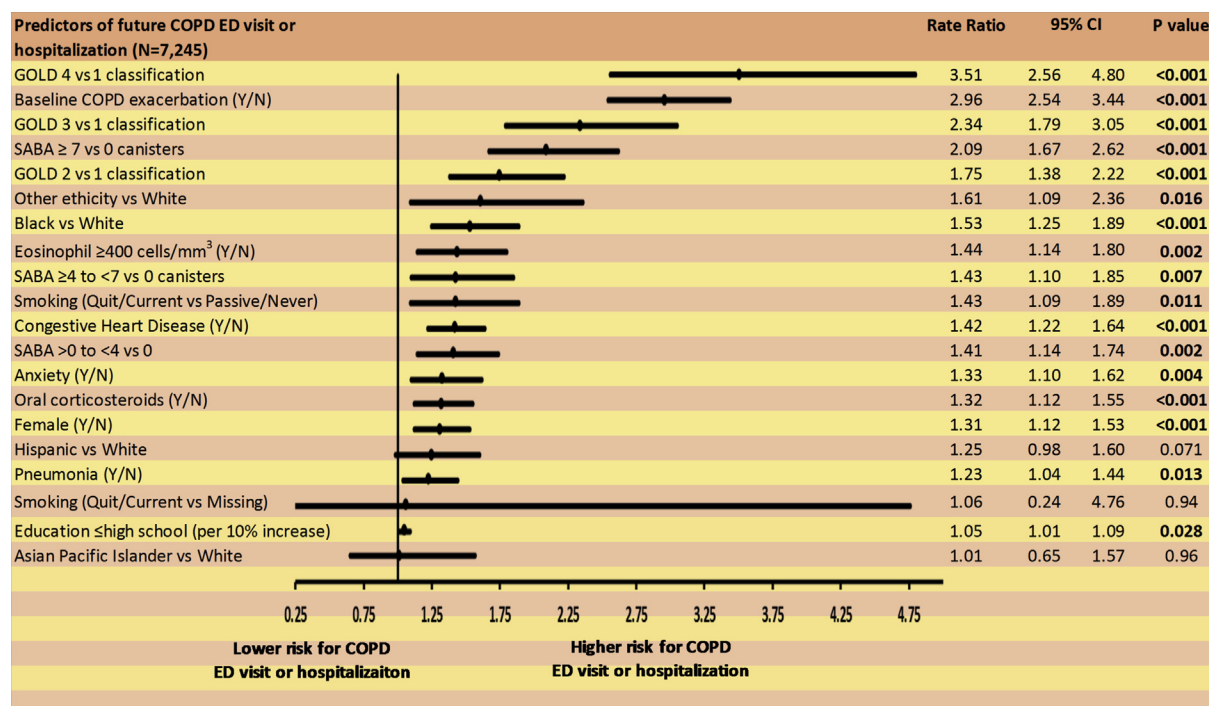


**FIGURE 4.** Adjusted RRs with 95% CIs by Poisson regression models with robust error variance for rate of COPD ED visits or hospitalizations in outcome year for each covariate (predictor) determined in baseline year in 7245 patients with COPD. *N*, No; *Y*, yes.

eosinophil counts (Figure 2, A). The rates of future COPD ED visits or hospitalizations were significantly increased (44% and 68%, respectively) for patients with greater versus lesser eosinophil counts at 400 cells/mm<sup>3</sup> and 500 cells/mm<sup>3</sup> cutoffs (Figure 2, B). Our study confirmed findings from a Danish study that reported that a blood eosinophil count of greater than or equal to 340 cells/mm<sup>3</sup> was associated with future COPD hospitalizations. That study, however, defined the COPD cohort based on *pre*bronchodilator spirometry measurement, and cannot fully exclude some individuals with more reversible airflow limitation.<sup>16</sup>

Airway inflammation is important in the pathophysiology of COPD and its exacerbations. Although neutrophilic lung inflammation is the hallmark of COPD, as shown in both biopsies and sputum,<sup>27</sup> eosinophilic inflammation is also present in the sputum of patients with COPD. Using blood and sputum biomarkers during acute COPD exacerbations, Bafadhel et al<sup>28</sup> determined 4 clusters of patients that confirmed the heterogeneity of the disease: bacterial (35%), viral (30%), eosinophilic (24%), and paucinflamatory with minimal inflammatory changes (11%). In COPD, evidence supports an elevated blood eosinophil count as a good biomarker for sputum eosinophils<sup>28-30</sup> and also for identifying patients with bronchial submucosal eosinophils.<sup>31</sup> Consistent with our findings, elevated eosinophil counts in blood and sputum are being recognized as a specific COPD eosinophilic phenotype that is associated with an increased risk of exacerbations.<sup>15,16,28</sup> In contrast, one study indicated that during 3-year follow-up, COPD exacerbations or hospitalizations were similar between patients with persistently elevated eosinophil counts (≥2%) compared with those without persistently elevated counts.<sup>29</sup> For patients with COPD

hospitalized for an exacerbation, elevated blood eosinophil count (≥300 cells/mm<sup>3</sup>)<sup>32,33</sup> in 2 studies, but not in another (≥200 cells/mm<sup>3</sup>),<sup>34</sup> was associated with more frequent readmission for another acute COPD exacerbation. Patients with COPD with elevated blood or sputum eosinophils also exhibit responsiveness to anti-inflammatory medications including ICS,<sup>35-37</sup> ICS/LABA,<sup>15,38-40</sup> OCS,<sup>14,41-43</sup> and biologics such as antieosinophil therapy.<sup>44</sup>

Blood eosinophil counts were relatively stable in COPD over a month (intraclass correlation of 0.8)<sup>30</sup> and in 80%, 70%, and 63% of patients with counts of greater than or equal to 340 cells/mm<sup>3</sup> remaining at or above those counts after 6, 9, and 12 months, respectively.<sup>45</sup> ICS treatment may have a small effect on blood eosinophil counts.<sup>46</sup> The relationship of elevated blood eosinophil count and exacerbations has also been reported for adults with persistent asthma,<sup>22,47</sup> severe asthma,<sup>48-50</sup> asthma and COPD diagnostic codes,<sup>51</sup> and children with asthma.<sup>52-54</sup> Taken together, evidence is growing that the COPD eosinophilic phenotype may exhibit type 2 inflammation similarities to asthma, and, as such, requires identification to institute more antieosinophilic interventions to prevent the increased risk of exacerbations.<sup>55</sup>

In addition to blood eosinophil count at a cutoff of greater than or equal to 400 cells/mm<sup>3</sup>, other predictors for COPD exacerbations were identified (Figure 3). The strongest predictors were GOLD levels 3 and 4, as reported earlier.<sup>7</sup> Other disease severity predictors included 7 or more SABA canisters dispensed, baseline COPD exacerbations, and oral corticosteroid use. Comorbidity predictors included pneumonia, anxiety, and congestive heart failure. Demographic predictors included females, blacks, smokers, and those at a lower education level (Figure 3).

These same variables were observed as predictors for future COPD-related ED visits or hospitalizations (Figure 4). More intensive interventions need to be directed at the above clinically modifiable risk factors to improve outcomes in COPD.

Unlike other retrospective administrative studies that did not use spirometry at all,<sup>11,33,56</sup> or only prebronchodilator FEV<sub>1</sub>/FVC ratio of less than 0.7<sup>16</sup> to identify patients with COPD, the present study gains its strength by using both HEDIS COPD coding and post-bronchodilator FEV<sub>1</sub>/FVC ratio of less than 0.7 to define COPD, as is recommended by COPD guidelines.<sup>4</sup> The representative nature of the present COPD cohort to other general COPD cohorts is supported by similar demographic characteristics,<sup>57</sup> frequency of comorbidities related to risk of mortality,<sup>23</sup> distribution of GOLD classifications,<sup>57,58</sup> and COPD-related hospitalizations.<sup>11</sup>

In unadjusted analyses, patients with greater compared with lesser blood eosinophil counts appeared to have lower frequency of overall death, and death with COPD as a cause of death (Table III). Conflicting data have been reported on this issue, supported by some<sup>59,60</sup> but not by others.<sup>32</sup> One potential explanation may be related to the greater prevalence of comorbidities associated with mortality in COPD (pneumonia, congestive heart failure, atrial fibrillation, liver cirrhosis, lung/bronchial/tracheal cancer, and anxiety) (Table E2) observed in patients with lesser blood eosinophil counts in the present study. Future studies are needed to better understand the dichotomy between the lesser death rate and greater exacerbation rate observed with greater blood eosinophil counts in COPD.

Our 2 exacerbation definitions attempted to capture more severe exacerbations and did not specifically include those only requiring antibiotics. Thus, the study may have underestimated the exacerbation rate, because some antibiotic uses may be for treatment of exacerbations.<sup>4</sup> However, the exacerbation rate in the present study is very similar to the rate found in a prospective observation study of COPD from Germany, which did include antibiotic use (0.38/y).<sup>61</sup> The similarity of the overall antibiotic use between blood eosinophil counts (Table II and Table E4) suggested no differential impact of any exacerbation rate underestimation on the relationship of eosinophil level and exacerbation.

The study's major limitation is its retrospective design and reliance on a single blood eosinophil measurement. However, as noted above, blood eosinophil counts exhibit modest stability during 1 to 6 months for patients with COPD.<sup>45</sup> Double and triple controller therapies were suboptimal at baseline according to COPD management guidelines.<sup>4</sup> Similarly, suboptimal treatment of COPD was reported in a large retrospective analysis of US managed care and Medicare patients,<sup>56</sup> the National Health and Nutrition Examination Survey data from 1999 to 2010,<sup>62</sup> and for patients with COPD treated in general practice.<sup>63</sup> It is not known to what degree, if any, better adherence to COPD guideline treatment might have affected the relationship found in the present study between elevated blood eosinophil counts and future COPD exacerbations. Caution is needed in comparing findings from this study with other COPD cohorts that had different background therapies or with those without a blood eosinophil determination. A more exhaustive pulmonary function characterization of the study cohort to help separate patients with COPD with emphysema versus other airway diseases was not possible because repeat pulmonary function laboratory spirometry and lung computed tomography studies are only intermittently performed in patients with COPD at KPSC. Despite the multivariable adjustment, there might still be some residual confounding especially by a high prevalence of associated

comorbidities, which may influence the association of eosinophilia and COPD exacerbations in poorly treated patients with COPD.

In summary, high blood eosinophil counts were an independent risk factor for future COPD exacerbations whether measured as a composite of moderate or severe exacerbations or as severe exacerbations (ED visit or hospitalization) (Figure 2, B), giving strength to the findings. These findings indicate a greater disease burden for a subset of patients with COPD with elevated blood eosinophils. Real-time identification of this eosinophilic subset of patients with COPD with an easily obtained blood test could lead to more intensive anti-inflammatory therapy directed at eosinophilic inflammation, which, in turn, could be beneficial in reducing future exacerbations.<sup>14,37,40,44</sup>

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## METHODS

Covariates were considered for multivariable analyses on the basis of their association with the outcomes of COPD exacerbations or COPD ED visits or hospitalizations. For COPD exacerbations, the following covariates in addition to eosinophil cutoff point were considered: sex, ethnicity, smoking status, any specialist visits, GOLD classifications, congestive heart failure, coronary artery disease, atrial fibrillation, chronic sinusitis, pneumonia, lung/bronchial/tracheal cancer, anxiety, depression, SABA canisters dispensed ( $\geq 7$ ,  $4 < 7$ ,  $> 0 < 4$  vs 0), any dispensing of a LABA, ICS, and OCS, neutrophils greater than 5,000 cells/mm<sup>3</sup>, percent with high school education or less, years of KP enrollment, and previous COPD exacerbations. For the outcome COPD ED visits or hospitalizations, the following baseline covariates were considered in addition to blood eosinophil cutoff point: sex, ethnicity, obesity, smoking status, any specialist visits, Charlson comorbidity index ( $\geq 2$ , 1 vs 0), GOLD classification, congestive heart failure, coronary artery disease, atrial fibrillation, pneumonia, peripheral vascular disease, any diabetes, lung/bronchial/tracheal cancer, anxiety, depression, SABA canisters dispensed ( $\geq 7$ ,  $4 < 7$ ,  $> 0 < 4$  vs 0), any OCS dispensed, blood neutrophils greater than 5,000 cells/mm<sup>3</sup>, percent with high school education or less, years of KP enrollment, and previous COPD exacerbations.

### Modeling

Final multivariate models used the blood eosinophil cutoff point intervals determined most related to COPD exacerbations. We assumed that potential confounders did not vary by the cutoff point of the blood eosinophil count and used the models involving the most robust eosinophil cutoff point to determine potential confounders. The covariates selected into

the final models of this cutoff point were applied to regression models of the same outcome with other blood eosinophil cutoff points. For robust Poisson models, Quasilikelihood under the Independence Model Criterion was used to compare any 2 models in a stepwise approach. The model with the smaller Quasilikelihood under the Independence Model Criterion was preferred.

The following *ICD-9* codes were used to identify specific conditions/diseases:

Gastroesophageal reflux disease: 530.81  
Pneumonia: 480.x thru 483.x, 485.x, 486.x  
Rhinitis: 472.0, 477.x  
Chronic sinusitis: 473.x  
Hypertension: 401.0x, 401.1x, 401.9x, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.x, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99  
Anxiety: 293.89, 300.00, 300.01, 300.02, 300.22, 300.23, 300.3x, 308.3x, 309.81  
Depression: 296.2x, 293.3x, 300.4x, 311.x  
Diabetes: 250.x, 357.2x, 362.0x, 366.41, 648.0x  
Ulcer disease: 531.x, 533.x, 532.9x  
Pulmonary fibrosis: 515.x, 516.31, J84.10  
Congestive heart failure: 428.x, 398.91  
Coronary artery disease: 414.x  
Atrial fibrillation: 427.31, 148.0x  
Peripheral vascular disease: 443.9x  
Diabetes with kidney disease: 250.40 thru 250.43  
Liver cirrhosis: 571.2x, 571.5x, 571.6x  
Lung/bronchial/trachea cancer: 162.x  
Breast/pancreatic/esophageal cancer: 150.x, 157.x, 174.x, 175.x

**TABLE E1.** Baseline demographic characteristics of the COPD cohort overall and stratified by index blood eosinophil cutoff point (cells/mm<sup>3</sup>)

| Demographic characteristic                  | Index blood eosinophil cutoff point (cells/mm <sup>3</sup> ) |                                |                                          |                                |                                |                                |                              |                                |                              |                                | Total<br>(N = 7,245)           |
|---------------------------------------------|--------------------------------------------------------------|--------------------------------|------------------------------------------|--------------------------------|--------------------------------|--------------------------------|------------------------------|--------------------------------|------------------------------|--------------------------------|--------------------------------|
|                                             | ≥50<br>(N = 5,817)                                           | <50<br>(N = 1,428)             | ≥150<br>(N = 3,463)                      | <150<br>(N = 3,782)            | ≥300<br>(N = 1,374)            | <300<br>(N = 5,871)            | ≥400<br>(N = 740)            | <400<br>(N = 6,505)            | ≥500<br>(N = 431)            | <500<br>(N = 6,814)            |                                |
| Age (y)                                     | 71.4 ± 9.6                                                   | 71.7 ± 9.6                     | 71.3 ± 9.6                               | 71.7 ± 9.5                     | 71.3 ± 9.6                     | 71.5 ± 9.6                     | 71.5 ± 9.3                   | 71.5 ± 9.6                     | 71.0 ± 9.1                   | 71.5 ± 9.6                     | 71.5 ± 9.6                     |
| Sex: male                                   | 3,364 (57.8) <sup>†</sup>                                    | 772 (54.1)                     | 2,106 (60.8) <sup>‡</sup>                | 2,030 (53.7)                   | 852 (62.0) <sup>‡</sup>        | 3,284 (55.9)                   | 455 (61.5)*                  | 3,681 (56.6)                   | 268 (62.2)*                  | 3,868 (56.8)                   | 4,136 (57.1)                   |
| Ethnicity                                   |                                                              |                                |                                          |                                |                                |                                |                              |                                |                              |                                |                                |
| White                                       | 4,204 (72.3)                                                 | 995 (69.7)                     | 2,527 (73.0)                             | 2,672 (70.7)                   | 993 (72.3)                     | 4,206 (71.6)                   | 521 (70.4)                   | 4,678 (71.9)                   | 305 (70.8)                   | 4,894 (71.8)                   | 5,199 (71.8)                   |
| Black                                       | 789 (13.6)*                                                  | 223 (15.6)                     | 416 (12.0) <sup>‡</sup>                  | 596 (15.8)                     | 157 (11.4) <sup>†</sup>        | 855 (14.6)                     | 86 (11.6)                    | 926 (14.2)                     | 49 (11.4)                    | 963 (14.1)                     | 1,012 (14.0)                   |
| Hispanic                                    | 494 (8.5)                                                    | 129 (9.0)                      | 300 (8.7)                                | 323 (8.5)                      | 132 (9.6)                      | 491 (8.4)                      | 79 (10.7)*                   | 544 (8.4)                      | 47 (10.9)                    | 576 (8.5)                      | 623 (8.6)                      |
| Asian                                       | 195 (3.4)                                                    | 53 (3.7)                       | 128 (3.7)                                | 120 (3.2)                      | 51 (3.7)                       | 197 (3.4)                      | 33 (4.5)                     | 215 (3.3)                      | 19 (4.4)                     | 229 (3.4)                      | 248 (3.4)                      |
| Others/unknown                              | 135 (2.3)                                                    | 28 (2.0)                       | 92 (2.7)                                 | 71 (1.9)                       | 41 (3.0)                       | 122 (2.1)                      | 21 (2.8)                     | 142 (2.2)                      | 11 (2.5)                     | 152 (2.2)                      | 163 (2.2)                      |
| Household income by geocoding               | 61,534 ± 26,219<br>(N = 5,807)                               | 60,403 ± 25,194<br>(N = 1,426) | 61,968 ± 27,101<br>(N = 3,459)           | 60,708 ± 24,982<br>(N = 3,774) | 61,301 ± 25,212<br>(N = 1,374) | 61,313 ± 26,211<br>(N = 5,859) | 60,683 ± 25,146<br>(N = 740) | 61,383 ± 26,121<br>(N = 6,493) | 60,205 ± 24,444<br>(N = 431) | 61,381 ± 26,119<br>(N = 6,802) | 61,311 ± 26,022<br>(N = 7,233) |
| Family education ≤grade 12 (%) by geocoding | 40.6 ± 17.7 <sup>†</sup><br>(N = 5,808)                      | 42.4 ± 18.2<br>(N = 1,426)     | 40.8 ± 17.6<br>(N = 3,460)               | 41.2 ± 18.0<br>(N = 3,774)     | 41.0 ± 17.5<br>(N = 1,374)     | 41.0 ± 17.9<br>(N = 5,860)     | 41.4 ± 17.5<br>(N = 740)     | 41.0 ± 17.9<br>(N = 6,494)     | 41.9 ± 17.5<br>(N = 431)     | 40.9 ± 17.8<br>(N = 6,803)     | 41.0 ± 17.8<br>(N = 7,234)     |
| Years of health plan enrollment             | 20.9 ± 13.0*<br>(N = 5,809) <sup>†</sup>                     | 21.7 ± 13.0<br>(N = 1,421)     | 20.7 ± 13.0*<br>(N = 3,459) <sup>†</sup> | 21.4 ± 13.1<br>(N = 3,771)     | 20.6 ± 13.1<br>(N = 1,373)     | 21.2 ± 13.0<br>(N = 5,857)     | 20.3 ± 13.0<br>(N = 739)     | 21.2 ± 13.1<br>(N = 6,491)     | 20.5 ± 13.1<br>(N = 430)     | 21.1 ± 13.0<br>(N = 6,800)     | 21.1 ± 13.0<br>(N = 7,230)     |
| Insurance                                   |                                                              |                                |                                          |                                |                                |                                |                              |                                |                              |                                |                                |
| Commercial                                  | 1,690 (29.1)                                                 | 416 (29.1)                     | 1,011 (29.2)                             | 1,095 (29.0)                   | 393 (28.6)                     | 1,713 (29.2)                   | 205 (27.7)                   | 1,901 (29.2)                   | 119 (27.6)                   | 1,987 (29.2)                   | 2,106 (29.1)                   |
| Medicaid                                    | 60 (1.0)                                                     | 9 (0.6)                        | 37 (1.1)                                 | 32 (0.8)                       | 12 (0.9)                       | 57 (1.0)                       | 7 (0.9)                      | 62 (1.0)                       | 3 (0.7)                      | 66 (1.0)                       | 69 (1.0)                       |
| Medicare                                    | 4,089 (70.3)                                                 | 1,005 (70.4)                   | 2,426 (70.1)                             | 2,668 (70.5)                   | 975 (71.0)                     | 4,119 (70.2)                   | 535 (72.3)                   | 4,559 (70.1)                   | 311 (72.2)                   | 4,783 (70.2)                   | 5,094 (70.3)                   |
| Smoking status                              |                                                              |                                |                                          |                                |                                |                                |                              |                                |                              |                                |                                |
| Current                                     | 506 (8.7)                                                    | 114 (8.0)                      | 315 (9.1)                                | 305 (8.1)                      | 132 (9.6)                      | 488 (8.3)                      | 75 (10.1)                    | 545 (8.4)                      | 51 (11.9)                    | 569 (8.4)                      | 620 (8.6)                      |
| Passive                                     | 37 (0.6)                                                     | 9 (0.6)                        | 22 (0.6)                                 | 24 (0.6)                       | 11 (0.8)                       | 35 (0.6)                       | 7 (0.9)                      | 39 (0.6)                       | 3 (0.7)                      | 43 (0.6)                       | 46 (0.6)                       |
| Quit                                        | 3,936 (67.8)                                                 | 904 (63.6)                     | 2,368 (68.5)                             | 2,472 (65.6)                   | 931 (67.8)                     | 3,909 (66.7)                   | 497 (67.3)                   | 4,343 (66.9)                   | 279 (64.9)                   | 4,561 (67.1)                   | 4,840 (66.9)                   |
| Never                                       | 1,330 (22.9)<br>(N = 5,809) <sup>†</sup>                     | 394 (27.7)<br>(N = 1,421)      | 754 (21.8)<br>(N = 3,459) <sup>†</sup>   | 970 (25.7)<br>(N = 3,771)      | 299 (21.8)<br>(N = 1,373)      | 1,425 (24.3)<br>(N = 5,857)    | 160 (21.7)<br>(N = 739)      | 1,564 (24.1)<br>(N = 6,491)    | 97 (22.6)<br>(N = 430)       | 1,627 (23.9)<br>(N = 6,800)    | 1,724 (23.8)<br>(N = 7,230)    |

Data presented as n (%) or mean ± SD.

P values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

\*P &lt; .05.

†P &lt; .01.

‡P &lt; .001.

**TABLE E2.** Baseline comorbidities of the COPD cohort overall and stratified by index blood eosinophil cutoff level (cells/mm<sup>3</sup>)

| Comorbidities                         | Index blood eosinophil count by cutoff point (cells/mm <sup>3</sup> ) |                           |                              |                           |                           |                             |                         |                             |                         |                             | Total<br>(N = 7,245)        |
|---------------------------------------|-----------------------------------------------------------------------|---------------------------|------------------------------|---------------------------|---------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|-----------------------------|-----------------------------|
|                                       | ≥50<br>(N = 5,817)                                                    | <50<br>(N = 1,428)        | ≥150<br>(N = 3,463)          | <150<br>(N = 3,782)       | ≥300<br>(N = 1,374)       | <300<br>(N = 5,871)         | ≥400<br>(N = 740)       | <400<br>(N = 6,505)         | ≥500<br>(N = 431)       | <500<br>(N = 6,814)         |                             |
| Charlson comorbidity index            | 3.5 ± 2.6†                                                            | 3.8 ± 2.7                 | 3.5 ± 2.5                    | 3.6 ± 2.7                 | 3.5 ± 2.5                 | 3.6 ± 2.6                   | 3.5 ± 2.6               | 3.6 ± 2.6                   | 3.4 ± 2.5               | 3.6 ± 2.6                   | 3.6 ± 2.6                   |
| GERD                                  | 1,384 (23.8)                                                          | 340 (23.8)                | 842 (24.3)                   | 882 (23.3)                | 347 (25.3)                | 1,377 (23.5)                | 170 (23.0)              | 1,554 (23.9)                | 100 (23.2)              | 1,624 (23.8)                | 1,724 (23.8)                |
| Obesity                               | 1,618 (27.9)‡<br>(N = 5,800)                                          | 304 (21.3)<br>(N = 1,426) | 1,005 (29.1)‡<br>(N = 3,452) | 917 (24.3)<br>(N = 3,774) | 391 (28.5)<br>(N = 1,371) | 1,531 (26.1)<br>(N = 5,855) | 184 (24.9)<br>(N = 738) | 1,738 (26.8)<br>(N = 6,477) | 101 (23.5)<br>(N = 429) | 1,821 (26.8)<br>(N = 6,797) | 1,922 (26.6)<br>(N = 7,226) |
| Chronic sinusitis                     | 490 (8.4)                                                             | 107 (7.5)                 | 311 (9.0)*                   | 286 (7.6)                 | 126 (9.2)                 | 471 (8.0)                   | 73 (9.9)                | 524 (8.1)                   | 50 (11.6)†              | 547 (8.0)                   | 597 (8.2)                   |
| Pneumonia                             | 1,109 (19.1)‡                                                         | 465 (32.6)                | 651 (18.8)‡                  | 923 (24.4)                | 273 (19.9)                | 1,301 (22.2)                | 141 (19.1)              | 1,433 (22)                  | 87 (20.2)               | 1,487 (21.8)                | 1,574 (21.7)                |
| Pulmonary fibrosis                    | 175 (3.0)                                                             | 54 (3.8)                  | 103 (3.0)                    | 126 (3.3)                 | 43 (3.1)                  | 186 (3.2)                   | 18 (2.4)                | 211 (3.2)                   | 11 (2.6)                | 218 (3.2)                   | 229 (3.2)                   |
| Congestive heart failure              | 1,138 (19.6)‡                                                         | 346 (24.2)                | 668 (19.0)*                  | 816 (21.6)                | 267 (19.4)                | 1,217 (20.7)                | 141 (19.1)              | 1,343 (20.6)                | 73 (16.9)               | 1,411 (20.7)                | 1,484 (20.5)                |
| Coronary artery disease               | 1,343 (23.1)                                                          | 303 (21.2)                | 823 (23.8)*                  | 823 (21.8)                | 329 (23.9)                | 1,317 (22.4)                | 163 (22.0)              | 1,483 (22.8)                | 93 (21.6)               | 1,553 (22.8)                | 1,646 (22.7)                |
| Atrial fibrillation                   | 873 (15.0)‡                                                           | 291 (20.4)                | 478 (13.8)‡                  | 686 (18.1)                | 166 (12.1)‡               | 998 (17.0)                  | 87 (11.8)‡              | 1,077 (16.6)                | 47 (10.9)†              | 1,117 (16.4)                | 1,164 (16.1)                |
| Hypertension                          | 4,426 (76.1)                                                          | 1,073 (75.1)              | 2,620 (75.7)                 | 2,879 (76.1)              | 1,056 (76.9)              | 4,443 (75.7)                | 558 (75.4)              | 4,941 (76.0)                | 326 (75.6)              | 5,173 (75.9)                | 5,499 (75.9)                |
| Ulcer disease                         | 108 (1.9)                                                             | 38 (2.7)                  | 70 (2.0)                     | 76 (2.0)                  | 27 (2.0)                  | 119 (2.0)                   | 13 (1.8)                | 133 (2.0)                   | 8 (1.9)                 | 138 (2.0)                   | 146 (2.0)                   |
| Peripheral vascular disease           | 610 (10.5)                                                            | 172 (12.0)                | 371 (10.7)                   | 411 (10.9)                | 157 (11.4)                | 625 (10.6)                  | 95 (12.8)               | 687 (10.6)                  | 49 (11.4)               | 733 (10.8)                  | 782 (10.8)                  |
| Any diabetes                          | 1,352 (23.2)*                                                         | 297 (20.8)                | 845 (24.4)†                  | 804 (21.3)                | 339 (24.7)                | 1,310 (22.3)                | 179 (24.2)              | 1,470 (22.6)                | 104 (24.1)              | 1,545 (22.7)                | 1,649 (22.8)                |
| Diabetic kidney disease               | 669 (11.5)                                                            | 151 (10.6)                | 436 (12.6)†                  | 384 (10.2)                | 165 (12.0)                | 655 (11.2)                  | 94 (12.7)               | 726 (11.2)                  | 51 (11.8)               | 769 (11.3)                  | 820 (11.3)                  |
| Liver cirrhosis                       | 76 (1.3)*                                                             | 30 (2.1)                  | 37 (1.1)†                    | 69 (1.8)                  | 15 (1.1)                  | 91 (1.5)                    | 9 (1.2)                 | 97 (1.5)                    | 4 (0.9)                 | 102 (1.5)                   | 106 (1.5)                   |
| Lung/bronchial/<br>tracheal cancer    | 356 (6.1)*                                                            | 111 (7.8)                 | 181 (5.2)‡                   | 286 (7.6)                 | 79 (5.7)                  | 388 (6.6)                   | 46 (6.2)                | 421 (6.5)                   | 27 (6.3)                | 440 (6.5)                   | 467 (6.4)                   |
| Breast/pancreas/<br>esophageal cancer | 166 (2.9)                                                             | 37 (2.6)                  | 101 (2.9)                    | 102 (2.7)                 | 40 (2.9)                  | 163 (2.8)                   | 17 (2.3)                | 186 (2.9)                   | 10 (2.3)                | 193 (2.8)                   | 203 (2.8)                   |
| Anxiety                               | 802 (13.8)*                                                           | 230 (16.1)                | 435 (12.6)‡                  | 597 (15.8)                | 156 (11.4)‡               | 876 (14.9)                  | 83 (11.2)*              | 949 (14.6)                  | 45 (10.4)*              | 987 (14.5)                  | 1,032 (14.2)                |
| Depression                            | 1,281 (22)                                                            | 320 (22.4)                | 765 (22.1)                   | 836 (22.1)                | 261 (19.0)†               | 1,340 (22.8)                | 140 (18.9)*             | 1,461 (22.5)                | 77 (17.9)*              | 1,524 (22.4)                | 1,601 (22.1)                |

GERD, Gastroesophageal reflux disease.

Data presented as n (%) or mean ± SD.

P values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis test for Charlson comorbidity index.\* $P < .05$ .† $P < .01$ .‡ $P < .001$ .

**TABLE E3.** Disease characteristics of the COPD cohort overall and stratified by index blood eosinophil cutoff point (cells/mm<sup>3</sup>)

| Disease characteristic                          | Index blood eosinophil count by cutoff point (cells/mm <sup>3</sup> ) |                    |                     |                     |                     |                     |                   |                     |                   |                     | Total<br>(N = 7,245) |
|-------------------------------------------------|-----------------------------------------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|-------------------|---------------------|-------------------|---------------------|----------------------|
|                                                 | ≥50<br>(N = 5,817)                                                    | <50<br>(N = 1,428) | ≥150<br>(N = 3,463) | <150<br>(N = 3,782) | ≥300<br>(N = 1,374) | <300<br>(N = 5,871) | ≥400<br>(N = 740) | <400<br>(N = 6,505) | ≥500<br>(N = 431) | <500<br>(N = 6,814) |                      |
| COPD exacerbations,                             |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| Incidence, rate/y<br>(95% CI)                   | 0.36 (0.34-0.38)‡                                                     | 0.49 (0.45-0.54)   | 0.38 (0.36-0.41)    | 0.39 (0.36-0.41)    | 0.45 (0.41-0.50)‡   | 0.37 (0.35-0.39)    | 0.51 (0.45-0.59)‡ | 0.37 (0.35-0.39)    | 0.55 (0.46-0.66)‡ | 0.37 (0.36-0.39)    | 0.38 (0.37-0.40)     |
| ≥1 exacerbation, n (%)                          | 1,471 (25.3)‡                                                         | 483 (33.8)         | 909 (26.2)*         | 1,045 (27.6)        | 409 (29.8)          | 1,545 (26.3)        | 243 (32.8)†       | 1,711 (26.3)        | 147 (34.1)*       | 1,807 (26.5)        | 1,954 (27.0)         |
| ≥2 exacerbations, n (%)                         | 389 (6.7)‡                                                            | 118 (8.3)          | 256 (7.4)           | 251 (6.6)           | 124 (9.0)*          | 383 (6.5)           | 72 (9.7)†         | 435 (6.7)           | 45 (10.4)*        | 462 (6.8)           | 507 (7.0)            |
| COPD ED visits or hospitalizations              |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| ≥1 ED visit, n (%)                              | 794 (13.6)‡                                                           | 315 (22.1)         | 497 (14.4)*         | 612 (16.2)          | 227 (16.5)          | 882 (15.0)          | 151 (20.4)‡       | 958 (14.7)          | 100 (23.2)‡       | 1,009 (14.8)        | 1,109 (15.3)         |
| ED visits, rate/y<br>(95% CI)                   | 0.17 (0.16-0.18)‡                                                     | 0.28 (0.25-0.31)   | 0.18 (0.17-0.20)    | 0.20 (0.18-0.22)    | 0.22 (0.19-0.26)*   | 0.18 (0.17-0.20)    | 0.29 (0.24-0.35)‡ | 0.18 (0.17- 0.19)   | 0.33 (0.27-0.42)‡ | 0.18 (0.17-0.19)    | 0.19 (0.18-0.20)     |
| ≥1 hospitalization, n (%)                       | 539 (9.3)‡                                                            | 279 (19.5)         | 343 (9.9)‡          | 475 (12.6)          | 153 (11.1)          | 665 (11.3)          | 109 (14.7)†       | 709 (10.9)          | 62 (14.4)*        | 756 (11.1)          | 818 (11.3)           |
| Hospitalizations,<br>rate/y (95% CI)            | 0.11 (0.10-0.12)‡                                                     | 0.23 (0.21-0.27)   | 0.12 (0.10-0.13)†   | 0.15 (0.13-0.16)    | 0.14 (0.11-0.16)    | 0.13 (0.12-0.14)    | 0.19 (0.15-0.23)‡ | 0.13 (0.12-0.14)    | 0.18 (0.14-0.24)* | 0.13 (0.12-0.14)    | 0.13 (0.12-0.14)     |
| ≥1 ED visit or hospitalization,<br>n (%)        | 901 (15.5)‡                                                           | 377 (26.4)         | 557 (16.1)‡         | 721 (19.1)          | 257 (18.7)          | 1,021 (17.4)        | 170 (23.0)‡       | 1,108 (17.0)        | 108 (25.1)‡       | 1,170 (17.2)        | 1,278 (17.6)         |
| ED visit or hospitalization,<br>rate/y (95% CI) | 0.19 (0.18-0.21)‡                                                     | 0.33 (0.30-0.37)   | 0.21 (0.19-0.23)*   | 0.23 (0.22-0.25)    | 0.25 (0.22-0.29)    | 0.21 (0.20-0.23)    | 0.33 (0.28-0.38)‡ | 0.21 (0.20-0.22)    | 0.36 (0.29-0.44)‡ | 0.21 (0.20-0.23)    | 0.22 (0.21-0.24)     |
| Specialist visit, n (%)                         |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| Pulmonologist                                   | 2,197 (37.8)                                                          | 509 (35.6)         | 1,306 (37.7)        | 1,400 (37.0)        | 496 (36.1)          | 2,210 (37.6)        | 262 (35.4)        | 2,444 (37.6)        | 158 (36.7)        | 2,548 (37.4)        | 2,706 (37.3)         |
| Allergist                                       | 148 (2.5)                                                             | 25 (1.8)           | 89 (2.6)            | 84 (2.2)            | 39 (2.8)            | 134 (2.3)           | 18 (2.4)          | 155 (2.4)           | 14 (3.2)          | 159 (2.3)           | 173 (2.4)            |
| Specialist                                      | 2,272 (39.1)                                                          | 518 (36.3)         | 1,350 (39.0)        | 1,440 (38.1)        | 517 (37.6)          | 2,273 (38.7)        | 269 (36.4)        | 2,521 (38.8)        | 164 (38.1)        | 2,626 (38.5)        | 2,790 (38.5)         |
| GOLD class, n (%)                               |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| 1 (≥80%)                                        | 1,454 (25.0)                                                          | 276 (19.3)         | 839 (24.2)          | 891 (23.6)          | 331 (24.1)          | 1,399 (23.8)        | 182 (24.6)        | 1,548 (23.8)        | 102 (23.7)        | 1,628 (23.9)        | 1,730 (23.9)         |
| 2 (50%-79%)                                     | 2,967 (51.0)                                                          | 707 (49.5)         | 1,780 (51.4)        | 1,894 (50.1)        | 722 (52.5)          | 2,952 (50.3)        | 372 (50.3)        | 3,302 (50.8)        | 222 (51.5)        | 3,452 (50.7)        | 3,674 (50.7)         |
| 3 (30%-49%)                                     | 1,182 (20.3)                                                          | 353 (24.7)         | 718 (20.7)          | 817 (21.6)          | 269 (19.6)          | 1,266 (21.6)        | 155 (20.9)        | 1,380 (21.2)        | 92 (21.3)         | 1,443 (21.2)        | 1,535 (21.2)         |
| 4 (<30%)                                        | 212 (3.6)                                                             | 91 (6.4)           | 124 (3.6)           | 179 (4.7)           | 52 (3.8)            | 251 (4.3)           | 31 (4.2)          | 272 (4.2)           | 15 (3.5)          | 288 (4.2)           | 303 (4.2)            |
|                                                 | (N = 5,815)‡                                                          | (N = 1,427)        | (N = 3,461)         | (N = 3,781)         | (N = 1,374)         | (N = 5,868)         | (N = 740)         | (N = 6,502)         | (N = 431)         | (N = 6,811)         | (N = 7,242)          |
| Blood cell count/mm <sup>3</sup> ,<br>mean ± SD |                                                                       |                    |                     |                     |                     |                     |                   |                     |                   |                     |                      |
| Leukocytes                                      | 8,716 ± 3,985‡                                                        | 10,138 ± 4,950     | 8,922 ± 3,563       | 9,064 ± 4,760       | 9,483 ± 4,098‡      | 8,882 ± 4,253       | 9,920 ± 4,487‡    | 8,891 ± 4,188       | 10,192 ± 4,627‡   | 8,921 ± 4,193       | 8,996 ± 4,231        |
| Neutrophils                                     | 5,899 ± 2,964‡                                                        | 8,264 ± 4,689      | 5,894 ± 2,855‡      | 6,797 ± 3,957       | 6,077 ± 3,061*      | 6,433 ± 3,596       | 6,203 ± 3,123     | 6,384 ± 3,543       | 6,319 ± 3,264     | 6,368 ± 3,518       | 6,365 ± 3,503        |
| Lymphocytes                                     | 1,826 ± 2,438‡                                                        | 1,168 ± 1,140      | 1,909 ± 1,528‡      | 1,502 ± 2,748       | 2,062 ± 1,971‡      | 1,611 ± 2,312       | 2,188 ± 2,406‡    | 1,640 ± 2,234       | 2,169 ± 2,478‡    | 1,666 ± 2,240       | 1,696 ± 2,258        |

*P* values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables. CIs for rates determined by robust Poisson regression.

\**P* < .05.

†*P* < .01.

‡*P* < .001.

**TABLE E4.** Medications dispensed in the baseline year to COPD cohort overall and stratified by index blood eosinophil cutoff level

| Medication dispensed  | Index blood eosinophil count by cutoff point (cells/mm3) |                 |                  |                  |                  |                  |                |                  |                |                  | Total (N = 7,245) |
|-----------------------|----------------------------------------------------------|-----------------|------------------|------------------|------------------|------------------|----------------|------------------|----------------|------------------|-------------------|
|                       | ≥50 (N = 5,817)                                          | <50 (N = 1,428) | ≥150 (N = 3,463) | <150 (N = 3,782) | ≥300 (N = 1,374) | <300 (N = 5,871) | ≥400 (N = 740) | <400 (N = 6,505) | ≥500 (N = 431) | <500 (N = 6,814) |                   |
| SABA singly           | 2,027 (34.8)†                                            | 445 (31.2)      | 1,211 (35.0)     | 1,261 (33.3)     | 469 (34.1)       | 2,003 (34.1)     | 254 (34.3)     | 2,218 (34.1)     | 160 (37.1)     | 2,312 (33.9)     | 2,472 (34.1)      |
| SAMA singly           | 147 (2.5)                                                | 36 (2.5)        | 83 (2.4)         | 100 (2.6)        | 25 (1.8)         | 158 (2.7)        | 8 (1.1)†       | 175 (2.7)        | 4 (0.9)*       | 179 (2.6)        | 183 (2.5)         |
| SABA-SAMA combination | 1,243 (21.4)                                             | 289 (20.2)      | 775 (22.4)*      | 757 (20.0)       | 325 (23.7)*      | 1,207 (20.6)     | 192 (25.9)‡    | 1,340 (20.6)     | 109 (25.3)*    | 1,423 (20.9)     | 1,532 (21.1)      |
| ≥7 SABA canisters     | 1,060 (18.2)*                                            | 302 (21.1)      | 657 (19.0)       | 705 (18.6)       | 298 (21.7)†      | 1,064 (18.1)     | 166 (22.4)†    | 1,196 (18.4)     | 101 (23.4)*    | 1,261 (18.5)     | 1,362 (18.8)      |
| LABA singly           | 30 (0.5)                                                 | 13 (0.9)        | 20 (0.6)         | 23 (0.6)         | 6 (0.4)          | 37 (0.6)         | 5 (0.7)        | 38 (0.6)         | 3 (0.7)        | 40 (0.6)         | 43 (0.6)          |
| LAMA singly           | 386 (6.6)                                                | 86 (6.0)        | 240 (6.9)        | 232 (6.1)        | 96 (7.0)         | 376 (6.4)        | 48 (6.5)       | 424 (6.5)        | 30 (7.0)       | 442 (6.5)        | 472 (6.5)         |
| ICS singly            | 1,183 (20.3)                                             | 264 (18.5)      | 706 (20.4)       | 741 (19.6)       | 307 (22.3)*      | 1,140 (19.4)     | 170 (23.0)*    | 1,277 (19.6)     | 107 (24.8)†    | 1,340 (19.7)     | 1,447 (20.0)      |
| Double therapy        | 1,113 (19.1)                                             | 261 (18.3)      | 693 (20.0)*      | 681 (18.0)       | 273 (19.9)       | 1,101 (18.8)     | 143 (19.3)     | 1,231 (18.9)     | 80 (18.6)      | 1,294 (19.0)     | 1,374 (19.0)      |
| Triple therapy        | 692 (11.9)                                               | 185 (13.0)      | 419 (12.1)       | 458 (12.1)       | 152 (11.1)       | 725 (12.3)       | 80 (10.8)      | 797 (12.3)       | 51 (11.8)      | 826 (12.1)       | 877 (12.1)        |
| Theophylline          | 77 (1.3)*                                                | 29 (2.0)        | 50 (1.4)         | 56 (1.5)         | 18 (1.3)         | 88 (1.5)         | 13 (1.8)       | 93 (1.4)         | 6 (1.4)        | 100 (1.5)        | 106 (1.5)         |
| Any OCS               | 2,166 (37.2)†                                            | 595 (41.7)      | 1,310 (37.8)     | 1,451 (38.4)     | 559 (40.7)*      | 2,202 (37.5)     | 315 (42.6)†    | 2,446 (37.6)     | 185 (42.9)*    | 2,576 (37.8)     | 2,761 (38.1)      |
| ≥5 mg/d               | 264 (4.5)‡                                               | 119 (8.3)       | 157 (4.5)†       | 226 (6.0)        | 71 (5.2)         | 312 (5.3)        | 42 (5.7)       | 341 (5.2)        | 22 (5.1)       | 361 (5.3)        | 383 (5.3)         |
| Antibiotics           | 3,364 (57.8)                                             | 849 (59.5)      | 1,994 (57.6)     | 2,219 (58.7)     | 823 (59.9)       | 3,390 (57.7)     | 447 (60.4)     | 3,766 (57.9)     | 262 (60.8)     | 3,951 (58.0)     | 4,213 (58.2)      |

SAMA, Short-acting muscarinic antagonist.

Data presented as n (%).

P values determined by  $\chi^2$  test or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Double therapy = 2 of 3 medications were dispensed: LABA, LAMA, or ICS; Triple therapy = LABA, LAMA, and ICS were dispensed.

\*P &lt; .05.

†P &lt; .01.

‡P &lt; .001.

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