

Characteristics and Outcomes of HEDIS-Defined Asthma Patients with COPD Diagnostic Coding



Robert S. Zeiger, MD, PhD^a, Michael Schatz, MD, MS^a, Qiaowu Li, MS^a, Wansu Chen, MS^a,

Deepak B. Khatry, PhD, MA, MSc^b, and Trung N. Tran, MD, PhD^c San Diego and Pasadena, Calif; and Gaithersburg, Md

What is already known about this topic? The asthma-COPD overlap syndrome (ACOS) is described clinically as persistent airflow limitation combined with features of both asthma and COPD. Patients with persistent asthma who also have a COPD diagnosis code (AS-COPD) may share clinical characteristics similar to ACOS. Patients with AS-COPD can be identified in administrative databases, but are not sufficiently understood or characterized.

What does this article add to our knowledge? Patients with AS-COPD exhibited, compared with those with persistent asthma only, significantly more comorbidities, a higher intensity of asthma treatments, and more uncontrolled asthma, based on both risk and impairment domains. Moreover, elevated blood eosinophil count in AS-COPD was a risk factor for future asthma exacerbations as previously reported for patients with persistent asthma only.

How does this study impact current management guidelines? These findings document a greater disease burden associated with elevated blood eosinophils in AS-COPD and suggest a common inflammatory component between AS-COPD and PA only.

BACKGROUND: Little is known of the disease burden of patients with persistent asthma (PA) who also have a chronic obstructive pulmonary disease (COPD) diagnosis code (AS-COPD).

OBJECTIVE: The objective of this study was to characterize and compare patients with AS-COPD with those with PA without COPD diagnosis, and determine in AS-COPD the relationship between blood eosinophil count and future asthma exacerbations.

METHODS: This retrospective cohort study used administrative pharmacy and health care utilization data to identify, characterize, and compare the burden and asthma exacerbations in adults with AS-COPD (N = 901) with those with PA (N = 2392). Negative binomial regression and Poisson regression models were used to evaluate the relationships between baseline blood eosinophil counts (high vs low) based on various cutoff points and asthma exacerbations in the follow-up year, adjusting for demographics, comorbidities, and asthma burden.

RESULTS: Compared with patients with PA, those with AS-COPD were significantly (all $P < .001$) older, more frequently female, less well educated, more likely to be or have been a smoker, had more comorbidities, received more asthma controller medications, and had greater rates and frequencies of asthma exacerbations, but had similar blood eosinophil counts. The rate of asthma exacerbations/person-year in AS-COPD during follow-up was 1.61 (95% CI, 1.18-2.20). Patients with AS-COPD with a blood eosinophil count ≥ 400 cells/mm³ had an increased rate of future asthma exacerbations compared with those whose blood eosinophil count was < 400 cells/mm³ (adjusted rate ratio, 1.44, 95% CI, 1.09-1.90).

CONCLUSIONS: Compared with patients with PA, those with AS-COPD had more disease burden, but a similar relationship of high blood eosinophil count to more future asthma exacerbations. These findings suggest a common inflammatory component between AS-COPD and PA. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:273-83)

Key words: Asthma; Asthma control; Asthma guidelines; Asthma impairment; Asthma risk; COPD; Eosinophils; GINA step-care level; Managed care

^aKaiser Permanente Southern California, San Diego and Pasadena, Calif

^bTranslational Sciences, MedImmune, Gaithersburg, Md

^cObservational Research Center, AstraZeneca, Gaithersburg, Md

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Corresponding author: Robert S. Zeiger, MD, PhD, Director of Allergy Research, Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Boulevard, San Diego, CA 92111. E-mail: robert.s.zeiger@kp.org.

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Abbreviations used

ACOS- Asthma-COPD overlap syndrome
 AS-COPD- Persistent asthma patients with ICD-9 diagnosis codes for chronic bronchitis, emphysema, chronic airway obstruction, or chronic obstructive asthma
 AMR- Asthma Medication Ratio
 COA- Chronic obstructive asthma
 COPD- Chronic obstructive pulmonary disease
 ED- Emergency department
 GINA- Global Initiative for Asthma
 HEDIS- Healthcare Effectiveness Data and Information Set
 ICD-9- The International Classification of Diseases, 9th Revision
 ICS- Inhaled corticosteroids
 KPSC- Kaiser Permanente Southern California
 LABA- Long-acting β_2 -agonist
 NCQA- National Committee of Quality Assurance
 PA- Persistent asthma without chronic obstructive pulmonary disease ICD-9 diagnosis codes
 RR- Rate ratio
 SABA- Short-acting β_2 -agonists

INTRODUCTION

The National Committee of Quality Assurance (NCQA) has developed the Healthcare Effectiveness Data and Information Set (HEDIS) tools to measure the performance and delivery of medical care between US health plans with an adoption rate of more than 90%. Specific HEDIS tools were created to identify persistent asthma (PA) and chronic obstructive pulmonary disease (COPD).¹ The 2-year administrative data HEDIS criteria to identify patients with PA require at least one of the following events to occur in each of 2 consecutive years: (1) 4 or more asthma rescue or controller medications dispensed, (2) 1 or more emergency department (ED) visits or hospitalizations with a diagnosis of asthma, or (3) 4 or more outpatient visits with a diagnosis of asthma and 2 or more asthma medications dispensed.¹ In addition to the above patient ascertainment for PA, HEDIS measures also require exclusion of patients with the International Classification of Diseases, 9th Revision Codes (ICD-9), for the spectrum of COPD, cystic fibrosis, and acute respiratory failure.¹ HEDIS applies the following ICD-9 codes administratively to identify patients with the COPD spectrum of illnesses (chronic airway obstruction [496], chronic obstructive asthma [COA] [493.2x], chronic bronchitis [491.x], or emphysema [492.x]).² Starting in 2013, NCQA decided to switch the COA diagnosis code (ICD-9, 493.2x) from the HEDIS PA specification measure to the COPD specification measure.³ Speculations for this change include that COA may more closely align clinically and physiologically to COPD than PA.

Electronic medical records frequently note physician diagnosis coding of asthma or COPD in the same patient at different times.⁴ Little is known of the disease characteristics and burden of patients with PA who also have received diagnosis coding for COPD (AS-COPD), and as such these patients need to be studied. Patients with AS-COPD identified administratively may share clinical characteristics similar to the asthma-COPD overlap syndrome (ACOS) that has been described clinically as persistent airflow limitation combined with features of both asthma and COPD.⁵⁻⁹

We recently reported the characteristics and asthma-related burden of an HEDIS defined adult PA cohort and suggested

that blood eosinophil counts of ≥ 400 cells/mm³ appeared to be an independent risk factor for future asthma exacerbations.¹⁰ The present report characterizes and compares administratively identified patients with AS-COPD with those with PA, and evaluates the relationship of blood eosinophil in patients with AS-COPD to future asthma exacerbations. We hypothesized that high blood eosinophil counts predict future exacerbations in patients with AS-COPD, as reported in patients with PA without a COPD diagnosis code.

METHODS**Study design**

We conducted a retrospective cohort study to characterize patients with AS-COPD and evaluated the relationship between blood eosinophil counts at baseline (2010) and asthma exacerbations in the following 12 months (2011). The Kaiser Permanente Southern California (KPSC) Research Data Warehouse captured pharmacy and health care utilization data that allowed identification of adults with either AS-COPD or PA (Figure 1, A). The study was approved by the KPSC Institutional Review Board, with waiver of written consent.

Patients

Adults between 18 and 64 years of age were identified with either HEDIS-defined 2-year PA (2009 and 2010)^{11,12} or AS-COPD if they had been excluded from the PA cohort by evidencing COPD ICD-9 diagnostic codes (chronic airway obstruction [496], COA [493.2x], chronic bronchitis [491.x], or emphysema [492.x])² during 2004-2010 (Figure 1, B). In addition, patients were required to have had continuous health plan enrollment and pharmacy benefit in 2009-2011 (no gap of >45 days within each calendar year).¹¹ Exclusions included encounter diagnoses of chronic conditions listed in the legend to Figure 1(A). The study included patients with a blood eosinophil determination in 2010.

Blood eosinophil counts

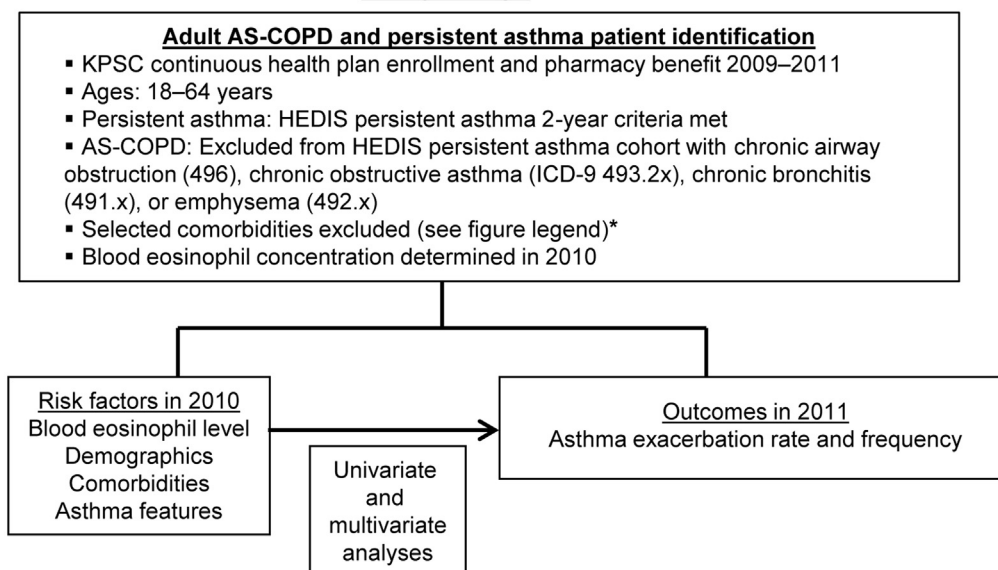
Blood eosinophil counts were calculated from the last complete blood count with differential obtained in 2010. The association between blood eosinophil count (high vs low) with cutoff points from 100 to 500 cells/mm³ by 50 cell/mm³ increments and asthma exacerbations in 2011 was determined for patients with AS-COPD. Four blood eosinophil cutoff points (150, 200, 300, and 400 cells/mm³) were used for multivariable analyses. Because oral corticosteroids and infections influence blood eosinophil counts, we conducted sensitivity analyses excluding blood eosinophil count measured within 15 days before systemic corticosteroid courses, infections, or systemic antibiotics and/or antiviral medications (restricted eosinophils).¹⁰

Study measures

Education count and household income were determined by using address information geocoded to the census block level and linked to block group-level information about socioeconomic status provided by Nielsen (www.nielsen.com). The Asthma Medication Ratio (AMR) was defined as the number of dispensed asthma controller units (inhaled controller medication canisters or 30-day supplies of oral controller medications) divided by the total number of controller units and short-acting β_2 -agonist (SABA) canisters dispensed and is an administrative data quality marker predictive of future ED and/or hospital care.¹³ A ratio of ≥ 0.5 is the minimum recommended cutpoint.¹³ ICS products were categorized into low,

A

Study design



B

AS-COPD and persistent asthma cohort identification from administrative data

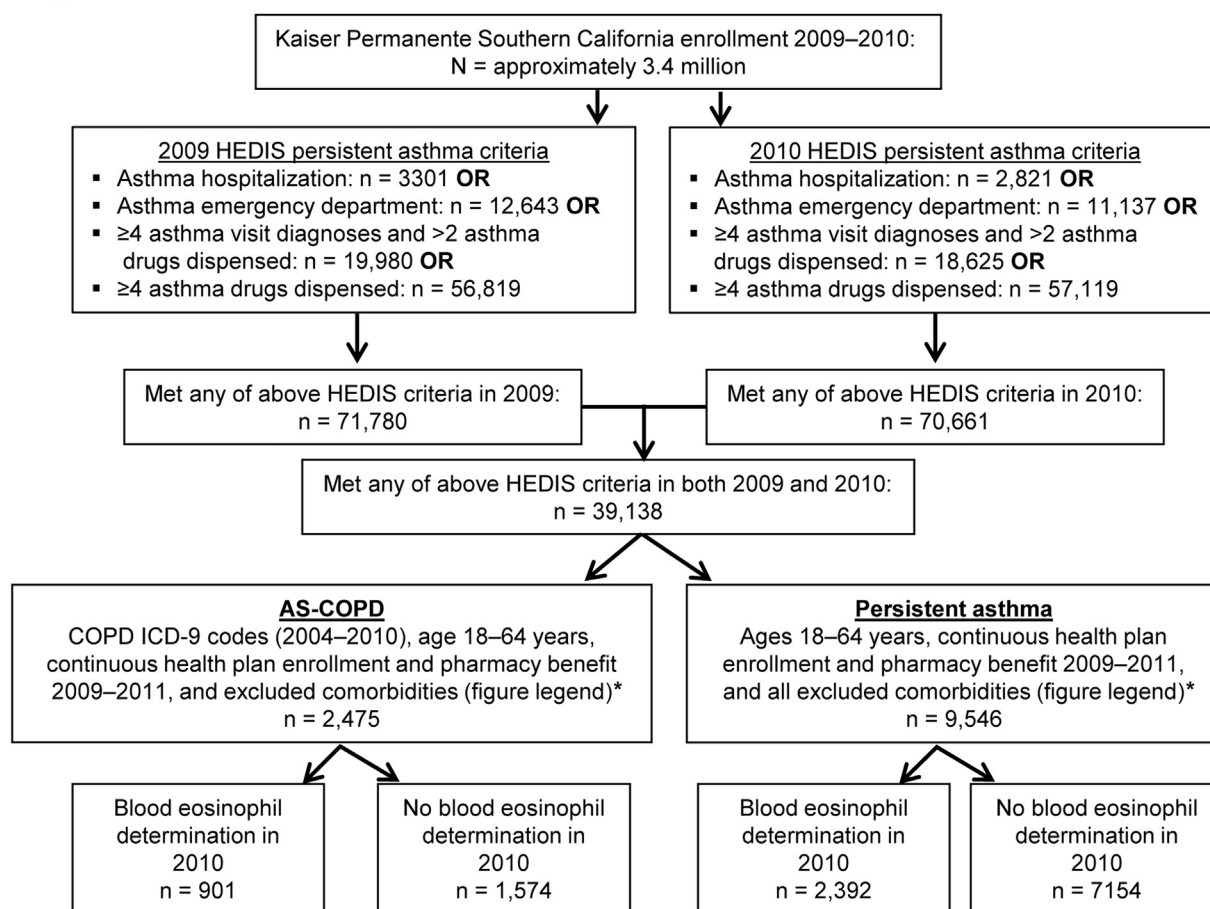


FIGURE 1. The study design and number of patients identified with administrative databases. **A**, Study design. *Excluded patients had encounter diagnoses of cystic fibrosis, bronchiectasis, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, sarcoidosis, pulmonary hypertension, cerebral palsy, transplantation of major organs (2004–2010), and other clinically relevant nonasthma pulmonary disorders such as autoimmunity, immune deficiency, immunosuppression treatments (procedural codes), cancer, HIV, drug addiction, and major psychiatric disorder (2009–2010). **B**, Administrative algorithm for identification of AS-COPD and adult persistent asthma cohorts.

medium, and high dosage, based on the calculated daily dosage and on individual potencies using the estimated comparative daily dosages for ICS recommended by the Global Initiative for Asthma (GINA) guideline for the diagnosis and management of adult asthma.¹⁴ The GINA medication step-care levels from 1 to 5 were determined at baseline (2010) by modifying an algorithm and formula previously reported¹⁴: step-care 1: no medication or only SABA; step-care 2: low-dosage inhaled corticosteroid (ICS) or leukotriene modifier; step-care 3: low-dosage ICS plus at least one of a long-acting β_2 -agonist (LABA), a leukotriene modifier, or theophylline, or medium- to high-dosage ICS alone; step-care 4: medium- or high-dosage ICS plus at least one of an LABA (including high-dosage ICS/LABA combination), a leukotriene modifier, or theophylline; and step-care 5: added to step-care 4: “regular” oral corticosteroid use, defined as dispensing of at least 3.65 g/year of prednisone equivalent or diagnosis of steroid-dependent asthma and/or omalizumab treatment. Asthma controller medications were considered to be in combination with an ICS when they were dispensed as a single combination inhaler or dispensed within ± 3 months of an ICS dispensing.

A level of controller units of 9 or greater dispensed per year equivalent to 75% adherence was used as a proxy for adherence to treatment.¹⁵ Asthma exacerbations were defined as worsening asthma requiring systemic corticosteroids ± 7 days of an outpatient visit using KPSC internal codes indicative of uncontrolled asthma status (ie, acute exacerbation, status asthmaticus, acute asthma attack, not controlled asthma, or asthmatic bronchitis), or an ED visit or hospitalization with a primary asthma diagnosis or second asthma diagnosis with a primary respiratory diagnosis based on ICD-9 coding. At least 8 days between episodes were required to define a new asthma exacerbation. Excessive SABA canisters dispensed was defined as ≥ 7 SABA dispensed canisters per year (equivalent to ≥ 4 puffs/day/year), and is an administrative marker for uncontrolled asthma.¹⁶

Statistical analyses

Patient demographics, comorbidities, asthma characteristics, and features in 2010 were compared between AS-COPD and PA by using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Negative binomial models (a method used to estimate overdispersed or high variability in event counts) were employed for unadjusted and adjusted rate ratios and their 95% confidence intervals (CIs). Poisson regression models with a robust error variance were applied to calculate the unadjusted and adjusted risk ratios and their 95% CIs.¹⁷ Covariates determined in 2010 and considered in model selection included age (continuous), sex, obesity (BMI ≥ 30 kg/m²), geocoded education, ethnicity, smoking status, insurance type, Charlson comorbidity index, COA, COPD diagnoses without COA, relevant comorbidities (gastroesophageal reflux, rhinitis, chronic sinusitis, pneumonia, nasal polyps, and eczema), GINA step-care level,¹⁸ ≥ 7 SABA canisters dispensed, history of asthma exacerbations, and blood eosinophil count in 2010. Age, sex, obesity, geocoded education, and blood eosinophil count were forced into the models. Outcomes determined in 2011 (ie, the future year) for the multivariable analyses were rate and risk of asthma exacerbation. For negative binomial regression, the likelihood ratio test was used to compare any 2 nested models in a stepwise approach with an α error set at 0.05. For robust Poisson models, Quasilikelihood under the Independence Model Criterion (QIC) was used to compare any 2 models in a stepwise approach. The model with the smaller QIC was preferred. We assumed that potential confounders did not vary

by the cutoff point of the blood eosinophil count and used the model involving the most robust eosinophil cutoff point (400 cells/mm³) to determine potential confounders. The covariates selected for the final model of this cutoff point were applied to regression models of the same outcome with other blood eosinophil cutoff points. All analyses were conducted with SAS (version 9.3 for Windows, SAS Institute, Cary, NC).

RESULTS

Identification of the AS-COPD cohort

Using administrative pharmacy and health care utilization data, we identified 2475 patients between ages 18 and 64 years who met the HEDIS 2-year criteria (2009 and 2010) for persistent asthma but also had COPD diagnostic codes (2004–2010) (Figure 1, B). Within this AS-COPD cohort, 901 (36.4%) had a blood eosinophil determination in 2010. Compared with patients with AS-COPD without eosinophil determinations, those with AS-COPD with eosinophil determinations were significantly more from minority groups, less well-educated, more obese, more Medicaid and Medicare insured, more frequently diagnosed with asthma, and had experienced more comorbidities, more asthma specialist care, and more asthma exacerbations (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

The AS-COPD cohort with eosinophil determinations consisted of patients with only a COA diagnosis ($n = 312$), a COPD diagnosis without COA ($n = 283$), or COA and one of the other COPD diagnoses ($n = 306$). These AS-COPD subgroups differed significantly by demographics, smoking status, comorbidities, asthma medication use, and asthma exacerbations (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The COA-only subgroup evidenced the greatest rate of asthma exacerbations among the subgroups, reaching a more than 2-fold greater rate (0.97, 95% CI, 0.81–1.16) than the AS-COPD without COA subgroup (0.39, 95% CI, 0.31–0.49) (Table E2).

Comparison of baseline characteristics between patients with AS-COPD and those with PA with blood eosinophil counts

The PA cohort of 2392 with blood eosinophil determination in 2010 identified during ascertainment of the AS-COPD cohort (Figure 1, B) has been reported.¹⁰ Compared with patients with PA, those with AS-COPD were significantly older (mean age 54.1 vs 47.0 years); more frequently white ethnically (55% vs 45%); lower in socioeconomic status; more likely to be current (19% vs 7%) and have been smokers (43% vs 27%); longer health plan enrollees (17.8 vs 16.5 years); greater in Charlson comorbidity indices; more frequently diagnosed with gastroesophageal reflux, chronic sinusitis, pneumonia, and nasal polyps; and more frequently seen by pulmonologists (23% vs 9%) (Table I). Physician-diagnosed asthma in either 2009 or 2010 was reported significantly less frequently for patients with AS-COPD (79.5%) than for patients with PA (93.1%). For the minority of patients with available spirometry data, post-bronchodilator FEV₁/FVC ratio < 0.7 , a measure of persistent airflow obstruction,¹⁹ occurred significantly more frequently in AS-COPD (60.1%, $n = 183$) than PA (29.3%, $n = 184$). With respect to asthma medication and disease burden, compared with PA, AS-COPD evidenced significantly greater GINA step-care

TABLE I. Comparison of demographics, comorbidities, and asthma burden in 2010 between patients with AS-COPD and PA with blood eosinophil determinations (data as n [%] or as noted)

Demographics/clinical features (2010)	AS-COPD (N = 901)	PA (N = 2392)	P value*
Age (y), mean $\pm$ SD	54.1 $\pm$ 8.8	47.0 $\pm$ 12.4	<.001
≥ 40 y	834 (92.6)	1752 (73.2)	<.001
Female sex	564 (62.6)	1684 (70.4)	<.001
Ethnicity			<.001
White	499 (55.4)	1085 (45.4)	
Black	174 (19.3)	420 (17.6)	
Hispanic	153 (17.0)	600 (25.1)	
Native American/Native Alaskan	2 (0.2)	7 (0.3)	
Asian/Pacific Islander	42 (4.7)	177 (7.4)	
Multiple, others	12 (1.3)	41 (1.7)	
Unknown	19 (2.1)	62 (2.6)	
Estimated household income by geocoding (US dollars), mean $\pm$ SD	62,990 $\pm$ 27,118	67,587 $\pm$ 29,633	<.001
Estimated education level < high school diploma among adults ≥ 25 y of age by geocoding, mean % $\pm$ SD	24.5 $\pm$ 16.3	23.0 $\pm$ 17.6	<.001
Length of health plan enrollment, y, mean $\pm$ SD	17.8 $\pm$ 10.5	16.5 $\pm$ 10.5	.001
Insurances†			
Commercial	725 (80.5)	2081 (87.0)	<.001
Medicaid or state sponsored	73 (8.1)	177 (7.4)	.50
Medicare	73 (8.1)	81 (3.4)	<.001
Private pay	46 (5.1)	125 (5.2)	.89
Smoking status			<.001
Current	171 (19.2)	155 (6.6)	
Passive	11 (1.2)	19 (0.8)	
Quit	387 (43.4)	644 (27.4)	
Never	322 (36.1) (n = 891)	1532 (65.2) (n = 2,350)	
Body mass index			
Mean $\pm$ SD	32.4 $\pm$ 8.6	32.1 $\pm$ 8.4	.39
Obese (≥ 30 kg/m ²)	486 (54.1) (n = 898)	1,276 (53.6) (n = 2381)	.79
Charlson Comorbidity Index, mean $\pm$ SD	1.7 $\pm$ 1.2	1.3 $\pm$ 0.9	<.001
Asthma ICD-9 code (2009 or 2010)	716 (79.5)	2226 (93.1)	<.001
Any rhinitis	323 (35.8)	865 (36.2)	.87
Gastroesophageal reflux	279 (31.0)	641 (26.8)	.02
Chronic sinusitis	207 (23.0)	448 (18.7)	.01
Pneumonia	128 (14.2)	162 (6.8)	<.001
Nasal polyps	38 (4.2)	51 (2.1)	.001
Eczema	12 (1.3)	63 (2.6)	.03
Allergist visit	198 (22.0)	548 (22.9)	.57
Pulmonologist visit	207 (23.0)	225 (9.4)	<.001
Any asthma specialist visit	357 (39.6)	695 (29.1)	<.001
Post-bronchodilator FEV ₁ /FVC <0.7	110 (60.1) (n = 183)	54 (29.3) (n = 184)	<.001
Blood eosinophil concentration, cells/mm ³ , mean $\pm$ SD	259 $\pm$ 257	263 $\pm$ 280	.25
12-month GINA step-care level			<.001
Step 1	70 (7.8)	244 (10.2)	
Step 2	73 (8.1)	317 (13.3)	
Step 3	258 (28.6)	768 (32.1)	
Step 4	467 (51.8)	1021 (42.7)	
Step 5	30 (3.3)	39 (1.6)	
Unclassified	3 (0.3)	3 (0.1)	

(continued)

TABLE I. (Continued)

Demographics/clinical features (2010)	AS-COPD (N = 901)	PA (N = 2392)	P value*
Any ICS dispensed			<.001
None	100 (11.1)	350 (14.6)	
Low dosage	87 (9.7)	397 (16.6)	
Medium dosage	427 (47.4)	1150 (48.1)	
High dosage	287 (31.9)	495 (20.7)	
Any ICS/LABA dispensed			<.001
None	417 (46.3)	1312 (54.8)	
Low dosage	35 (3.9)	146 (6.1)	
Medium dosage	217 (24.1)	532 (22.2)	
High dosage	232 (25.7)	402 (16.8)	
Leukotriene modifiers	206 (22.9)	538 (22.5)	.82
Theophylline	31 (3.4)	44 (1.8)	.01
Omalizumab	1 (0.1)	6 (0.3)	.68
Controller equivalent canisters dispensed, mean $\pm$ SD	8.8 $\pm$ 7.1	7.4 $\pm$ 5.9	<.001
≥ 9 controller canisters dispensed	422 (46.8)	880 (36.8)	<.001
Asthma Medication Ratio ≥ 0.5	515 (57.2)	1467 (61.3)	.03
SABA canisters dispensed, mean $\pm$ SD	7.9 $\pm$ 7.6	5.6 $\pm$ 5.3	<.001
≥ 7 SABA canisters dispensed	402 (44.6)	771 (32.2)	<.001
Asthma exacerbations, rate/y (95% CI)	0.72 (0.64-0.81)	0.54 (0.50-0.58)	<.001
≥ 1 asthma exacerbation	330 (36.6)	786 (32.9)	.04
≥ 2 asthma exacerbations	166 (18.4)	287 (12.0)	<.001
≥ 1 asthma ED visit or hospitalization	166 (18.4)	306 (12.8)	<.001

AS-COPD, Persistent asthma with coding for COPD spectrum diagnoses; ED, emergency department; GINA, Global Initiative for Asthma; ICD-9, the International Classification of Diseases, 9th Revision; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; PA, persistent asthma; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: χ^2 test (categorical), Wilcoxon rank sum test (continuous), and χ^2 test based on likelihood ratio for exacerbation rate comparisons.

†Patients may have more than 1 insurance plan.

level treatment, greater dosages of ICS monotherapy and ICS/LABA combination, more controller equivalent canisters dispensed, more excessive SABA use, and greater rates and frequencies of asthma exacerbations and asthma ED visits or hospitalizations. Blood eosinophil counts were similar between patients with AS-COPD and those with PA.

Characteristics of AS-COPD by blood eosinophil count

By varying the blood eosinophil cutoff point by 50 cell/mm³ increments, in crude analysis, blood eosinophil count in 2010 appeared to have begun being associated with asthma exacerbation (yes/no) in 2011 at the 350 cell/mm³ cutoff point ($P = .04$) for any blood eosinophil determination and at the 400 cell/mm³ cutoff point ($P = .03$) for restricted eosinophil determinations (Table II).

AS-COPD with blood eosinophil counts ≥ 400 cells/mm³ ($n = 169$, 18.8%) compared with those < 400 cells/mm³ ($n = 732$, 81.2%) at baseline in 2010 were significantly (1) more male; (2) afflicted more frequently with rhinitis, chronic sinusitis, and nasal polyps and less with pneumonia; and (3) suffered more burdensome asthma manifested by greater rates and frequencies of asthma exacerbations (Table III).

Relationship of blood eosinophil counts in 2010 to asthma outcomes in 2011 in AS-COPD

Univariate analyses. Compared with a blood eosinophil count < 400 cells/mm³, blood eosinophils ≥ 400 cells/mm³ in 2010 in AS-COPD was associated in 2011 with a significantly

TABLE II. Relationship between the last blood eosinophil count (high vs low) in 2010 at various cutoff points in AS-COPD and asthma exacerbations in 2011

Blood eosinophil cutoff point/mm ³	Any blood eosinophil determination (n = 901)		Restricted blood eosinophil determination* (n = 563)	
	χ^2	P value	χ^2	P value
≥ 100 cells/mm ³ vs < 100 cells/mm ³	0.33	.57	1.33	.25
≥ 150 cells/mm ³ vs < 150 cells/mm ³	0.27	.60	0.72	.40
≥ 200 cells/mm ³ vs < 200 cells/mm ³	0.96	.33	2.53	.11
≥ 250 cells/mm ³ vs < 250 cells/mm ³	1.12	.29	2.84	.09
≥ 300 cells/mm ³ vs < 300 cells/mm ³	0.62	.43	0.66	.42
≥ 350 cells/mm ³ vs < 350 cells/mm ³	4.32	.04	2.43	.12
≥ 400 cells/mm ³ vs < 400 cells/mm ³	6.37	.01	4.60	.03
≥ 450 cells/mm ³ vs < 450 cells/mm ³	4.91	.03	5.18	.02
≥ 500 cells/mm ³ vs < 500 cells/mm ³	1.38	.24	1.43	.23

AS-COPD, Persistent asthma with coding for COPD spectrum of diagnoses.

Bold values indicate significant differences between comparisons at $P < .05$.

*Restricted blood eosinophil determinations excluded those blood counts associated with systemic corticosteroid course, infection, or antiviral or antibiotic medication in the prior 15 d.

greater unadjusted rate ratio (RR) of asthma exacerbations (1.61; 95% CI, 1.18-2.20, $P = .003$) and greater unadjusted risk ratios for at least 1 (1.35, 95% CI, 1.08-1.68, $P = .01$) and 2 or more

TABLE III. Comparison of demographics, comorbidities, and asthma burden in 2010 in patients with AS-COPD with blood eosinophil cutoff point $\geq 400/\text{mm}^3$ vs $< 400/\text{mm}^3$ (data as n [%] or as noted)

Demographics/clinical features (2010)	Blood eosinophils $\geq 400/\text{mm}^3$ (n = 169)	Blood eosinophils $< 400/\text{mm}^3$ (n = 732)	P value*
Age (y), mean $\pm$ SD	53.2 $\pm$ 9.1	54.3 $\pm$ 8.7	.09
≥ 40 y	154 (91.1)	680 (92.9)	.43
Female sex	94 (55.6)	470 (64.2)	.04
Ethnicity			.41
White	87 (51.5)	412 (56.3)	
Black	33 (19.5)	141 (19.3)	
Hispanic	29 (17.2)	124 (16.9)	
Native American/Native Alaskan	0 (0)	2 (0.3)	
Asian/Pacific Islander	13 (7.7)	29 (4.0)	
Multiple, others	3 (1.8)	9 (1.2)	
Unknown	4 (2.4)	15 (2.0)	
Estimated household income by geocoding (US dollars), mean $\pm$ SD	65,545 $\pm$ 28,479	62,402 $\pm$ 26,781	.20
Estimated family education level < high school diploma by geocoding, mean % $\pm$ SD	23.8 $\pm$ 16.8	24.6 $\pm$ 16.2	.40
Length of health plan enrollment, y, mean $\pm$ SD	16.5 $\pm$ 10.4	18.1 $\pm$ 10.5	.054
Insurances†			
Commercial	138 (81.7)	587 (80.2)	.66
Medicaid and other state sponsored	14 (8.3)	59 (8.1)	.92
Medicare	12 (7.1)	61 (8.3)	.60
Private pay	6 (3.6)	40 (5.5)	.31
Smoking status			.01
Current	21 (12.5)	150 (20.7)	
Passive	4 (2.4)	7 (1.0)	
Quit	69 (41.1)	318 (44.0)	
Never	74 (44.0)	248 (34.3)	
	(n = 168)	(n = 723)	
Body mass index			
Mean $\pm$ SD	31.7 $\pm$ 7.7	32.6 $\pm$ 8.8	.28
Obese (≥ 30 kg/m ²)	87 (51.5)	399 (54.7)	.44
	(n = 169)	(n = 729)	
Charlson Comorbidity Index, mean $\pm$ SD	1.5 $\pm$ 1.0	1.7 $\pm$ 1.2	.16
Asthma ICD-9 code (2009 or 2010)	141 (83.4)	575 (78.6)	.16
Any rhinitis	76 (45.0)	247 (33.7)	.01
Gastroesophageal reflux	42 (24.9)	237 (32.4)	.06
Chronic sinusitis	50 (29.6)	157 (21.4)	.02
Pneumonia	15 (8.9)	113 (15.4)	.03
Nasal polyps	20 (11.8)	18 (2.5)	<.001
Eczema	3 (1.8)	9 (1.2)	.58
Allergist visit	44 (26.0)	154 (21.0)	.16
Pulmonologist visit	40 (23.7)	167 (22.8)	.81
Any asthma specialist visit	76 (45.0)	281 (38.4)	.11
Post-bronchodilator FEV ₁ /FVC <0.7	16 (51.6)	94 (61.8)	.29
	(n = 31)	(n = 152)	
Blood eosinophil concentration in cells/mm ³ , mean $\pm$ SD	684 $\pm$ 283	161 $\pm$ 106	Not applicable
12-mo GINA step-care level			.002
Step 1	8 (4.7)	62 (8.5)	
Step 2	15 (8.9)	58 (7.9)	
Step 3	43 (25.4)	215 (29.4)	
Step 4	88 (52.1)	379 (51.8)	
Step 5	14 (8.3)	16 (2.2)	
Unclassified	1 (0.6)	2 (0.3)	

(continued)

TABLE III. (Continued)

Demographics/clinical features (2010)	Blood eosinophils $\geq 400/\text{mm}^3$ (n = 169)	Blood eosinophils $< 400/\text{mm}^3$ (n = 732)	P value*
Any ICS dispensed			.69
None	15 (8.9)	85 (11.6)	
Low dosage	15 (8.9)	72 (9.8)	
Medium dosage	81 (47.9)	346 (47.3)	
High dosage	58 (34.3)	229 (31.3)	
Any ICS/LABA dispensed			.83
None	77 (45.6)	340 (46.4)	
Low dosage	6 (3.6)	29 (4.0)	
Medium dosage	38 (22.5)	179 (24.5)	
High dosage	48 (28.4)	184 (25.1)	
Leukotriene modifiers	46 (27.2)	160 (21.9)	.13
Theophylline	8 (4.7)	23 (3.1)	.31
Omalizumab	0 (0)	1 (0.1)	1.00
Controller equivalent canisters dispensed, mean $\pm$ SD	8.9 $\pm$ 6.3	8.8 $\pm$ 7.3	.35
≥ 9 controller canisters dispensed	86 (50.9)	336 (45.9)	.24
Asthma Medication Ratio ≥ 0.5	101 (59.8)	414 (56.6)	.45
SABA canisters dispensed, mean $\pm$ SD	8.1 $\pm$ 7.0	7.9 $\pm$ 7.7	.39
≥ 7 SABA canisters dispensed	79 (46.7)	323 (44.1)	.54
Asthma exacerbations, rate/y (95% CI)	1.08 (0.84-1.38)	0.64 (0.56-0.73)	<.001
≥ 1 asthma exacerbation	78 (46.2)	252 (34.4)	.004
≥ 2 asthma exacerbations	48 (28.4)	118 (16.1)	<.001
≥ 1 asthma ED visit or hospitalization	37 (21.9)	129 (17.6)	.20

ED, Emergency department; GINA, Global Initiative for Asthma; ICD-9, the International Classification of Diseases, 9th Revision; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: χ^2 test (categorical), Wilcoxon rank sum test (continuous), and χ^2 test, based on likelihood ratio for exacerbation rate comparisons.

†Patients may have more than 1 insurance plan.

TABLE IV. Unadjusted rate or risk ratio of asthma outcomes in 2011 for patients with AS-COPD with blood eosinophils ≥ 400 cells/ mm^3 vs < 400 cells/ mm^3 in 2010

Asthma outcomes in 2011	Eosinophils ≥ 400 cells/ mm^3 (n = 169)	Eosinophils < 400 cells/ mm^3 (n = 732)	Unadjusted rate or risk ratio (95% CI)*	P value*
Asthma exacerbation, rate/y (95% CI)	0.81 (0.61-10.5)	0.50 (0.43-0.57)	1.61 (1.18-2.20)	.003
Any asthma exacerbation, n (%)	65 (38.5)	209 (28.6)	1.35 (1.08-1.68)	.01
≥ 2 asthma exacerbations, n (%)	36 (21.3)	87 (11.9)	1.79 (1.26-2.54)	.001
Any asthma ED/hospitalization, n (%)	17 (10.1)	73 (10.0)	1.01 (0.61-1.66)	.97
≥ 7 SABA canisters dispensed, n (%)	73 (43.2)	282 (38.5)	1.12 (0.92-1.36)	.25

ED, Emergency department; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*Negative binomial and Poisson regression models with robust error variance were used to estimate the rate ratio and risk ratio, respectively, their 95% CIs, and to derive the P values.

asthma exacerbations (1.79, 95% CI, 1.26-2.54, $P = .001$). An analysis including patients with AS-COPD without a COA diagnosis (n = 283) yielded a similar RR for asthma exacerbations (1.51; 95% CI, 0.71-3.23). No differences in asthma ED visits or hospitalizations or ≥ 7 SABA canisters dispensed in 2011 were observed at the blood eosinophil 400 cell/ mm^3 cutoff (Table IV). A blood eosinophil cutoff point ≥ 300 cells/ mm^3 compared with < 300 cell/ mm^3 also evidenced an increased rate and risk of 2 or more asthma exacerbations, although appeared to be a smaller increase versus the 400 cells/ mm^3 cutoff (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Multivariable analyses. In multivariable analyses that examined the relationship between blood eosinophil levels and future asthma exacerbation, an eosinophil cutoff point of ≥ 400 cells/ mm^3 was associated with a 44% increase in rate of asthma exacerbations (RR, 1.44; 95% CI, 1.09-1.90, $P = .01$) (Table V). There appeared to be an elevated risk of at least 1 asthma exacerbation (risk ratio, 1.20; 95% CI, 0.98-1.48, $P = .08$) in 2011; however, it did not reach statistical significance (Table V). The following baseline (2010) covariates remained statistically significant at the .05 level in the final multivariable model estimating the RR of asthma exacerbation in 2011, with the eosinophil cutoff categorized as ≥ 400 cells/ mm^3 versus

TABLE V. Unadjusted and adjusted effects of blood eosinophils at various cutoff points in 2010 on rate ratio* and risk ratio† of asthma exacerbations in 2011 in AS-COPD (n = 901)

Eosinophil cutoff points as cells/mm ³ , % of patients	Unadjusted rate ratio* (95% CI)	P value	Adjusted rate ratio*,‡ (95% CI)	P value§	Unadjusted risk ratio† (95% CI)	P value	Adjusted risk ratio†, (95% CI)	P value
≥150 (60.0%) vs <150 (40.0%)	0.98 (0.76-1.28)	.91	0.91 (0.72-1.16)	.46	0.95 (0.78-1.16)	.60	0.90 (0.75-1.08)	.27
≥200 (47.2%) vs <200 (52.8%)	1.20 (0.93-1.56)	.16	1.03 (0.81-1.31)	.79	1.10 (0.91-1.34)	.33	0.99 (0.83-1.19)	.91
≥300 (28.9%) vs <300 (71.1%)	1.36 (1.03-1.80)	.03	1.13 (0.88-1.46)	.33	1.09 (0.88-1.35)	.43	0.98 (0.81-1.19)	.81
≥400 (18.8%) vs <400 (81.2%)	1.61 (1.18-2.20)	.003	1.44 (1.09-1.90)	.01	1.35 (1.08-1.68)	.01	1.20 (0.98-1.48)	.08

Bold values indicate significant differences between comparisons at $P < .05$.

*Negative binomial regression was used to estimate the unadjusted and the adjusted rate ratio.

†Poisson regression with robust error variance was applied to estimate the unadjusted and the adjusted risk ratio.

‡Age, sex, body mass index, geocoded education, and eosinophil cut point are forced into the model, ethnicity, smoking, insurance status, gastroesophageal reflux, rhinitis, sinusitis, pneumonia, Global Initiative for Asthma step-care level, ≥ 7 short-acting β_2 -agonists (SABA) canisters dispensed, controller equivalent canisters dispensed, 2010 asthma exacerbation, allergist visit, diagnoses of chronic obstructive asthma (COA) or chronic obstructive pulmonary disease are in the candidate pool, and stepwise variable selection was used.

§After stepwise variable selection, final negative binomial adjusted for age, sex, obesity, geocoded education, ethnicity, COA, ≥ 7 SABA canisters dispensed, and history of prior asthma exacerbations in 2010.

||Poisson regression models adjusted for age, sex, obesity, geocoded education, ethnicity, COA, ≥ 9 controller equivalent canisters dispensed, ≥ 7 SABA canisters dispensed, and history of prior asthma exacerbations in 2010.

<400 cell/mm³ for female sex (RR, 1.34; 95% CI, 1.03-1.74, $P = .03$), obesity (RR, 1.33; 95% CI, 1.04-1.70, $P = .02$), COA (RR, 1.65; 95% CI, 1.23-2.21, $P < .001$), prior year asthma exacerbations (RR, 3.37; 95% CI, 2.63-4.31, $P < .001$), and ≥ 7 SABA canisters dispensed in the prior year (RR, 1.35; 95% CI, 1.07-1.71, $P = .01$). The sensitivity analyses in those patients with only restricted eosinophil determinations confirmed the relationship between blood eosinophil cutoff points and both the rate and risk of at least 1 asthma exacerbation (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

We demonstrated that the group of adult patients excluded from the HEDIS-defined PA cohort because of occurrences of COPD diagnostic coding (AS-COPD) was frequent. Furthermore, these patients also had increased frequencies of comorbidities and disease burden compared with patients with PA. Yet, this AS-COPD population was often understudied either by being excluded or included but not discriminated from those with PA or COPD. The AS-COPD cohort probably includes some patients with true asthma, some with true COPD, and some with an overlap of the two. The significantly greater asthma exacerbation rate in AS-COPD versus PA (Table I) may at least partly be a result of the particularly high rate observed for patients with COA diagnosis (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). In addition, a physician diagnosis of asthma in 2009 or 2010 was observed for 93% of the PA cohort, but was also frequently noted for the AS-COPD cohort as a whole (80%), especially in the COA subset (95%), and less often in the COPD without COA subset (63%) (Table I and Table E2).

Findings such as these provide evidence for the difficulties and challenges faced in real-world clinical settings by physicians in discriminating between asthma and COPD based principally on history, symptoms, and response to medication, without the benefit of spirometry. In the present study, post-bronchodilator FEV₁/FVC was captured administratively in only a minority of patients with AS-COPD and PA (Table I). A level less than 0.7

for this spirometry measure, which is a marker for persistent airway obstruction and a physiologic hallmark for COPD,²⁰ was observed more often for patients with AS-COPD than for those with PA (Table I). Physicians should measure and health plans need to steadfastly promote efforts to obtain lung function in patients with persistent obstructive lung disease for accurate diagnosis and better management. It is discouraging to note only a small increase (from 36.1% in 2006 to 42.5% in 2013) in the frequency health plans that show compliance with the HEDIS quality measure to obtain spirometry in newly diagnosed or newly active COPD.²¹

The accuracy of diagnoses listed in administrative data depends on the certainty and accuracy of clinical diagnoses. However, many challenges persist for the accurate diagnosis of asthma and COPD, and the existence of ACOS complicates the situation even more. The AS-COPD cohort, particularly those with a COA diagnosis, exhibited several characteristics similar to those found in ACOS.²⁰ Similar to ACOS, many patients with AS-COPD were at least 40 years old (93%); had frequent, persistent airflow limitation, when measured (60%); frequent physician diagnosis of asthma (80%); and a more than 2-fold greater asthma exacerbation rate within the COA than AS-COPD subgroups without COA (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). However, the lack of a gold standard clinical definition for ACOS, the difficulty in differentiating it from asthma or COPD clinically, and the absence of clinical and laboratory information (eg, lung function) in administrative data likely translate into formidable challenges in identifying and differentiating these patients in a database setting. Therefore, caution must be taken in studying and interpreting ACOS using administrative data.

In the current study, we demonstrated through multivariable analyses that a high blood eosinophil count was a risk factor for future asthma exacerbations in AS-COPD (Table V). We and others have reported a similar relationship of blood eosinophils to asthma exacerbations in PA^{10,22,23} and in COPD.²⁴⁻²⁶ Airway inflammation plays a critical role in the pathophysiology of both asthma and COPD and its associated exacerbations. The principal type of lung inflammation in PA is eosinophilic and in COPD is neutrophilic,²⁷ but variations in inflammatory cell

signature in both diseases exist. Eosinophilic inflammation is also encountered in sputum of patients with COPD, and, when present, appears to be associated with corticosteroid responsiveness.²⁸ Biomarker measurement in blood and sputum during acute COPD exacerbations identified 4 major patient clusters during exacerbations: bacterial (35%), viral (30%), eosinophilic (24%), and pauci-inflammatory with minimal inflammatory changes (11%).²⁴ Peripheral blood eosinophil count may be a predictor for sputum eosinophilia²⁴ and helped guide a treatment strategy that significantly reduced the number of exacerbations treated with systemic corticosteroids without increasing symptom burden during COPD exacerbations.²⁹ The heterogeneity of COPD is apparent from these studies and as reviewed recently.³⁰

The current study's major limitation is the certainty of COPD diagnoses, especially because they were based solely on an encounter diagnosis code and reliance on a single blood eosinophil measurement (which was captured for only 36% of the otherwise eligible patients with AS-COPD). However, patients with AS-COPD versus without a blood eosinophil measurement manifested features of more severe disease, including more asthma exacerbations and comorbidities (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The relationship of blood eosinophil count to asthma exacerbations observed in this AS-COPD cohort with blood eosinophil determination may, therefore, not be generalizable to AS-COPD without blood eosinophil determination, as one can only speculate how the subgroup without a blood eosinophil determination would affect the association of eosinophil level with future exacerbations, if an eosinophil determination had been made. Although the entire AS-COPD cohort met the HEDIS criteria for asthma, the subgroup with only a COA diagnosis compared with the AS-COPD cohort without a COA diagnosis appears to represent patients with characteristics more consistent with an asthma than a COPD phenotype (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Because of the sample size limitations of the AS-COPD subgroups, it remains uncertain to what extent the COA subgroup influences the association of elevated eosinophil count with asthma exacerbations noted in the entire AS-COPD cohort. Unfortunately, there was insufficient spirometry data to include in the multivariable analyses, and, as with most administrative data studies, relevant variables may be absent for adjustment. However, we included important variables known to influence asthma exacerbations.³¹

In summary, we found that patients with AS-COPD excluded from an HEDIS-defined PA cohort consist of a mix of patients with probably true asthma, true COPD, and a combination of the two. The AS-COPD cohort was sizable and exhibited greater numbers of comorbidities and disease burden than a PA cohort, suggesting that more study should be directed at the AS-COPD population. We also found in this novel administrative data study that high blood eosinophil counts were a risk factor for increased future asthma exacerbations in both unadjusted and adjusted models of data from adults with AS-COPD, as we previously reported in adults¹⁰ and children³² with PA. These findings support a greater disease burden associated with elevated blood eosinophils in both AS-COPD and PA, suggesting a common inflammatory component between these 2 diagnostic classifications. Particularly important, a simple biomarker like blood eosinophil count may enhance identification of patients with many variations of obstructive respiratory diseases at greater

risk for exacerbations in whom institution of more intensive anti-inflammatory therapy directed at eosinophilic inflammation may be beneficial in reducing future exacerbations.³³

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TABLE E1. Comparison of demographics, comorbidities, and asthma burden in 2010 among patients with AS-COPD with or without blood eosinophil determinations (data as n [%] or as noted)

Demographics/clinical features (2010)	With eosinophils (n = 901)	Without eosinophils (n = 1574)	P value*
Age (y), mean $\pm$ SD	54.1 $\pm$ 8.8	53.9 $\pm$ 9.2	.98
≥ 40 y	834 (92.6)	1447 (91.9)	.57
Female sex	564 (62.6)	898 (57.1)	.01
Ethnicity			.01
White	499 (55.4)	945 (60.0)	
Black	174 (19.3)	225 (14.3)	
Hispanic	153 (17.0)	235 (14.9)	
Native American/Native Alaskan	2 (0.2)	4 (0.3)	
Asian/Pacific Islander	42 (4.7)	88 (5.6)	
Multiple, others	12 (1.3)	27 (1.7)	
Unknown	19 (2.1)	50 (3.2)	
Estimated household income by geocoding (US dollars), mean $\pm$ SD	62,990 $\pm$ 27,118	65,894 $\pm$ 27,535	.01
Estimated education level < high school diploma among adults ≥ 25 y of age by geocoding, mean % $\pm$ SD	24.5 $\pm$ 16.3	23.2 $\pm$ 16.8	.01
Length of health plan enrollment, y, mean $\pm$ SD	17.8 $\pm$ 10.5	18.1 $\pm$ 10.2	.26
Insurances†			
Commercial	725 (80.5)	1322 (84.0)	.03
Medicaid or state sponsored	73 (8.1)	59 (3.7)	<.001
Medicare	73 (8.1)	80 (5.1)	.002
Private pay	48 (5.1)	103 (6.5)	.15
Smoking status			.07
Current	171 (19.2)	351 (23.5)	
Passive	11 (1.2)	12 (0.8)	
Quit	387 (43.4)	606 (40.6)	
Never	322 (36.1) (n = 891)	525 (35.1) (n = 1494)	
Body mass index			
Mean $\pm$ SD	32.4 $\pm$ 8.6	30.9 $\pm$ 7.5	<.001
Obese (≥ 30 kg/m ²)	486 (54.1) (n = 898)	743 (48.0) (n = 1548)	.004
Charlson Comorbidity Index, mean $\pm$ SD	1.7 $\pm$ 1.2	1.3 $\pm$ 0.9	<.001
Asthma ICD-9 code (2009 or 2010)	716 (79.5)	1133 (72.0)	<.001
Any rhinitis	323 (35.8)	473 (30.1)	.003
Gastroesophageal reflux	279 (31.0)	269 (17.1)	<.001
Chronic sinusitis	207 (23.0)	280 (17.8)	.002
Pneumonia	128 (14.2)	70 (4.4)	<.001
Nasal polyps	38 (4.2)	48 (3.0)	.13
Eczema	12 (1.3)	28 (1.8)	.40
Allergist visit	198 (22.0)	283 (18.0)	.02
Pulmonologist visit	207 (23.0)	203 (12.9)	<.001
Any asthma specialist visit	357 (39.6)	447 (28.4)	<.001
Postbronchodilator FEV ₁ /FVC <0.7	110 (60.1) (n = 183)	120 (63.8) (n = 188)	.46
12-mo GINA step-care level			.06
Step 1	70 (7.8)	167 (10.6)	
Step 2	73 (8.1)	132 (8.4)	
Step 3	258 (28.6)	456 (29.0)	
Step 4	467 (51.8)	786 (49.9)	
Step 5	30 (3.3)	30 (1.9)	
Unclassified	3 (0.3)	3 (0.2)	

(continued)

TABLE E1. (Continued)

Demographics/clinical features (2010)	With eosinophils (n = 901)	Without eosinophils (n = 1574)	P value*
Any ICS dispensed			.18
None	100 (11.1)	209 (13.3)	
Low dosage	87 (9.7)	176 (11.2)	
Medium dosage	427 (47.4)	728 (46.3)	
High dosage	287 (31.9)	461 (29.3)	
Any ICS/LABA dispensed			0.59
None	417 (46.3)	756 (48.0)	
Low dosage	35 (3.9)	72 (4.6)	
Medium dosage	217 (24.1)	371 (23.6)	
High dosage	232 (25.7)	375 (23.8)	
Leukotriene modifiers	206 (22.9)	286 (18.2)	.005
Theophylline	31 (3.4)	58 (3.7)	.75
Omalizumab	1 (0.1)	4 (0.3)	.66
Controller equivalent canisters dispensed, mean $\pm$ SD	8.8 $\pm$ 7.1	8.7 $\pm$ 6.6	.75
≥ 9 controller canisters dispensed	422 (46.8)	750 (47.6)	.70
Asthma Medication Ratio ≥ 0.5	515 (57.2)	930 (59.1)	.35
SABA canisters dispensed, mean $\pm$ SD	7.9 $\pm$ 7.6	7.5 $\pm$ 7.0	.35
≥ 7 SABA canisters dispensed	402 (44.6)	688 (43.7)	.66
Asthma exacerbations, rate/y (95% CI)	0.72 (0.64-0.81)	0.36 (0.32-0.40)	<.001
≥ 1 asthma exacerbation	330 (36.6)	345 (21.9)	<.001
≥ 2 asthma exacerbations	166 (18.4)	125 (7.9)	<.001
≥ 1 asthma ED visit or hospitalization	166 (18.4)	66 (4.2)	<.001

ED, Emergency department; GINA, Global Initiative for Asthma; ICD-9, the International Classification of Diseases, 9th Revision; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: χ^2 test (categorical), Wilcoxon rank sum test (continuous), and χ^2 test based on likelihood ratio for exacerbation rate comparisons.

†Patients may have more than 1 insurance plan.

TABLE E2. Comparison of demographics, comorbidities, and asthma burden in 2010 in AS-COPD categorized as only COA, AS-COPD without COA, or COA with any COPD diagnosis (data as n [%] or as noted)

Demographics/clinical features (2010)	COA only (n = 312)	AS-COPD without COA (n = 283)	COA with any other COPD diagnosis (n = 306)	P value*
Age (y), mean $\pm$ SD	51.5 $\pm$ 9.9	54.9 $\pm$ 8.4	56.1 $\pm$ 7.2	<.001
≥ 40 y	277 (88.8)	263 (92.9)	294 (96.1)	
Female sex	205 (65.7)	163 (57.6)	196 (64.1)	.10
Ethnicity				.01
White	144 (46.2)	176 (57.6)	179 (58.5)	
Black	80 (25.6)	42 (14.8)	52 (17.0)	
Hispanic	60 (19.2)	46 (16.3)	47 (15.4)	
Native American/Native Alaskan	1 (0.3)	0 (0.0)	1 (0.3)	
Asian/Pacific Islander	18 (5.8)	8 (2.8)	16 (5.2)	
Multiple, others	4 (1.2)	2 (0.7)	6 (1.9)	
Unknown	5 (1.6)	9 (3.2)	5 (1.6)	
Estimated household median income by geocoding (US dollars), mean $\pm$ SD	64,550 $\pm$ 28,065	61,705 $\pm$ 24,940	62,593 $\pm$ 28,065	.48
Estimated education level < high school diploma among adults ≥ 25 y of age by geocoding, mean % $\pm$ SD	24.5 $\pm$ 17.0	24.8 $\pm$ 16.4	24.2 $\pm$ 15.7	.89
Length of health plan enrollment, y, mean $\pm$ SD	18.7 $\pm$ 10.8	17.0 $\pm$ 10.3	17.5 $\pm$ 10.3	.14
Insurances†				
Commercial	246 (78.8)	229 (80.9)	250 (81.7)	.65
Medicaid or state sponsored	34 (10.9)	19 (6.7)	20 (6.5)	.08
Medicare	20 (6.4)	17 (6.0)	36 (11.8)	.02
Private pay	13 (4.2)	16 (5.7)	17 (5.6)	.65
Smoking status				<.001
Current	32 (10.3)	64 (23.1)	75 (24.8)	
Passive	4 (1.3)	3 (1.1)	4 (1.3)	
Quit	111 (35.7)	124 (44.8)	152 (50.2)	
Never	164 (52.7)	86 (31.0)	72 (23.8)	
	(n = 311)	(n = 277)	(n = 306)	
Body mass index				
Mean $\pm$ SD	33.5 $\pm$ 9.2	31.1 $\pm$ 7.9	32.6 $\pm$ 8.4	.01
Obese (≥ 30 kg/m ²)	180 (57.9)	138 (49.1)	168 (54.9)	.10
	(n = 311)	(n = 281)	(n = 306)	
Charlson Comorbidity Index, mean $\pm$ SD	1.5 $\pm$ 1.0	1.6 $\pm$ 1.2	1.9 $\pm$ 1.3	<.001
Asthma ICD-9 code (2009 or 2010)	296 (94.9)	179 (63.3)	241 (78.8)	<.001
Any rhinitis	133 (42.6)	80 (28.3)	110 (35.9)	.001
Gastroesophageal reflux	93 (29.8)	80 (28.3)	106 (34.6)	.21
Chronic sinusitis	91 (29.2)	47 (16.6)	69 (22.5)	.001
Pneumonia	30 (9.6)	41 (14.5)	57 (18.6)	.01
Nasal polyps	20 (6.4)	13 (4.6)	5 (1.6)	.01
Eczema	7 (2.2)	1 (0.4)	4 (1.3)	.13
Allergist visit	95 (30.4)	40 (14.1)	63 (20.6)	<.001
Pulmonologist visit	59 (18.9)	51 (18.0)	97 (31.7)	<.001
Any asthma specialist visit	136 (43.6)	82 (29.0)	139 (45.4)	<.001
Post-bronchodilator FEV ₁ /FVC <0.7	25 (56.8)	33 (55.0)	52 (65.8)	.38
	(n = 44)	(n = 60)	(n = 79)	
Blood eosinophil concentration in cells/mm ³ , mean $\pm$ SD	294 $\pm$ 274	247 $\pm$ 266	236 $\pm$ 224	.003
12-month GINA step-care level				<.001
Step 1	15 (4.8)	37 (13.1)	18 (5.9)	
Step 2	22 (7.1)	27 (9.5)	24 (7.8)	
Step 3	88 (28.2)	87 (30.7)	83 (27.1)	
Step 4	168 (53.8)	127 (44.9)	172 (56.2)	
Step 5	18 (5.8)	3 (1.1)	9 (2.9)	
Unclassified	1 (0.3)	2 (0.7)	0 (0)	

(continued)

TABLE E2. (Continued)

Demographics/clinical features (2010)	COA only (n = 312)	AS-COPD without COA (n = 283)	COA with any other COPD diagnosis (n = 306)	P value*
Any ICS dispensed				<.001
None	25 (8.0)	48 (17.0)	27 (8.8)	
Low dosage	24 (7.7)	33 (11.7)	30 (9.8)	
Medium dosage	145 (46.5)	140 (49.5)	142 (46.4)	
High dosage	118 (37.8)	62 (21.9)	107 (35.0)	
Any ICS/LABA dispensed				<.001
None	135 (43.3)	155 (54.8)	127 (41.5)	
Low dosage	9 (2.9)	12 (4.2)	14 (4.6)	
Medium dosage	68 (21.8)	70 (24.7)	79 (25.8)	
High dosage	100 (32.1)	46 (16.3)	86 (28.1)	
Leukotriene modifiers	88 (28.2)	42 (14.8)	76 (24.8)	<.001
Theophylline	10 (3.2)	11 (3.9)	10 (3.3)	.88
Omalizumab	1 (0.3)	0 (0)	0 (0)	1.0
Controller equivalent canisters dispensed, mean $\pm$ SD	9.4 $\pm$ 8.0	7.7 $\pm$ 6.0	9.2 $\pm$ 7.0	.02
≥ 9 controller canisters dispensed	152 (48.7)	126 (44.5)	144 (47.1)	.59
Asthma Medication Ratio ≥ 0.5	192 (61.5)	155 (54.8)	168 (54.9)	.15
SABA canisters dispensed, mean $\pm$ SD	7.2 $\pm$ 6.8	7.4 $\pm$ 7.3	9.1 $\pm$ 8.4	.009
≥ 7 SABA canisters dispensed	127 (40.7)	115 (40.6)	160 (52.3)	.01
Asthma exacerbations, rate/y (95% CI)	0.97 (0.81-1.16)	0.39 (0.31-0.49)	0.77 (0.64-0.93)	<.001
≥ 1 asthma exacerbation	144 (46.2)	72 (25.4)	114 (37.3)	<.001
≥ 2 asthma exacerbations	83 (26.6)	24 (8.5)	59 (19.3)	<.001
≥ 1 asthma ED visit or hospitalization	76 (24.4)	23 (8.1)	67 (21.9)	<.001

COA, Chronic obstructive asthma; COPD, chronic obstructive pulmonary disease; ED, emergency department; GINA, Global Initiative for Asthma; ICD-9, The International Classification of Diseases, 9th Revision; ICS, inhaled corticosteroids; LABA, Long-acting β_2 -agonist; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: χ^2 test (categorical), Wilcoxon rank sum test (continuous), and χ^2 test based on likelihood ratio for exacerbation rate comparisons.

†Patients may have more than 1 insurance plan.

TABLE E3. Unadjusted rate or risk ratio of asthma outcomes in 2011 among patients with AS-COPD with blood eosinophils ≥ 300 cells/mm³ vs < 300 cells/mm³ in 2010

Asthma outcomes (2011)	Eosinophils ≥ 300 cells/mm ³ (n = 260)	Eosinophils < 300 cells/mm ³ (n = 641)	Unadjusted rate or risk ratio (95% CI)*	P value*
Asthma exacerbation, rate/y (95% CI)	0.68 (0.54-0.86)	0.50 (0.43-0.59)	1.36 (1.03-1.80)	.03
Any asthma exacerbation, n (%)	84 (32.3)	190 (29.6)	1.09 (0.88-1.35)	.43
≥ 2 asthma exacerbations, n (%)	45 (17.3)	78 (12.2)	1.42 (1.01-1.99)	.04
Any asthma ED/hospitalization, n (%)	24 (9.2)	66 (10.3)	0.90 (0.57-1.40)	.63
≥ 7 SABA canisters dispensed, n (%)	110 (42.3)	245 (38.2)	1.11 (0.93-1.32)	.25

ED, Emergency department; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*Negative binomial and Poisson regression models with robust error variance were used to estimate the rate ratio and risk ratio, respectively, their 95% CIs, and to derive the P value.

TABLE E4. Unadjusted and adjusted effects of restricted blood eosinophils (excluded blood counts associated with systemic corticosteroid course, infection, or antiviral or antibiotic medication in the prior 15 d) at various cutoff points in 2010 on rate ratio* and risk ratio† of asthma exacerbations in 2011 in AS-COPD (n = 563)

Eosinophil cutoff points as cells/mm ³ , % of patients	Unadjusted rate ratio* (95% CI)	P value	Adjusted rate ratio* (95% CI)	P value‡	Unadjusted risk ratio† (95% CI)	P value	Adjusted risk ratio† (95% CI)	P value§
≥150 (66.1%) vs <150 (33.9%)	1.23 (0.85-1.77)	.28	1.05 (0.75-1.48)	.77	1.13 (0.85-1.52)	.40	1.0 (0.76-1.31)	.98
≥200 (51.7%) vs <200 (48.3%)	1.39 (0.99-1.97)	.06	1.11 (0.80-1.53)	.55	1.25 (0.95-1.64)	.11	1.03 (0.79-1.34)	.82
≥300 (30.6%) vs <300 (69.4%)	1.55 (1.09-2.22)	.02	1.31 (0.94-1.83)	.11	1.13 (0.85-1.49)	.41	1.01 (0.77-1.33)	.93
≥400 (20.1%) vs <400 (79.9%)	1.74 (1.17-2.58)	.01	1.58 (1.11-2.26)	.01	1.40 (1.04-1.88)	.03	1.28 (0.96-1.70)	.09

Bold indicates comparisons are statistically significant.

*Negative binomial regression was used to estimate the unadjusted and the adjusted rate ratio.

†Poisson regression with robust error variance was applied to estimate the unadjusted and the adjusted risk ratio.

‡After stepwise variable selection, final negative binomial adjusted for age, sex, obesity, geocoded education, ethnicity, chronic obstructive asthma (COA) diagnosis, ≥7 short-acting β₂-agonists (SABA) canisters dispensed, and history of prior asthma exacerbation in 2010.

§Poisson regression models adjusted for age, sex, obesity, geocoded education, ethnicity, COA diagnosis, ≥9 controller equivalent dispensed canisters, ≥7 SABA canisters dispensed, and history of prior asthma exacerbation in 2010.

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