

Original Article

High Blood Eosinophil Count Is a Risk Factor for Future Asthma Exacerbations in Adult Persistent Asthma

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What is already known about this topic? Eosinophilic inflammation hallmarks several phenotypes, and high blood eosinophil counts appear associated with uncontrolled asthma. However, it is not known whether knowledge of blood eosinophil counts will help to identify patients with persistent asthma at increased risk for future asthma exacerbations in asthma population care management.

What does this article add to our knowledge? High blood eosinophil counts in adults with persistent asthma were associated with increased future asthma risk (exacerbations) and excessive short-acting β_2 -agonist use (impairment) in a large managed care organization administrative database study.

How does this study impact current management guidelines? Population care management programs and clinical practice should consider measurement of blood eosinophil count as an additional biologic marker to assist in the identification of persistent adult patients with asthma and with higher risk for future exacerbations and excessive short-acting β_2 -agonist use.

BACKGROUND: Exacerbation-associated uncontrolled asthma represents a major public health problem. The relationship of elevated blood eosinophils to this process needs study.

OBJECTIVE: To determine whether a high blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma.

METHODS: By using electronic pharmacy and health care data from Kaiser Permanente Southern California, 2392 patients, ages 18 to 64 years, were identified who met the Health Effectiveness

Data and Information Set 2-year criteria for persistent asthma, did not manifest chronic obstructive pulmonary disease and other major illnesses, and had a blood eosinophil determination in 2010. Exacerbations (primary outcome) were defined as asthma outpatient visits that required systemic corticosteroid dispensing within ± 7 days or asthma emergency department visits or hospitalizations. A period of ≥ 8 days defined a new exacerbation. Multivariate modelling used negative binomial and Poisson regression to examine the association between a blood eosinophil count determined in 2010 and risk of exacerbations, and ≥ 7 short-acting β_2 -agonist (SABA) canisters dispensed (secondary outcome) in 2011 by adjusting for demographics, comorbidities, and asthma burden.

RESULTS: The rate of asthma exacerbations in 2011 was 0.41 events per person year (95% CI, 0.37-0.45). Eosinophil count $\geq 400/\text{mm}^3$ in 2010 was a risk factor for asthma exacerbations in 2011 (adjusted rate ratio 1.31 [95% CI, 1.07-1.60]; $P = .009$) and ≥ 7 SABA dispensed (adjusted risk ratio 1.17 [95% CI, 1.03-1.33]; $P = .015$).

CONCLUSION: A high blood eosinophil count is a risk factor for increased future asthma exacerbations and excessive short-acting β_2 -agonist use after adjustment of potential confounders in adults with persistent asthma, which suggests a higher disease burden in patients with asthma and with high blood eosinophil counts. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

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Abbreviations used

ED- Emergency department
 GINA- Global Initiative for Asthma
 HEDIS- Healthcare Effectiveness Data and Information Set
 ICS- Inhaled corticosteroid
 KPSC- Kaiser Permanente Southern California
 LABA- Long-acting β_2 -agonist
 MCO- Managed care organization
 PREDUNA- Predictors of Uncontrolled Asthma
 RR- Rate ratio
 SABA- Short-acting β_2 -agonist

Exacerbation-driven uncontrolled asthma is a public health concern¹ and is often associated with unremitting eosinophilic inflammation.² However, the understanding of the relationship of blood eosinophilia to exacerbations remains incomplete. Studies have reported that high blood eosinophil counts are associated with bronchial hyperreactivity and late-phase asthmatic reactions,³ age-dependent interaction with atopy,⁴ airways inflammation in children with a history of wheeze,⁵ uncontrolled asthma,^{6,7} and specific phenotypic asthma clusters⁸⁻¹⁰; and may function as a marker for favorable spirometric and clinical responses to specific asthma medications in adults¹¹⁻¹⁵ and children with persistent asthma.¹⁶⁻¹⁸ Population asthma care management in managed care organizations (MCO) institute programs that use health care utilization and pharmacy dispensing information to (1) find subscribers with persistent asthma by using Healthcare Effectiveness Data and Information Set (HEDIS) definitions,^{19,20} (2) identify and track markers of uncontrolled asthma,²¹ (3) determine amounts of medication dispensing,²² and (4) report asthma quality markers²³ to the National Committee for Quality Assurance. Specific administrative markers predictive of poor asthma outcomes include documented prior year asthma exacerbations (which represents the risk domain of asthma control)^{24,25} and excessive short-acting β_2 -agonist (SABA) canister dispensings (impairment domain of asthma control).²⁶⁻²⁹

Recent studies report responsiveness of moderate-to-severe asthma adults to several biologic antiasthma medications based on total blood eosinophil counts.^{11,30,31} Given these findings, we were interested in understanding the relationship of blood eosinophil counts at different cutoff points to subsequent asthma burden in a cohort of adult patients with persistent asthma. This information could help recognize the blood eosinophil count as a practical biologic marker to identify patients with persistent asthma who are at increased risk for future asthma exacerbations. To address this objective, we conducted a retrospective cohort study, the Predictors of Uncontrolled Asthma (PREDUNA) study, to determine the relationship of blood eosinophil counts to future asthma exacerbations by using administrative data in a large MCO. We hypothesized that a high blood eosinophil count is a relevant risk factor for future exacerbations in adult patients with persistent asthma.

METHODS**PREDUNA study protocol**

The PREDUNA study was a retrospective cohort study that examined the relationship between the blood eosinophil count at baseline (2010) and asthma exacerbations in the following 12 months (2011). The study used the Kaiser Permanente Southern

California (KPSC) research data warehouse to capture pharmacy and health care utilization data to identify patients with persistent asthma and to determine asthma-related outcomes (Figure 1, A). The KPSC Institutional Review Board approved the study with a waiver of written consent.

PREDUNA patients

Patients ages 18 to 64 years were identified with HEDIS-defined 2-year persistent asthma (2009 and 2010)^{19,20} and continuous health plan enrollment and pharmacy benefit in 2009 to 2011 (no gap of ≥ 45 days within each calendar year).¹⁹ Exclusions included encounter diagnoses of chronic obstructive pulmonary disease and other chronic conditions that are listed in the legend to Figure 1, A. The final cohort consisted of patients with a complete blood count with differential in 2010 to allow calculation of a total blood eosinophil count.

Blood eosinophil counts

Total peripheral blood eosinophil counts were calculated from the last complete blood count with differential obtained from each patient in 2010. The unadjusted relationship of blood eosinophil counts in 2010 to the frequency of asthma exacerbations in 2011 was determined by analyzing blood eosinophil cutoff points, from 100/mm³ to 500/mm³ by 50/mm³ increments to subsequent exacerbation. In multivariate analyses, we studied 4 blood eosinophil cutoff points of 150/mm³, 200/mm³, 300/mm³, and 400/mm³. Given that blood eosinophil counts can be influenced by asthma medication, especially oral corticosteroids and infection, we performed sensitivity analyses in a subgroup of patients for whom blood eosinophil counts were excluded if associated with systemic corticosteroid courses, infections, or systemic antibiotics and/or antiviral medications in the prior 15 days (named restricted eosinophil cohort) (see this article's Online Repository at www.jaci-inpractice.org).

Outcome measures

The objective was to determine whether blood eosinophil counts obtained in 2010 are associated with an increased risk of future asthma exacerbations in 2011 (primary analysis) and 7 or more SABA canister dispensings in 2011, equivalent to ≥ 4 puffs/d/y and an administrative marker for uncontrolled asthma²⁶ (secondary analysis). Asthma exacerbations were defined as worsening asthma that required systemic corticosteroids ± 7 days of an outpatient visit by using KPSC extension codes indicative of uncontrolled asthma status (ie, acute exacerbation, status asthmaticus, acute asthma attack, uncontrolled asthma, or asthmatic bronchitis) or an emergency department (ED) visit or hospitalization with a primary asthma diagnosis or secondary asthma diagnosis when there was a primary respiratory diagnosis based on the International Classification of Diseases, Ninth Revision coding.³² A period of at least 8 days between episodes defined a new exacerbation.

Asthma medication step-care levels

Determination of a patient's Global Initiative for Asthma (GINA) medication step-care level at baseline (2010) used an algorithm and formula previously reported (see this article's Online Repository at www.jaci-inpractice.org).³³ Patients with asthma were categorized into GINA step-care levels as follows: step-care 1, no medication or SABA only; step-care 2, low-dose inhaled corticosteroid (ICS), leukotriene modifier or theophylline; step-care 3, low-dose ICS plus at least 1 of a long-acting

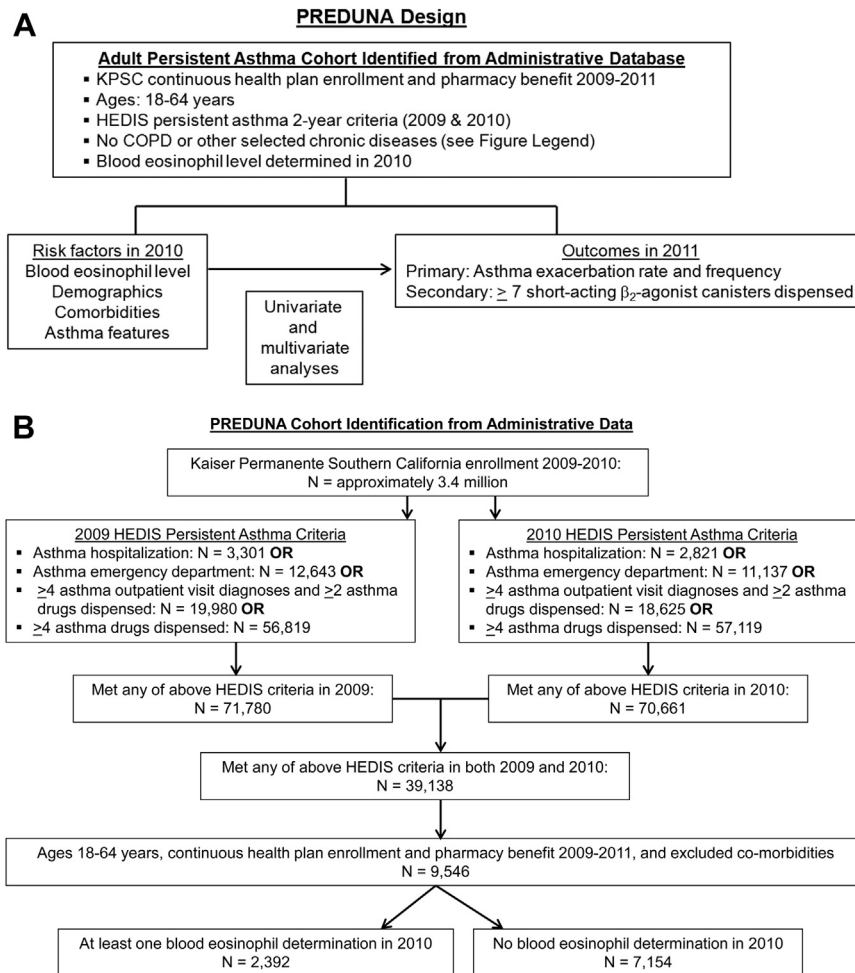


FIGURE 1. The study design, administrative logistics for patient identification, and number of patients identified with administrative databases. A, Summary of study design. Excluded patients had encounter diagnoses of chronic obstructive lung disease; emphysema; cystic fibrosis; chronic bronchitis; bronchiectasis; Churg Strauss syndrome; Wegener syndrome; 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, An administrative algorithm for patient identification of the adult persistent asthma cohort.

β_2 -agonist (LABA), a leukotriene modifier or theophylline, or medium- to high-dose ICS alone; step-care 4, medium- or high-dose ICS plus at least 1 of an LABA (including high-dose 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/y of prednisone equivalent or a diagnosis of steroid-dependent asthma and/or omalizumab treatment. 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.

Statistical analyses

Patient demographics, comorbidities, asthma characteristics, and features in 2010 between the patients with and those without eosinophil determinations or by blood eosinophil count were compared by using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. The unadjusted and the adjusted rate ratios (RR) and the 95% CIs were estimated by using negative binomial models (a method used to

estimate overdispersed or high variability in event counts). Poisson regression models with a robust error variance were applied to calculate the unadjusted and the adjusted risk ratios and their 95% CIs.³³ Covariates determined in 2010 and considered in model selection included age (continuous), sex, obesity (yes or no), geocoded education,³³ enrollment duration, ethnicity, smoking status, insurance type, Charlson comorbidity index, relevant comorbidities (gastroesophageal reflux, rhinitis, chronic sinusitis, nasal polyps, eczema), medication dispensings (leukotriene modifiers, theophylline, omalizumab, and ≥ 7 SABA canisters dispensed), HEDIS-defined asthma treatment adherence (≥ 9 vs < 9 controllers per year),³⁴ GINA step-care level, history of asthma exacerbations, and blood eosinophil count. Age, sex, obesity, geocoded education, and blood eosinophil count were forced into the models. For negative binomial regression, the likelihood ratio test was used to compare any 2 nested models in a stepwise approach with the alpha count being set at .05. For robust Poisson models, quasi-likelihood under the independence model criterion was used to compare any 2 models

TABLE I. Comparison of demographics, comorbidities, and asthma features at baseline in 2010 among adult patients with persistent asthma and with blood eosinophil levels $\geq 400/\text{mm}^3$ vs $< 400/\text{mm}^3$

Demographics and clinical features	Blood eosinophils $\geq 400/\text{mm}^3$ (n = 437)	Blood eosinophils $< 400/\text{mm}^3$ (n = 1955)	Total patients (n = 2392)	P value*
Age (y), mean $\pm$ SD	44.8 $\pm$ 13.28	47.4 $\pm$ 12.19	47.0 $\pm$ 12.43	<.001
Female sex, no. (%)	310 (70.9)	1374 (70.3)	1684 (70.4)	.79
Race and/or ethnicity, no. (%)				.03
White	192 (43.9)	893 (45.7)	1085 (45.4)	
Black	61 (14.0)	359 (18.4)	420 (17.6)	
Hispanic	119 (27.2)	481 (24.6)	600 (25.1)	
Native American/Native Alaskan	2 (0.5)	5 (0.3)	7 (0.3)	
Asian and/or Pacific Islander	38 (8.7)	139 (7.1)	177 (7.4)	
Multiple, others	10 (2.3)	31 (1.6)	41 (1.7)	
Unknown	15 (3.4)	47 (2.4)	62 (2.6)	
Estimated household income by geocoding (\$), mean $\pm$ SD	67,300 $\pm$ 28,239	67,652 $\pm$ 29,942	67,587 $\pm$ 29,633	.87
Estimated family education level $\leq$ grade 12 by geocoding (%), mean $\pm$ SD	23.8 $\pm$ 17.8	22.9 $\pm$ 17.5	23.0 $\pm$ 17.6	.33
Body mass index (kg/m^2), mean $\pm$ SD	32.0 $\pm$ 8.9	32.2 $\pm$ 8.3	32.1 $\pm$ 8.4	.48
Obese $\geq 30 \text{ kg}/\text{m}^2$, no. (%)	228 (52.2)	1048 (53.6)	1276 (53.3)	.61
Missing body mass index, no. (%)	1 (0.2)	10 (0.5)	11 (0.5)	
Smoking status, no. (%)				.24
Yes	26 (5.9)	129 (6.6)	155 (6.5)	
Passive	6 (1.4)	13 (0.7)	19 (0.8)	
Quit	117 (26.8)	527 (27.0)	644 (26.9)	
Never	276 (63.2)	1256 (64.2)	1532 (64)	
Missing	12 (2.7)	30 (1.5)	42 (1.8)	
Length of health plan enrollment (y), mean $\pm$ SD	15.8 $\pm$ 11.0	16.7 $\pm$ 10.3	16.5 $\pm$ 10.5	.03
Insurances, no. (%)†				
Commercial	395 (90.4)	1686 (86.2)	2081 (87.0)	.02
Medicaid	22 (5)	155 (7.9)	177 (7.4)	.04
Medicare	10 (2.3)	71 (3.6)	81 (3.4)	.16
Private pay	19 (4.3)	106 (5.4)	125 (5.2)	.36
Charlson comorbidity index, mean $\pm$ SD	1.3 $\pm$ 0.83	1.3 $\pm$ 0.94	1.3 $\pm$ 0.92	.90
Rhinitis, no. (%)	160 (36.6)	705 (36.1)	865 (36.2)	.83
Gastroesophageal reflux, no. (%)	93 (21.3)	548 (28.0)	641 (26.8)	.004
Chronic sinusitis, no. (%)	74 (16.9)	374 (19.1)	448 (18.7)	.29
Pneumonia, no. (%)	29 (6.6)	133 (6.8)	162 (6.8)	.90
Eczema, no. (%)	21 (4.8)	42 (2.1)	63 (2.6)	.002
Nasal polyps, no. (%)	22 (5.0)	29 (1.5)	51 (2.1)	<.001
Allergist visit, no. (%)	94 (21.5)	454 (23.2)	548 (22.9)	.44
12-Mo GINA step-care level, no. (%)				.003
1	34 (7.8)	210 (10.7)	244 (10.2)	
2	53 (12.1)	264 (13.5)	317 (13.3)	
3	122 (27.9)	646 (33)	768 (32.1)	
4	214 (49)	807 (41.3)	1021 (42.7)	
5	13 (3)	26 (1.3)	39 (1.6)	
Unclassified	1 (0.2)	2 (0.1)	3 (0.1)	
Any ICS dispensed, no. (%)				.07
Low dose	73 (16.7)	324 (16.6)	397 (16.6)	
Medium dose	210 (48.1)	940 (48.1)	1150 (48.1)	
High dose	105 (24)	390 (19.9)	495 (20.7)	
None	49 (11.2)	301 (15.4)	350 (14.6)	
Any ICS-LABA dispensed, no. (%)				.001
Low dose	32 (7.3)	114 (5.8)	146 (6.1)	
Medium dose	112 (25.6)	420 (21.5)	532 (22.2)	
High dose	90 (20.6)	312 (16.0)	402 (16.8)	
None	203 (46.5)	1109 (56.7)	1312 (54.8)	

(continued)

TABLE I. (Continued)

Demographics and clinical features	Blood eosinophils ≥400/mm ³ (n = 437)	Blood eosinophils <400/mm ³ (n = 1955)	Total patients (n = 2392)	P value*
Leukotriene modifiers, no. (%)	95 (21.7)	443 (22.7)	538 (22.5)	.68
Theophylline, no. (%)	7 (1.6)	37 (1.9)	44 (1.8)	.68
Omalizumab, no. (%)	3 (0.7)	3 (0.2)	6 (0.3)	.04
Controller equivalent canisters dispensed, mean ± SD	7.4 ± 5.7	7.4 ± 6.0	7.4 ± 5.9	.71
≥9 Controller equivalent canisters dispensed, no. (%)	147 (33.6)	733 (37.5)	880 (36.8)	.13
≥7 SABA canister dispensed, no. (%)	170 (38.9)	601 (30.7)	771 (32.2)	.001
No. asthma exacerbations, mean ± SD	0.7 ± 1.2	0.5 ± 1.0	0.5 ± 1.0	<.001
Rate of asthma exacerbations (95% CI)	0.7 (0.62-0.85)	0.5 (0.46-0.54)	0.5 (0.51-0.58)	<.001
≥1 Asthma exacerbation, no. (%)	176 (40.3)	610 (31.2)	786 (32.9)	<.001
≥2 Asthma exacerbations, no. (%)	76 (17.4)	211 (10.8)	287 (12.0)	<.001
Any asthma emergency visit or hospitalization, no. (%)	74 (16.9)	232 (11.9)	306 (12.8)	.004

*Determined by the χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.

†Patients may have more than 1 insurance plan.

TABLE II. Relationship of blood eosinophil level cutoff points for patients with all or restricted blood eosinophil determinations in 2010 to frequency of asthma exacerbations in 2011

Blood eosinophil cutoff point/mm ³	All blood eosinophil determinations (n = 2392)		Restricted blood eosinophil determinations (n = 1667)*	
	χ^2 test	P value	χ^2 test	P value
<100 vs ≥100	1.08	.30	0.13	.72
<150 vs ≥150	0.55	.46	0.11	.74
<200 vs ≥200	2.02	.16	0.05	.82
<250 vs ≥250	4.44	.04	2.09	.15
<300 vs ≥300	4.87	.03	2.46	.12
<350 vs ≥350	8.96	.003	2.57	.11
<400 vs ≥400	14.31	<.001	6.36	.01
<450 vs ≥450	14.62	<.001	7.47	.01
<500 vs ≥500	13.16	<.001	4.90	.03

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

in a stepwise approach. The model with the smaller quasi-likelihood under the independence model criterion was preferred. To simplify the design, we assumed that potential confounders do not vary by the cutoff point of the blood eosinophil count and used the models that involved the most-robust eosinophil cutoff point to determine potential confounders. The covariates selected for the final models of this cutoff point were applied to regression models of the same outcome with other blood eosinophil cutoff points. Interaction (cross product) terms were attempted and were kept in the models if they were statistically significant ($P < .05$, 2-tailed). All analyses were conducted by using SAS (version 9.2 for Windows; SAS Institute, Cary, NC).

RESULTS

Identification of patients with persistent asthma

When applying HEDIS criteria for persistent asthma, 71,780 and 70,661 patients of all ages with persistent asthma were identified in 2009 and 2010, respectively, with 55% ($n = 39,138$) fulfilling the 2-year definition of persistent asthma (Figure 1, B). After exclusion of patients due to noncontinuous membership or pharmacy benefit, age limitation, and specific diseases, 9546 adults 18 to 64 years of age with persistent asthma were identified, with 2392 (25.1%) having had at least 1 blood cell count with an eosinophil count in 2010. Patients with eosinophil determinations compared with those without eosinophil determinations in 2010

evidenced different demographic frequencies, more comorbidities, and burdensome asthma (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Characteristics of the persistent asthma cohort with eosinophil counts

The study cohort ($n = 2392$) had a mean age of 47 years, 71% women, predominately nonwhite (52%); the majority were obese (mean body mass index, 32.1 kg/m²), infrequent current smokers (6.5%), had a mean family income of approximate \$67,600, were long-term health plan members (16.5 years), were predominately commercial insurance members (87%), had high frequencies of comorbidities (ie, rhinitis, gastroesophageal reflux disease, and chronic sinusitis), and frequent features of uncontrolled asthma (Table I).

Characteristics of the cohort by blood eosinophil count

Statistically significant associations were observed between the eosinophil count in 2010 and exacerbation frequency (yes or no) in 2011 starting at ≥250/mm³ in all eosinophil determinations and at ≥400/mm³ in restricted eosinophils (no systemic corticosteroids, infections, or systemic antibiotics and/or antiviral medications within 15 days before the blood cell count) ($P < .01$) blood eosinophil determinations (Table II). Given this

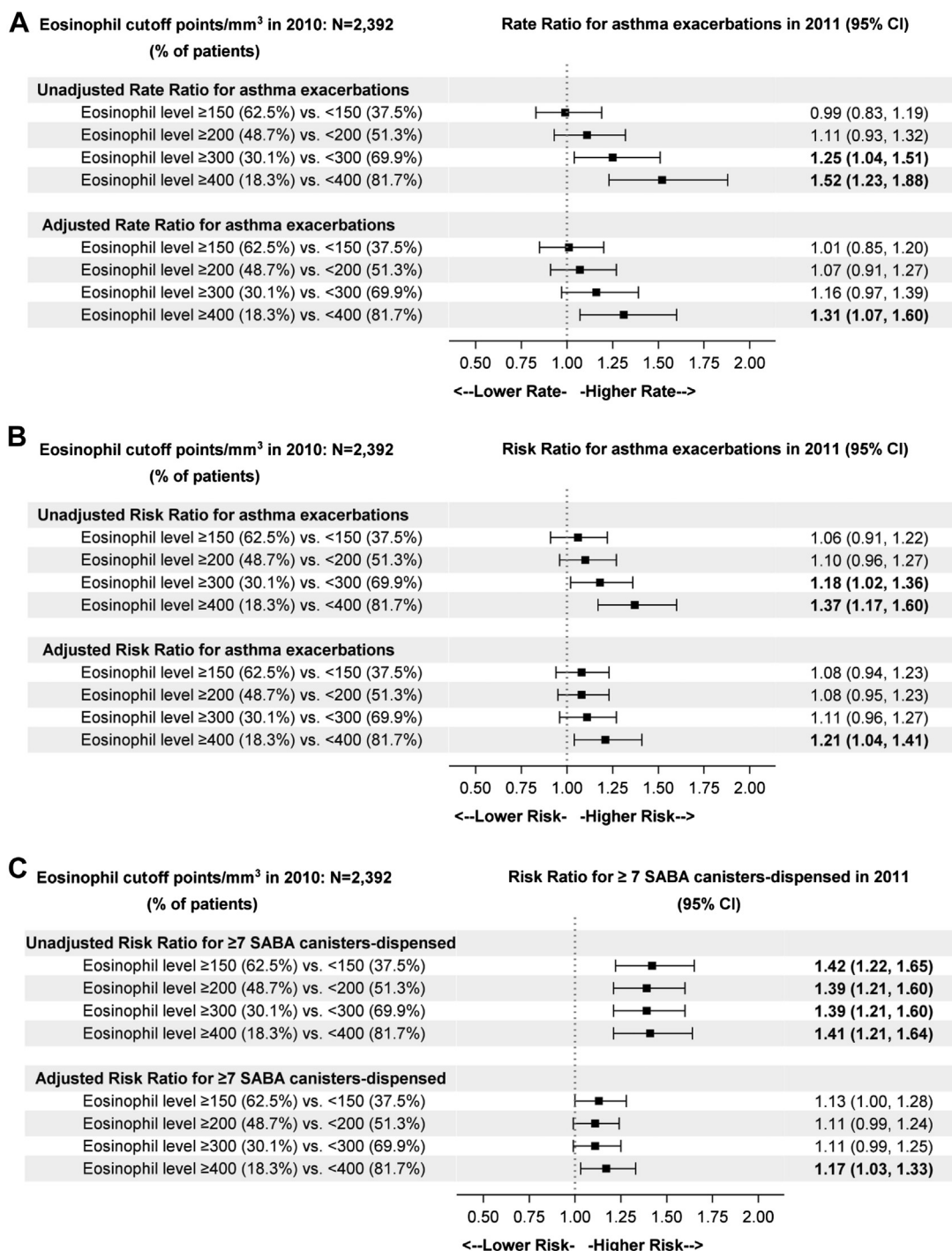


FIGURE 2. Unadjusted and adjusted effects of various eosinophil cutoff points in 2010 on asthma exacerbations and ≥7 SABA canisters dispensed in 2011. A, A negative binomial model was used, and the covariates in the adjusted models were age, sex, obesity, geocoded education, ethnicity, GINA step-care level, ≥7 SABA canisters dispensed, and a history of prior asthma exacerbation in 2010. B, A Poisson model with a robust error variance was used, and the covariates in the adjusted models were age, sex, obesity, geocoded education, race and/or ethnicity, GINA step-care level, ≥7 SABA canisters dispensed, and a history of prior asthma exacerbation in 2010. C, A Poisson model with a robust error variance was used, and the covariates in the adjusted models were age, sex, obesity, geocoded education, eczema, rhinitis, and ≥7 SABA canisters dispensed in 2010.

finding, we constructed final multivariate models by using the blood eosinophil cutoff point of $400/\text{mm}^3$ and applied the selected covariates to other models of the same outcome with other blood eosinophil cutoff points.

At baseline, in 2010, patients with blood eosinophil counts $\geq 400/\text{mm}^3$ versus $<400/\text{mm}^3$ were significantly (1) younger; (2) health plan members of shorter duration; (3) more commercial and fewer Medicaid insurance subscribers; (4) had gastroesophageal reflux disease less frequently, but nasal polyps and eczema more frequently; and (5) a history in 2010 of more burdensome asthma manifested by higher GINA step-care levels, more-frequent dispensing of ICS-LABA combinations, higher rates and frequency of asthma exacerbations, and higher frequencies of asthma ED visits, hospitalization, and ≥ 7 SABA canisters dispensed in 2010 (Table I).

Relationship of blood eosinophil counts in 2010 to asthma outcomes 2011

We next determined the relationship of the blood eosinophil count in 2010 at 4 selected cutoff points ($150/\text{mm}^3$, $200/\text{mm}^3$, $300/\text{mm}^3$, and $400/\text{mm}^3$) to the rate and frequency of future asthma exacerbation in 2011 and the frequency of patients with ≥ 7 SABA canisters dispensed in 2011.

Exacerbations in 2011. In unadjusted analyses, high blood eosinophil counts were associated with an increased rate as well as frequency (% of patients) of future exacerbations in 2011, starting at $\geq 300/\text{mm}^3$, and the associations were strongest at the $\geq 400/\text{mm}^3$ blood eosinophil cutoff point (Figure 2, A and B). Patients with blood eosinophil counts $\geq 400/\text{mm}^3$ compared with those with counts $<400/\text{mm}^3$ exhibited more uncontrolled asthma in 2011 as documented by higher rates and frequency of asthma exacerbations (both $P < .001$), ≥ 2 asthma exacerbations ($P = .02$), asthma ED visits ($P < .001$), asthma hospitalizations ($P = .004$), and ≥ 7 SABA canister dispensings ($P < .001$) (Table III). The blood eosinophil cutoff point of $\geq 300/\text{mm}^3$ also was associated with these increased outcomes, but with relatively smaller effect sizes (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

In multivariate analyses, after adjusting for age, sex, obesity, geocoded education, race and/or ethnicity, GINA step-care level, ≥ 7 SABA canisters dispensed, and a history of asthma exacerbations in 2010, an eosinophil cutoff point of $\geq 400/\text{mm}^3$ was associated with an approximately 30% increase in asthma exacerbation rate (RR 1.31 [95% CI, 1.07-1.60], $P = .009$) (Figure 2, A) and an approximately 20% increase in frequency of any asthma exacerbation (risk ratio 1.21 [95% CI, 1.04-1.41], $P < .02$) in 2011 (Figure 2, B). Among the studied blood eosinophil cutoff points, both unadjusted and adjusted associations with rate and frequency of future exacerbations appeared stronger as cutoff points increased. These findings were confirmed in sensitivity analyses of those patients with only restricted eosinophil determinations (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

For the rate and risk of asthma exacerbations in 2011, the following variables were selected for both final models: a history of asthma exacerbations in 2010 ($P < .001$), GINA step-care levels 4 and 5 versus steps-care levels 1 and 2 ($P \leq .01$), female sex ($P \leq .01$), ≥ 7 SABA canisters dispensed in 2010 ($P \leq .02$), and black versus non-Hispanic white race ($P \leq .02$). Obesity versus not obese ($P = .02$) was associated only with the rate of

asthma exacerbation, and Asian versus non-Hispanic white race ($P = .04$) was associated only with the frequency of any exacerbations in 2011 (Table IV).

≥ 7 SABA canisters dispensed in 2011. Univariate analyses noted that eosinophil cutoff points that started at $\geq 150/\text{mm}^3$ compared with lower values were significantly associated with ≥ 7 SABA canisters dispensed in 2011 (Figure 2, C) and was confirmed in sensitivity analyses by using restricted blood eosinophil determinations (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). In multivariate analyses, all examined eosinophil cutoff points appeared to associate with an increased risk of excessive SABA use in 2011, although only the cutoff point of $\geq 400/\text{mm}^3$ remained statistically significant in the overall analyses (Figure 2, C) and in the sensitivity analysis of restricted blood eosinophil determination ($P < 0.01$) (Table E4 in this article's Online Repository at www.jaci-inpractice.org). In multivariate analyses, prior year ≥ 7 SABA canisters dispensed ($P < .001$) and a diagnosis of eczema ($P < .01$) were associated with an increased relative risk, whereas a diagnosis of rhinitis was associated with a decreased relative risk of ≥ 7 SABA canister dispensings in 2011 (see in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Eosinophilia in blood (tissues also) is a biologic inflammatory marker that links asthma to a specific pathophysiologic phenotype^{3-5,35} and responsiveness to specific medications.^{15-18,36} The PREDUNA study provides evidence that high blood eosinophil counts of adults with persistent asthma are associated with increased risk for future asthma exacerbations and excessive SABA canisters dispensed after adjustments for covariates. High blood eosinophil count was hypothesized as a marker for future asthma exacerbations based on prior studies,^{2,6} but remaining a risk factor after multiple adjustments is a particular novel finding of the present study. In multivariate analysis, the magnitude of increased rate of asthma exacerbations conferred by blood eosinophil counts $\geq 400/\text{mm}^3$ (RR 1.31 [95% CI, 1.07-1.60]) was of the same magnitude as other reported risk factors for increased exacerbations, such as ≥ 7 SABA canister dispensings (RR 1.29 [95% CI, 1.08-1.53]), female sex (RR 1.36 [95% CI, 1.12-1.65]), black versus white race (RR 1.33 [95% CI, 1.06-1.68]), and obesity (RR 1.22 [95% CI, 1.03-1.45]), but markedly less than a history of asthma exacerbation in the baseline year (RR 3.02 [95% CI, 2.55-3.57]), consistently shown to be the strongest risk factor for future asthma exacerbations.^{25,37}

Recently, blood eosinophil counts are being recognized as an important biomarker to help identify patients with moderate-to-severe uncontrolled asthma who appear to experience favorable responses in clinical trials to biologics that reduce blood and tissue eosinophils, such as mepolizumab,¹¹ dupilumab,³¹ lebrikizumab,³⁸ reslizumab,³⁹ or reduce IgE.³⁰ Recently Katz et al¹¹ reported in a *post hoc* clinical trial analysis that a blood eosinophil count $\geq 150/\text{mm}^3$ was a useful biologic marker to predict a favorable response to an anti-IL-5 treatment. Wenzel et al³¹ reported that a blood eosinophil count of $\geq 300/\text{mm}^3$ helped to identify patients with uncontrolled moderate-to-severe asthma who exhibited a favorable clinical response to dupilumab, an inhibitor of the IL-4 receptor.³¹ In the PREDUNA study, we demonstrated that high blood eosinophil counts are associated with more uncontrolled asthma and also higher GINA step-care levels. Other studies report that sputum eosinophilia predicts uncontrolled asthma better than blood

TABLE III. Asthma outcomes with unadjusted rate ratio or risk ratio in 2011 by blood eosinophil cutoff point of 400/mm³ in 2010

Asthma outcomes in 2011	Eosinophil $\geq 400/\text{mm}^3$, no. (%) (n = 437)	Eosinophil $< 400/\text{mm}^3$, no. (%) (n = 1955)	Unadjusted rate ratio or risk ratio (95% CI)*	P value*
Asthma exacerbation	0.57†	0.37†	1.52 (1.23-1.88)	<.001
Any asthma exacerbation	142 (32.5)	465 (23.8)	1.37 (1.17-1.60)	<.001
≥ 2 Asthma exacerbations	50 (11.4)	154 (7.9)	1.45 (1.07-1.96)	.02
Any asthma ED visit	46 (10.5)	116 (5.9)	1.77 (1.28-2.46)	<.001
Any asthma hospitalization	19 (4.3)	38 (1.9)	2.24 (1.30-3.84)	.004
Any asthma ED and/or hospitalization	46 (10.5)	120 (6.1)	1.71 (1.24-2.37)	.001
≥ 7 SABA canisters dispensed	150 (34.3)	475 (24.3)	1.41 (1.21-1.64)	<.001

*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.

†Data are rate/y.

TABLE IV. Adjusted rate ratio and risk ratio of covariates in 2010 in addition to an eosinophil cutoff point $\geq 400/\text{mm}^3$ associated with rate and frequency of asthma exacerbations in 2011 in adults with persistent asthma (n = 2392)

Factors in 2010 in the 400/mm ³ models associated with asthma exacerbations in 2011	Adjusted rate ratio (95% CI)*	P value†	Adjusted risk ratio (95% CI)†	P value‡
History of asthma exacerbation vs no asthma exacerbation	3.02 (2.55-3.57)	<.001	2.49 (2.16-2.87)	<.001
GINA step-care levels 4 and 5 vs 1 and 2	1.45 (1.16-1.82)	.001	1.27 (1.06-1.53)	.01
Female vs male sex	1.36 (1.12-1.65)	.002	1.24 (1.06-1.46)	.01
≥ 7 SABA vs < 7 SABA canisters dispensed	1.29 (1.08-1.53)	.005	1.18 (1.03-1.35)	.02
Black vs non-Hispanic white race	1.33 (1.06-1.68)	.02	1.33 (1.11-1.59)	.002
Asian vs non-Hispanic white race	1.24 (0.90-1.72)	.19	1.30 (1.02-1.67)	.04
Body mass index $\geq 30 \text{ kg/m}^2$ (obese) vs $< 30 \text{ kg/m}^2$ (not obese)	1.22 (1.03-1.45)	.02	1.16 (0.77-1.75)	.48

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

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

‡After stepwise variable selection, both negative binomial and Poisson regression final models adjusted age, sex, obesity, geocoded education, race and/or ethnicity, GINA step-care level, ≥ 7 SABA canisters dispensed, and history of asthma exacerbation in 2010.

Age, P > .25 for both analyses.

eosinophilia^{6,40} but only blood eosinophil counts are available for population care management and routine clinical care. The present study provided proof of concept that high blood eosinophil counts are associated with both the increased risk of future asthma exacerbations and excessive SABA canister dispensings. The increasing RRs and risk ratios for future asthma exacerbations with increasing blood eosinophil cutoff points aligned with findings from a recent study that used data from the National Health and Nutrition Examination Survey, which showed that patients with asthma and with higher blood eosinophil counts compared with lower counts had more frequent prior asthma attacks.⁴¹ In the PREDUNA study of the blood eosinophil cutoff points selected for analyses, 400/mm³ was most related in the present cohort compared with 3 other studied blood eosinophil cutoff points (150/mm³, 200/mm³, and 300/mm³). Other cutoff points may be more relevant, depending on outcome selected, age group, asthma severity level, and setting (clinical vs research), and when adjustments for covariates are not practical.

Effective population asthma care management in MCOs relies on accurately identifying patients at high risk to implement effective therapy to improve outcomes.^{24,42} We and other investigators reported specific demographic characteristics, disease activity counts, patient-centered measurements, physiologic assessments, and biologic markers (fractional exhaled nitric oxide) that help to identify patients at increased risk for future poor asthma outcomes. Risk factors for future poor asthma outcomes identified or confirmed in large epidemiologic studies in MCOs and routinely assessable from

electronic pharmacy and health care databases include (1) demographic factors (female sex of adults, low socioeconomic status, specific ethnicities, smoking status, obesity, and types of health insurance)⁴³⁻⁴⁶; (2) high disease activity (prior year history of asthma exacerbations and increased asthma-specific health care utilization, excessive SABA canister dispensing, and high GINA step-care level)^{22,25,47}; and (3) poor treatment adherence.⁴⁸ Other patient risk factors that have been found in prospective cohort studies in MCOs and other settings to be associated with future uncontrolled asthma (risk, asthma exacerbation; impairment, excessive SABA use) include the following: (1) patient-centered assessments (ie, validated asthma control and asthma-specific quality of life surveys),^{20,49,50} (2) physiologic measurements (spirometry),^{51,52} and (3) biologic markers (fractional exhaled nitric oxide).^{32,53,54} However, these latter measures are not routinely captured at KPSC among patients with asthma.

The PREDUNA study is limited by being retrospective and relying on a single blood eosinophil determination during 2010 and determined in only 25% of the identified adults with persistent asthma; however, the patients studied represent a subgroup with features of more high-risk asthma, including higher frequency of obesity, more frequent comorbidities, and features of troublesome and uncontrolled asthma. As such, the findings apply to adult patients with persistent asthma and with more active disease but may not be generalizable to all health plan enrollees with asthma, nor to children. An ongoing prospective cohort study will test the validity of the present findings in a cohort

similar to that studied in the PREDUNA study. We did not have sufficient data on spirometry to include it in the multivariate analyses because, as already noted; spirometry is not routinely performed in our MCO, separate from asthma specialty care settings. Although the persistent asthma definition used in the PREDUNA study did not include spirometry, the 2-year HEDIS criteria for persistent asthma uses asthma diagnoses, acute asthma ED and hospitalization utilization coding, and repeated asthma medication dispensings, and is a recognized and accepted administrative definition of asthma.^{19,55} Similar to other administrative studies, relevant variables may have been missed for adjustment; however, the PREDUNA study adjusted for the important variables previously shown in administrative data studies to relate to future uncontrolled asthma.

In summary, the PREDUNA retrospective administrative database study provides evidence and proof of concept that a high blood eosinophil count in adults with persistent asthma is a relevant biologic marker associated with future uncontrolled asthma (exacerbations and excessive SABA use) after adjusting for many demographic, comorbidities, and asthma disease severity characteristics previously shown to relate to future uncontrolled asthma. Although routine determination of asthma control or quality of life by validated testing and lung function by spirometry would be appropriate for patients with persistent asthma, the widespread implementation of these assessments has been met with repeated obstacles in large MCOs. Given that patient-centered assessments have been shown predictive of future asthma outcomes, it is recommended for health care organizations to institute patient-centered assessment programs for their patients with asthma.^{22-26,48-50} However, institution of routine blood testing at least yearly in adults with persistent asthma to identify patients with high eosinophil counts may represent a simple and potentially cost-effective addition to population care management and also be useful for asthma care in general. Blood eosinophil cutoff points need to be determined for specific situations such as clinical trials and general asthma care when adjustments for multiple confounders are not practical. Moreover, with the advent of highly efficient electronic medical records and robust computer-generated pharmacy and encounter databases, opportunities exist to use these systems to promote real-time identification of patients with asthma who are at high risk and to intervene, as we previously reported.⁵⁶

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METHODS**HEDIS 2-year persistent asthma definition:**

HEDIS (Healthcare Effectiveness Data and Information Set) defined persistent asthma in 2009 and 2010 (two year criteria)¹ using HEDIS specific Tables² to identify members as having persistent asthma who met at least one of the following criteria during 2009 and 2010. Criteria need not be the same across both years.

- At least one ED visit (Table ASM-B) with asthma as the principal diagnosis (Table ASM-A)
- At least one acute inpatient claim/encounter (Table ASM-B) with asthma as the principal diagnosis (Table ASM-A)
- At least four outpatient asthma visits (Table ASM-B) with asthma as one of the listed diagnoses (Table ASM-A) and at least two asthma medication dispensing events (Table ASM-C)
- At least four asthma medication dispensing events (Table ASM-C).

Determination of GINA Step-level care

Asthma drug dispensing was determined using the KPSC Pharmacy Information Management System (PIMS)³ in which the prescription directions for use, specific drug class and name, and quantities dispensed are available. The daily dosage of ICS was calculated using the following formula as reported previously:⁴

Daily dosage equals:

$$\frac{(\# \text{ of canisters}) \times (\# \text{ of puffs/canister}) \times (\text{strength in mcg/puff})}{\# \text{ of days supply}}$$

Different ICS were categorized into low-, medium-, and high-dose, based on the calculated daily dosage and on their individual potency using the estimated comparative daily dosages for ICS recommended by the GINA guideline for the diagnosis and management of asthma for patients' ages at least 12 years of age and adults.

RESULTS**Multivariate analyses for ≥ 7 canister dispensings in 2011**

The following 2010 adjustors were significant in addition to an eosinophil cutoff point of $\geq 400/\text{mm}^3$ (relative risk, 1.17; 95% CI, 1.03-1.33, $P = 0.02$) in influencing ≥ 7 canister dispensings in 2011: (1) ≥ 7 canister dispensings (relative risk, 7.17; 95% CI, 6.04-8.51, $P < 0.001$); diagnosis of eczema (relative risk, 1.60; 95% CI, 1.19-2.15, $P < 0.01$); and diagnosis of rhinitis (relative risk, 0.84; 95% CI, 0.74-0.96, $P < 0.01$).

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TABLE E1. Demographics at baseline and asthma features in baseline year 2010 by availability of blood eosinophil counts

Demographics and clinical features	Eosinophil count (n = 2392)	No eosinophil count (n = 7154)	Total patients (n = 9546)	P value*
Age (y), mean $\pm$ SD	47.0 $\pm$ 12.4	45.7 $\pm$ 12.8	46.0 $\pm$ 12.7	<.001
Female sex, no. (%)	1684 (70.4)	4208 (58.8)	5892 (61.7)	<.001
Race and/or ethnicity, no. (%)				<.001
White	1085 (45.4)	3271 (45.7)	4356 (45.6)	
Black	420 (17.6)	894 (12.5)	1314 (13.8)	
Hispanic	600 (25.1)	1789 (25)	2389 (25)	
Native American/Native Alaskan	7 (0.3)	18 (0.3)	25 (0.3)	
Asian and/or Pacific Islander	177 (7.4)	575 (8.0)	752 (7.9)	
Multiple and others	41 (1.7)	179 (2.5)	220 (2.3)	
Unknown	62 (2.6)	428 (6.0)	490 (5.1)	
Estimated household income by geocoding (\$), mean $\pm$ SD	67,587 $\pm$ 29,633	69,358 $\pm$ 28,823	68,915 $\pm$ 29,037	.002
Estimated family education level $\leq$ grade 12 by geocoding (%), mean $\pm$ SD	23.0 $\pm$ 17.6	22.3 $\pm$ 17.4	22.5 $\pm$ 17.4	.06
Body mass index (kg/m ²), mean $\pm$ SD	32.1 $\pm$ 8.4	31.0 $\pm$ 7.5	31.3 $\pm$ 7.7	<.001
Obese, $\geq$ 30 kg/m ² , no. (%)	1276 (53.3)	3365 (47.0)	4641 (48.6)	<.001
Missing body mass index data, no. (%)	11 (0.5)	206 (2.9)	217 (2.3)	
Smoking status, no. (%)				.001
Yes	155 (6.5)	524 (7.3)	679 (7.1)	
Passive	19 (0.8)	94 (1.3)	113 (1.2)	
Quit	644 (26.9)	1549 (21.7)	2193 (23)	
Never	1532 (64)	4431 (61.9)	5963 (62.5)	
Missing	42 (1.8)	556 (7.8)	598 (6.3)	
Length of health plan membership (y), mean $\pm$ SD	16.5 $\pm$ 10.5	16.3 $\pm$ 10.3	16.3 $\pm$ 10.4	.37
Insurance, no. (%)†				
Commercial	2081 (87.0)	6491 (90.7)	8572 (89.8)	<.001
Medicaid	177 (7.4)	228 (3.2)	405 (4.2)	<.001
Medicare	81 (3.4)	131 (1.8)	212 (2.2)	<.001
Private pay	125 (5.2)	412 (5.8)	537 (5.6)	.33
Charlson comorbidity index, mean $\pm$ SD	1.3 $\pm$ 0.9	1.0 $\pm$ 0.7	1.1 $\pm$ 0.8	<.001
Rhinitis, no. (%)	865 (36.2)	2021 (28.2)	2886 (30.2)	<.001
Gastroesophageal reflux, no. (%)	641 (26.8)	805 (11.3)	1446 (15.1)	<.001
Chronic sinusitis, no. (%)	448 (18.7)	928 (13.0)	1376 (14.4)	<.001
Pneumonia, no. (%)	162 (6.8)	147 (2.1)	309 (3.2)	<.001
Eczema, no. (%)	63 (2.6)	126 (1.8)	189 (2.0)	.01
Nasal polyps, no. (%)	51 (2.1)	110 (1.5)	161 (1.7)	.05
Allergist visit, no. (%)	548 (22.9)	1189 (16.6)	1737 (18.2)	<.001
12-Mo GINA step-care level, no. (%)				<.001
1	244 (10.2)	738 (10.3)	982 (10.3)	
2	317 (13.3)	1052 (14.7)	1369 (14.3)	
3	768 (32.1)	2567 (35.9)	3335 (34.9)	
4	1021 (42.7)	2765 (38.6)	3786 (39.7)	
5	39 (1.6)	21 (0.3)	60 (0.6)	
Unclassified	3 (0.1)	11 (0.2)	14 (0.1)	
Any ICS dispensed, no. (%)				<.001
Low dose	397 (16.6)	1386 (19.4)	1783 (18.7)	
Medium dose	1150 (48.1)	3627 (50.7)	4777 (50.0)	
High dose	495 (20.7)	1090 (15.2)	1585 (16.6)	
None	350 (14.6)	1051 (14.7)	1401 (14.7)	
Any ICS-LABA dispensed, no. (%)				<.001
Low dose	146 (6.1)	546 (7.6)	692 (7.2)	
Medium dose	532 (22.2)	1648 (23)	2180 (22.8)	
High dose	402 (16.8)	832 (11.6)	1234 (12.9)	
None	1312 (54.8)	4128 (57.7)	5440 (57)	

(continued)

TABLE E1. (Continued)

Demographics and clinical features	Eosinophil count (n = 2392)	No eosinophil count (n = 7154)	Total patients (n = 9546)	P value*
Leukotriene modifiers, no. (%)	538 (22.5)	1206 (16.9)	1744 (18.3)	<.001
Theophylline, no. (%)	44 (1.8)	147 (2.1)	191 (2)	.52
Omalizumab, no. (%)	6 (0.3)	9 (0.1)	15 (0.2)	.18
Controller equivalent canisters dispensed, mean $\pm$ SD	7.4 $\pm$ 5.9	7.4 $\pm$ 5.8	7.4 $\pm$ 5.8	.86
≥ 9 Controller equivalent canisters dispensed, no. (%)	880 (36.8)	2656 (37.1)	3536 (37.0)	.77
≥ 7 SABA canisters dispensed, no. (%)	771 (32.2)	2291 (32)	3062 (32.1)	.85
No. Asthma exacerbations, mean $\pm$ SD	0.5 $\pm$ 1.0	0.3 $\pm$ 0.7	0.4 $\pm$ 0.8	<.001
Rate of asthma exacerbations (95% CI)	0.5 (0.50-0.58)	0.3 (0.31-0.34)	0.4 (0.37-0.39)	<.001
Any asthma exacerbation, no. (%)	786 (32.9)	1642 (23)	2428 (25.4)	<.001
≥ 2 asthma exacerbations, no. (%)	287 (12.0)	464 (6.5)	751 (7.9)	<.001
Any asthma emergency visit or hospitalization, no. (%)	306 (12.8)	326 (4.6)	632 (6.6)	<.001

*Determined by χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables.

†Patients may have more than 1 insurance plan.

TABLE E2. Asthma outcomes with unadjusted rate ratio or risk ratio in 2011 by blood eosinophil cutoff point of 300/mm³ in 2010

Asthma outcomes in 2011	Eosinophil $\geq 300/\text{mm}^3$, no. (%) (n = 719)	Eosinophil $< 300/\text{mm}^3$, no. (%) (n = 1673)	Unadjusted rate ratio or risk ratio (95% CI)	P value*
Asthma exacerbation	0.48†	0.38†	1.25 (1.04-1.51)	.02
Any asthma exacerbation	204 (28.4)	403 (24.1)	1.18 (1.02-1.36)	.03
≥ 2 Asthma exacerbations	71 (9.9)	133 (7.9)	1.24 (0.94-1.63)	.12
Any asthma ED visit	70 (9.7)	92 (5.5)	1.77 (1.31-2.39)	<.001
Any asthma hospitalization	27 (3.8)	30 (1.8)	2.09 (1.25-3.50)	.005
Any asthma ED and/or hospitalization	71 (9.9)	95 (5.7)	1.74 (1.30-2.34)	<.001
≥ 7 SABA canisters dispensed	234 (32.5)	391 (23.4)	1.39 (1.21-1.60)	<.001

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

†Data are rate/y.

TABLE E3. Unadjusted and adjusted effects of restricted blood eosinophils* at various cutoff points in 2010 on rate (rate ratio) and frequency (risk ratio) of asthma exacerbations in 2011 in adults with persistent asthma (n = 1667)

Eosinophil cutoff points as cells/mm ³ (% 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 (65.6) vs < 150 (34.4)	1.10 (0.86-1.39)	.45	0.99 (0.78-1.24)	.91	1.03 (0.85-1.25)	.74	0.99 (0.82-1.20)	.94
≥ 200 (50.2) vs < 200 (49.8)	1.05 (0.84-1.31)	.70	0.99 (0.80-1.23)	.94	1.02 (0.85-1.22)	.82	0.98 (0.82-1.17)	.81
≥ 300 (30.9) vs < 300 (69.1)	1.20 (0.95-1.52)	.14	1.11 (0.88-1.40)	.38	1.17 (0.96-1.41)	.11	1.10 (0.92-1.32)	.30
≥ 400 (18.2) vs < 400 (81.8)	1.48 (1.13-1.94)	.005	1.34 (1.03-1.74)	.03	1.32 (1.07-1.63)	.01	1.22 (1.00-1.50)	.052

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

†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, both final negative binomial and Poisson regression models adjusted for age, sex, obesity, geocoded education, race and/or ethnicity, GINA step-care level, ≥ 7 SABA canisters dispensed, and history of prior asthma exacerbation in 2010.

TABLE E4. Unadjusted and adjusted effects of restricted blood eosinophils* at various cutoff points in 2010 to frequency of ≥ 7 SABA canisters dispensed in 2011 in adults with persistent asthma (n = 1667)

Eosinophil cutoff points as cells/mm ³ (% patients)	Unadjusted risk ratio (95% CI) [†]	P value	Adjusted risk ratio (95% CI) [†]	P value [‡]
≥ 150 (65.6) vs <150 (34.4)	1.50 (1.23-1.82)	<.001	1.14 (0.97-1.34)	.11
≥ 200 (50.2) vs <200 (49.8)	1.41 (1.19-1.67)	<.001	1.07 (0.93-1.23)	.33
≥ 300 (30.9) vs <300 (69.1)	1.44 (1.22-1.70)	<.001	1.09 (0.95-1.25)	.24
≥ 400 (18.2) vs <400 (81.8)	1.53 (1.28-1.84)	<.001	1.22 (1.05-1.42)	.01

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

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

[‡]After stepwise variable selection, the final multivariate models adjusted for age, sex, obesity, geocoded education, eczema, rhinitis, and ≥ 7 SABA canisters dispensed in 2010.