

The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma

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Clinical Implications

- Blood eosinophil counts of 300/mm³ or more in children with persistent asthma may identify children at increased risk for future asthma exacerbations, indicating a possible higher disease burden among these patients.

TO THE EDITOR:

Eosinophilic pulmonary inflammation is a major asthma phenotype associated with exacerbation-driven uncontrolled asthma.¹ We recently reported that high blood eosinophil counts were a risk factor for increased future asthma exacerbations in adults with persistent asthma after controlling for other factors that may confound this relationship.² It is unknown whether a similar relationship exists in children with persistent asthma. To address this issue, we conducted a retrospective study (see [Figure E1, A](#), in this article's Online Repository at www.jaci-inpractice.org) using administrative data from a large medical care organization to determine whether blood eosinophil levels in children with persistent asthma are an independent risk factor for future asthma exacerbations. Electronic pharmacy and health care data from Kaiser Permanente Southern California identified 2451 children aged 5 to 11 years who met the Health Effectiveness Data and Information Set 2-year criteria for persistent asthma in 2009 and 2010, did not manifest cystic fibrosis and other major illnesses ([Figure E1, B](#)), and were continuously enrolled health plan members with pharmacy benefit from 2009 to 2011.² Of these 2451 identified children, 333 (13.6%) also had a total blood eosinophil count determined from the last complete blood cell count with differential obtained in 2010 ([Figure E1, B](#)). *Exacerbations*, the study's primary outcome, were defined as asthma outpatient visits requiring systemic corticosteroid dispensing within ± 7 days or asthma emergency department (ED) visits or hospitalizations. A period of 8 or more days between episodes was required to define a new exacerbation. Negative binomial and Poisson regression were applied to examine the association between blood eosinophil counts using cutoff points of 150/mm³, 200/mm³, 300/mm³, and 400/mm³ determined in 2010 and the rate and risk of exacerbations in 2011 after controlling for demographic characteristics, comorbidities, and asthma burden (see this article's Online Repository at www.jaci-inpractice.org).² SAS (version 9.2 for Windows, SAS Institute, Cary, NC) was used for all analyses, with the statistical significance level set at $P < .05$, 2-tailed.

Children with ($N = 333$) compared with those without ($N = 2118$) eosinophil determinations in 2010 evidenced

generally similar demographic characteristics, but more frequent comorbidities, allergist visits, and uncontrolled asthma (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). The present study's subgroup with eosinophil determination ($N = 333$) was aged 7.7 ± 1.9 years, 72% boys, about 75% nonwhite, from households with median incomes of about \$63,000, long-term health plan enrollees (6.7 ± 2.4 years), and possessed mainly commercial insurance, with 25.8% covered by Medicaid or other state programs ([Table I](#)). During the baseline year (2010), this subgroup had frequent comorbidities, including rhinitis (56.2%), pneumonia (30.6%), and eczema (15.0%), received inhaled corticosteroids (88.9%) and leukotriene modifiers (32.4%), and was Global Initiative for Asthma (GINA) step-care level 3 or higher^{2,3} (59.1%). Of the study subgroup with eosinophil determination, 61.9% and 29.1% experienced at least 1 and 2 asthma exacerbations, respectively, and 32.7% required an asthma-related ED visit or hospitalization ([Table I](#)). Children with eosinophil counts of less than 300/mm³ during the baseline year (2010) exhibited generally similar characteristics than did those children with eosinophil counts of 300/mm³ or more, except that the latter more frequently visited an allergist ($P = .003$) and received inhaled corticosteroid/long-acting β_2 -agonist ($P = .001$), but less frequently experienced pneumonia ($P = .002$) ([Table I](#)).

The rate of asthma exacerbations in 2011 was 0.64 events per person-year (95% CI, 0.54-0.76). Compared with children with a blood eosinophil count of less than 300/mm³, children with counts of 300/mm³ or more in 2010 experienced a higher rate (0.82/y vs 0.53/y; $P = .01$) and risk (49.6% vs 34.3%; $P = .01$) of asthma exacerbations in 2011. However, no difference was found in asthma ED visits or hospitalizations or excessive short-acting β_2 -agonist (SABA) dispensings (≥ 7 canisters dispensed/y) between the 2 stratified eosinophil subgroups ([Table II](#)).

We further explored the relationship of blood eosinophil counts in 2010 (yes/no) using cutoff points of 150/mm³, 200/mm³, 300/mm³, and 400/mm³ with the rate and risk of future asthma exacerbation in 2011. Blood eosinophil counts of 300/mm³ or more and 400/mm³ or more were associated with both increased rate ([Figure 1, A](#)) and risk (% of children) ([Figure 1, B](#)) for future exacerbations in 2011. After adjusting for age, sex, obesity, geocoded education, ethnicity, GINA step-care level, 7 or more SABA canisters dispensed, and history of asthma exacerbations in 2010,² multivariate analyses revealed that an eosinophil cutoff point of 300/mm³ or more was associated in 2011 with a 52% increase in asthma exacerbation rate (rate ratio, 1.52; 95% CI, 1.12-2.07; $P = .01$) ([Figure 1, A](#)) and a 40% increase in the frequency of any asthma exacerbation (risk ratio, 1.40; 95% CI, 1.09-1.79; $P < .01$) ([Figure 1, B](#)). Slightly higher point estimates were observed in terms of the rate or risk ratio when comparing the effects of eosinophils on asthma exacerbations using a cutoff point of 300/mm³ or more versus a cutoff point of 400/mm³ or more. However, because of overlap of the 95% CIs, comparisons on the risk of exacerbations between these 2 cutoff points cannot be made ([Figure 1, A and B](#)).

Other variables selected in the final rate and risk models at the 300/mm³ eosinophil cutoff point that were associated with an increase in asthma exacerbations were (1) a history of asthma exacerbations in 2010 ($P < .001$ for both ratios), (2) decreasing

TABLE I. Comparison of demographic characteristics, comorbidities, and asthma features at baseline in 2010 among 5- to 11-y-old children with persistent asthma stratified by blood eosinophil levels of 300/mm³ or more vs less than 300/mm³*

Demographic characteristic/clinical feature	Blood eosinophils $\geq 300/\text{mm}^3$ (N = 123)	Blood eosinophils $< 300/\text{mm}^3$ (N = 210)	Total (N = 333)	P†
Age (y), mean $\pm$ SD	7.9 $\pm$ 2.0	7.6 $\pm$ 1.9	7.7 $\pm$ 1.9	0.13
Boys	80 (65.0)	126 (60.0)	206 (61.9)	0.36
Race and/or ethnicity				0.34
White	35 (28.5)	47 (22.4)	82 (24.6)	
Black	21 (17.1)	37 (17.6)	58 (17.4)	
Hispanic	55 (44.7)	96 (45.7)	151 (45.3)	
Asian/Pacific Islander	8 (6.5)	16 (7.6)	24 (7.2)	
Multiple, others	4 (3.3)	9 (4.3)	13 (3.9)	
Unknown	0 (0)	5 (2.4)	5 (1.5)	
Median household income by geocoding (\$), mean $\pm$ SD	62,363 $\pm$ 25,626	63,366 $\pm$ 26,168	62,995 $\pm$ 25,935	0.74
% resident education level $\leq$ grade 12 by geocoding, mean % $\pm$ SD	27.0 $\pm$ 19.2	29.1 $\pm$ 18.8	28.3 $\pm$ 18.9	0.23
BMI (percentile), mean $\pm$ SD	68.1 $\pm$ 30.32	68.0 $\pm$ 31.29	68.0 $\pm$ 30.89	0.70
Obese ($\geq$ 95th percentile)	31 (25.2)	59 (28.1)	90 (27.0)	0.57
Smoking status				0.30
Yes	0 (0)	1 (0.5)	1 (0.3)	
Passive	14 (11.4)	33 (15.7)	47 (14.1)	
Quit	3 (2.4)	1 (0.5)	4 (1.2)	
Never	101 (82.1)	170 (81.0)	271 (81.4)	
Missing	5 (4.1)	5 (2.4)	10 (3.0)	
Length of health plan enrollment (y), mean $\pm$ SD	7.0 $\pm$ 2.5	6.5 $\pm$ 2.4	6.7 $\pm$ 2.4	0.10
Insurances‡				
Commercial	89 (72.4)	152 (72.4)	241 (72.4)	1.00
Medicaid and other state programs	31 (25.2)	55 (26.2)	86 (25.8)	0.84
Private pay	4 (3.3)	4 (1.9)	8 (2.4)	0.44
Charlson comorbidity index, mean $\pm$ SD	1.0 $\pm$ 0.2	1.0 $\pm$ 0.3	1.0 $\pm$ 0.3	0.88
Rhinitis	77 (62.6)	110 (52.4)	187 (56.2)	0.07
Gastroesophageal reflux	6 (4.9)	4 (1.9)	10 (3)	0.12
Chronic sinusitis	18 (14.6)	24 (11.4)	42 (12.6)	0.40
Pneumonia	25 (20.3)	77 (36.7)	102 (30.6)	0.002
Eczema	22 (17.9)	28 (13.3)	50 (15.0)	0.26
Nasal polyps	1 (0.8)	0 (0)	1 (0.3)	0.19
Allergist visit	58 (47.2)	65 (31)	123 (36.9)	0.003
12-mo GINA step-care level				0.84
Step 1	10 (8.1)	14 (6.7)	24 (7.2)	
Step 2	38 (30.9)	74 (35.2)	112 (33.6)	
Step 3	51 (41.5)	81 (38.6)	132 (39.6)	
Step 4	24 (19.5)	40 (19.0)	64 (19.2)	
Step 5	0 (0)	1 (0.5)	1 (0.3)	
Any ICS dispensed				0.73
Low dose	56 (45.5)	100 (47.6)	156 (46.8)	
Medium dose	43 (35)	79 (37.6)	122 (36.6)	
High dose	8 (6.5)	10 (4.8)	18 (5.4)	
None	16 (13.0)	21 (10.0)	37 (11.1)	
Any ICS/LABA dispensed				0.001
Low dose	14 (11.4)	5 (2.4)	19 (5.7)	
Medium dose	10 (8.1)	15 (7.1)	25 (7.5)	
High dose	5 (4.1)	2 (1)	7 (2.1)	
None	94 (76.4)	188 (89.5)	282 (84.7)	
Leukotriene modifiers	39 (31.7)	69 (32.9)	108 (32.4)	0.83
Controller equivalent canisters dispensed, mean $\pm$ SD§	6.9 $\pm$ 6.4	6.8 $\pm$ 5.4	6.8 $\pm$ 5.8	0.70

(continued)

TABLE I. (Continued)

Demographic characteristic/clinical feature	Blood eosinophils $\geq 300/\text{mm}^3$ (N = 123)	Blood eosinophils $< 300/\text{mm}^3$ (N = 210)	Total (N = 333)	P†
≥ 9 controller equivalent canisters dispensed§	32 (26.0)	58 (27.6)	90 (27.0)	0.75
≥ 7 SABA canisters dispensed	28 (22.8)	31 (14.8)	59 (17.7)	0.06
Number of asthma exacerbations, mean $\pm$ SD	1.2 $\pm$ 1.2	1.0 $\pm$ 1.2	1.1 $\pm$ 1.2	0.23
Rate of asthma exacerbations (95% CI)	1.17 (0.97-1.41)	1.03 (0.88-1.19)	1.08 (0.96-1.22)	0.28
≥ 1 asthma exacerbation	80 (65.0)	126 (60.0)	206 (61.9)	0.36
≥ 2 asthma exacerbations	39 (31.7)	58 (27.6)	97 (29.1)	0.43
≥ 1 asthma ED visit or hospitalization	37 (30.1)	72 (34.3)	109 (32.7)	0.43

BMI, Body mass index; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist.

*Data presented as frequency, n (%), which may not add to 100% because of rounding, unless specified otherwise.

†P values determined by using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables.

‡Patients may have more than 1 insurance plan.

§The number of asthma controller units (canisters of inhaled controller medications or 30-d supplies of oral controller medications).

TABLE II. Asthma outcomes with unadjusted rate or risk ratio in 2011 by blood eosinophil cutoff point of $300/\text{mm}^3$ in 2010 in 5- to 11-y-old children with persistent asthma

Asthma outcomes in 2011	Ages 5-11 y			P*
	Eosinophil count $\geq 300/\text{mm}^3$ (N = 123)	Eosinophil count $< 300/\text{mm}^3$ (N = 210)	Unadjusted rate or risk ratio (95% CI)*	
Asthma exacerbation, rate/y	0.82	0.53	1.55 (1.12-2.16)	.01
≥ 1 asthma exacerbation, n (%)	61 (49.6)	72 (34.3)	1.45 (1.12-1.87)	.01
≥ 2 asthma exacerbations, n (%)	24 (19.5)	28 (13.3)	1.46 (0.89-2.41)	.13
≥ 1 asthma ED visit/hospitalization, n (%)	13 (10.6)	25 (11.9)	0.89 (0.47,1.67)	.71
≥ 7 SABA canisters dispensed, n (%)	18 (14.6)	25 (11.9)	1.23 (0.70-2.16)	.47

*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.

age ($P = .01$ for both ratios), (3) GINA step-care levels 4 and 5 versus step-care levels 1 and 2 ($P = .04$ for rate ratio), (4) 7 or more SABA canisters dispensed ($P = .05$ for rate ratio), (5) Asian versus non-Hispanic white ethnicity ($P = .03$ for both ratios), and (6) Hispanic versus non-Hispanic white ethnicity ($P = .03$ for risk ratio) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). The above findings were similar in sensitivity analyses in which the covariates allergist visits, pneumonia, and 9 or more controller equivalent canister dispensing were added to the multivariate modeling (see this article's Online Repository at www.jaci-inpractice.org). It is known that a history of exacerbations is a strong predictor for subsequent exacerbations.³ In our study, eosinophil counts of $300/\text{mm}^3$ or more and $400/\text{mm}^3$ or more were associated with the occurrence of a future exacerbation even after we controlled for the history of an exacerbation. Knowledge of blood eosinophil counts may encourage physicians to target and treat patients with elevated eosinophil counts, even if the patients do not have a history of exacerbations. To our knowledge, this is the first study using administrative data to demonstrate in children with persistent asthma the association of blood eosinophil count thresholds with future asthma exacerbations. The estimated rate ratio and risk ratio after controlling for potential confounders were 1.52 and 1.40, respectively; however, the 95% CIs were fairly wide, in part, because of the limited sample size of the study population. These findings are consistent with our earlier report that specific blood eosinophil counts were a risk factor for future asthma exacerbations in adults with persistent asthma.² It also supports previous findings of the association

between blood eosinophil counts and asthma exacerbations in children from a small clinical study⁴ and a post hoc analysis of a large clinical trial.⁵ The study is limited by its sample size, as noted above, and single blood eosinophil determination. Children in whom blood cell counts (with eosinophil levels) were ordered, accounting for only approximately 14% of the total children in the cohort with persistent asthma, may have presented with an illness or condition in which the physician decided that a blood cell count would be clinically useful. This is supported by significantly more comorbidities and asthma exacerbations in children with blood eosinophil counts (Table E1), which would increase the opportunity for direct physician contact and increase the chance to order blood tests. This suggests that our study findings may not be generalizable to children with less burdensome asthma. In addition, spirometry was unavailable on most children, although the Health Effectiveness Data and Information definition of asthma, which does not capture spirometry, is routinely used to identify children with persistent asthma for administrative data studies and regulatory activities.⁶ Our administrative database may not have captured all relevant variables for adjustment in the multivariate analyses; however, these analyses adjusted for the most important administrative data variables related to asthma exacerbations. We did not find an association of blood eosinophil counts with the number of SABA canisters dispensed or asthma ED visits/hospitalizations as was found in our study of adults with persistent asthma.² This may be due to reduced study power because the present cohort with blood cell counts was 85% smaller than our adult persistent asthma cohort.²

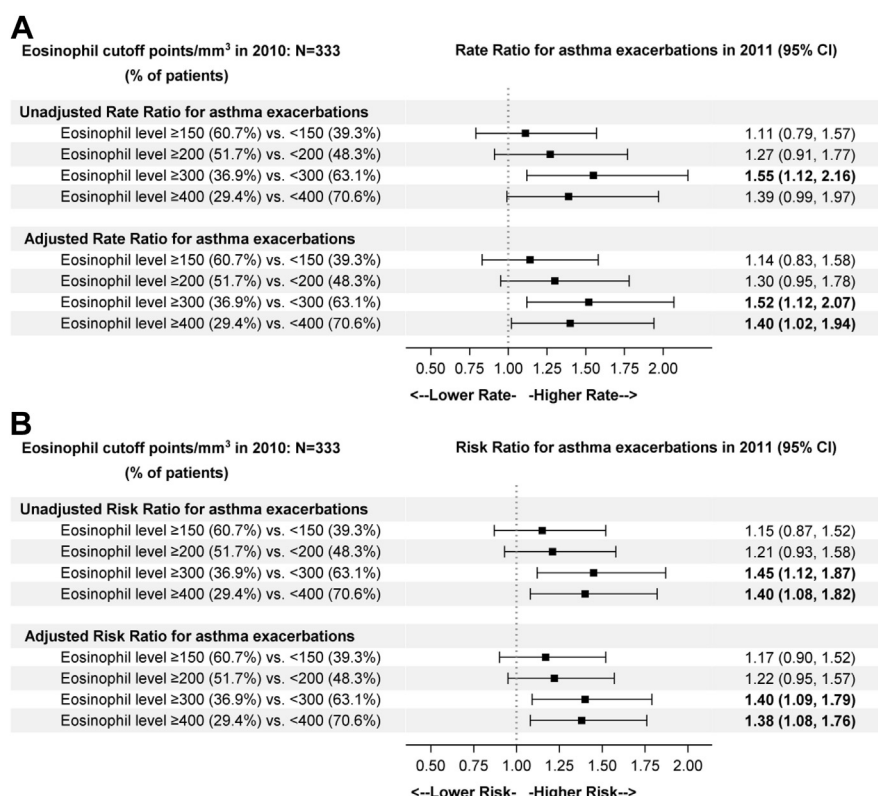


FIGURE 1. Unadjusted and adjusted relationships of eosinophil cutoff points in 2010 with asthma exacerbations in 2011. **A**, Negative binomial modeling. **B**, Poisson modeling with a robust error variance. Both modeling methods used the following covariates: age, sex, obesity, geocoded education, ethnicity, history of asthma exacerbation, GINA step-care level, and 7 or more SABA canisters dispensed in 2010.

The present study's novel finding that blood eosinophil count thresholds are a risk factor for future asthma exacerbations in children with persistent asthma, after accounting for many other relevant factors, adds further support to the integral role of eosinophils in asthma pathophysiology and their association with uncontrolled asthma, its disease burden,¹ and specific asthma phenotypes.⁷ Before these findings are used to support the consideration of implementing blood eosinophil counts for population care management and clinical care in children with persistent asthma, confirmation is needed including evidence that such determinations improve asthma outcomes to justify the increase in costs.

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This study was funded by a research grant from MedImmune, Gaithersburg, Md, to the Southern California Permanente Medical Group. The sponsor contributed to the study with comments to the protocol, data analysis, and manuscript.

Conflicts of interest: R. S. Zeiger has received research support from MedImmune, Genentech, GlaxoSmithKline, Aerocrine, Merck, MedImmune, and AstraZeneca; has received consultancy fees from GlaxoSmithKline for membership on the Steering Committee for Food and Drug Administration-mandated long-acting beta agonist safety study; has received consultancy fees from Genentech and Novartis; and has received consultancy fees from the National Heart, Lung, and

Blood Institute/Penn State for serving on the Data and Safety Monitoring Board. M. Schatz has received research support from MedImmune and GlaxoSmithKline. Q. Li has received research support from AstraZeneca. W. Chen has received research support from Kaiser Permanente Southern California. D. B. Khatri is employed by and owns stock and stock options in MedImmune/AstraZeneca and has a patent with MedImmune (Patent Pub. No. US 2012/0328606 A1; Pub. Date: December 27, 2012). D. Gossage was employed by MedImmune/AstraZeneca within 36 months of writing this article; is currently employed by and owns stock in Gilead Sciences; and has a patent from MedImmune (Patent Pending Pub. No. US 2012/0328606 A1; Pub. Date: December 27, 2012; MedImmune is the licensee; Title: Methods of diagnosing and testing pulmonary diseases or disorders). T. N. Tran is employed by and owns stock/stock options in AstraZeneca.

Received for publication September 3, 2014; revised October 4, 2014; accepted for publication October 21, 2014.

Available online January 15, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2014.10.009>

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METHODS

Census block group-level household and education attainment data were obtained through geocoding, a technique that maps members' addresses into census geographic areas (block, block group, and tract).

Statistical analyses

The chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables were used to compare demographic characteristics, comorbidities, and asthma features in 2010 between children with and without eosinophil determinations or by blood eosinophil cutoff points. Negative binomial models estimated unadjusted and adjusted rate ratios and 95% CIs, which accounted for overdispersion or high variability in event counts. Poisson regression models with a robust error variance calculated unadjusted and adjusted risk ratios and their 95% CIs. Similar to the modeling done in our study with adults,¹ the covariates determined in 2010 and considered in model selection were age (continuous), sex, obesity (yes/no), geocoded education, enrollment duration, race/ethnicity, smoking status, insurance type, Charlson comorbidity index, relevant comorbidities (gastroesophageal reflux, rhinitis, chronic sinusitis, nasal polyps, and eczema), medication dispensings (leukotriene modifiers, theophylline, omalizumab, and ≥ 7 SABA canisters dispensed), Health Effectiveness Data and Information—defined asthma treatment adherence (≥ 9 vs < 9 controllers equivalent canisters dispensed per year), GINA step-care level, history of asthma exacerbations, and blood eosinophil count.¹ We forced age, sex, obesity, geocoded education, and blood eosinophil count into the models. Negative binomial regression used the likelihood ratio test to compare any 2 nested models in a stepwise approach, with alpha count being set at .05. Robust Poisson models used Quasi-likelihood under the independence model criterion to compare any 2 models in a stepwise approach. Smaller Quasi-likelihood under the independence model criterion modeling was preferred. Similar to our study in adults with persistent asthma,¹ we assumed that potential confounders were not affected by the eosinophil cutoff point. Models with the most robust eosinophil cutoff point were used to determine potential confounders. These selected covariates were applied to regression models with other blood eosinophil cutoff points to determine asthma rate ratios and risk ratios. Interaction analyses were kept in the models if statistically significant ($P < .05$).

RESULTS

Multivariate analyses for asthma exacerbations in 2011

The following variables were also selected for significance in both the final rate and risk models for the $300/\text{mm}^3$ cutoff point as factors associated with an increase in asthma exacerbations: (a) age (per each 1-year decrease in age: rate ratio, 1.12, 95% CI, 1.03-1.22, $P < .001$, and risk ratio, 1.10, 95% CI, 1.02-1.18, $P = .01$), (b) a history of asthma exacerbations in 2010 (rate ratio, 2.35, 95% CI, 1.61-3.44, $P < .001$, and risk ratio, 1.94, 95% CI, 1.37-2.73, $P < .001$), (c) GINA step-care levels 4 and 5 versus 1 and 2 in 2010 (rate ratio, 1.55, 95% CI, 1.02-2.36, $P = .04$), (d) 7 or more SABA canisters dispensed in 2010 (rate ratio, 1.45, 95% CI, 1.00-2.11, $P = .05$), (e) Asian versus non-Hispanic white ethnicity (rate ratio, 2.01, 95% CI, 1.08-3.74, $P = .03$, and risk ratio, 1.75, 95% CI, 1.06-2.88, $P = .03$), and (f) Hispanic versus non-Hispanic white ethnicity (risk ratio, 1.53, 95% CI, 1.03-2.25, $P = .03$).

Sensitivity analyses

Sensitivity analyses were conducted by adding allergist visit, pneumonia, and, as an adherence marker, 9 or more controller canister equivalents dispensed in 2010 (number of asthma controller units as canisters of inhaled controller medications or 30-day supplies of oral controller medications) to the original asthma exacerbation rate ratio and risk ratio models. Allergist visit was significant ($P = .002$) in the exacerbation rate ratio model but increased the rate ratio only by less than 10% for eosinophil count in the model using a blood eosinophil cutoff point of $300/\text{mm}^3$ or more. Pneumonia was significant ($P = .044$) but became not significant when allergist visit was in the model. Dispensing of 9 or more controller canister equivalents was not significant in any model. These 3 variables were not significant when added to the exacerbation risk ratio model.

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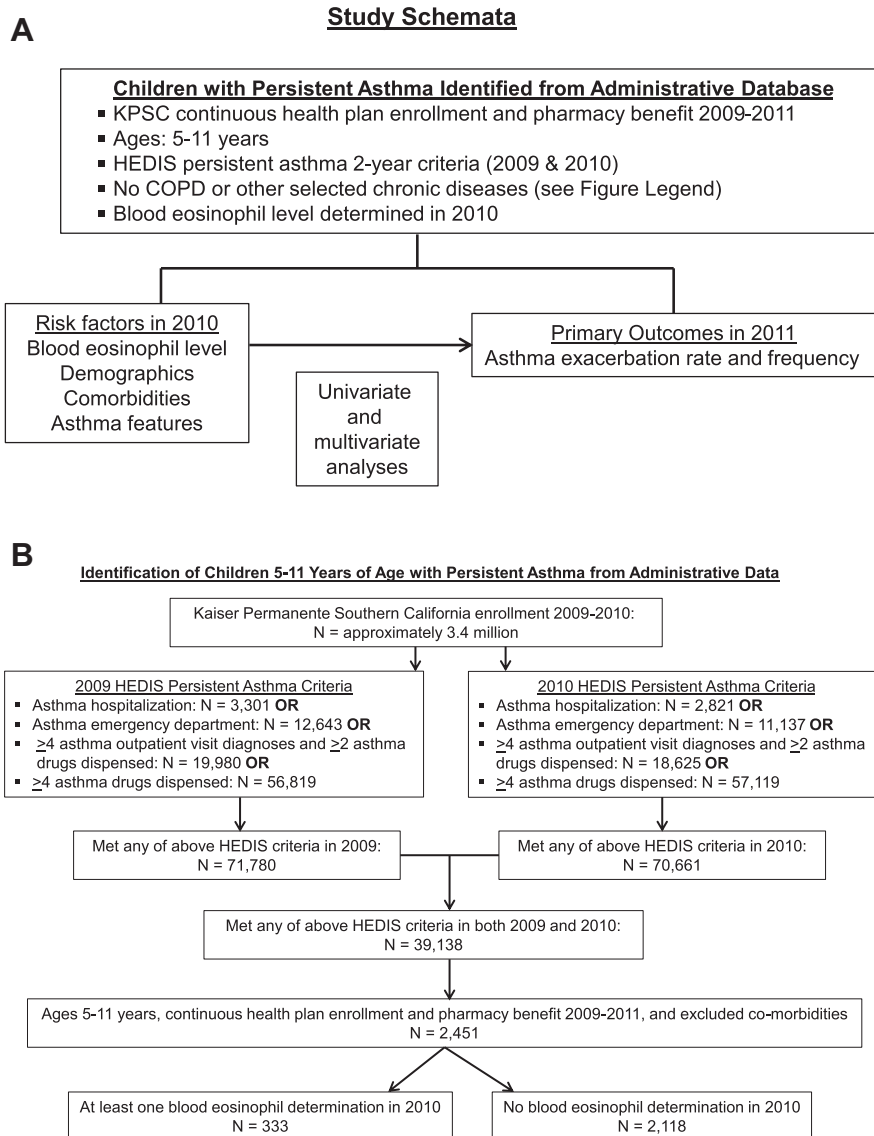


FIGURE E1. Study design and patient identification from administrative databases (modified with permission from Zeiger et al^{E1}). **A**, Study design schemata. *Exclusions: encounter diagnoses of chronic obstructive lung disease, emphysema, cystic fibrosis, chronic bronchitis, bronchiectasis, Churg Strauss, Wegener's, sarcoidosis, pulmonary hypertension, cerebral palsy, transplantation of major organs (2004-2010), 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**, Algorithm for patient identification of children aged 5 to 11 years with persistent asthma. *COPD*, Chronic obstructive lung disease; *HEDIS*, Healthcare Effectiveness Data and Information Set; *KPSC*, Kaiser Permanente Southern California.

TABLE E1. Demographic characteristics and asthma features in baseline year 2010 by availability of blood eosinophil counts in 5- to 11-y-old children with persistent asthma*

Demographic characteristic/clinical feature	Eosinophil count (N = 333)	No eosinophil count (N = 2118)	Total (N = 2451)	P†
Age (y), mean $\pm$ SD	7.7 $\pm$ 1.9	7.9 $\pm$ 2.0	7.8 $\pm$ 2.0	.15
Boys	206 (61.9)	1419 (67.0)	1625 (66.3)	.06
Race and/or ethnicity				.05
White	82 (24.6)	396 (18.7)	478 (19.5)	
Black	58 (17.4)	423 (20.0)	481 (19.6)	
Hispanic	151 (45.3)	932 (44.0)	1083 (44.2)	
Native American/Alaskan	0 (0)	6 (0.3)	6 (0.2)	
Asian/Pacific Islander	24 (7.2)	218 (10.3)	242 (9.9)	
Multiple and others	13 (3.9)	67 (3.1)	80 (3.3)	
Unknown	5 (1.5)	76 (3.6)	81 (3.3)	
Median household income by geocoding (\$), mean $\pm$ SD	62,995 $\pm$ 25,935	64,663 $\pm$ 28,627	64,436 $\pm$ 28,277	.53
% resident education level $\leq$ grade 12 by geocoding, mean % $\pm$ SD	28.3 $\pm$ 18.9	27.4 $\pm$ 19.1	27.5 $\pm$ 19.1	.29
BMI (percentile), mean $\pm$ SD	68.0 $\pm$ 30.89	68.3 $\pm$ 30.27	68.3 $\pm$ 30.35	.92
Obese ($\geq$ 95th percentile)	90 (27.0)	550 (26.0)	640 (26.1)	.43
	(N = 333)	(N = 2108)	(N = 2441)	
Smoking status				.40
Yes	1 (0.3)	7 (0.3)	8 (0.3)	
Passive	47 (14.1)	261 (12.3)	308 (12.6)	
Quit	4 (1.2)	19 (0.9)	23 (0.9)	
Never	271 (81.4)	1719 (81.2)	1990 (81.2)	
Missing	10 (3.0)	112 (5.3)	122 (5.0)	
Length of health plan membership (y), mean $\pm$ SD	6.7 $\pm$ 2.4	6.8 $\pm$ 2.4	6.8 $\pm$ 2.4	.82
Insurances‡				
Commercial	241 (72.4)	1558 (73.6)	1799 (73.4)	.65
Medicaid and other state programs	86 (25.8)	525 (24.8)	611 (24.9)	.68
Private pay	8 (2.4)	54 (2.5)	62 (2.5)	.87
Charlson comorbidity index, mean $\pm$ SD	1.0 $\pm$ 0.3	0.9 $\pm$ 0.3	0.9 $\pm$ 0.3	.01
Rhinitis	187 (56.2)	963 (45.5)	1150 (46.9)	<.001
Gastroesophageal reflux	10 (3.0)	35 (1.7)	45 (1.8)	.09
Chronic sinusitis	42 (12.6)	109 (5.1)	151 (6.2)	<.001
Pneumonia	102 (30.6)	304 (14.4)	406 (16.6)	<.001
Eczema	50 (15)	247 (11.7)	297 (12.1)	.08
Nasal polyps	1 (0.3)	1 (0)	2 (0.1)	.13
Allergist visit	123 (36.9)	625 (29.5)	748 (30.5)	.01
12-mo GINA step-care level				.26
Step 1	24 (7.2)	140 (6.6)	164 (6.7)	
Step 2	112 (33.6)	827 (39.0)	939 (38.3)	
Step 3	132 (39.6)	822 (38.8)	954 (38.9)	
Step 4	64 (19.2)	325 (15.3)	389 (15.9)	
Step 5	1 (0.3)	4 (0.2)	5 (0.2)	
Any ICS dispensed				.60
Low dose	156 (46.8)	1052 (49.7)	1208 (49.3)	
Medium dose	122 (36.6)	739 (34.9)	861 (35.1)	
High dose	18 (5.4)	87 (4.1)	105 (4.3)	
None	37 (11.1)	240 (11.3)	277 (11.3)	
Any ICS/LABA dispensed				.02
Low dose	19 (5.7)	119 (5.6)	138 (5.6)	
Medium dose	25 (7.5)	84 (4.0)	109 (4.4)	
High dose	7 (2.1)	27 (1.3)	34 (1.4)	
None	282 (84.7)	1888 (89.1)	2170 (88.5)	

(continued)

TABLE E1. (Continued)

Demographic characteristic/clinical feature	Eosinophil count (N = 333)	No eosinophil count (N = 2118)	Total (N = 2451)	P†
Leukotriene modifiers	108 (32.4)	625 (29.5)	733 (29.9)	.28
Controller equivalent canisters dispensed§	6.8 ± 5.8	6.6 ± 5.0	6.7 ± 5.1	.71
≥9 controller equivalent canisters dispensed§	90 (27.0)	598 (28.2)	688 (28.1)	.65
≥7 SABA canisters dispensed	59 (17.7)	444 (21.0)	503 (20.5)	.17
Number of asthma exacerbations, mean ± SD	1.1 ± 1.2	0.7 ± 1.0	0.8 ± 1.1	<.001
Rate of asthma exacerbations (95% CI)	1.08 (0.96-1.22)	0.75 (0.71-0.79)	0.79 (0.75-0.84)	<.001
≥1 asthma exacerbation	206 (61.9)	1001 (47.3)	1207 (49.2)	<.001
≥2 asthma exacerbations	97 (29.1)	389 (18.4)	486 (19.8)	<.001
≥1 asthma ED visit or hospitalization	109 (32.7)	335 (15.8)	444 (18.1)	<.001

BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist.

*Data presented as frequency, n (%), which may not add to 100% because of rounding, unless specified otherwise.

†P values determined by using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables.

‡Patients may have more than 1 insurance plan.

§The number of asthma controller units (canisters of inhaled controller medications or 30-d supplies of oral controller medications).

TABLE E2. Adjusted rate ratio and risk ratio of covariates in 2010 in addition to eosinophil cutoff point of 300/mm³ or more vs less than 300/mm³ associated with rate and frequency (risk) of asthma exacerbations in 2011 in 5- to 11-y-old children with persistent asthma (N = 333)

Factors in 2010 associated with asthma exacerbations in 2011	Adjusted rate ratio* (95% CI)	P‡	Adjusted risk ratio† (95% CI)	P‡
Age (per each 1-y decrease in age)	1.12 (1.03-1.21)	.01	1.10 (1.02-1.17)	.01
History of asthma exacerbation vs no asthma exacerbation	2.35 (1.61-3.44)	<.001	1.94 (1.37-2.73)	<.001
GINA step-care levels 4 and 5 vs 1 and 2	1.55 (1.02-2.36)	.04	1.30 (0.92-1.84)	.13
≥7 SABA vs <7 SABA canisters dispensed	1.45 (1.00-2.11)	.05	1.26 (0.94-1.71)	.13
Asian vs non-Hispanic white ethnicity	2.01 (1.08-3.74)	.03	1.75 (1.06-2.88)	.03
Hispanic vs non-Hispanic white ethnicity	1.48 (0.94-2.33)	.09	1.53 (1.03-2.25)	.03
Black vs non-Hispanic white ethnicity	1.25 (0.74-2.09)	.40	1.25 (0.81-1.94)	.31
Boys vs girls	0.96 (0.70-1.31)	.78	1.05 (0.81-1.35)	.73
Body mass index ≥95 percentile (obese) vs <95 percentile (nonobese)	1.14 (0.80-1.63)	.47	1.12 (0.85-1.48)	.42

*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, ethnicity, GINA step-care level, ≥7 SABA canisters dispensed, and history of asthma exacerbation in 2010.

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