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High blood eosinophil count is associated with more frequent asthma attacks in asthma patients

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ABSTRACT

Background: The clinical importance of eosinophils in asthma has been shown by the observation of frequent exacerbation in patients with high sputum eosinophil counts and a corresponding decrease in exacerbations when anti-inflammatory therapy was adjusted to maintain low sputum eosinophil percentages. However, less is known of the relation between blood eosinophilia and asthma exacerbation.

Objective: To examine whether patients with asthma and a higher blood eosinophil count have more asthma attacks than those with a lower count.

Methods: The authors analyzed data from the National Health and Nutrition Examination Survey, an annual cross-sectional survey of the US general population. Patients with asthma and asthma attacks were identified based on participants' self-report or parental report. A high blood eosinophil count was defined using 200, 300, or 400 cells/ μ L as cutoffs. The primary analysis used data from 2001 through 2010 after adjusting for demographic variables, obesity, smoking, neutrophil level, and past treatment for wheezing. A secondary analysis used data from 2007 through 2010 and included recent treatment for asthma and fraction of exhaled nitric oxide level as additional adjustment variables.

Results: In survey years 2001 through 2010, 3,162 patients with asthma had blood eosinophil data and approximately half (54% of children and 52% of adults) reported an asthma attack in the previous year. In the primary analysis, higher blood eosinophil counts were associated with more asthma attacks in children but not in adults. The secondary analysis suggested an association in both children and adults.

Conclusion: Patients with asthma with higher blood eosinophil counts experienced more asthma attacks than those with lower eosinophil counts.

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Introduction

Asthma is characterized by variable airflow obstruction, airway hyper-responsiveness, and chronic airway inflammation. Inflammation in asthma exhibits different phenotypes that can be characterized by the persistence at varying degrees of eosinophilic and neutrophilic infiltrations.^{1–3} Eosinophilic asthma has been categorized based on larger numbers of eosinophils in bronchoalveolar lavage, airway tissue biopsies, or induced sputum in patients with clinical asthmatic symptoms and airway hyper-responsiveness.⁴

Knowledge of the epidemiology and disease burden of eosinophilic vs noneosinophilic asthma is still accumulating. Although

noneosinophilic asthma can be severe and can present a significant burden,⁵ the clinical importance of eosinophils in asthma has been shown by the observation of frequent exacerbations of the disease in patients with sputum eosinophil counts higher than 3%.^{6,7} Clinical asthma studies of inhaled anti-inflammatory therapy designed to maintain sputum eosinophils below 2% or 3% have resulted in fewer exacerbations of the disease.^{8,9} Patients with refractory asthma with a recalcitrant high sputum eosinophil count on standard therapy also have shown improvement after therapy with anti-interleukin-5 monoclonal antibody that lowers airway and blood eosinophils.^{10–12}

It is evident that a complete blood cell count can be performed at substantially lower cost and with greater accessibility than induced sputum.¹³ However, patients with high tissue or sputum eosinophil levels do not always have high blood eosinophil levels,¹⁴ although the correlation between blood and sputum eosinophilia in patients with asthma generally tends to be positive.^{15–17} Given the indication from several smaller studies that higher sputum eosinophil levels might be positively associated with frequent

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asthma exacerbations⁶ and that eosinophil levels in sputum and blood are positively correlated, the authors hypothesized that higher blood eosinophil counts would be positively associated with more frequent self-reported asthma attacks in a general population of patients with asthma. To address this hypothesis, they examined the association between blood eosinophil counts and frequency of asthma attacks in patients with self-identified asthma in the National Health and Nutrition Examination Survey (NHANES) covering 10 survey years from 2001 through 2010.

Methods

NHANES Dataset

The NHANES is an annual survey of a nationally representative sample of the noninstitutionalized US civilian population. It is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. Each survey consists of a combination of an in-home interview, an examination at a mobile examination center, and laboratory tests. In each survey, participants are selected using a complex stratified multistage cluster sampling scheme. Ten survey years from 2001 through 2010 were used in this analysis.

Definition of Asthma, Eosinophilic Asthma, and Asthma Attack

The NHANES “medical conditions” file contains questions related to the medical history of participants. Patients with asthma were defined as providing an affirmative response to these questions: “Has a physician or other health professional ever told you that you have asthma?” and “Do you still have asthma?” Participants with a prior diagnosis of asthma but responding that they no longer had it were excluded from the analysis. In all survey years, participants had their complete blood cell count data recorded, which included absolute cell counts (cells per microliter) of eosinophils and neutrophils. Different eosinophil cutoffs (ie, 200, 300, and 400 cells/ μ L) to define patients with asthma with high vs low levels of blood eosinophils were investigated in the analyses. Asthma attack (ie, worsening of asthma symptoms) was identified by an affirmative response of patients with asthma to the question: “In the past year, did you have an asthma attack?” Those who reported having an asthma attack also were asked if they had an emergency department (ED) visit because of asthma in the past year.

Independent Variables

For all survey years (2001–2010), background characteristic variables, such as age, sex, race/ethnicity, and education, were extracted from the “demographic variable” file. Smoking history was extracted from “smoking cigarettes use” file and a participant was defined as a nonsmoker if the participant reported “ever smoked less than 100 cigarettes in life.” Survey participants who smoked at least 100 cigarettes were classified as current or ex-smokers. Children were considered nonsmokers.¹⁸ Body mass index (BMI) data from the “body measurements” file were used to define obesity status. In children, obesity was defined as a BMI greater than or equal to the 95th percentile, and overweight was defined as a BMI between the 85th and 95th percentiles of the corresponding age and sex reference group.¹⁹ In adults, study participants with a BMI greater than or equal to 30 kg/m² were considered obese and those with a BMI from 25 to lower than 30 kg/m² were considered overweight. A high blood neutrophil count was defined using the 95th percentile value for each age group in the general NHANES population as the cutoff (ie, 7,000 cells/ μ L for children and 8,400 cells/ μ L for adults). The “respiratory health and disease” file contained questions on whether participants had wheezing or whistling in the past year and whether they had taken treatment for wheezing or whistling in the past year. Participants

Table 1

Characteristics of study population by age group

	Children (6–17 y old) (n = 1,441)	Adults (18–64 y old) (n = 1,721)
Age (y)		
Mean (SE)	12 (0.1)	40 (0.4)
Median	12	40
Age at asthma onset (y)		
Mean (SE)	5 (0.1)	21 (0.6)
Median	4	17
Sex, n (%) ^a		
Male	790 (54)	609 (37)
Female	651 (46)	1,112 (63)
Race/ethnicity, n (%) ^a		
Hispanic	409 (17)	330 (9)
Non-Hispanic white	382 (55)	864 (72)
Non-Hispanic black	579 (22)	447 (14)
Other	71 (6)	80 (5)
Education, n (%) ^a		
$\geq$ High school	N/A	1,198 (83)
<High school		420 (17)
Smoking status, n (%) ^a		
Current smoker	0 (0)	483 (29)
Ex-smoker	0 (0)	339 (23)
Nonsmoker	1,441 (100)	710 (48)
Body mass index (kg/m ²)		
Mean (SE)	22 (0.2)	30 (0.3)
Median	21	29
Eosinophil count (cells/ μ L)		
Mean (SE)	318 (11)	248 (6)
Median	200	157
25th percentile	87	75
75th percentile	368	267
Range	0–2,200	0–2,300
Neutrophil count (cells/ μ L)		
Mean (SE)	3,780 (69)	4,540 (50)
Median	3,437	4,210
25th percentile	2,513	3,227
75th percentile	4,654	5,377
95th percentile	7,084	7,883
Range	700–12,000	700–17,300
Wheezing/whistling in past year, n (%) ^a		
Yes	878 (64)	1,130 (67)
No	563 (36)	591 (33)
Treatment for wheezing/whistling in past year in those with wheezing/whistling, n (%) ^a		
Yes	774 (91)	875 (80)
No	82 (9)	223 (20)
Any asthma attack in past year, n (%) ^a		
Yes	780 (56)	890 (53)
No	661 (44)	831 (47)
Any asthma ED visit in past year in those with asthma attack, n (%) ^a		
Yes	250 (27)	272 (25)
No	530 (73)	618 (75)
Taking prescribed medication for asthma in past 3 mo (data from 2007–2010 only), n (%) ^a		
Yes	365 (73)	518 (67)
No	154 (27)	241 (33)

Abbreviations: ED, emergency department; N/A, not applicable.

^aPercentage adjusted taking into account the multistage sampling of the National Health and Nutrition Examination Survey.

who reported using oral or inhaled corticosteroid in the month before the survey were excluded from analyses because some asthma medications, particularly oral corticosteroids,^{14,20,21} can decrease blood eosinophil counts. In the 4 survey years from 2007 through 2010, participants also were asked specifically if they had taken prescribed medication for asthma in the past 3 months. In these survey years, fraction of exhaled nitric oxide (FeNO) also was measured (“examination data” file). The mean of 2 reproducible FeNO measurements were used as the final value in the analyses.

Table 2

Proportion (percentage^a) of patients with asthma with high blood eosinophil count using different cutoffs

Eosinophil count	Children (6–17 y old) (n = 1,441) (%)	Adults (18–64 y old) (n = 1,721) (%)
≥200 cells/μL	871 (61)	1,030 (62)
≥300 cells/μL	602 (42)	561 (33)
≥400 cells/μL	402 (27)	308 (18)

^aPercentage adjusted taking into account the multistage sampling of the National Health and Nutrition Examination Survey.

Study participants were categorized into high, intermediate, or normal FeNO levels according to American Thoracic Society guidelines.²² In children younger than 12 years, FeNO values of 20 to 35 and higher than 35 ppb were considered intermediate and high levels, respectively. In participants at least 12 years old, the corresponding cutoffs were 25 and 50 ppb.

Statistical Analysis

Univariate analysis was used to describe the frequency of asthma attack rate in the past 12 months in eosinophilic and noneosinophilic asthma (defined using previously stated blood eosinophil cutoffs). Multivariate logistic regression was used to examine the association between blood eosinophil level and asthma attack in the past year. Separate analyses were conducted for children (6–17 years old) and adults (18–64 years old). Models for children used blood eosinophil level as the main independent variable and simultaneously adjusted for age, sex, race/ethnicity, survey year, blood neutrophil level, obesity status, age of asthma onset, and treatment for wheezing/whistling in the past year. Models for adults used education and smoking history as additional independent variables beyond those for children. In a secondary analysis, which included data only from 2007 through 2010, 2 newly measured additional variables were used: whether the patient received “prescribed medication for asthma in the past 3 months” and whether the patient had high exhaled FeNO levels. Analyses were repeated using data from 2001 through 2010 and associations between blood eosinophil level and ED visits for asthma were examined. All analyses took into account the complex multistage sampling and sampling weights provided by the NHANES. All analyses were conducted with SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

Study Population

There were 1,441 children 6 to 17 years old and 1,721 adults 18 to 64 years old who self-identified as currently having asthma from 2001 through 2010 in this study. Mean age was 12 and 40 years for the pediatric and adult groups, respectively (Table 1). In children,

there were more male than female patients (54% vs 46%), whereas the reverse was true in adults (63% vs 37%). Most patients were non-Hispanic white (55% of children and 72% of adults). Approximately two thirds of patients with asthma reported wheezing or whistling in the past year (64% of children and 67% of adults), whereas slightly more than half reported at least 1 asthma attack in the past year (56% of children and 53% of adults). Of those who reported an asthma attack, only approximately one fourth (27% of children and 25% of adults) had an ED visit because of asthma. Most patients who reported wheezing or whistling reported receiving treatment in the past year (91% of children and 80% of adults). The median eosinophil count in children (200 cells/μL) was higher than in adults (157 cells/μL; Table 1).

Proportion of Patients with Asthma with High Blood Eosinophil Levels

The proportion of patients with asthma with high blood eosinophil counts defined by different blood eosinophil cutoffs is presented in Table 2. At the cutoff of 200 cells/μL, the proportion was similar between children and adults (ie, ~61%). However, it was higher in children than in adults at higher cutoffs (42% vs 33% at 300-cells/μL cutoff and 27% vs 18% at 400-cells/μL cutoff, respectively). Table 3 presents the distribution of high, intermediate, and normal FeNO levels by blood eosinophil levels (data available for 2007–2010 only). Patients with higher blood eosinophil counts also were more likely to have higher FeNO levels and the relative difference appeared stronger in adults than in children.

Association of Blood Eosinophil Level and Asthma Attack

In univariate analysis, patients with asthma with higher eosinophil counts appeared to report more asthma attacks than those with lower eosinophil counts, and the difference was more pronounced in children than in adults (Table 4). The median blood eosinophil count was 300 cells/μL in children who reported an asthma attack and it was 200 cells/μL in those who did not. The corresponding figure in adults was 200 cells/μL in the 2 groups.

Three separate multivariate logistic regression models were used separately for children and adults (Table 5). In each age group, each of the 3 models contained the same set of independent variables except for different blood eosinophil count cutoffs, as mentioned earlier. High eosinophil count was associated with more frequent asthma attacks only in models with the 300- and 400-cells/μL cutoffs but not in the model with the 200-cells/μL cutoff in children using all 10 survey years (2001–2010). In adults, no clear association was observed between blood eosinophil level and asthma attack in data from the 10 survey years. When the analysis was restricted to data from 2007 through 2010, with additional adjustment for levels of exhaled FeNO and treatment for asthma in the prior 3 months, similar associations and trends were observed in children, although the estimates were less precise. In adults,

Table 3

Distribution of FeNO by blood eosinophil levels (data from 2007–2010)

Blood eosinophil level	Children (6–17 y old)				Adults (18–64 y old)			
	FeNO level, n (%) ^a			P value	FeNO level, n (%) ^a			P value
	High (>35 ppb)	Intermediate (20–35 ppb)	Normal (<20 ppb)		High (>50 ppb)	Intermediate (25–50 ppb)	Normal (<25 ppb)	
<200 cells/μL	15 (9)	17 (7)	183 (84)	<.01	4 (1)	31 (14)	274 (85)	<.01
≥200 cells/μL	69 (18)	45 (16)	190 (66)		53 (12)	77 (18)	321 (70)	
<300 cells/μL	22 (7)	26 (9)	258 (84)	<.01	13 (3)	66 (15)	443 (82)	<.01
≥300 cells/μL	62 (24)	36 (18)	115 (58)		44 (16)	42 (19)	152 (65)	
<400 cells/μL	34 (9)	38 (10)	302 (81)	<.01	26 (5)	85 (16)	511 (79)	<.01
≥400 cells/μL	50 (29)	24 (19)	71 (52)		31 (18)	23 (20)	84 (62)	

Abbreviation: FeNO, fraction of exhaled nitric oxide.

^aPercentage adjusted taking into account the multistage sampling of the National Health and Nutrition Examination Survey.

Table 4

Frequency of asthma attacks in previous year by eosinophil level

Variables	Frequency of asthma attack in previous year, n (%) ^a	
	Children (6–17 y old) (n = 1,441)	Adults (18–64 y old) (n = 1,721)
Blood eosinophil level (cutoff 200 cells/ μ L)		
High	490 (56.3)	547 (53.1)
Low	290 (50.9)	343 (49.6)
Blood eosinophil level (cutoff 300 cells/ μ L)		
High	361 (60.0)	311 (55.4)
Low	419 (49.9)	579 (49.9)
Blood eosinophil level (cutoff 400 cells/ μ L)		
High	250 (62.2)	172 (55.8)
Low	530 (51.0)	718 (50.8)
Total	780 (54.1)	890 (51.7)

^aPercentage adjusted taking into account the multistage sampling of the National Health and Nutrition Examination Survey.

there was a clearer tendency of an increase of asthma attacks, which was strongest in the model with the 300-cells/ μ L cutoff. No association between blood eosinophil count and asthma-related ED visit was observed in children and adults (data not shown).

Discussion

The authors' hypothesis was that in patients with asthma, a higher blood eosinophil count would be positively associated with more frequent asthma attacks. After controlling for potential confounders, the authors observed that higher blood eosinophil counts were associated with more frequent self-reported asthma attacks in children but not in adults in the analysis using 10 years of data. The association also was observed in adult patients when 2 additional potential confounders (FeNO and prescription for asthma in the past 3 months) as available in the most recent 4 years of data were taken into account. The observed association was stronger in children with higher eosinophil cutoffs. These results suggest that an increased frequency of self-reported asthma attack might be present in patients with a blood eosinophil count of 300 cells/ μ L or higher. Previous studies also using NHANES data have suggested that patients with higher blood eosinophil counts in the general population are more likely to have self-reported asthma,^{18,23} asthma attacks, and asthma-related ED visits.¹⁸ The present study investigated whether these associations would be observed specifically in patients with self-identified asthma (versus the general population).

The authors expected the secondary analysis based on data from fewer survey years (ie, 2007–2010 instead of 2001–2010) to have lower study power (Table 5). However, the authors also assumed that reporting of treatment for asthma and high exhaled FeNO values would correlate with asthma attacks and might be correlated with blood eosinophil level and, thus, might be important potential confounding variables for inclusion in the multivariate adjustment. The inconsistent findings between the primary (10-year data) and secondary (4-year data) analyses in adult patients suggest the importance of controlling for these 2 additional variables in assessing an association between high blood eosinophil counts and asthma attacks. Although the overall trends of the association were similar, potential differences observed between pediatric and adult patients in this study may need further consideration. Higher blood eosinophil counts might play a different role in children with asthma than in adults with asthma.²⁴ In addition, the ability to control for smoking history could play a role. More than 50% of the surveyed adults were current or ex-smokers, whereas all children were assumed to be nonsmokers. It has been shown that smoking

Table 5
Association^a between blood EOS level and past asthma attack in multivariate analysis

	Children (6–17 y old)		Adults (18–64 y old)	
	Model 1 (cutoff 200 cells/ μ L for high/low EOS level)	Model 2 (cutoff 300 cells/ μ L for high/low EOS level)	Model 3 (cutoff 400 cells/ μ L for high/low EOS level)	Model 2 (cutoff 300 cells/ μ L for high/low EOS level)
Blood EOS level ^{b,c} (data from 2001–2010, n = 1,301 in children and 1,609 in adults)				
High	1.11 (0.79–1.56)	1.35 (1.01–1.80)	1.65 (1.04–2.61)	1.15 (0.87–1.52)
Low	Ref	Ref	Ref	Ref
Blood EOS level ^{b,d} (data from 2007–2010, n = 352 in children and 556 in adults)				
High	0.93 (0.50–1.71)	1.24 (0.80–1.92)	1.65 (0.91–3.00)	1.84 (1.11–3.05)
Low	Ref	Ref	Ref	Ref

Abbreviations: EOS, eosinophil; Ref, reference.

^aAnalysis took into account multistage sampling of the National Health and Nutrition Examination Survey.

^bUsed cutoffs of 200, 300, and 400 cells/ μ L in models 1, 2, and 3, respectively.

^cIn children, other variables included in the model were age and age at asthma onset as continuous variables and sex, race/ethnicity, year of survey, blood neutrophil level, body mass index, and treatment for wheezing or whistling in past year as categorical variables. In adults, the model also included education and smoking status (as categorical variables).

^dIn children, other variables included in the model were age and age at asthma onset as continuous variables and sex, race/ethnicity, year of survey, blood neutrophil level, body mass index, treatment for wheezing or whistling in past year, fraction of exhaled nitric oxide, and prescribed medication for asthma in past 3 months as categorical variables. In adults, the model also included education and smoking status (as categorical variables).

has a suppressive effect on eosinophilic inflammation.²⁵ In addition, it is important to note that the NHANES asthma population was self-identified from the general population surveyed. Thus, patients with asthma of different severity levels might have been drawn into the sample, including an unknown proportion with mild asthma. Lack of treatment information, including the dosing level of medication and the authors' inability to control for severity of asthma, could have influenced the estimate of the true association.

The authors did not observe an association between high blood eosinophil level and asthma-related ED visits in patients with asthma. Asthma-related ED visits can be interpreted as a more severe type of asthma attack. However, one can argue that this is not always the case because it depends on care-seeking practice of the individuals, which leads to a debatable interpretation of its meaning. In addition, although the authors could not rule out that a higher blood eosinophil count might not be associated with more severe asthma attacks, the low frequency of asthma-related ED visits in the NHANES asthma population (ie, 15% in children and 13% in adults) and the potential confounding effect of asthma severity might in part explain the observed lack of association in children and adults.

In this study, 3,162 patients 6 to 64 years old with asthma and available blood eosinophil data were included. The relatively large sample of the general asthmatic population from the sampled general US population helps ensure the stability of the study population's blood eosinophil estimates and improves the study's generalizability. The findings of this study need to be interpreted with caution. Owing to its cross-sectional nature, asthma attack was self-reported for events that occurred in the past year, before the blood sample was taken and the blood eosinophil count was measured. Therefore, although eosinophil counts may be associated with a past asthma attack, they might not be predictive of a future asthma attack. Of note, because asthma attack was defined as worsening of asthma symptoms, a measurement of loss of asthma control, it might or might not meet the definition of a moderate to severe exacerbation requiring treatment with oral corticosteroids or events leading to hospitalization or ED visits.²⁶ It also has been proposed that neither a single blood eosinophil count nor a single sputum sample is a reliable marker for eosinophilic asthma.^{27,28} Future studies should examine the relation between blood eosinophil level and risk of future asthma attack, taking into account the influence of severity of asthma and treatment. Despite these potential caveats, the present findings agree with recent preliminary findings from studies in the United Kingdom and the United States suggesting that patients with asthma with a blood eosinophil count higher than 400 cells/ μ L have increased future exacerbation and poorer asthma control (Zeiger R, personal communication, 2014),²⁹ and that moderate to severe asthma is associated with increased odds of eosinophil elevation.³⁰ Together, these studies provide mounting evidence that patients with asthma and a higher blood eosinophil level might have more frequent asthma exacerbations and greater disease burden than those with a lower eosinophil level.

Previous clinical studies have relied on induced sputum to identify eosinophilic phenotypes, a laboratory method that is not easily transferred from the research setting to routine use in the clinic^{13,31} because sputum collection and processing are time consuming and require specialized personnel and training.¹⁴ Other less invasive and simpler tests, such as FeNO and peripheral blood eosinophil counts, have been studied to find alternative predictive markers for sputum eosinophil counts.^{32,33} Indeed, the present findings support the need to further explore the role of FeNO in combination with peripheral blood eosinophil levels on asthma exacerbation. Recently, the US National Institutes of Health and federal agencies convened an expert group to propose biomarkers that should be assessed in future clinical asthma research studies

and concluded that (1) analysis of blood eosinophils by an automated complete blood cell counter provides useful information to characterize study populations for prospective clinical studies in asthma and (2) blood eosinophil counts can be used as a biomarker to monitor the systemic biological effects of pharmacologic and immunologic interventions in patients with asthma.³⁴ The positive association between blood eosinophilia and asthma attack as found in this study provides further support of the use of blood eosinophil levels in assessing asthma status.

In conclusion, high blood eosinophil counts appeared to be associated with more frequent asthma attacks in children with asthma. Increased frequency of asthma attacks was more pronounced at higher blood eosinophil counts. A similar association might be present in adults, although it was not as clear in the data analyzed. These data support the use of blood eosinophil count as a potential practical marker of asthma outcomes. Additional studies are needed to confirm a potential increase in disease severity and burden associated with higher blood eosinophil counts in patients with asthma.

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