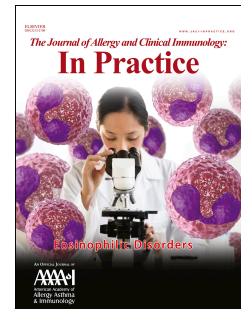


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**Associations Between Individual Characteristics and Blood Eosinophil Counts in Adults with
Asthma or COPD**

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29 **Conflict of Interest**

30 CSA and TNT are employees of AstraZeneca. HC was an employee of AstraZeneca at the time this
31 work was completed. BEC has served as an advisor for consult and as a speaker for AstraZeneca,
32 Boehringer Ingelheim, Circassia, Genentech, Novartis, Regeneron, Sanofi, and Teva. RSZ reports
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35 Theravance BioPharma, Regeneron Pharmaceuticals, and Patara Pharma outside the submitted work.

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40

41 **Abstract**

42 *Background*

43 Elevated blood eosinophil (bEOS) counts are markers of inflammation associated with poorer
44 outcomes in individuals with asthma and chronic obstructive pulmonary disease (COPD). However,
45 little is known about factors impacting the variability of bEOS counts in individuals with these
46 conditions.

47 *Objective*

48 To determine the association between individual characteristics and bEOS counts in individuals with
49 asthma, COPD, and non-asthma/COPD controls.

50 *Methods*

51 Participants in the National Health and Nutrition Examination Surveys (NHANES; 2001-2016) aged
52 ≥ 18 years with asthma or COPD and non-asthma/COPD controls were identified based on diagnoses
53 by health care practitioners. Associations between bEOS counts and age, sex, race/ethnicity, body
54 mass index (BMI), and smoking status were investigated. Statistical analyses incorporated NHANES
55 multistage sampling and sampling weights.

56 *Results*

57 bEOS counts were significantly higher in individuals with asthma than in non-asthma/COPD controls.
58 There was no significant difference between individuals with COPD and non-asthma/COPD controls.
59 Across all 3 populations, median bEOS counts were consistently higher in men (15–20%) and those
60 with higher BMI (~5–25%) and lower in individuals of black race (15–20%). bEOS counts increased
61 with age in non-asthma/COPD controls but not in individuals with asthma or COPD. Among non-
62 asthma/COPD controls and individuals with asthma, bEOS counts were higher in current and former

smokers compared with never smokers, but no such association was found between bEOS counts and smoking status in individuals with COPD.

Conclusion

In individuals with asthma or COPD, sex, race, and BMI should be considered when interpreting bEOS counts. Smoking history should also be considered in individuals with asthma. Future research should evaluate the association between bEOS counts adjusted for demographic factors and clinical outcomes, such as asthma or COPD exacerbations.

Highlights

1. What is already known about this topic?

Reducing exacerbations of asthma and COPD improves patient outcomes and lowers health care costs. Elevated blood eosinophil (bEOS) counts have been associated with risk of asthma exacerbations, though their role in COPD remains unclear.

2. What does this article add to our knowledge?

We showed that certain demographic and clinical characteristics were associated with bEOS counts in individuals with asthma or COPD compared with healthy controls. Individuals with asthma had higher baseline bEOS counts than healthy controls.

3. How does this study impact current management guidelines?

Some individual characteristics (e.g., sex, race, BMI) affect baseline bEOS counts in patients with asthma or COPD. Understanding these correlations can help interpret clinical data to better personalize treatment plans for these diseases.

Keywords (max: 10): NHANES, biomarkers, demographics, eosinophil, asthma, COPD

86

87 **Abbreviations**

88 bEOS, blood eosinophil
89 BMI, body mass index
90 CI, confidence interval
91 COPD, chronic obstructive pulmonary disease
92 FeNO, fractional exhaled nitric oxide
93 FEV₁, forced expiratory volume in 1 second
94 HCP, health care provider
95 ICS, inhaled corticosteroids
96 IgE, immunoglobulin E
97 N/A, not applicable
98 NHANES, National Health and Nutrition Examination Surveys
99 ppb, parts per billion

Introduction

Exacerbations of asthma or chronic obstructive pulmonary disease (COPD) can incur considerable health care costs as well as lost productivity and reduced quality of life.^{1,2} Elevated blood eosinophil (bEOS) counts have been associated with increased risk of asthma exacerbations.^{3,4} In individuals with severe uncontrolled eosinophilic asthma, eosinophil depletion with a variety of newly-available monoclonal antibody therapies has demonstrated improved outcomes.⁵⁻¹³ A number of studies have found a similar association between bEOS counts and exacerbations in COPD, but evidence is somewhat conflicting.¹⁴⁻¹⁶ Individuals with COPD who had eosinophilic inflammation responded better to inhaled corticosteroids (ICS) than those with lower baseline eosinophil counts,¹⁷ but it is unclear whether lowering bEOS count correlates with better outcomes in individuals with COPD.^{18,19} Furthermore, absolute bEOS counts can be variable within the same individual over time,²⁰⁻²³ even during the course of a single day. Despite the role bEOS counts play in asthma, and potentially COPD, it is not well understood how they are associated with individual patient characteristics.

The objective of the current study was to examine whether bEOS counts were associated with demographic characteristics (age, sex, race/ethnicity), body mass index (BMI), and smoking history in individuals with asthma or COPD, and a control population of individuals without asthma or COPD. We hypothesized that these individual demographic characteristics and clinical risk factors may affect bEOS counts.

Methods

Study Population

Data were extracted from National Health and Nutrition Examination Surveys (NHANES), cross-sectional surveys of nationally representative samples of the non-institutionalized U.S. civilian population. The NHANES program assesses the health and nutritional status of both adults and children in the U.S. by conducting in-home interviews followed the next day by standardized physical examinations and laboratory testing in specially equipped mobile examination centers.²⁴ NHANES samples approximately 5,000 individuals each year. Our analysis included data from NHANES participants from 2001 (when respiratory disease symptoms began to be collected in a systematic and stable fashion) to 2016 (the latest data available when the data were downloaded in April 2018).

Individuals with asthma were identified as NHANES participants aged 18 to 64 years who were ever told by a doctor or other health care provider (HCP) that they had asthma and reported having asthma at the time of the interview. Individuals with COPD were identified as individuals aged ≥ 40 years who were ever told by a doctor or other HCP that they had chronic bronchitis and had chronic bronchitis at the time of the interview, or were ever told by a doctor or other HCP that they had emphysema. Non-asthma/COPD controls were defined as NHANES participants aged ≥ 18 years, without report of a diagnosis of asthma, emphysema, or chronic bronchitis. Participants who coughed or brought up phlegm during most of the days during the last 3 months were excluded from the population of non-asthma/COPD controls. Participants who reported ≥ 1 of the following conditions were also excluded from the analysis: history of lung, windpipe, or larynx cancer; flu during the last 3 months; pneumonia or ear infections that started during the last 30 days. Women who reported being pregnant or tested positive to a laboratory pregnancy test were also excluded from the analysis.

Complete blood counts were carried out with Beckman Coulter analyzers (Miami, FL, USA) that were located in 4 NHANES mobile examination centers. bEOS were generated as the product of total white blood cell count by the percent of eosinophils.⁴ Coulter controls were run at the beginning of the shift. NHANES laboratories subscribed to College of American Pathologist proficiency surveys. In this study, bEOS counts are reported as medians with 95% confidence intervals (95% CI) to correct for the skewness to the right of the original distributions.

Individual Characteristics

Demographics included age (18-39, 40-64, or ≥ 65 years for controls; 18-39 and 40-64 years for asthma; 40-64 and ≥ 65 years for COPD), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other). Clinical risk factors of interest were smoking status and BMI. Individuals were characterized as current smokers, former smokers (smoked ≥ 100 cigarettes in life but had stopped smoking when the interview was completed), or never smokers. BMI was broken down into 3 categories: normal weight ($\text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), or obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). bEOS counts were also analyzed as a function of the timing of the blood draw as reported by NHANES: morning, afternoon, or evening. Disease-relevant variables for asthma were age at onset (≤ 18 or > 18 years), emergency care visit because of asthma or asthma attack over the past year, fractional exhaled nitric oxide (FeNO), use of ICS within the last 30 days, ≥ 1 elevated allergen-specific immunoglobulin E (IgE) and total IgE. FeNO measurements were categorized as low (< 25 ppb), medium ($25 \leq \text{FeNO} \leq 50$ ppb), and high (≥ 50 ppb).²⁵ Allergen-specific IgE to any of the 9 tested perennial allergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat epithelium and dander, dog dander, German cockroach, Alternaria alternata, Aspergillus fumigatus, rat and mouse

urine proteins) were considered elevated when ≥ 0.35 U/mL.²⁶ Total IgE was considered elevated when ≥ 100 U/mL.²⁶ Disease-relevant variables for COPD included duration of illness (based on age at current diagnosis; <10 years vs ≥ 10 years), cough and phlegm during the last 3 months, use of ICS within the last 30 days, and elevated total IgE.

Statistical Analysis

Distributions of bEOS counts were first compared between the 2 populations of interest and controls of the same age: all patients with asthma versus non-asthma/COPD controls aged 18-64 years, and all patients with COPD versus non-asthma/COPD controls aged ≥ 40 years. Subsequently, to examine associations with asthma and COPD independently, 3 populations within the same category of aged 40-64 years (asthma only, COPD only, and asthma and COPD) were compared to non-asthma/COPD controls aged 40-64 years. No adjustment for multiplicity was made because the categorical comparisons involved 3 or fewer comparisons conducted in independent samples. Associations between demographics, clinical characteristics, and bEOS distributions were analyzed independently among non-asthma/COPD controls, all patients with asthma, and all patients with COPD; individuals with both asthma and COPD were not examined due to the small sample size. The association of each factor with bEOS count was tested against the residual variance estimate with an F test. Figures present crude bEOS distributions, but all statistical comparisons between populations and all associations with demographics and clinical characteristics were tested after adjustment for other covariates as described below.

All data analysis procedures took into account the complex multistage sampling of the survey, as well as the sampling weights provided by NHANES. bEOS counts were ranked among the total population

191 retained for analysis to control for the skewness of distribution. The ranks were fitted with
192 multivariable linear regressions that adjusted for individual characteristics (age, sex, race/ethnicity,
193 smoking status, BMI) and timing of blood draw (morning, afternoon, evening), then disease-relevant
194 variables (e.g., age of onset for asthma, duration of illness for COPD) were analyzed one by one
195 (controlling also for individual characteristics). All statistical analyses were conducted with SAS®
196 version 9.4 (SAS Institute, North Carolina).

197

198

Results

Study Populations

A total of 37,575 NHANES participants from 16 survey years were analyzed, including 2,366 individuals with asthma, 1,307 individuals with COPD, and 34,181 non-asthma/COPD controls; 279 participants reported both asthma and COPD (**Supplementary Figure E1**). The distribution of demographic/clinical characteristics in the retained populations is shown in **Table 1**. Females accounted for 63% and 53% of individuals with asthma and individuals with COPD respectively versus 49% in the non-asthma/COPD controls. More individuals with asthma and COPD were white (48% and 66% respectively) compared with those in the non-asthma/COPD control group (42%). Obesity occurred in 26% of individuals with asthma and 25% of those with COPD, whereas 33% of controls were obese. The majority of individuals with COPD were current or former smokers (77%) compared with 50% in those with asthma and 43% in the control group. Among former smokers in the asthma, COPD, and control groups, 31% to 39% of subjects reported having quit smoking in the previous 1-9 years, 23% to 28% reported quitting in the previous 10-19 years, and 33% to 43% quit smoking ≥ 20 years in the past.

Comparisons Between Populations

Median (95% CI) bEOS counts were significantly higher in individuals with asthma (median, 196 [95% CI, 188-204] cells/ μ L) than in non-asthma/COPD controls aged 18-64 years (154 [151-156] cells/ μ L; $p < 0.001$; **Figure 1A**). In contrast, there was no significant difference in bEOS counts between individuals with COPD and non-asthma/COPD controls aged ≥ 40 years (**Figure 1B**) after adjustment on demographics. When individuals with asthma and COPD aged 40-64 years were re-categorized into 3 mutually exclusive populations (asthma only, COPD only, and asthma and COPD) and compared with non-asthma/COPD controls aged 40-64 years (157 [154-160] cells/ μ L), bEOS

counts were higher in individuals with asthma only (202 [191-213] cells/ μ L; $p < 0.001$) and those with both asthma and COPD (206 [188-255] cells/ μ L; $p < 0.001$), but did not reach statistical significance in those with COPD only (157 [131-183] cells/ μ L; $p = 0.06$; **Figure 1C**).

Distribution of bEOS Counts in Non-asthma/COPD Controls

In the population of non-asthma/COPD controls, median (95% CI) bEOS count was significantly associated with all demographic and clinical characteristics (all $p < 0.001$). bEOS count increased with increasing age (median, 151 [95% CI, 148-153] cells/ μ L for ages 18-39 years, 157 [154-160] cells/ μ L for ages 40-64 years, and 168 [164-173] cells/ μ L for ages ≥ 65 years; **Figure 2A**) and was higher in men than women (170 [168-173] cells/ μ L for men vs 145 [143-147] cells/ μ L for women; **Figure 2B**), as well as in current smokers compared with former or never smokers (187 [181-193] cells/ μ L for current smokers vs 161 [158-165] cells/ μ L for former smokers and 147 [144-150] cells/ μ L for never smokers; **Figure 2C**). bEOS counts were lower in non-Hispanic blacks (138 [134-142] cells/ μ L) than in other racial/ethnic groups (white, 159 [157-161] cells/ μ L; Hispanic, 156 [152-160] cells/ μ L; other, 163 [158-168] cells/ μ L; **Figure 2D**), and bEOS count increased with increasing BMI (normal weight, 139 [136-142] cells/ μ L; overweight, 156 [152-159] cells/ μ L; obese, 173 [170-177] cells/ μ L; **Figure 2E**). The association between bEOS count and timing of blood draw was U-shaped, with higher bEOS counts when blood was drawn in the morning (159 [156-162] cells/ μ L) or in the evening (163 [158-168] cells/ μ L) versus in the afternoon (150 [146-153] cells/ μ L; **Figure 2F**).

bEOS Counts in Individuals with Asthma

Associations between bEOS counts and individual characteristics were generally consistent between individuals with asthma and non-asthma/COPD controls. Median (95% CI) bEOS counts were higher in men with asthma than women with asthma (median, 226 [95% CI, 214-238] cells/ μ L for men vs 180

[168-192] cells/ μ L for women; $p < 0.001$; **Figure 2B**) and in current smokers compared with former or never smokers (209 [193-226] cells/ μ L for current smokers vs 201 [178-224] cells/ μ L for former smokers and 187 [178-197] cells/ μ L for never smokers; $p = 0.02$; **Figure 2C**). bEOS counts were lower in non-Hispanic blacks (170 [158-183] cells/ μ L) than other races (white, 200 [191-209] cells/ μ L; Hispanic, 207 [196-218] cells/ μ L; other, 196 [177-215] cells/ μ L; $p < 0.001$; **Figure 2D**). bEOS counts also increased with increasing BMI (normal weight, 164 [148-180] cells/ μ L; overweight, 204 [189-220] cells/ μ L; obese, 209 [196-222] cells/ μ L; $p < 0.001$; **Figure 2E**). However, no significant associations were observed between bEOS counts and age or the timing of blood draw (**Figure 2A, 2F**).

Analysis of the relationship between bEOS counts and the disease-relevant variables for asthma showed that bEOS count increased with elevations in FeNO ($p < 0.001$), when ≥ 1 allergen-specific IgE was elevated ($p < 0.01$), or when total IgE was ≥ 100 U/mL ($p = 0.01$), and was higher among individuals who had used ICS within the last 30 days ($p < 0.01$; **Table 2**). There were no significant associations between bEOS count and other disease-relevant variables for asthma.

bEOS Counts in Individuals with COPD

The associations between individual characteristics and bEOS counts were also generally consistent with those observed in non-asthma/COPD controls (**Figures 2A to 2F**). Median (95% CI) bEOS counts were higher in men with COPD than women with COPD (median, 205 [95% CI, 186-223] cells/ μ L for men vs 168 [153-183] cells/ μ L for women; $p < 0.01$; **Figure 2B**), but were lower in non-Hispanic black individuals (159 [142-177] cells/ μ L) than other races (white, 186 [173-198] cells/ μ L; Hispanic, 193 [181-204] cells/ μ L; other, 201 [185-217] cells/ μ L; $p = 0.02$; **Figure 2D**). bEOS counts

also increased with increasing BMI (normal weight, 161 [139-183] cells/ μ L; overweight, 185 [162-208] cells/ μ L; obese, 194 [173-215] cells/ μ L; $p < 0.001$ **Figure 2E**). However, there were no associations between bEOS counts and age, smoking status, or timing of blood draw (**Figures 2A, 2C, and 2F**, respectively). In addition, unlike for asthma, no associations were observed between bEOS count and any of the disease-relevant variables for COPD (**Table 2**). Results of the multivariable analysis of bEOS counts and each demographic and clinical characteristic after adjustment for other covariates are shown in **Table 3**.

Discussion

The present NHANES analysis of bEOS counts demonstrates that an individual's demographic and clinical characteristics may affect blood eosinophil counts, which may be particularly important to consider when focusing on absolute bEOS thresholds (e.g., >150 cells/ μ L, >300 cells/ μ L, >400 cells/ μ L) to define elevated bEOS counts. For all three populations evaluated (individuals with asthma, individuals with COPD, and controls without asthma or COPD), bEOS counts were higher in men than in women and in obese individuals, and lower among blacks than among individuals of another race or ethnicity.

In the large population of non-asthma/COPD controls, we further found that older age, smoking, and morning or evening blood draws were associated with elevated baseline bEOS counts. Similar trends with these factors were observed among individuals with asthma and COPD but did not always reach statistical significance, likely due to more limited statistical power. Among individuals with asthma, increased bEOS counts were also associated with other markers of allergy and inflammation, including specific IgE, total IgE, and FeNO, consistent with previous studies.²⁷⁻²⁹

Several earlier studies in individuals with asthma have shown an association between bEOS counts and the risk of asthma exacerbations.^{3, 4, 30, 31} A 2015 study conducted in patients with asthma in the United Kingdom demonstrated that elevated bEOS counts were associated with younger age, male sex, smoking, and having more severe exacerbations.³ Interestingly, this result is similar to our findings for some demographic variables, but we did not observe a significant association between age and elevated bEOS counts in the U.S. NHANES population for individuals with asthma.

Associations between bEOS counts and characteristics of individuals with COPD were investigated in a smaller sample of participants in the NHANES surveys from 2007 to 2010, in which older age and male sex were associated with elevated bEOS counts.³² Furthermore, a 2017 study of U.K. patients showed that elevated bEOS counts in former smokers were associated with increased exacerbation risk in patients with COPD.³³ Similar to the findings in patients with asthma, our results are generally consistent with the literature, although we also did not find an association between age and bEOS count for U.S. patients with COPD. Associations between bEOS counts and timing of the blood draw have also been previously described, as well as circadian changes in the sputum of patients with asthma and healthy controls^{34, 35}.

Our analysis was conducted in a relatively large sample considered to be representative of the general population of U.S. residents. Diagnoses of HCP-diagnosed asthma and COPD (emphysema or chronic bronchitis) were derived from patient self-report during a systematic interview conducted by trained personnel, consistent with the NHANES procedures manuals and previous studies^{36, 37}. To increase the diagnosis specificity, our analysis of the populations of individuals with asthma and COPD was restricted to NHANES participants aged 18 to 64 years and aged ≥ 40 years, respectively. However, a

limitation of our analysis is that we could not validate the patient-reported diagnoses in the NHANES dataset³⁶. There are other limitations with the available data, such as an inability to quantify pack-years of smoking history, the variable timing of the bEOS count measurements that we adjusted for in our analyses, and limited data on the medications individuals were taking at the time of the survey. The prevalence of current or former smoking reported for our population of individuals with asthma is high but consistent with estimates from a large population of US individuals with asthma described by the Behavioral Risk Factor Surveillance System (BRFSS)³⁸.

Based on the current findings, future clinical studies of eosinophilic inflammation in asthma and COPD should consider that comparable levels of eosinophilic airway inflammation could be associated with differential bEOS counts based on differences in individual demographic and clinical characteristics. One area for further exploration is whether the use of certain demographic factors (e.g., sex, race, BMI, and smoking history) to derive an “adjusted” bEOS count would result in improved correlations with exacerbation risk in asthma or COPD. Alternatively, different thresholds for elevated bEOS counts as a function of a patient’s demographic and clinical characteristics could be identified, for instance, a lower threshold in women than men. Further standardizing of the conditions for the laboratory examinations—with blood drawn more systematically in morning hours—would also facilitate consistent interpretation of the bEOS counts.

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Figure Captions

Figure 1. Distribution of blood EOS counts in each population. The distributions of blood eosinophil counts are shown for A) individuals aged 18-64 years with asthma compared with age-matched non-asthma/COPD controls; B) individuals aged ≥ 40 years with COPD compared with age-matched non-asthma/COPD controls; C) individuals aged 40-64 years with asthma only, COPD only, both asthma and COPD, and non-asthma/COPD controls.

* $p < 0.001$ (comparison vs. control group).

COPD, chronic obstructive pulmonary disease.

<<Note for journal editor: We suggest this be printed as a 2-column image.>>

Figure 2. Blood eosinophil counts by key demographic and clinical characteristics for individuals with asthma, COPD, and controls without asthma or COPD. The median (95% CI) blood eosinophil counts are shown for individuals by: A) age; B) sex; C) smoking status; D) race/ethnicity; E) BMI; F) time of blood draw.

*Comparisons between the defined categories (eg, age groups 18 to 39 vs. 40 to 64 vs. ≥ 65 years old) within each study sample population (eg, individuals with asthma) – adjusted p-value: $p < 0.05$.

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

<<Note for journal editor: We suggest this be printed as full-page image.>>

Table 1. Distributions of Key Demographic and Clinical Characteristics by Population.^a

	Non-asthma/COPD controls % (n)	Individuals with asthma % (n)	Individuals with COPD % (n)
Age (years)	n = 34,181	n = 2,366	n = 1,307
18 to 39	40% (13,570)	48% (1,129)	N/A
40 to 64	38% (13,148)	52% (1,237)	48% (627)
65 and older	22% (7,463)	N/A	52% (680)
Sex	n = 34,181	n = 2,366	n = 1,307
Male	51% (17,327)	37% (871)	47% (612)
Female	49% (16,854)	63% (1,495)	53% (695)
Race/ethnicity	n = 34,181	n = 2,366	n = 1,307
White	42% (14,517)	48% (1,133)	66% (868)
Black	21% (7,231)	26% (621)	16% (215)
Hispanic	27% (9,301)	19% (439)	11% (149)
Other	9% (3,132)	7% (173)	6% (75)
Smoking status	n = 32,216	n = 2,187	n = 1,306
Current smoker	19% (6,194)	29% (643)	35% (461)
Former smoker	24% (7,644)	21% (459)	42% (552)
Never smoker	57% (18,378)	50% (1,085)	22% (293)
Missing data	1,965	179	1
BMI (kg/m²)	n = 33,599	n = 2,336	n = 1,265
<25 (normal weight)	34% (11,288)	47% (1,108)	44% (560)
25 ≤ to <30 (overweight)	34% (11,314)	26% (609)	30% (385)
≥30 (obesity)	33% (10,997)	26% (619)	25% (320)
Missing data	582	30	42
Timing of blood draw	n = 34,181	n = 2,366	n = 1,307
Morning	48% (16,572)	47% (1,119)	50% (655)
Afternoon	35% (12,244)	37% (873)	39% (517)
Evening	16% (5,365)	16% (374)	10% (135)

^aNot all percentages sum to 100 due to rounding.

N/A, not applicable.

Table 2. Median (95% CI) Blood EOS Count as a Function of Disease-relevant Variables for Asthma and for COPD.^a

Severity indicators for asthma	Eosinophils (cells/ μ L) median [95% CI]	P-value
Age at onset (years)		
≤ 18 (n = 1,311 [56%])	199 [188-210]	$p = 0.14$
> 18 (n = 1,025 [44%])	190 [177-204]	
Visit to an emergency room or urgent care center because of asthma over past year		
Yes (n = 354 [15%])	206 [182-231]	$p = 0.14$
No (n = 2,012 [85%])	195 [188-203]	
Asthma attack in past year		
Yes (n = 1,179 [50%])	200 [189-212]	$p = 0.17$
No (n = 1,185 [50%])	192 [182-202]	
FeNO		
< 25 ppb (n = 599 [74%])	174 [158-190]	$p < 0.001$
$25 \leq \text{FeNO} \leq 50$ (n = 141 [17%])	225 [200-251]	
> 50 (n = 67 [8%])	371 [304-439]	
Use of ICS during the last 30 days^b		
Yes (n = 382 [19%])	216 [184-249]	$p < 0.01$
No (n = 1,654 [81%])	195 [186-205]	
≥ 1 Elevated allergen-specific IgE^c		
Yes (n = 171 [64%])	246 [202-289]	$p < 0.01$
No (n = 97 [36%])	168 [126-211]	
Total IgE (U/mL)^c		
≥ 100 (n = 133 [52%])	266 [196-335]	$p = 0.01$
< 100 (n = 124 [48%])	202 [164-239]	
Severity indicators for COPD	Eosinophils (cells/μL) median [95% CI]	P-value
Duration of illness		
< 10 years (n = 293 [36%])	159 [136-182]	$p = 0.36$
≥ 10 years (n = 532 [64%])	189 [172-205]	
Cough most days during the last 3 months		
Yes (n = 404 [41%])	190 [175-206]	$p = 0.26$
No (n = 573 [59%])	171 [153-190]	
Phlegm most days during the last 3 months		
Yes (n = 371 [38%])	190 [173-208]	$p = 0.52$
No (n = 605 [62%])	178 [162-193]	
Use of ICS during the last 30 days^b		
Yes (n = 245 [22%])	204 [181-228]	$p = 0.13$
No (n = 892 [78%])	179 [165-194]	
Total IgE (U/mL)^c		
≥ 100 (n = 43 [31%])	198 [171-226]	$p = 0.56$
< 100 (n = 97 [69%])	198 [179-218]	

^aNot all percentages sum to 100 due to rounding.^bData missing in 2015 and 2016.^cData available in 2005 and 2006; unadjusted linear regression.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin.

Table 3. Factors Associated with Blood Eosinophil Counts (cells/ μ L) Based on Multivariable Analysis.^a

	Non-asthma/COPD controls (n = 34,181)	Individuals with asthma (n = 2,366)	Individuals with COPD (n = 1,307)
Age (years)	28.76 $\pm$ 4.00 <i>p</i> <0.001	2.21 $\pm$ 1.25 <i>p</i> = 0.08	2.05 $\pm$ 1.22 <i>p</i> = 0.10
Sex			
Male	2,006 $\pm$ 148 - (ref)	219 $\pm$ 36 - (ref)	84.7 $\pm$ 28.9 - (ref)
Female	<i>p</i> <0.001	<i>p</i> <0.001	<i>p</i> <0.01
Race/ethnicity			
Black	- (ref)	- (ref)	- (ref)
Other (White, Hispanic, Other)	2,229 $\pm$ 145 <i>p</i> <0.001	166 $\pm$ 37 <i>p</i> <0.001	77 $\pm$ 33 <i>p</i> = 0.02
Smoking status^a	-1,542 $\pm$ 98 <i>p</i> <0.001	-44.3 $\pm$ 19.4 <i>p</i> = 0.02	-14.8 $\pm$ 18.3 <i>p</i> = 0.42
BMI (kg/m²)	204 $\pm$ 9 <i>p</i> <0.001	8.60 $\pm$ 2.03 <i>p</i> <0.001	7.39 $\pm$ 1.74 <i>p</i> <0.001
Time of blood draw			
Morning	-586 $\pm$ 202	-33.9 $\pm$ 53.0	-6.9 $\pm$ 47.8
Afternoon	-1,526 $\pm$ 201	-80.1 $\pm$ 54.7	-31.3 $\pm$ 50.5
Evening	- (ref) <i>p</i> <0.001	- (ref) <i>p</i> = 0.28	- (ref) <i>p</i> = 0.72

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

^aEstimated regression coefficient and standard error after rank transformation. The magnitude of parameter estimates varies between controls, individuals with asthma, and individuals with COPD because the models fit ranks from 1 to 34,181 for controls, 1 to 2,366 for individuals with asthma, and 1 to 1,307 for individuals with COPD, consistent with the total N for each population.

^bSmoking status was considered as an ordinal variable with decreasing blood eosinophils counts from current smokers (code: 1) to former smokers (code: 2) and never smokers (code: 3).

