

Associations between blood eosinophils and decline in lung function among adults with and without asthma

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Take Home Message: Blood eosinophils are associated with lung function decline even in people without asthma or wheeze.

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Abstract

Eosinophilic inflammation and airway remodelling are characteristic features of asthma, but the association between them is unclear. We assessed associations between blood eosinophils and lung function decline in a population-based cohort of young adults.

We used linear mixed models to analyse associations between blood eosinophils and spirometry at 21, 26, 32, and 38 years adjusting for sex, smoking, asthma, and spirometry at age 18. We further analysed associations between mean eosinophil counts and changes in spirometry from ages 21 to 38 years.

Higher eosinophils were associated with lower FEV₁/FVC ratios and lower percent-predicted FEV₁ values for both pre- and post-bronchodilator spirometry (all p values ≤ 0.048). Although eosinophil counts were higher in participants with asthma, the associations between eosinophils and spirometry were similar among participants without asthma or wheeze. Participants with mean eosinophil counts >0.4 × 10⁹/L between ages 21 and 38 had greater declines in FEV₁/FVC ratios (1.8%; 95% CI 0.7, 2.9; p=0.001) and FEV₁ values (3.4 %predicted; 95% CI 1.5, 5.4); p=0.001) than those with lower counts.

Blood eosinophils are associated with airflow obstruction and enhanced decline in lung function independently of asthma and smoking. Eosinophilia is a risk factor for airflow obstruction even in those without asthma or symptoms.

Abstract words: 200

Introduction

Eosinophilic airway inflammation and airway remodelling leading to persistent airflow obstruction are characteristic features of asthma, but the link between them is unclear.[1]

Although tissue eosinophils are associated with remodelling of the airway wall, it has not been established whether this is a causal association.[2-4] Controlling eosinophilic inflammation with inhaled corticosteroids reduces exacerbations,[5-7] but has not yet been shown to prevent the development of fixed airflow obstruction.[1]

One reason for the uncertainty is that measurement of eosinophilic airway inflammation using induced sputum is unsuitable for routine clinical practice or large-scale epidemiological studies.[7, 8] Peripheral blood eosinophil counts have emerged as a promising and easily measured marker of eosinophilic airway inflammation.[9-12] High blood eosinophils are associated with poor asthma control and risk for exacerbations.[13-15] Blood eosinophil counts also predict the response to inhaled corticosteroids in patients with COPD,[16-18] and the response to anti-IL5 therapy in asthma.[19] Blood eosinophil counts have been associated with lower FEV₁ values in participants with and without asthma,[13, 20-23] but not all studies have found this.[24] Blood eosinophils did not predict an enhanced decline in FEV₁ in asthmatic adults,[22, 25, 26] but a greater decline in FEV₁ was observed in COPD patients with high blood eosinophil counts who were not treated with inhaled corticosteroids.[18]

We investigated associations between blood eosinophil counts and lung function in a population-based birth cohort of young adults. We hypothesised that eosinophilic inflammation would be associated with airflow obstruction and a decline in lung function among participants with asthma.

Methods

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behaviour in an unselected population-based cohort of individuals born in the only maternity hospital in Dunedin in 1972/73 (<http://dunedinstudy.otago.ac.nz>).[27, 28] The cohort was formed when 1,037 children living in the greater Dunedin area (91% of eligible births) were assessed at age 3 years. Study members represent the full range of socio-economic status in the South Island of New Zealand and are primarily of New Zealand/European ethnicity. The study has a high rate of follow-up: 95% of living study members participated in the most recent assessment at age 38. Written informed consent was obtained for each assessment. The Otago Ethics Committee approved the study.

Childhood asthma was defined as a parent-reported diagnosis of asthma with compatible symptoms or asthma medication within the previous year at 9, 11, or 13 years.[28] Adult asthma was defined as a self-reported diagnosis with compatible symptoms or medication within the previous year at ages 21, 26, 32, or 38 years. Wheeze included all episodes of reported wheeze in the previous year, excluding only one or two episodes lasting less than one hour.[27] Inhaled corticosteroid use was recorded at each age. Current smoking was defined as daily smoking for at least one month in the previous year. Cumulative tobacco exposure was quantified in pack-years (equivalent to 20 cigarettes/day for one year).[28]

At ages 21, 26, 32, and 38 years, blood was drawn at the end of the assessment day. Eosinophil counts were obtained from automated complete blood counts and were reported to two decimal places at ages 21, 26, and 32 but to one decimal place at age 38. Eosinophil counts $>0.4 \times 10^9/L$ were regarded as high.[15]

Spirometry was performed at ages 18, 21, 26, 32, and 38 years. This was repeated after inhaled salbutamol at 18, 26, 32, and 38.[28] Height was measured at each assessment. Skin-prick tests

for 11 common aeroallergens were done at ages 21 and 32.[29] Participants were considered to have atopic sensitisation if they had at least one positive test (weal diameter ≥ 2 mm greater than negative control) at either age.

Statistical analyses

We compared sex, asthma, atopy, smoking, and lung function at age 38 among those with and without complete eosinophil data. Non-parametric (Spearman) correlations, intraclass correlations and the persistence of high ($>0.4 \times 10^9/L$) counts between ages were used to assess the consistency of eosinophil counts between ages.

Eosinophil counts were transformed with natural logarithms to approximate normal distributions. To allow transformation of zero values, 0.1 was added before transformation and later deducted from the geometric mean values. Linear mixed models were used to assess predictors of log-eosinophil counts with fixed effects for age and a random effect for participants to accommodate repeated measurements. These models included current smoking, childhood asthma, adult asthma, atopic sensitisation, inhaled corticosteroid use, and sex as predictors.

Linear mixed models with fixed effects for age and a random effect for participants were also used to assess whether log-eosinophil counts were associated with airflow obstruction. The primary outcome measure was the pre-bronchodilator FEV₁/FVC ratio from ages 21 to 38 years. Secondary outcome measures were percent predicted FEV₁ and FVC and post-bronchodilator spirometry.[30] Analyses adjusted for spirometry measurements at age 18, sex, childhood and adult asthma, inhaled corticosteroids, and pack-years. Analyses tested for interactions between eosinophils and asthma diagnoses. Additional separate analyses were done for those with and without adult asthma. Body Mass Index (BMI) is associated with lower FEV₁/FVC ratios among women in this cohort [31] and because atopic sensitisation was associated with higher eosinophil counts, further analyses adjusted for these factors. We also tested for interactions between

eosinophils and smoking. The models were repeated with adjustment for childhood and adult wheeze instead of diagnosed asthma. Spirometry data were approximately normally distributed and were not transformed before analysis. Models were checked by inspection of histograms of residuals and scatterplots of residuals against fitted values.

To further assess whether eosinophil counts were associated with decline in lung function, changes in FEV₁/FVC ratio and FEV₁ from age 21 to 38 years were plotted with respect to the mean eosinophil counts across these ages. Changes in lung function were compared between those with and without mean eosinophil counts >0.4x10⁹/L using t-tests.

Analyses used Stata 13 (College Station, TX). Spirometry from pregnant women and one implausible measurement were excluded. Otherwise, analyses used all available data. Two-sided p values<0.05 were considered statistically significant.

Results

Characteristics of the participants are shown in Table 1. Those who missed at least one blood sample had similar rates of asthma, atopy, and FEV₁/FVC ratios, but were more likely to smoke and had lower FEV₁ values (Online Table 1). Geometric mean eosinophil counts at each age are shown in Table 2.

Eosinophil counts differed between ages (Wald p<0.001): counts were higher at age 21 than older ages (all pairwise p≤0.001) but were not significantly different between ages 26, 32, and 38 (all pairwise p≥0.054). Twenty-one-year-olds did not have higher eosinophils when these were expressed as a percentage of total leukocytes. Among 691 participants who had eosinophils measured at all four assessments, geometric mean (95% CI) eosinophil counts were 0.25 (0.23,

0.27) $\times 10^9$ cells/L for those with adult asthma and 0.17 (0.17, 0.18) $\times 10^9$ cells/L for those without (t-test $p < 0.001$).

Spearman correlations between counts at each age are shown in Table 2. Correlations were similar among those with and without asthma (Online Table 2). The interclass correlation coefficient for individual eosinophil counts was 0.58 ($p < 0.001$) over the 17-year follow-up. High eosinophils ($> 0.4 \times 10^9$ cells /L) were found in 193 of 961 measurements (20%) among 269 participants with adult asthma and 200/2424 measurements (8%) among 701 participants without (chi-square $p < 0.001$). Among those with high eosinophils, the count remained high at the next measurement for 52% of those with asthma and 42% of those without. For participants with complete eosinophil data, 81/201 (40%) of those with asthma and 96/490 (20%) without asthma had at least one count above 0.4×10^9 cells /L (chi-square $p < 0.001$), but only 13 (6%) of those with asthma and 5 (1%) of those without had high counts at every assessment (chi-square $p < 0.001$). Thirty-five (17%) of those with asthma and 30 (6%) of those without had mean eosinophil counts $> 0.4 \times 10^9$ cells /L across the four tests (chi-square $p < 0.001$).

Childhood and adult asthma, atopic sensitisation, current smoking, and inhaled corticosteroid use were associated with higher eosinophil counts (Table 3). Smokers did not have higher eosinophils when these were expressed as a percentage of total leukocytes (Online Table 3).

Eosinophil counts were associated with lower pre- and post-bronchodilator FEV₁/FVC ratios and FEV₁ values (Table 4). There were no interactions between adult asthma and eosinophil counts for any spirometry measure (all interaction $p \geq 0.359$): when analysed separately, eosinophil counts were associated with lower FEV₁/FVC ratios and FEV₁ values among those with and without asthma, although these associations were not statistically significant for post-bronchodilator FEV₁. Adjustments for atopic sensitisation and BMI made no material difference

to the analyses (not shown). There were no interactions between current or cumulative smoking and eosinophil counts for any spirometry measure (all interaction $p \geq 0.166$).

Eosinophil counts were associated with lower pre- and post-bronchodilator FEV₁/FVC ratios and FEV₁ values in analyses adjusting for wheeze and for pre-bronchodilator values in the subgroups with and without wheeze. Post-bronchodilator FEV₁/FVC ratios and FEV₁ values were only significantly associated with eosinophils among those reporting wheeze although there was a tendency ($p=0.081$) for an association with lower FEV₁/FVC ratios among those without wheeze (Table 5).

Scatterplots of the associations between mean eosinophil counts and the changes in FEV₁/FVC ratios and FEV₁ values between ages 21 and 38 are shown in the figure. The coefficients of the fitted regression lines were not different for those with and without asthma (interaction p values ≥ 0.638) and were statistically significant for both groups (all p values ≤ 0.033). Participants with mean eosinophil counts $>0.4 \times 10^9/L$ had mean excess declines of 1.8% in FEV₁/FVC (95% CI: 0.7, 2.9%; $p=0.002$) and 3.3% in predicted FEV₁ (95% CI: 1.3, 5.3; $p=0.001$) between ages 21 and 38 compared to those with lower eosinophil counts. By comparison, those who smoked ≥ 10 pack-years had mean excess declines of 2.4% in FEV₁/FVC (95% CI: 1.6, 3.2%; $p<0.001$) and 3.5% in predicted FEV₁ (95%CI: 2.0, 4.9; $p<0.001$).

Discussion

In this population-based cohort of young adults, blood eosinophil counts were associated with lower FEV₁/FVC ratios and lower FEV₁ values. These associations were found for both pre- and post-bronchodilator measurements and were independent of childhood or adult asthma diagnoses, cumulative smoking exposure, and lung function measured at the beginning of

adulthood. Higher eosinophil counts were also associated with a greater decline in FEV₁/FVC ratios and FEV₁ values. The declines in FEV₁ and FEV₁/FVC among those with high mean eosinophil counts across the four assessments were of a similar magnitude to the declines observed among those who smoked 10 pack-years or more over the same time. The findings demonstrate that blood eosinophilia is associated with airflow obstruction and indicate that it may be an important risk factor for lung function decline.

As far as we are aware, this is the first study to explore longitudinal associations between blood eosinophils and lung function in a general population sample. Although participants with asthma had higher mean eosinophil counts, blood eosinophil counts were associated with worse lung function and similar declines in FEV₁ and FEV₁/FVC among participants with and without asthma and even among those who did not report wheezing symptoms. This suggests that eosinophilic inflammation contributes to lung function decline and airflow obstruction even among those without diagnosed airway disease or relevant symptoms. This is consistent with evidence from some cross-sectional studies that high blood eosinophil counts are associated with lower FEV₁ values in non-asthmatics.[20, 21, 23] although this was not observed in the large NHANES III study.[24] Findings from previous longitudinal research on eosinophils and lung function have been inconsistent.[22, 23, 26, 32] The largest study found that although blood eosinophils were associated with lower FEV₁ values at baseline among adults with asthma, they did not predict lung function decline over 12 years,[22] while a post hoc analysis of the placebo arm of an inhaled corticosteroid trial found that COPD patients with high blood eosinophils had a more rapid decline in FEV₁. [18] Differences in the characteristics of the populations studied, cut-offs for defining high blood eosinophils, and potential treatment responses may explain some of the inconsistencies between these studies.

We used blood eosinophils as a marker of airway eosinophilic inflammation. Studies of lung function decline and direct markers of airway eosinophilia are limited to smaller asthmatic cohorts and the findings are inconsistent. One study found that neither blood nor sputum eosinophils predicted FEV₁ decline over 5 years in difficult to treat asthma,[25] whereas a study of asthmatics with fixed airflow obstruction found that sputum eosinophils predicted 5-year FEV₁ decline.[33] Another study found that patients who had experienced a rapid decline in FEV₁ over 8 years had higher blood and sputum eosinophils.[34] The variability in sputum eosinophils counts, rather than persistently high levels, was found to be associated with a greater decline in FEV₁ over 6 years in patients with refractory asthma.[35] Bronchial biopsy studies have found that lung function decline is associated with inflammatory changes, including the numbers of CD4 and CD8 positive cells, but not with eosinophils.[34, 36, 37] These inconsistencies may also be due to differences in the characteristics of the asthmatic sub-groups studied and potential treatment responses, as well as small sample sizes and the difficulties in directly measuring airway inflammation.

As this is an observational study, we cannot prove that eosinophilic inflammation causes airflow obstruction or whether this could be prevented with treatment. Sputum eosinophil counts are associated with asthma exacerbations and treatment with inhaled corticosteroids reduces this risk,[5-7] but the finding that blood eosinophils were associated with lower lung function among participants without either asthma or wheeze makes it highly unlikely that the association can be explained by recurrent asthma exacerbations among those with high blood eosinophils.

Our findings suggest that long-term eosinophilic airway inflammation may worsen lung function decline and increase the risk for COPD. This is important because it may be possible to prevent this with treatment. A post hoc analysis of the ISOLDE study found that inhaled fluticasone appeared to reduce the decline in FEV₁ in COPD patients with high blood eosinophils.[18] We

need information from prospective randomised controlled trials to establish whether treating eosinophilic inflammation with inhaled corticosteroids would improve long-term outcomes for lung function in either COPD or asthma.[1, 38]

Few factors are known to cause lung function decline among healthy young adults: only exposure to pollutants (including tobacco smoke) has been consistently found to lead to airflow obstruction at a population level. Our findings suggest that eosinophilic inflammation may be another factor, and this effect appears to be independent of asthma. The drivers of this inflammation are unknown but it is plausible that exposure to environmental or occupational allergens contribute to this. Atopic sensitisation was not an independent predictor of lung function, however, and adjusting the analyses for atopic sensitisation made no material difference to the findings. Higher BMI has been found to be associated with lower FEV₁/FVC ratios in women in this cohort,[31] but was not associated with eosinophil counts and adjusting the analyses for BMI did not alter the findings for either sex.

Blood eosinophils were moderately correlated between ages. This is consistent with previous reports,[10, 22] and extends the period of observation to 17-years and to young adults with and without asthma. There was considerable variability around our pre-specified cut point of 0.4×10^9 cells/L. Variability around this and other cut points has been noted in other studies, indicating that a single test is insufficient to characterise long-term eosinophilia.[39] As anticipated, atopic sensitisation and asthma were associated with higher counts. In keeping with other observations,[32] we found that smokers had higher absolute eosinophils counts than non-smokers but this could be explained by higher total leukocyte counts. Total leukocyte and eosinophil counts were also higher at age 21 years than older ages, but percentage eosinophil counts were similar. We analysed absolute eosinophil counts as recommended,[40] but repeating the analyses using percentage eosinophils made no material differences to the findings.

The study has a number of strengths including measurements of eosinophils and spirometry on four occasions over 17 years with a high rate of follow-up. We adjusted for many potential covariates or effect modifiers including childhood and adult asthma, symptoms of wheeze, smoking exposure, and spirometry at age 18. There are also some limitations, however.

Peripheral blood eosinophil counts are only a proxy measure of airway eosinophilia, although obtaining direct measurements of airway eosinophils in this large epidemiological study would be unfeasible with current techniques. Asthma diagnoses were self-reported and this may have led to some misclassification. We do not have post-bronchodilator measures of lung function at age 21. Participants who missed one or more blood samples were more likely to smoke and had slightly lower FEV₁ values, but restricting the analyses to those who had eosinophil counts at every age made no material difference to the findings. Eosinophils counts were only reported to one decimal place ($\times 10^9/L$) at age 38, but restriction of the analyses to ages 21 to 32 also made little difference to the findings. So far, we have only followed the cohort to early mid-adult life and we cannot extrapolate the findings to older adults or the risk for clinically diagnosed COPD.

The implications for clinical practice are not yet clear. We need to know the long-term risk of developing COPD among people with high blood eosinophil counts and whether anti-inflammatory treatment alters this risk. The finding that blood eosinophils are associated with airflow obstruction in people without asthma or wheeze raises questions about the role of asymptomatic eosinophilia. Could eosinophils allow us to identify asymptomatic individuals at high risk of developing chronic lung disease and facilitate targeted prevention strategies? We also need to understand more about the intrinsic and environmental drivers of eosinophilic inflammation and whether these are amenable to intervention at individual or population-based levels.

In summary, we have found that blood eosinophil counts are moderately stable across young adult life and that high counts are associated with airflow obstruction. Although eosinophil counts were higher in participants with asthma, associations between blood eosinophil counts and airflow obstruction were present in those without asthma or symptoms of wheeze. The findings suggest that persistent blood eosinophilia is an independent risk factor for the development of airflow obstruction even in those without respiratory disease.

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Figure legend.

Scatter plots of changes in FEV₁/FVC ratios and FEV₁ between ages 21 and 38 years and mean eosinophil counts between ages 21 and 38.

Participants reporting asthma at any age between 21 and 38 are indicated by cross symbols and dashed lines. a) The coefficient for change in FEV₁/FVC ratio for participants without asthma is -5.6% per 1×10^9 /L eosinophils ($p < 0.001$). For those with asthma, the coefficient is -4.5% per 1×10^9 /L eosinophils ($p = 0.034$). b) The coefficient for change in FEV₁ for participants without asthma is -0.38L per 1×10^9 /L eosinophils ($p < 0.001$). For those with asthma, the coefficient is -0.30L per 1×10^9 /L eosinophils ($p = 0.048$).

Table 1 Participant characteristics

Male (n/N (%))	495/971 (51%)
Smoker at 21, 26, 32, or 38 years (n/N (%))	439/971 (45%)
Pack-years smoking by age 38 (n=439) (median (IQR))*	12.7 (6.9-18.9)
Asthma at 21, 26, 32, or 38 years (n/N (%))	269/971 (27%)
Wheeze at 21, 26, 32, or 38 years (n/N (%))	609/971 (37%)
Atopy at 21 or 32 years (n/N (%))	660/959 (69%)
Pre-bronchodilator spirometry at age 38 years (n=912)†:	
Percent predicted FEV ₁ (mean (SD))	97.4% (12.6)
Percent predicted FVC (mean (SD))	103.7% (11.8)
FEV ₁ /FVC ratio % (mean (SD))	76.2% (6.8)
Post-bronchodilator spirometry at age 38 years (n=898)†:	
Percent predicted FEV ₁ (mean (SD))	101.6% (12.2)
Percent predicted FVC (mean (SD))	103.1% (11.6)
FEV ₁ /FVC ratio % (mean (SD))	79.9% (6.5)

The table includes 971 surviving participants with at least one eosinophil measurement between 21 and 38 years. *Non-smokers between 21 and 38 years are excluded from analysis of pack-years. †Pregnant women age 38 are excluded from lung function measurements. IQR = interquartile range.

Table 2 Eosinophil counts at each age and correlations between ages.

Age	Eosinophil counts at each age			Spearman correlations between ages (rho)		
	n	Geometric Mean	95% CI	21	26	32
21	773	0.21	0.20, 0.22			
26	849	0.19	0.18, 0.20	0.579		
32	866	0.20	0.19, 0.21	0.533	0.662	
38	898	0.19	0.19, 0.20	0.498	0.552	0.642

Excludes pregnant women at each age. Spearman correlations between ages are all statistically significant (p values <0.0001)

Table 3 Predictors of blood eosinophil counts

	Coeff	95% CI	P
Male Sex	0.016	-0.030, 0.062	0.490
Age (yrs)	-0.002	-0.003, 0.000	0.059
Current Smoker	0.080	0.044, 0.116	<0.001
Atopic sensitisation	0.075	0.024, 0.126	0.004
Adult asthma (21 to 38)	0.164	0.099, 0.230	<0.001
Childhood asthma (9 to 13)	0.071	0.001, 0.141	0.047
Inhaled corticosteroid use	0.081	0.020, 0.143	0.009

Analyses by a random effects linear regression model using 2888 observations from 815 individuals. Coefficients represent the difference in log-eosinophil counts associated with each independent predictor.

Table 4 Association between eosinophil counts and pre- and post-bronchodilator spirometry in participants with and without asthma.

		FEV ₁ /FVC ratio (%)			FEV ₁ % predicted			FVC % predicted		
	n	Coef	95% CI	p	Coef	95% CI	p	Coef	95% CI	p
Pre-bronchodilator										
All participants*	729	-0.84	-1.24, -0.44	<0.001	-1.53	-2.26, -0.80	<0.001	-0.34	-1.04, 0.35	0.328
No Asthma	527	-0.75	-1.18, -0.31	<0.001	-1.46	-2.29, -0.63	<0.001	-0.39	-1.20, 0.42	0.349
Asthma	202	-1.01	-1.89, -0.14	0.024	-1.77	-3.29, -0.25	0.023	-0.38	-1.74, 0.99	0.587
Post-bronchodilator										
All Participants*	722	-0.95	-1.38, -0.51	<0.001	-0.87	-1.74, -0.01	0.048	0.30	-0.52, 1.11	0.475
No Asthma	523	-0.86	-1.34, -0.38	<0.001	-0.65	-1.64, 0.35	0.205	0.35	-0.62, 1.32	0.479
Asthma	199	-1.26	-2.18, -0.35	0.007	-1.67	-3.42, 0.07	0.060	0.13	-1.39, 1.65	0.863

Coefficients represent the difference in spirometry values associated with blood eosinophil counts in natural logarithm units. Analyses use spirometry and blood eosinophil data from ages 21, 26, 32, and 38 years and adjust for pre- or post-bronchodilator spirometry values at age 18, sex, age, inhaled corticosteroid use, childhood asthma at ages 9 to 13 years, and cumulative smoking history. *The All Participants analyses also adjust for reported asthma at any age between 21 to 38 years.

Table 5 Association between eosinophil counts and pre- and post-bronchodilator spirometry in participants with and without wheeze.

	n	FEV ₁ /FVC ratio (%)			FEV ₁ % predicted			FVC % predicted		
		Coef	95% CI	p	Coef	95% CI	p	Coef	95% CI	p
Pre-bronchodilator										
All participants*	738	-0.91	-1.30, -0.51	<0.001	-1.63	-2.36, -0.91	<0.001	-0.33	-1.02, 0.36	0.345
No wheeze	269	-0.94	-1.54, -0.34	0.002	-1.26	-2.42, -0.09	0.035	0.10	-1.02, 1.22	0.865
Wheeze	469	-0.85	-1.37, -0.34	0.001	-1.94	-2.86, -1.01	<0.001	-0.69	-1.57, 0.19	0.122
Post-bronchodilator										
All Participants*	728	-1.03	-1.46, -0.60	<0.001	-0.97	-1.83, -0.10	0.028	0.31	-0.50, 1.11	0.457
No wheeze	265	-0.62	-1.32, 0.08	0.081	-0.07	-1.35, 1.49	0.927	0.71	-0.63, 2.04	0.299
Wheeze	463	-1.25	-1.80, -0.71	<0.001	-1.62	-2.71, -0.53	0.004	0.01	-1.02, 1.01	0.989

Coefficients represent the difference in spirometry values associated with blood eosinophil counts in natural logarithm units. Analyses use spirometry and blood eosinophil data from ages 21, 26, 32, and 38 years and adjust for pre- or post-bronchodilator spirometry values at age 18, sex, age, inhaled corticosteroid use, childhood wheeze at ages 9 to 13, and cumulative smoking history. *The All Participants analyses also adjust for reported wheeze at any age between 21 to 38 years.