Blood leukocyte concentrations, FEV_1 decline, and airflow limitation: a 15-year longitudinal study of WTC-exposed firefighters

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MDW conceived of the study, and designed it in conjunction with RZO, TKA, CBH and DJP. RZO, MDW, AS and TS analyzed and interpreted the data. RZO, AS and MDW drafted the first manuscript with critical revisions from CBH, DJP, MPW, HWC, AN and KJK. All authors approved the final manuscript. MDW, RZO and DJP agree to be accountable for all aspects of the work so that questions related to the accuracy and integrity of the research are appropriately investigated and resolved.

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ABSTRACT

Rationale: Rescue/recovery work at the World Trade Center (WTC) disaster site caused a proximate decline in lung function in Fire Department of the City of New York (FDNY) firefighters. A subset of this cohort experienced an accelerated rate of lung function decline over 15 years of post-9/11 follow-up. **Objectives:** To determine if early post-exposure blood leukocyte concentrations are biomarkers for subsequent forced expiratory volume (FEV_1) decline and incident airflow limitation. **Methods:** Individual rates of FEV_1 change were calculated for 9,434 firefighters using 88,709 spirometric measurements taken between 9/11/2001 (9/11) and 9/10/2016. We categorized FEV_1 change rates into three trajectories: accelerated FEV_1 decline (FEV_1 loss >64 ml/year), expected FEV_1 decline (FEV_1 loss between 0–64 ml/year), and improved FEV_1 (positive rate of change >0 ml/year). Occurrence of $FEV_1/FVC<0.70$ after 9/11 defined incident airflow limitation. Regression models assessed associations of post-9/11 blood eosinophil and neutrophil concentrations with subsequent FEV_1 decline and airflow limitation, adjusted for age, race, smoking, height, WTC exposure level, weight change and baseline lung function. **Results:** Accelerated FEV_1 decline occurred in 12.7% of participants (1,199/9,434), while post-9/11 FEV_1 improvement occurred in 8.3% (780/9,434). Higher blood eosinophil and neutrophil concentrations were each associated with accelerated FEV_1 decline after adjustment for covariates (OR: 1.10 per 100 eosinophils/μl, 95% CI: 1.05-1.15; and OR: 1.10 per 1,000 neutrophils/μl, 95% CI: 1.05-1.15). Multivariable-adjusted linear regression models showed that a higher blood neutrophil concentration was associated with a faster rate of FEV_1 decline (1.14 ml/year decline per 1,000 neutrophils/μl, 95% CI: 0.69-1.60 ml/year, $p<0.001$). Higher blood

eosinophil concentrations were associated with a faster rate of FEV_1 decline in ever-smokers (1.46 ml/year decline per 100 eosinophils/μl, 95% CI: 0.65-2.26 ml/year, p<0.001) but not in never-smokers (p for interaction=0.004). Higher eosinophil concentrations were also associated with incident airflow limitation (adjusted HR: 1.10 per 100 eosinophils/μl, 95% CI: 1.04-1.15). Compared with the expected FEV_1 decline group, individuals experiencing accelerated FEV_1 decline were more likely to have incident airflow limitation (adjusted OR: 4.12, 95% CI: 3.30-5.14). **Conclusions:** Higher post-9/11 blood neutrophil and eosinophil concentrations were associated with subsequent accelerated FEV_1 decline in WTC-exposed firefighters. Both higher blood eosinophil concentrations and accelerated FEV_1 decline were associated with incident airflow limitation in WTC-exposed firefighters.

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Introduction

The collapse of the World Trade Center (WTC) on September 11, 2001 (9/11) produced an immense dust cloud containing large-sized particulate matter. Fire Department of the City of New York (FDNY) rescue and recovery workers who were exposed to the caustic dust and products of combustion experienced high rates of upper and lower airway injury, evidenced by an excessive loss of lung function (1). Yearly declines in forced expiratory volume at one second (FEV_1) in this population eventually stabilized to an average age-related loss of 32 ml/year. The population included some individuals who continued to experience significantly greater than expected rates of decline in FEV_1, and others who rebounded and experienced an annual improvement in lung function rather than a decline. We previously identified a group that had an accelerated rate of FEV_1 decline, defined as greater than 64 ml/year FEV_1 loss during follow-up, which was more than twice the cohort average (2).

Inflammatory biomarkers in WTC-exposed FDNY firefighters are risk factors in the development of abnormal FEV_1 (3-6). Additionally, blood leukocytes, including eosinophils and neutrophils, were associated with COPD exacerbations in non-WTC-exposed patients (7, 8). Lower airway eosinophil concentrations were correlated with WTC exposure (9). Eosinophil concentration was also identified as a risk factor for airflow obstruction in WTC-exposed community residents (10), and for upper airway injury in WTC-exposed firefighters (11). The association between blood leukocyte concentrations and development of lung function abnormalities, therefore, warrants examination among this population as well as others.

The primary aim of this study was to investigate whether blood eosinophil and neutrophil concentrations, measured during post-9/11 medical monitoring examinations, were associated with the rate of FEV_1 decline in WTC-exposed male FDNY firefighters, adjusted for post-exposure lung function and smoking status. The rate of change in FEV_1 was defined using pulmonary function test (PFT) data from the first 15 years after 9/11, and classified into one of three post-9/11 FEV_1 trajectories: accelerated decline in FEV_1 greater than 64 ml/year, expected age-related decline, and improved FEV_1 or positive rate of post-9/11 FEV_1 change. To better define the nature of the FEV_1 trajectories, we tested their association with incident airflow limitation, defined as having an FEV_1/FVC ratio <0.70. Finally, we assessed the association between leukocyte concentrations and incident airflow limitation. Some of the results of this study were previously reported in abstract form (12, 13).

Methods

Study Population The flow diagram (Figure 1) shows those excluded from the source population of 9,939 male firefighters who were actively employed by FDNY on 9/11, and who first arrived to work at the WTC site between 9/11 and September 24, 2001. All active duty firefighters and those who are currently retired but WTC-exposed are scheduled to have PFTs and complete blood counts (CBCs) every 12-18 months, during routine medical monitoring examinations conducted at FDNY. To ensure sufficient PFT data for the estimation of post-9/11 rates of FEV_1 decline, firefighters with fewer than 3 post-9/11 PFTs were excluded (N=433). Those remaining who did not have CBCs measured on their first post-9/11 monitoring examination were also excluded (N=72). Participants provided written informed consent. The Montefiore

Medical Center/Albert Einstein College of Medicine Institutional Review Board approved this study. None of the sources of funding for this study had a role in its conception, design, conduct, or analyses, and none modified or approved the manuscript.

Demographics, Smoking and WTC Exposure Demographic data were retrieved from the FDNY employee database, and individual height and weight measurements were recorded during routine FDNY monitoring. Participants reported their earliest WTC arrival time and current and former cigarette smoking via health questionnaires that were administered during the monitoring exam. Individuals were classified as former smokers if they reported being a former cigarette smoker on their most recent questionnaire, and as current smokers if they reported current cigarette smoking at that time. Those who consistently reported never smoking cigarettes were classified as never-smokers. Each participant's first post-9/11 questionnaire provided his WTC arrival time. WTC exposure level was defined as it was in our 13-year study (2), with individuals categorized as having high, moderate or low exposure based on their time of initial arrival. We were able to obtain complete covariate data on all study participants.

CBC Cell Concentrations We obtained eosinophil and neutrophil concentration measurements from the first post-9/11 CBC, drawn during the monitoring examination. This CBC coincided with the first post-9/11 PFT. The median first CBC date was 1/9/2002 (interquartile range: 11/26/2001-12/27/2002). Pre-WTC exposure CBC data were available on 4,303 individuals.

Outcome FEV_1 and forced vital capacity (FVC) measurements were obtained from spirometry data collected during the monitoring exams. Spirometry was conducted and

graded via the process detailed in our 13-year (2) and 7-year (1) studies. We included spirometries with quality grades of 'B' or higher, according to American Thoracic Society classification; among spirometries measured post-9/11 (9/11/2001-9/10/2016), 88,709 had a quality grades of 'B' or higher and were included all analyses, while 4,509 were excluded due to grades lower than a 'B'. Post-9/11 rates of FEV_1 decline were estimated using the first post-9/11 PFT and all subsequent PFTs for each participant. These individual rates of post-9/11 FEV_1 decline, used to classify participants as having either accelerated FEV_1 decline (>64 ml/year FEV_1 loss), expected FEV_1 decline (FEV_1 loss between 0 and 64 ml/year), or improved FEV_1 (<0 ml/year loss), were estimated by fitting a linear regression model examining the effect of follow up time on FEV_1 for each study participant. We used an additional 5,771 spirometric measurements (N=5,384) from routine medical monitoring examinations performed between 9/11/2000 and 9/10/2001 to determine pre-exposure lung function and trans-9/11 FEV_1 change (the average FEV_1 in the last pre-9/11 year to the average FEV_1 in the first post-9/11 year).

Incident airflow limitation was defined as two consecutive FEV_1/FVC ratios <0.70; we required that measurements be at least one year apart. Pre-9/11 FEV_1/FVC ratio <0.70 was defined as a single FEV_1/FVC ratio <0.70 between 9/11/1997 and 9/10/2001. Since the GOLD definition of airflow limitation requires a post-bronchodilator FEV_1/FVC ratio <0.70 (14), we conducted a secondary analysis using a subset of participants who had a post-bronchodilator PFT at a hospital-based referral pulmonary function laboratory (the "post-bronchodilator PFT subpopulation", N=2,103). Participants who had a FEV_1/FVC ratio <0.70 on at least one post-bronchodilator PFT were defined as having airflow limitation for this secondary analysis.

Statistical Analyses Demographic and other characteristics for the study population were assessed as proportions, means (±SD) and medians (and interquartile range). Linear mixed models were used to estimate either absolute FEV_1 or FEV_1 percent predicted (15) over time in subsets of the population defined by post-9/11 FEV_1 trajectories (accelerated decline, expected decline or improved FEV_1). Mean absolute FEV_1 and FEV_1 percent predicted values were estimated for each one-year period between 9/11/2000 and 9/10/2016. In the model that had absolute FEV_1 as the outcome, age on 9/11, height and race were used as fixed effects, with age and height centered at the mean values for the cohort (40 years and 177 centimeters, respectively). Random intercepts accounted for between-subject variability and repeated measures correlations. Multivariate logistic regression models determined the associations of eosinophil and neutrophil concentrations at first post-9/11 exam with the categorical outcome of post-9/11 FEV_1 trajectory, and linear regression models were used to examine if blood leukocyte concentrations were associated with post-9/11 rate of FEV_1 decline as a continuous measure. Analyses were conducted with eosinophil and neutrophil concentrations included in the models as continuous variables. We assessed the linearity of the associations between blood leukocyte measurements and FEV_1 decline rate by examining residuals of the multivariable-adjusted linear model as a function of eosinophil and neutrophil concentrations (Figure E1 in data supplement). We also performed an analysis with blood leukocyte concentrations as binary variables (elevated eosinophil concentration ≥300 cells/μl and elevated neutrophil concentration ≥4,500 cells/μl). To control for confounding, models included smoking status (current, former or never), age on 9/11, race, height, annual post-9/11 weight change, WTC

exposure level, and first post-9/11 FEV_1 percent predicted. Covariates were selected based on theory. Additionally, we tested for interactions between smoking status and the blood leukocyte concentrations that justified stratification by smoking status.

To address the possibility that pre-exposure blood leukocyte concentrations could indicate a predisposition to accelerated FEV_1 decline, we carried out analyses in the subpopulation of 4,303 firefighters who had had both pre- and post-9/11 CBCs. Spearman correlation coefficients were used to determine if the pre- and post-9/11 blood leukocyte concentrations were associated. We then ran multivariate logistic and linear regression models that examined the associations between the pre-9/11 measurements and FEV_1 decline, adjusting for the same covariates that were included in our primary analyses. Finally, we investigated the effect of inflammatory response to WTC exposure on FEV_1 decline, independent of pre-exposure inflammatory status, by adjusting multivariable models of the post-9/11 blood leukocyte concentration – FEV_1 decline association for pre-9/11 CBC data.

We calculated the post-9/11 incidence rates for $FEV_1/FVC<0.70$ on screening spirometry and estimated confidence intervals using the Poisson distribution; person-time was calculated from 9/11 to the earliest date of the following events: the first of two consecutive FEV_1/FVC measurements <0.70, or the last monitoring exam taken by 9/10/2016. Individuals who had a FEV_1/FVC ratio<0.70 on any PFT prior to 9/11 were excluded from the incident airflow limitation analyses (N=158). Multivariable logistic regression analyses determined the relationship between FEV_1 trajectories (accelerated decline, expected decline, improved FEV_1) and incident airflow limitation, adjusted for blood leukocyte concentrations, age on 9/11, race, height, annual post-9/11 weight

change, smoking status, WTC exposure level, and first post-9/11 FEV_1 percent predicted. Multivariable Cox proportional hazards regression models were conducted to assess the association between post-9/11 blood leukocyte concentrations and incident airflow limitation, adjusting for age on 9/11, race, height, annual post-9/11 weight change, smoking, WTC exposure level, and first post-9/11 FEV_1 percent predicted. We also tested for interactions between smoking status and both blood leukocyte concentrations in these models. The Cox regression model used for our primary incident airflow limitation analysis was censored at either the date of the first of two consecutive FEV_1/FVC measurements <0.70, or the date of the final monitoring exam. For the secondary analysis of airflow limitation, we used data from the post-bronchodilator PFT subpopulation (N=2,103), censoring the Cox regression model at either the date of the first post-bronchodilator PFT with FEV_1/FVC<0.70 or the date of the last monitoring exam. The proportional hazards assumption was evaluated using tests and diagnostics based on weighted Schoenfeld residuals (16).

In order to rule out possible selection bias, we performed sensitivity analyses that included the data of firefighters who had two post-9/11 PFTs (Total N=9,643). The linear and multivariate logistic regression analyses modeling post-9/11 FEV_1 decline rate and FEV_1 trajectory, respectively, were repeated in this population; model results are presented in the supplemental tables (Tables E5 and E6).

Data analyses were performed using SAS version 9.4. Reported p values are two-sided and considered significant at the <0.05 level. We created Figures 2,3 and 4 using Prism 7.

Table 1: Baseline Characteristics

Variable	Study Cohort N=9,434	Bronchodilator PFT N=2,103
Age on 9/11*	40.14 ± 7.38	41.16 ± 6.78
Smoking status†		
Never	6,361 (67.43)	1,360 (64.67)
Former	2,785 (29.52)	673 (32.00)
Current	288 (3.05)	70 (3.33)
Race†		
White	8,889 (94.22)	1,982 (94.25)
Black	218 (2.31)	49 (2.33)
Hispanic	300 (3.18)	70 (3.33)
Other	27 (0.29)	2 (0.10)
WTC Arrival Time†		
Morning of 9/11	1,543 (16.36)	419 (19.92)
Afternoon on 9/11 - 9/12	6,755 (71.60)	1,490 (70.85)
9/13 – 9/24	1,136 (12.04)	194 (9.22)
FEV_1 (L)*‡	4.01 ± 0.66	3.87 ± 0.69
FEV_1 % predicted*‡	96.88 ± 13.27	93.70 ± 14.25
Eosinophils/µl blood, hundreds*‡	1.88 ± 1.31	1.99 ± 1.46
Neutrophils/µl blood, thousands*‡	3.63 ± 1.32	3.71 ± 1.39

*Mean ± standard deviation
† N (%)
‡Value on first post-9/11 monitoring exam

Results

Characteristics of WTC-exposed firefighters. Demographic and other characteristics of the 9,434 firefighters in the final study population are displayed in **Table 1**. Following the initial trans-9/11 decline, 12.7% of participants (N=1,199) had accelerated FEV_1 decline in the 15 years after 9/11, while 8.3% of the population (N=780) experienced an improvement in FEV_1. Eighty-three percent (N=7,853) of the study cohort had their first post-exposure FEV_1 and CBC measurements between 9/11 and 9/10/2002, and 85% (N=8,018) had one or more PFTs from 9/11/2014 to 9/10/2016. The median amount of time between 9/11 and date of first post-exposure measurements (FEV_1 and CBC) was similar (three and four months, respectively) and did not vary by the three FEV_1 trajectory groups (accelerated FEV_1 decline, expected decline, and improved FEV_1). The study population was similar to the source population of all active FDNY male firefighters in demographic and other characteristics (see **Table E1** in data supplement). The post-bronchodilator PFT subpopulation (N=2,103) was observed to have a greater proportion of smokers, higher levels of WTC exposure, higher post-9/11 concentrations of blood eosinophils and neutrophils, and lower post-exposure FEV_1 than the rest of the study cohort (**Table 1**). These are descriptive data, as no statistical comparisons of the two groups were performed.

Longitudinal FEV_1 We used linear mixed models to display longitudinal lung function from 9/11/2000 to 9/10/2016 in the three FEV_1 trajectory groups (**Figure 2A** for FEV_1 in liters and **Figure 2B** for FEV_1 percent predicted). Overall, pre-9/11 FEV_1 percent predicted was above 100% and not clinically different across the accelerated FEV_1 decline, expected FEV_1 decline, and improved FEV_1 groups (mean ± standard error

(SE), respectively: 105.94±0.55%, 104.40±0.20%, and 102.63±0.60%). In the post-9/11 accelerated FEV_1 decline group, decline in FEV_1 from the year prior to 9/11 exposure to the year after exposure (trans-9/11 decline) was minimal (39 ml), but was followed by a higher annual rate of FEV_1 decline over the rest of follow-up (85.2 ml/year, 95% CI: 83.9-86.5 ml/year). The final FEV_1 measurement for this group was, on average, 3.15 L. In the post-9/11 expected FEV_1 decline group, there was a larger trans-9/11 decline of 335 ml. This was followed by an annual longitudinal decline of 32.0 ml/year (95% CI: 31.7 to 32.3 ml/year), the expected age-related rate of decline, resulting in an average final FEV_1 of 3.54 L at the end of follow-up. The post-9/11 improved FEV_1 group had the largest trans-9/11 decline (691 ml), but then experienced an annual improvement in FEV_1 in the years between the first post-9/11 monitoring exam and end of this study (14.2 ml/year increase, 95% CI: 12.8-15.7 ml/year); this trajectory resulted in the highest average final FEV_1 of the three groups: 3.77 L. At the end of follow-up, this group had an FEV_1 percent predicted (mean ± SE) of 100.90±0.60%, which was close to its pre-9/11 level (102.63±0.60%). The accelerated and expected decline groups did not experience similar recovery of lung function.

Table 2: Multivariable Logistic Regression Models of Associations Between Blood Leukocyte Concentrations and Post-9/11 FEV_1 Trajectory *†

Variable	Accelerated Decline (vs. Expected)			Improved FEV_1 (vs. Expected)		
	OR	95% CI	P	OR	95% CI	P
Eosinophils per 100 cells/ µl‡	1.10	1.05-1.15	<0.001	1.01	0.95-1.07	0.71
Neutrophils per 1000 cells/ µl‡	1.10	1.05-1.15	<0.001	0.98	0.92-1.05	0.60

*Adjusted for race, age, smoking status, WTC exposure, first post-9/11 percent predicted, height, and post-9/11 weight change; †Likelihood ratio: Chi-square=1537, df=26, p<0.001; ‡First post 9/11 measurement.

Eosinophils, neutrophils and post-9/11 FEV_1 trajectory When examining the relationship between blood leukocyte concentrations and post-9/11 FEV_1 trajectory, we found that higher post-9/11 eosinophil concentrations (OR: 1.10, 95% CI: 1.05-1.15, p<0.001) and higher neutrophil concentrations (OR: 1.10, 95% CI: 1.05-1.15, p<0.001) were each associated with an increased risk of accelerated FEV_1 decline in a multivariable analysis adjusted for age on 9/11, race, height, annual post-9/11 weight change, WTC exposure level, smoking status and first post-9/11 FEV_1 percent predicted (**Table 2** and data supplement **Table E2**). We did not observe any significant interactions between leukocyte concentrations and smoking status. The analysis that used binary variables to indicate elevated eosinophil and neutrophil levels showed that individuals with eosinophil concentration ≥300 cells/µl and/or neutrophil concentration ≥4,500 cells/µl were associated with a higher risk of accelerated FEV_1 decline than those with lower concentrations (OR: 1.31, 95% CI: 1.10-1.56, p=0.002, and OR: 1.37, 95% CI: 1.17-1.60, p<0.001, respectively, data not shown). Neither eosinophil nor

neutrophil concentrations were significantly associated with improved FEV_1 vs. expected decline.

We observed a significant correlation between pre- and post-9/11 eosinophil values (rho: 0.64, p<0.001), and also between pre- and post-9/11 neutrophil values (rho: 0.55, p<0.001) in the subpopulation of 4,303 firefighters who had had CBCs both before and after WTC exposure. Greater pre-9/11 eosinophil and neutrophil concentrations were associated with an increased risk of accelerated vs. expected FEV_1 decline (OR: 1.11 per 100 eosinophils/μl, 95% CI: 1.03-1.20, p=0.009 and OR: 1.18 per 1000 neutrophils/μl, 95% CI: 1.10-1.26, p<0.001, respectively) adjusting for the same covariates listed above. When investigating whether pre-9/11 blood leukocyte concentrations confounded the associations of post-9/11 concentrations with accelerated decline, we found that adjustment for pre-9/11 CBC data in addition to the other covariates resulted in associations between post-9/11 leukocyte counts and accelerated decline similar to those from our model in Table 2 (OR: 1.11 per 100 eosinophils/μl, 95% CI: 1.01-1.23, p=0.03 and OR: 1.07 per 1,000 neutrophils/μl, 95% CI: 0.99-1.16, p=0.11).

Table 3: Multivariable Linear Regression Models examining Associations between Blood Leukocyte Concentrations and Post-9/11 Rate of FEV_1 Change (ml/year)*

Variable	Study Cohort N=9,434			Ever-Smokers N=3,073			Never-Smokers N=6,361		
	Adjusted Mean annual FEV_1 decline (mL)	95% CI	P	Adjusted Mean annual FEV_1 decline (mL)	95% CI	P	Adjusted Mean annual FEV_1 decline (mL)	95% CI	P
Eosinophils per 100 cells/ µl†	-0.7	-1.2, -0.3	0.001	-1.5	-2.3, -0.7	<0.001	-0.4	-0.9, 0.2	0.19
Neutrophils per 1000 cells/ µl†	-1.1	-1.6, -0.7	<0.001	-1.5	-2.2, -0.8	<0.001	-0.9	-1.4, -0.3	0.005

*Adjusted for race, age, smoking status, WTC exposure, first post-9/11 percent predicted, height, and post-9/11 weight change; †First post 9/11 measurement.

Eosinophils, neutrophils and FEV_1 rate of decline Since the definitions of accelerated FEV_1 decline, expected FEV_1 decline and FEV_1 improvement are based on thresholds derived from clinical judgment, we also tested the associations between blood eosinophil and neutrophil concentrations and post-9/11 rate of FEV_1 decline as a continuous outcome in a multivariable linear model. Post-9/11 eosinophil and neutrophil concentrations were significantly associated with subsequent annual FEV_1 decline (0.7 ml/year decline per 100 eosinophils/µl, 95% CI: 0.3-1.2 ml/year, p=0.001 and 1.1 ml/year decline per 1000 neutrophils/µl, 95% CI: 0.7-1.6 ml/year, p<0.001), adjusting for the other leukocyte concentration, age, race, height, annual post-9/11 weight change, WTC exposure level, smoking and first post-9/11 FEV_1 percent predicted (**Table 3** and data supplement **Table E3**).

There was a significant interaction between smoking and eosinophil concentration (p=0.004), and also between smoking and neutrophil concentration (p=0.01). To assess the nature of these interactions, we performed an analysis stratified by smoking status (**Table 3** and **Table E3**; **Figure 3A** for eosinophil concentration and **Figure 3B** for neutrophil concentration). Eosinophil concentration was associated with FEV_1 decline in ever-smokers, but not in never-smokers (1.5 ml/year decline per 100 eosinophils/μl, 95% CI: 0.7-2.3 ml/year, p<0.001, vs. 0.4 ml/year decline per 100 eosinophils/μl, 95% CI: -0.2–0.9 ml/year, p=0.19, respectively). The association between neutrophil concentration and subsequent FEV_1 decline was stronger in ever-smokers (1.5 ml/year decline per 1000 neutrophils/μl, 95% CI: 0.8-2.2 ml/year, p<0.001) than in never-smokers (0.9 ml/year decline per 1000 neutrophils/μl, 95% CI: 0.3-1.4 ml/year, p=0.005).

In the subset of firefighters with both pre- and post-exposure CBC measurements, similar magnitude post-9/11 blood leukocyte concentrations – FEV_1 decline associations to those shown in Table 3 were found after adjustment for pre-9/11 blood leukocyte concentrations and other potential confounders (0.6 ml/year decline per 100 eosinophils/μl, 95% CI: -0.3–1.5 ml/year, p=0.18 and 1.1 ml/year decline per 1,000 neutrophils/μl, 95% CI: 0.2-1.8 ml/year, p=0.01).

FEV_1 trajectories and airflow limitation We examined the associations between post-9/11 FEV_1 trajectories and incident FEV_1/FVC ratio <0.70 measured on at least two consecutive monitoring PFTs. The rate of incident airflow limitation in the accelerated FEV_1 decline group was 11.6 (95% CI: 10.2-13.4) per 1,000 person-years, vs. 4.2 (95% CI: 3.9-4.4) per 1,000 person-years in those with expected decline and 3.9 (95% CI:

3.1-4.8) per 1,000 person-years in the improved FEV_1 group. After adjusting for potential confounders, we found that individuals in the accelerated FEV_1 decline subpopulation were more than four times as likely to have had incident airflow limitation as those who had expected FEV_1 decline (OR: 4.12, 95% CI: 3.30-5.14, p<0.001, **Figure 4A**), while the improved FEV_1 group had a significantly lower risk of this outcome (OR: 0.38, 95% CI: 0.26-0.55, p<0.001). Our secondary analysis among the 2,103 firefighters who had post-bronchodilator FEV_1/FVC ratio measured showed similar results. Compared with the expected FEV_1 decline group, the accelerated FEV_1 decline group had a 2.5-fold increase (OR: 2.50, 95% CI: 1.81-3.46, p<0.001) and the improved FEV_1 group had a 54% reduction in odds of airflow limitation on post-bronchodilator PFT (OR: 0.46, 95% CI: 0.27-0.76, p=0.003) (**Figure 4B**).

Table 4: Cox Proportional Hazards Regression Models for Associations between Blood Leukocyte Concentrations and Incident post-9/11 Airflow Limitation*

Variable	Screening Spirometry N=9,276			Post-Bronchodilator PFT N=2,103		
	HR	95% CI	P	HR	95% CI	P
Eosinophils per 100 cells/ µl†	1.10	1.04-1.15	<0.001	1.10	1.03-1.17	0.004
Neutrophils per 1000 cells/ µl†	1.05	0.99-1.11	0.08	1.03	0.96-1.11	0.40

*Also adjusted for race, age, smoking status, WTC exposure, first post-9/11 percent predicted, height, and post-9/11 weight change; † First post 9/11 measurement; HR = hazard ratio.

Eosinophils, neutrophils and incident airflow limitation. We used multivariable Cox models to test the associations between post-9/11 blood eosinophil and neutrophil concentrations and incident airflow limitation. Higher eosinophil concentrations were associated with an increased incidence of airflow limitation (HR: 1.10 per 100 eosinophil/µl, 95% CI: 1.04-1.15, p<0.001), adjusting for neutrophil concentration, age on 9/11, annual post-9/11 weight change, height, WTC exposure level, first post-9/11 FEV_1 percent predicted and smoking status (**Table 4** and data supplement **Table E4)**. Blood neutrophil concentration, however, was not significantly associated with incident airflow limitation after adjusting for eosinophil concentration and the other potential confounders. Results from the secondary analysis using the post-bronchodilator FEV_1/FVC ratio were similar (HR: 1.10 per 100 eosinophil/µl, 95% CI: 1.03-1.17, p=0.004) (**Tables 4** and **E4**). There were no significant interactions between smoking and eosinophil or neutrophil concentration in either of these analyses. Checks of the

proportional hazards assumption using weighted residuals (16) showed that the significant effect of eosinophils on airflow limitation was entirely from the first nine years of follow-up. The HR in Table 4 therefore represents the average association over the whole time interval, with the strong effect during the first nine years and little if any effect afterwards.

Discussion

The collapse of the WTC towers produced an intense irritant exposure to caustic dust among FDNY firefighters, most of whom experienced a substantial acute drop in lung function without recovery. However, after the initial insult, some improved, while others continued to experience greater than expected rates of FEV_1 decline for years after 9/11. In the first 15 years following 9/11, 8.3% of WTC-exposed firefighters experienced FEV_1 improvement, while 12.7% experienced accelerated FEV_1 decline (>64 ml/year), defined as more than twice the cohort average loss of 32 ml/year (2). Post-9/11 blood leukocyte concentrations were independently associated with these lung function trajectories. Elevated first post-9/11 eosinophil concentration was associated with both accelerated FEV_1 decline and incident airflow limitation, after adjusting for neutrophil concentration, WTC exposure level, smoking status, and other potential confounders. Elevated post-9/11 neutrophil concentration was also a risk factor for the accelerated FEV_1 decline trajectory. Post-9/11 lung function trajectory is clinically meaningful, as we found it to be associated with the development of airflow limitation. These findings demonstrate that blood leukocyte concentrations are associated with future loss of lung function.

Elevated post-exposure eosinophil and neutrophil concentrations were independently associated with a greater rate of subsequent FEV_1 decline. In the subgroup of 4,303 individuals with both pre- and post-exposure CBC measurements available, there is a strong correlation between pre- and post-9/11 blood leukocyte concentrations. As expected with significantly correlated longitudinal data, pre-exposure eosinophil and neutrophil concentrations are also associated with post-9/11 accelerated

FEV_1 decline. One possible interpretation of this finding is that pre-9/11 blood leukocyte concentrations represent a latent risk factor, which was activated by WTC irritant exposure. Another possible interpretation is that those who had an exaggerated inflammatory response to WTC irritant exposure, manifest by elevated post-9/11 eosinophil and/or neutrophil concentrations, were susceptible to accelerated FEV_1 decline. This possibility is supported by the observed associations between post-9/11 blood leukocyte concentrations and FEV_1 decline in analyses that were adjusted for pre-exposure inflammatory status. These two possibilities are not mutually exclusive. Since only 45% of the cohort had both pre- and post-9/11 CBC measures available, these results are subject to selection bias. Nevertheless, the subgroup of firefighters who experienced accelerated FEV_1 decline had pre-9/11 FEV_1 above 100% predicted, which suggests that some phenomena related to WTC exposure prompted a marked change in lung function trajectory that has persisted for 15 years after the exposure.

We have previously shown that WTC dust may have been present in the lungs 10 months after exposure (9) and that WTC dust is pro-inflammatory (17). Greater retention of WTC dust in the lungs of those with accelerated FEV_1 decline could be a possible explanation for their more rapid rates of longitudinal FEV_1 decline. Alternatively, FEV_1 associated epigenetic changes may be associated with accelerated FEV_1 decline post-9/11, similar to what has been observed after particulate matter exposure or cigarette smoking (18-23).

In non-WTC-exposed populations with smoking-related COPD, elevated eosinophils are known risk factors for poor outcomes (7, 8, 24-26); this observation is consistent with the association of eosinophils with FEV_1 decline in ever-smokers, and

with incident airflow limitation among ever- and never-smokers. The fact that FEV_1 decline was associated with airflow limitation in this cohort is consistent with the genetic observations that FEV_1, FEV_1/FVC ratio and COPD have shared risk alleles (27-29). Parallels between this WTC-exposed cohort and non-WTC-exposed cohorts regarding FEV_1 loss and airflow limitation exist; exposure to WTC irritants produced changes in lung function similar to those seen in other irritant-exposed cohorts. Intense occupational irritant exposure associated with smelting has been found to yield a rate of airflow limitation of 20 cases per 1,000 person years (20), similar to the rate observed in ever-smoking WTC-exposed firefighters with accelerated FEV_1 decline. Given this similarity, the pathways to abnormal lung function are likely to be similar in populations with less intense irritant exposures, such as cigarette smoking and air pollution.

There are limitations to this study. The FDNY study cohort is overwhelmingly white, male, previously healthy, and experienced a massive caustic particulate exposure. This may limit generalizability. However, even though the FDNY cohort differs from the general population, a wide range of our findings have been replicated in more diverse WTC-exposed cohorts. A second limitation may be our decision to use an FEV_1 decline rate of greater than 64 ml/year to define accelerated FEV_1 decline. This a priori threshold represented twice the cohort's average decline rate. To address possible issues related to having predefined cutoffs, we modeled the association between post-9/11 blood leukocyte concentrations and FEV_1 decline as a continuous outcome and still observed that eosinophil and neutrophil concentrations were associated with longitudinal FEV_1 decline in ever-smokers and in the full cohort, respectively. Third, the cohort analysis of incident airflow limitation used screening spirometry without post-

bronchodilator data. To increase the specificity of this analysis, our definition of airflow limitation required persistence of FEV_1/FVC ratio less than 0.70 on two consecutive measurements more than one year apart. The similarity of the associations between eosinophils and incident airflow limitation in the primary and secondary (post-bronchodilator) analyses suggests that our primary analysis in the full cohort accurately represented those who developed airflow limitation. Finally, the post 9/11 blood leukocyte concentrations were obtained over an extended period post-exposure, and the evolving inflammatory response could have potentially introduced bias into the analysis. However, this would bias the results towards the null, because as we have previously reported, blood leukocyte concentrations were elevated during the first 18 months following 9/11 but then returned to pre-9/11 levels (11).

The final limitation is the possibility that the change in FEV_1 over time, particularly for the improved group, represents regression to the mean. When compared with the expected FEV_1 decline group, the group with accelerated FEV_1 decline had a blunted trans-9/11 FEV_1 decline (39 ml), while the improved FEV_1 group had a substantial one (691 ml). After 15 years of follow-up, however, the final FEV_1 in the accelerated FEV_1 decline group was more than 350 ml lower than that of the expected decline group, while those with improved FEV_1 had a final FEV_1 that was, on average, 288 ml higher. The large differences in the average final FEV_1 measurements of the three groups argues against regression to the mean as the full explanation of the inverse association between first post-9/11 FEV_1 and subsequent FEV_1 decline.

The data from the FDNY WTC Health Program is a valuable resource for understanding irritant-induced airways disease. Above-average blood leukocyte

concentrations may serve as a biomarker for increased vulnerability to post-irritant exposure airway injury. Ever-smokers have biological differences compared with never-smokers; the former are likely predisposed to exaggerated inflammation and/or poor counter-regulatory responses to inflammation that affect the rate of FEV_1 decline. Since eosinophils and neutrophils were measured early in the process of disease evolution, when lung function was still preserved, there is potential for targeting specific inflammatory pathways for early interventions.

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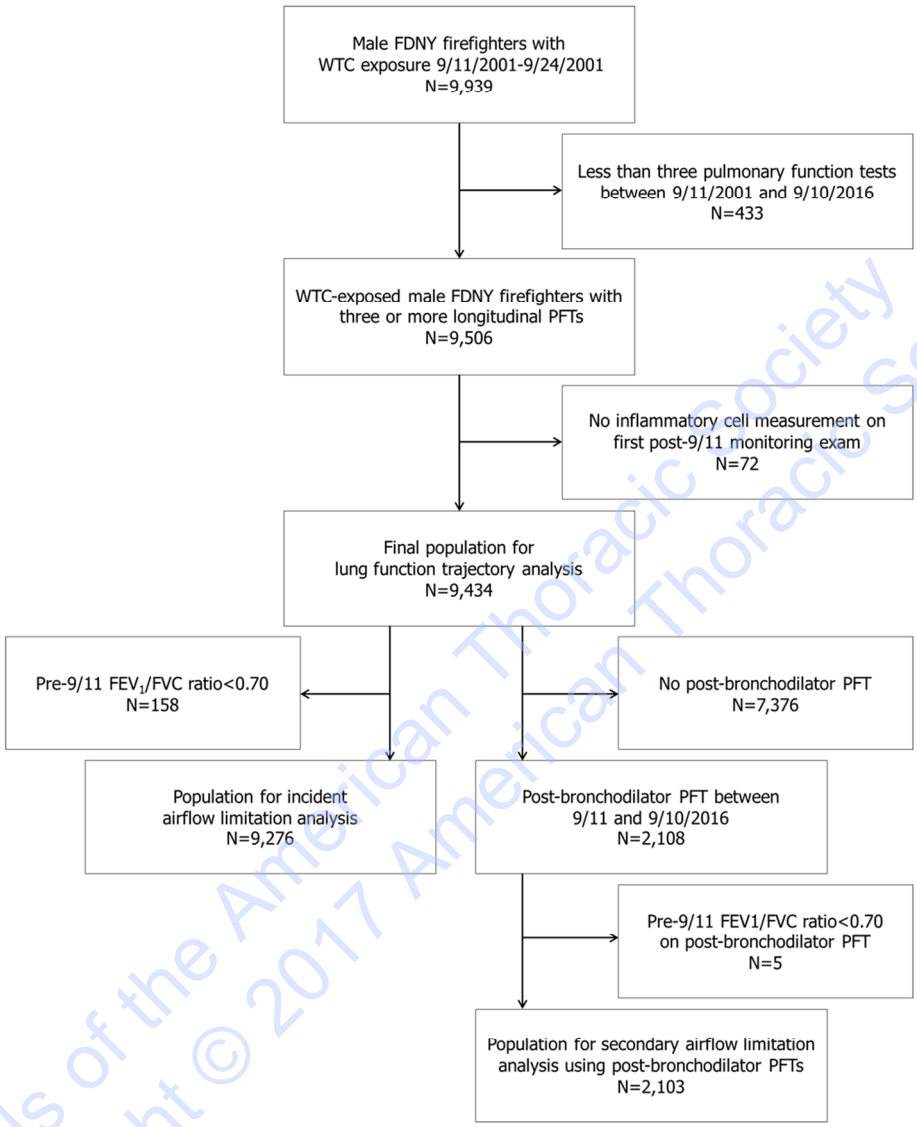
Figure 1. Firefighters who participated in the lung function trajectory study. Shown are the total number of male firefighters who were employed by the Fire Department of the City of New York (FDNY) on September 11, 2001 and present at the WTC between September 11 and September 24, 2001, the number included in the final study cohort, and the population for our secondary analysis using post-bronchodilator PFT data.

Figure 2. Lung function over time according to post-9/11 FEV_1 trajectory. Panel A shows yearly mean forced expiratory volume at one second (FEV_1) in liters in WTC-exposed FDNY firefighters from September 11, 2000 to September 10, 2016, adjusted for race, height and age on September 11, 2001, according to post-9/11 FEV_1 trajectory: accelerated decline (red), expected decline (blue) and improved FEV_1 (green). SEM is shown by error bars; it is not shown if it is less than the size of the symbol. Numbers below the x-axis represent the sample size at each time point. **Panel B** shows yearly mean FEV_1 percent predicted. The dashed vertical line in Panels A and B represents September 11, 2001.

Figure 3. Predicted post-9/11 FEV_1 decline rate according to blood leukocyte concentrations and smoking status. Panel A shows the associations between eosinophil concentration at the first post-9/11 PFT and predicted FEV_1 decline rate (FEV_1 slope) in ml/year in never-smokers (green) and ever-smokers (black). FEV_1 slope is adjusted for individual level variables listed in the footnote of Table 3. Dashed lines show 95% CI. P for interaction = 0.004. **Panel B** shows the association between neutrophil (PMN) concentration at the first post-9/11 PFT and predicted FEV_1 slope in ml/year in never-smokers and ever-smokers. P for interaction = 0.01.

Figure 4. Incident airflow limitation according to post-9/11 FEV_1 trajectory. Panel A shows adjusted cumulative incidence of airflow limitation, defined as having two consecutive FEV_1/FVC measurements less than 0.70 between September 11, 2001 and

September 10, 2016, according to post-9/11 FEV_1 trajectory: accelerated decline (red), expected decline (blue) and improved FEV_1 (green). **Panel B** shows adjusted cumulative incidence of airflow limitation on post-bronchodilator PFT, defined as at least one post-bronchodilator FEV_1/FVC ratio less than 0.70 between September 11, 2001 and September 10, 2016, according to post-9/11 FEV_1 trajectory.



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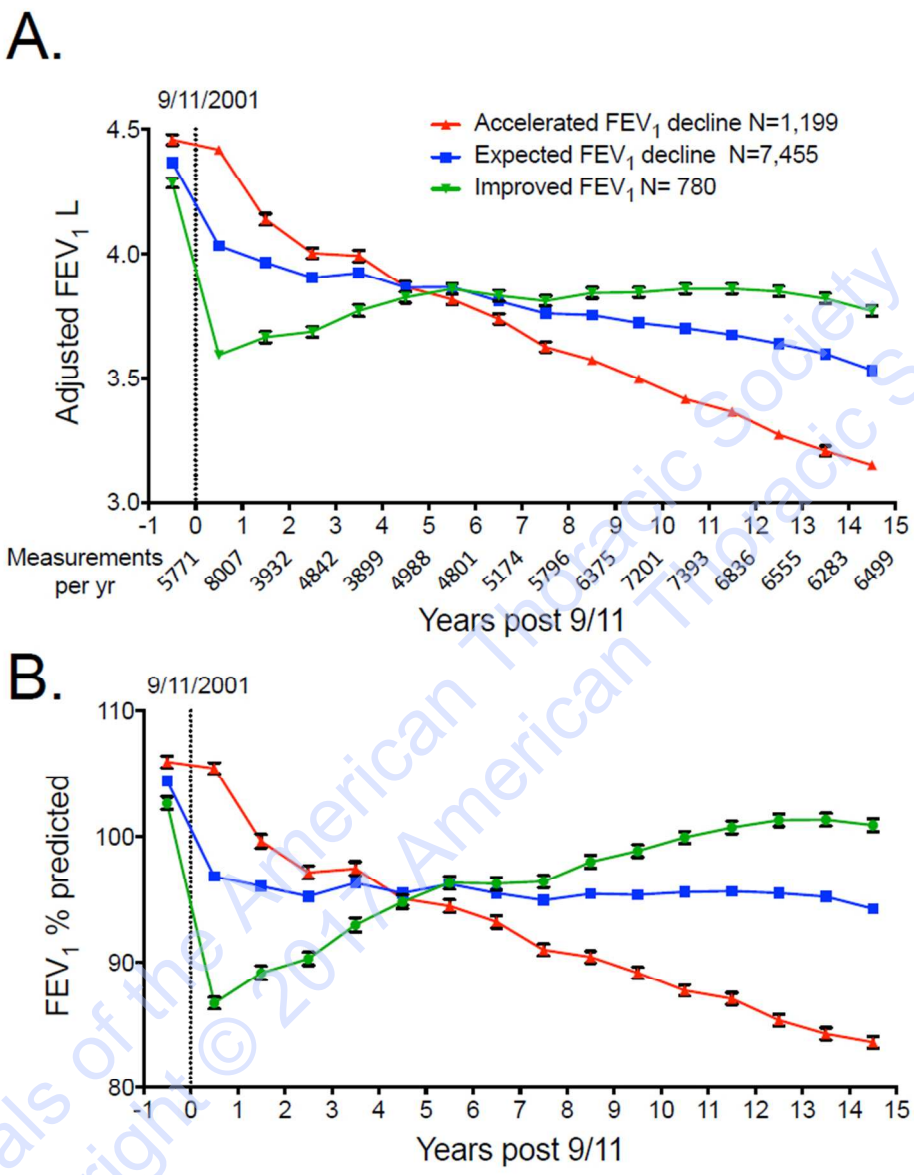

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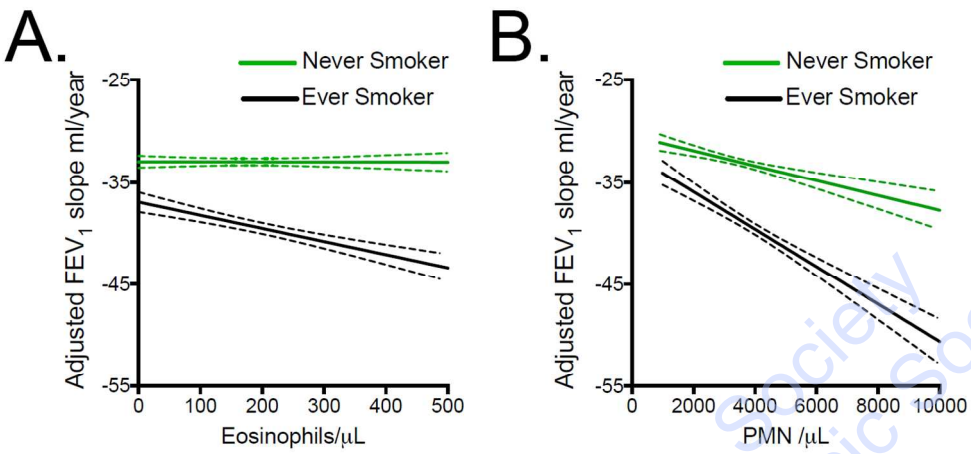
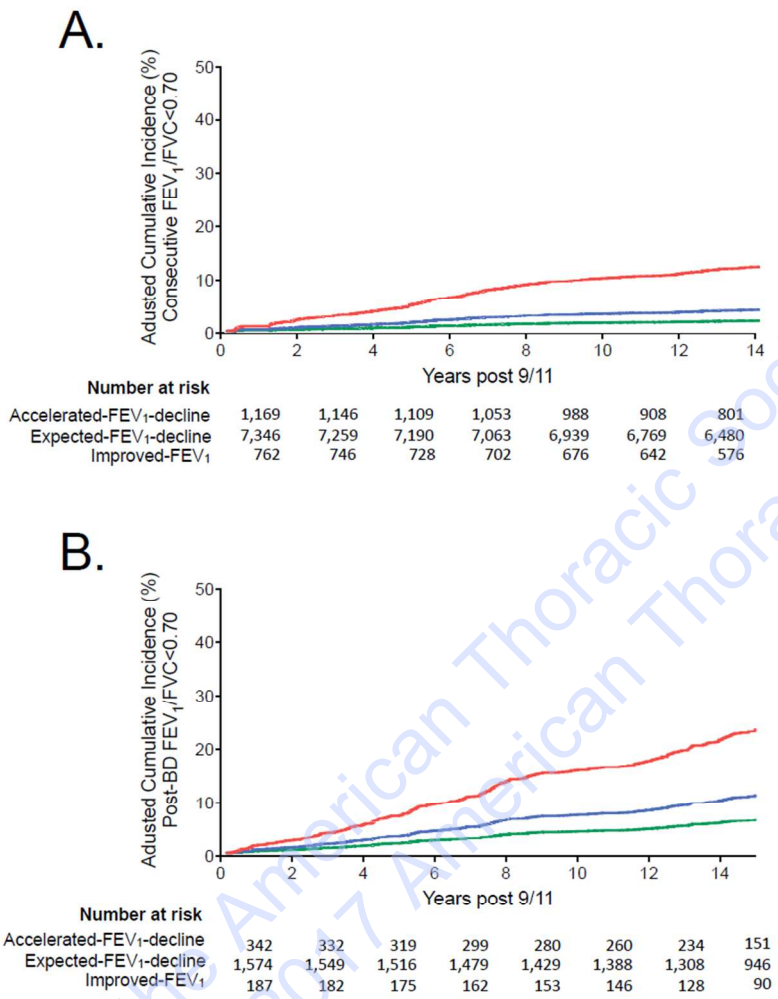


Figure 3. Post-9/11 FEV1 decline rate according to inflammatory cell concentrations and smoking status. Panel A shows the association between eosinophil concentration at the first post-9/11 PFT and adjusted FEV1 decline rate (FEV1 slope) in ml/year in never-smokers (green) and ever-smokers (black). FEV1 slope is adjusted for individual level variables listed in the footnote of Table 3. Dashed lines show 95% CI. Panel B shows the association between neutrophil (PMN) concentration at the first post-9/11 PFT and adjusted FEV1 slope in ml/year in never-smokers and ever-smokers.



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Data Supplement

Inflammatory cell concentrations, FEV_1 decline and airflow limitation: a 15-year longitudinal study of WTC-exposed firefighters

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Table E1: Baseline characteristics of source population of WTC-exposed male FDNY firefighters who were active on 9/11

Variable	WTC-Exposed Male FDNY Firefighters Active on 9/11 N=9,939	Study Cohort N=9,434
Age on 9/11*	40.33 ± 7.40	40.14 ± 7.38
Smoking status†§		
Never	6662 (67.03)	6,361 (67.43)
Former	2,928 (29.46)	2,785 (29.52)
Current	346 (3.48)	288 (3.05)
Race†		
White	9,342 (93.99)	8,889 (94.22)
Black	246 (2.48)	218 (2.31)
Hispanic	323 (3.25)	300 (3.18)
Other	28 (0.28)	27 (0.29)
WTC Arrival Time†		
Morning of 9/11	1,637 (16.47)	1,543 (16.36)
Afternoon on 9/11 - 9/12	7,078 (71.21)	6,755 (71.60)
9/13 – 9/24	1,224 (12.32)	1,136 (12.04)
FEV_1 (L)*‡‖	4.00 ± 0.67	4.01 ± 0.66
FEV_1 % predicted*‡‖	96.67 ± 13.38	96.88 ± 13.27
Eosinophils/µl blood, hundreds*‡¶	1.88 ± 1.30	1.88 ± 1.31
Neutrophils/µl blood, thousands*‡**	3.64 ± 1.33	3.63 ± 1.32

*Mean ± standard deviation
† N (%)
‡Value on first post-9/11 monitoring exam
§N=9,936
‖N=9,926
¶N=9,862
**N=9,849

Table E2: Multivariate Multiple Logistic Regression Model of Association Between Inflammatory Biomarker Concentrations and Post-9/11 FEV_1 Trajectory (Ref: Expected FEV_1 Decline)*†

Variable	Accelerated Decline (vs. Expected)			Improved FEV1 (vs. Expected)		
	OR	95% CI	P	OR	95% CI	P
Eosinophils per 100 cells/ µl‡	1.10	1.05-1.15	<0.001	1.01	0.95-1.07	0.71
Neutrophils per 1000 cells/ µl‡	1.10	1.05-1.15	<0.001	0.98	0.92-1.05	0.60
Age on 9/11 per 10 years	1.84	1.68-2.02	<0.001	0.66	0.58-0.74	<0.001
Baseline FEV_1 % predicted‡	1.06	1.05-1.06	<0.001	0.94	0.93-0.94	<0.001
Never smoker		Ref			Ref	
Former smoker	1.49	1.30-1.72	<0.001	0.87	0.72-1.04	0.12
Current smoker	2.98	2.19-4.06	<0.001	0.47	0.27-0.84	0.01
Low WTC exposure		Ref			Ref	
Mod. WTC exposure	1.08	0.89-1.33	0.44	1.22	0.94-1.59	0.14
High WTC exposure	1.16	0.91-1.49	0.23	1.48	1.09-1.99	0.01
Annual post-9/11 weight change, lbs	1.34	1.28-1.40	<0.001	0.74	0.70-0.79	<0.001
Height, cm	1.06	1.05-1.07	<0.001	1.00	0.98-1.01	0.52

*Also adjusted for race; †Likelihood ratio: Chi-square=1537, df=26, p<0.001; ‡First post 9/11 measurement.

Table E3: Multivariable Linear Regression Modeling the Effect of Inflammatory Biomarker Concentrations on Post-9/11 Rate of FEV_1 Change (ml/year)*

Variable	Study Cohort N=9,434			Ever-Smokers N=3,073			Never-Smokers N=6,361		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Eosinophils per 100 cells/ μl†	-0.7	-1.2, -0.3	0.001	-1.5	-2.3, -0.7	<0.001	-0.4	-0.9, 0.2	0.19
Neutrophils per 1000 cells/ μl†	-1.1	-1.6, -0.7	<0.001	-1.5	-2.2, -0.8	<0.001	-0.9	-1.4, -0.3	0.005
Age on 9/11 per 10 years	-7.5	-8.3, -6.7	<0.001	-9.1	-10.5, -7.8	<0.001	-6.5	-7.5, -5.5	<0.001
Baseline FEV_1 % predicted†	-0.9	-0.9, -0.8	<0.001	-0.8	-0.9, -0.8	<0.001	-0.9	-0.9, -0.8	<0.001
Never smoker		Ref			NA			NA	
Former smoker	-3.9	-5.2, -2.6	<0.001		Ref			NA	
Current smoker	-16.4	-19.9, -13.0	<0.001	-12.1	-15.8, -8.4	<0.001		NA	
Low WTC exposure		Ref			Ref			Ref	
Mod. WTC exposure	-0.1	-1.9, 1.7	0.91	0.4	-2.9, 3.6	0.83	-0.3	-2.5, 1.9	0.79
High WTC exposure	1.1	-1.1, 3.3	0.32	0.5	-3.5, 4.4	0.82	1.4	-1.2, 4.1	0.29
Annual post-9/11 weight change, lbs	-4.5	-4.9, -4.1	<0.001	-4.2	-4.7, -3.7	<0.001	-4.9	-5.6, -4.1	<0.001
Height, cm	-0.5	-0.6, -0.4	<0.001	-0.5	-0.6, -0.4	<0.001	-0.6	-0.8, -0.5	<0.001

*Also adjusted for race; † First post 9/11 measurement.

Table E4: Cox Proportional Hazards Regression Modeling post-9/11 Airflow Limitation*

Variable	Screening Spirometry N=9,276			Post-Bronchodilator PFT N=2,103		
	HR	95% CI	P	HR	95% CI	P
Eosinophils per 100 cells/ µl†	1.10	1.04-1.15	<0.001	1.10	1.03-1.17	0.004
Neutrophils per 1000 cells/ µl†	1.05	0.99-1.11	0.08	1.03	0.96-1.11	0.40
Age on 9/11 per 10 years	1.36	1.21-1.52	<0.001	1.62	1.37-1.91	<0.001
Baseline FEV_1 % predicted†	0.94	0.94-0.95	<0.001	0.95	0.95-0.96	<0.001
Never smoker		Ref			Ref	
Former smoker	1.49	1.25-1.77	<0.001	1.69	1.34-2.14	<0.001
Current smoker	2.00	1.42-2.81	<0.001	1.65	1.00-2.75	0.05
Low WTC exposure		Ref			Ref	
Moderate WTC exposure	0.98	0.76-1.25	0.86	0.79	0.56-1.11	0.17
High WTC exposure	0.86	0.63-1.17	0.34	0.69	0.46-1.04	0.07
Annual post-9/11 weight change, lbs	0.93	0.89-0.98	0.01	0.95	0.89-1.02	0.16
Height, cm	1.02	1.01-1.03	0.007	1.02	1.00-1.03	0.08

* Also adjusted for race; † First post 9/11 measurement.

Table E5: Multivariate Multiple Logistic Regression Model of Association Between Inflammatory Biomarker Concentrations and Post-9/11 FEV_1 Trajectory (Ref: Expected FEV_1 Decline) in Firefighters with 2+ Post-9/11 PFTs (N=9,643)*†

Variable	Accelerated Decline (vs. Expected)			Improved FEV_1 (vs. Expected)		
	OR	95% CI	P	OR	95% CI	P
Eosinophils per 100 cells/ µl‡	1.10	1.05-1.15	<0.001	1.01	0.95-1.07	0.84
Neutrophils per 1000 cells/ µl‡	1.10	1.05-1.15	<0.001	0.99	0.93-1.05	0.78
Age on 9/11 per 10 years	1.84	1.68-2.01	<0.001	0.70	0.62-0.78	<0.001
Baseline FEV_1 % predicted‡	1.05	1.04-1.06	<0.001	0.94	0.93-0.94	<0.001
Never smoker		Ref			Ref	
Former smoker	1.50	1.31-1.72	<0.001	0.86	0.73-1.03	0.10
Current smoker	3.23	2.43-4.31	<0.001	0.59	0.36-0.98	0.04
Low WTC exposure		Ref			Ref	
Mod. WTC exposure	1.06	0.88-1.29	0.54	1.20	0.93-1.55	0.16
High WTC exposure	1.16	0.92-1.47	0.21	1.48	1.10-1.99	0.01
Annual post-9/11 weight change, lbs	1.32	1.26-1.37	<0.001	0.76	0.72-0.80	<0.001
Height, cm	1.06	1.05-1.07	<0.001	1.00	0.99-1.01	0.65

*Also adjusted for race; †Likelihood ratio: Chi-square=1592, df=26, p<0.001; ‡First post 9/11 measurement.

Table E6: Multivariable Linear Regression Modeling the Effect of Inflammatory Biomarker Concentrations on Post-9/11 Rate of FEV_1 Change (ml/year) in Firefighters with 2+ Post-9/11 PFTs (N=9,643)*

Variable	Total N=9,643			Ever-Smokers N=3,166			Never-Smokers N=6,477		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Eosinophils per 100 cells/ µl†	-0.8	-1.2, -0.4	0.001	-1.3	-2.2, -0.4	0.01	-0.5	-1.0, 0.1	0.10
Neutrophils per 1000 cells/ µl†	-1.3	-1.8, -0.9	<0.001	-1.9	-2.8, -0.9	<0.001	-1.0	-1.4, -0.5	0.004
Age on 9/11 per 10 years	-8.1	-8.6, -7.5	<0.001	-10.4	-11.9, -9.0	<0.001	-6.7	-7.8, -5.6	<0.001
Baseline FEV_1 % predicted†	-0.9	-0.9, -0.8	<0.001	-0.8	-0.9, -0.8	<0.001	-0.9	-0.9, -0.8	<0.001
Never smoker		Ref			NA			NA	
Former smoker	-4.3	-5.5, -3.1	<0.001		Ref			NA	
Current smoker	-18.7	-21.4, -15.9	<0.001	-13.9	-18.3 -9.5	<0.001		NA	
Low WTC exposure		Ref			Ref			Ref	
Mod. WTC exposure	0.5	-1.4, 2.3	0.65	3.5	-0.5, 7.4	0.07	-1.2	-3.5, 1.1	0.35
High WTC exposure	2.5	-0.1, 5.0	0.06	5.7	0.9, 10.5	0.02	0.7	-2.3, 3.6	0.65
Annual post-9/11 weight change, lbs	-5.6	-6.0, -5.2	<0.001	-6.2	-7.2, -5.2	<0.001	-5.1	-5.8, -4.3	<0.001
Height, cm	-0.6	-0.7, -0.5	<0.001	-0.9	-1.0, 0.8	<0.001	-0.5	-0.6, -0.4	<0.001

*Also adjusted for race; † First post 9/11 measurement.

Figure E1. Residual Plots from Linear Model of Inflammatory Biomarkers and Post-9/11 FEV1 Decline Rate. The top panel shows the residuals of the multivariable-adjusted linear regression model as a function of post-9/11 eosinophil concentration, and the bottom panel shows the residuals from the same model as a function of neutrophil concentration.

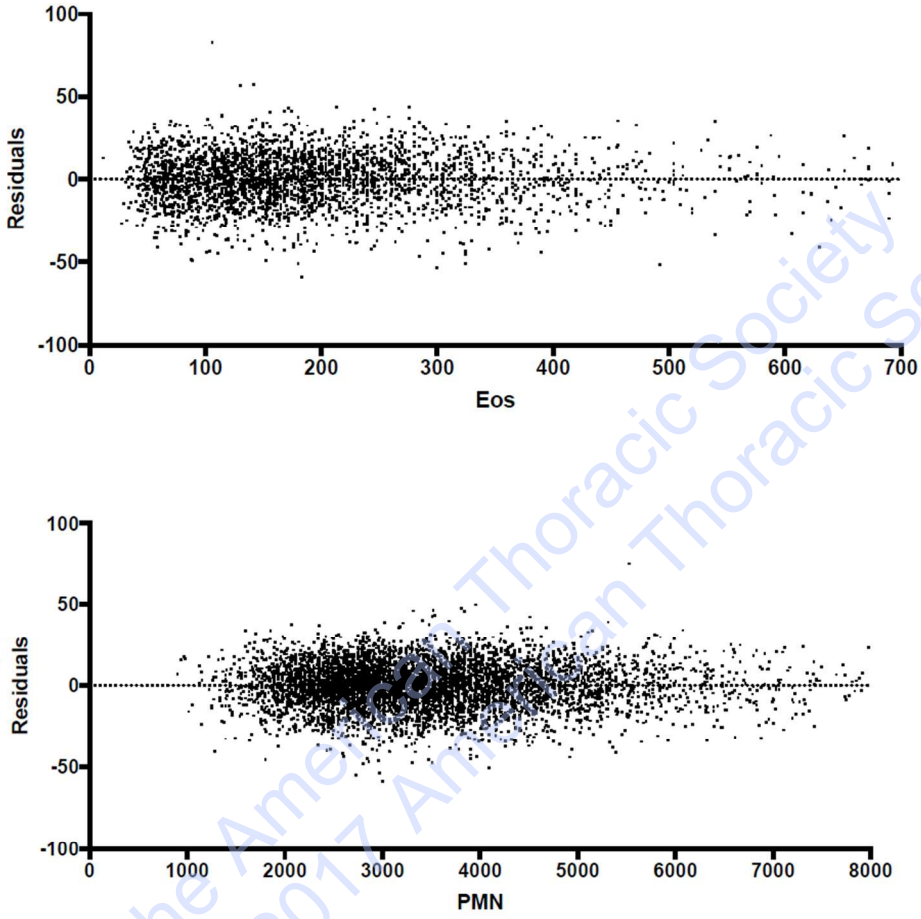

Figure E1. Residual Plots from Linear Model of Inflammatory Biomarkers and Post-9/11 FEV1 Decline Rate. The top panel shows the residuals of the multivariable-adjusted linear regression model as a function of post-9/11 eosinophil concentration, and the bottom panel shows the residuals from the same model as a function of neutrophil concentration.