CHEST

Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure

A Longitudinal Study

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BACKGROUND: Previously healthy firefighters with World Trade Center (WTC) dust exposure developed airway disease. Risk factors for irritant-associated asthma/COPD overlap are poorly defined.

METHODS: This study included 2,137 WTC-exposed firefighters who underwent a clinically indicated bronchodilator pulmonary function test (BD-PFT) between 9/11/2001 and 9/10/2017. A post-BD FEV_1 increase of $>$ 12% and 200 mL from baseline defined asthma, and a post-BD FEV_1/FVC ratio $<$ 0.7 identified COPD cases. Participants who met both criteria had asthma/COPD overlap. Eosinophil levels were measured on screening blood tests performed shortly after 9/11/2001 and prior to BD-PFT; a subgroup of participants also had serum IgE and 21 cytokines measured (n = 215). Marginal Cox regression models for multiple events assessed the associations of eosinophil levels or serum biomarkers with subsequent diagnosis, with age, race, smoking, WTC exposure, first post-9/11 FEV_1/FVC ratio, and BMI included as covariates.

RESULTS: BD-PFT diagnosed asthma/COPD overlap in 99 subjects (4.6%), isolated-asthma in 202 (9.5%), and isolated-COPD in 215 (10.1%). Eosinophil concentration $\geq$ 300 cells/μL was associated with increased risk of asthma/COPD overlap (hazard ratio [HR], 1.85; 95% CI, 1.16-2.95) but not with isolated-asthma or isolated-COPD. Serum IL-4 also predicted asthma/COPD overlap (HR, 1.51 per doubling of cytokine concentration; 95% CI, 1.17-1.95). Greater IL-21 concentration was associated with both isolated-asthma and isolated-COPD (HRs of 1.73 [95% CI, 1.27-2.35] and 2.06 [95% CI, 1.31-3.23], respectively).

CONCLUSIONS: In WTC-exposed firefighters, elevated blood eosinophil and IL-4 levels are associated with subsequent asthma/COPD overlap. Disease-specific T-helper cell type 2 biomarkers present years before diagnosis suggest patient-intrinsic predisposition to irritant-associated asthma/COPD overlap.

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KEY WORDS: asthma; airway obstruction; biomarkers; COPD; eosinophils

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ABBREVIATIONS: BD = bronchodilator; FDNY = Fire Department of the City of New York; HR = hazard ratio; IFN = interferon; PFT = pulmonary function test; RV = residual volume; T_h = T-helper cell type; TLC = total lung capacity; WTC = World Trade Center

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The collapse of the World Trade Center (WTC) on September 11, 2001 (9/11), exposed the Fire Department of the City of New York (FDNY) rescue and recovery workers to caustic dust and products of combustion.[1] Subsequently, WTC-exposed rescue and recovery workers had high rates of airway injury, including excessive loss of lung function,[2] obstructive ventilatory defect,[3] and airway hyperreactivity.[4] Firefighters with elevated postexposure blood eosinophil concentrations were at increased risk of developing COPD.[5]

Asthma/COPD overlap is a recently defined endotype of COPD,[6-8] with patients experiencing a poorer quality of life and higher mortality compared with patients who have either isolated-COPD or isolated-asthma.[9-11] Risk factors for asthma/COPD overlap are poorly defined, but among those with smoking-related COPD, elevated eosinophils in sputum and blood are biomarkers for this condition.[12,13] Longitudinal studies are needed to define risk factors for asthma/COPD overlap.[14]

The aim of the present study was to determine early predictors of asthma/COPD overlap among WTC-exposed firefighters with at least one post-9/11 clinically indicated pulmonary function test (PFT) with bronchodilator (BD) measurement (N = 2,137). The main predictors of interest were blood biomarkers collected during participants' post-9/11 FDNY medical monitoring examination. We also examined these measurements in association with isolated-asthma and with isolated-COPD as a way to understand the unique predictors of asthma/COPD overlap.

Methods

Study Population

The source population consisted of 9,598 male firefighters who were actively employed by the FDNY on 9/11; first arrived at the WTC between 9/11/2001 and 9/24/2001; and had ≥ 3 post-9/11 FEV_1 measurements from routine medical monitoring PFTs taken at FDNY.[5] A subset of this population received at least one clinically indicated BD-PFT performed according to American Thoracic Society standards[15] at a hospital-based pulmonary function laboratory between 9/11/2001 and 9/10/2017. We excluded 57 participants whose BD-PFT occurred before their first post-9/11 medical monitoring examination. The final study population included 2,137 firefighters (Fig 1).

Participants provided written informed consent. The Montefiore Medical Center (FWA #00002558)/Albert Einstein College of Medicine (FWA #00023382) Institutional Review Board approved this study.

Baseline Characteristics

Demographic data were retrieved from the FDNY employee database. Participants' height, weight, self-reported smoking status (current, former, or never-smoker), and time of initial arrival at the WTC site were assessed during routine medical monitoring examinations at FDNY (both active duty firefighters and WTC-exposed retirees are scheduled to have a monitoring examination once every 12 to 18 months). Individuals were classified as having high (morning of 9/11), moderate (afternoon on 9/11 to 9/12), or low (9/13 to 9/24) WTC exposure based on their WTC site arrival time.[4] Current and former smokers were grouped together as ever-smokers in these analyses. Those who consistently self-reported no cigarette smoking were classified as never-smokers.

Blood and Serum Biomarkers

Eosinophil concentration was measured from blood drawn shortly after 9/11, during the first post-9/11 monitoring examination. The median first post-9/11 blood draw date was 1/10/2002 (interquartile range: 11/26/2001 to 12/27/2002). We also had pre-9/11 blood data (eosinophil concentration) for the 1,008 participants who had blood drawn at a pre-9/11 monitoring examination. Serum biomarkers from the first post-9/11 blood draw, including IgE and cytokines, were available for a subgroup of the study cohort (n = 215). Serum was stored at –80°C; IL-4 and interferon (IFN)-γ were assayed with MilliporeSigma HSTCMAG28SPMX21 and IgE with HGAMMAG-303E.

Pulmonary Function

Participants' most recent BD-PFT from the 9/11/2001 to 9/10/2017 period provided the pre- and post-BD FEV_1 and FVC measurements used to define our main outcome. A BD response of > 12% and 200 mL increase from baseline FEV_1 diagnosed asthma.[16] COPD was defined according to the Global Initiative for Obstructive Lung Disease criteria, which requires a FEV_1/FVC ratio < 0.7 on a post-BD PFT.[7] We classified individuals who had a BD response and FEV_1/FVC ≥ 0.7 as having isolated-asthma, and those who had FEV_1/FVC < 0.7 and no BD response as having isolated-COPD. Individuals who met the criteria for both asthma and COPD had asthma/COPD overlap.

Total lung capacity (TLC) and residual volume (RV) measurements were also available from the BD-PFT data; these were measured prior to BD administration. We used spirometric measurements from 22,737 routine monitoring PFTs (always done without BD) taken between 9/11/2001 and 9/10/2017 to assess post-9/11 FEV_1 trajectories. FEV_1 values from post-9/11 monitoring PFTs that occurred prior to the BD-PFT were used to determine whether patients with asthma and/or COPD had accelerated (> 64 mL/y) or expected (≤ 64 mL/y) FEV_1 decline post-9/11 but prior to our outcome determination; for individuals who had neither

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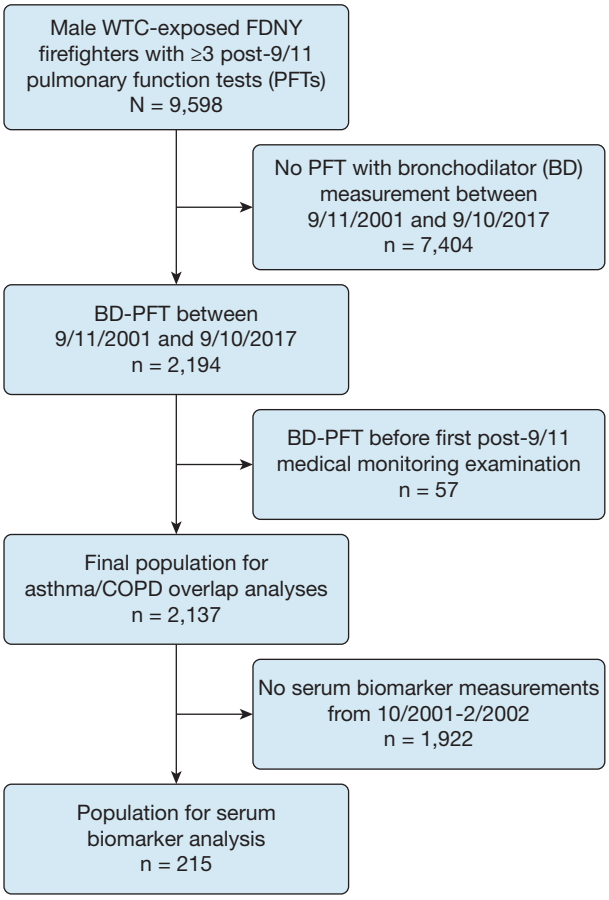

Figure 1 – *Firefighters who participated in the asthma/COPD overlap study. Shown is the source population of male firefighters who were employed by the FDNY on 9/11/2001, present at the WTC site between 9/11/2001 and 9/24/2001, and had at least three routine monitoring PFTs taken between 9/11/2001 and 9/10/2017 for FEV_1 slope measurement. The final study population included those who had received a post-9/11/2001 clinically indicated PFT with BD measurement. The serum biomarker population was a subgroup who had biomarkers measured on serum drawn between 10/2001 and 2/2002. BD = bronchodilator; FDNY = Fire Department of the City of New York; PFT = pulmonary function test; WTC = World Trade Center.*

diagnosis, all post-9/11 FEV_1 values were included in the FEV_1 decline rate calculation. Pre-9/11 FEV_1 and FVC measurements were available from 1,265 spirometries performed at FDNY monitoring in the year prior to 9/11 (9/11/2000 to 9/10/2001).

Statistical Analyses

Demographic and other characteristics of the study population and serum biomarker subgroup were assessed as proportions and means ± SD, with independent sample Student *t* tests or χ^2 tests used to evaluate differences, as appropriate. Longitudinal FEV_1 % predicted, FEV_1/FVC ratio, and post-9/11 rate of FEV_1 change were estimated in four subsets of the population defined according to outcome (isolated-asthma, isolated-COPD, asthma/COPD overlap, or neither condition) using linear mixed effects models with random intercepts. Participants' age on 9/11, height, and race were included as fixed effects in the models with the absolute FEV_1 or FEV_1/FVC ratio as the outcome. Mean FEV_1 % predicted and FEV_1/FVC ratio values in the four groups were estimated for each 1-year period between 9/11/2000 and 9/10/2017, and mean rates of FEV_1 change were determined by using the post-9/11 spirometry data.

Log-rank Mantel-Cox tests were performed to examine the univariable associations of post-9/11 FEV_1 trajectory (accelerated vs expected FEV_1 decline), eosinophil concentration, and smoking status with incident asthma/COPD overlap, followed by multivariable marginal Cox regression models for multiple events to evaluate shared and distinct risk factors for isolated-asthma, isolated-COPD, and asthma/COPD overlap. Censoring occurred at the time of the BD-PFT. Blood eosinophil concentration was assessed first as a binary variable (≥ 300 cells/μL vs < 300 cells/μL) and then as a continuous variable. Two sensitivity analyses were conducted: one that excluded individuals with an FEV_1/FVC ratio < 0.7 on a pre-9/11 monitoring PFT (n = 69) and another that examined the relationship between pre-9/11 eosinophil concentration and the outcomes of interest (n = 1,008). Absolute change in eosinophil concentration from pre-9/11 to post-9/11 was also investigated.

A multivariable-adjusted Cox regression analysis for multiple events data was also performed in the serum biomarker subpopulation (n = 215) to determine whether log_2-transformed serum IgE and 21 cytokines were associated with isolated-asthma, isolated-COPD, or asthma/COPD overlap. After Bonferroni correction, the significance cutoff for the serum biomarker analyses was set at a two-sided *P* value of .0024. For all other analyses, reported *P* values are two-sided and considered significant at the < .05 level. Multivariable models included age, race, smoking status, WTC exposure, first post-9/11 FEV_1/FVC ratio, and BMI as covariates. Covariates were selected based on theory. Data analyses were performed by using SAS version 9.4 (SAS Institute, Inc). Figures were created by using Prism 7 (GraphPad Software).

Results

Baseline Characteristics

Demographic and other characteristics of the 2,137 firefighters with clinically indicated post-9/11 BD-PFT in the final study population (Fig 1) and those without BD-PFT are presented in Table 1. Compared with WTC-exposed firefighters who did not have a BD-PFT, the study population was slightly different in that it was older, had a higher BMI and post-9/11 blood eosinophil concentration, and a greater proportion of ever-smokers. These differences were more pronounced in those who would develop a post-BD FEV_1/FVC ratio < 0.70. The serum biomarker subgroup was similar to the study population, with the exception of having a smaller proportion of ever-smokers.

Lung Function on Monitoring and BD-PFTs

Clinically indicated BD-PFT diagnosed isolated-asthma in 202 individuals (9.5%), isolated-COPD in 215 (10.1%), and asthma/COPD overlap in 99 (4.6%) (Fig 2). At the time of BD-PFT, the asthma/COPD

TABLE 1] Population Characteristics and Longitudinal Lung Function

Variable	WTC-Exposed No BD-PFT (N = 7,404)	BD-PFT Study Population (N = 2,137)		Subpopulation With Serum Biomarkers (n = 215)	*P* Value[a]
		Post-BD $FEV_1/FVC \geq 0.7$ (n = 1,823)	Post-BD $FEV_1/FVC < 0.7$ (n = 314)		
Age on 9/11, y[b]	39.9 ± 7.6	40.5 ± 6.7	44.0 ± 6.8	41.0 ± 6.8	< .001
BMI, kg/m^2[b,c]	28.7 ± 3.4	29.2 ± 3.5	28.5 ± 3.3	28.7 ± 3.3	< .001
Smoking status, No. (%)[c]					
Never	5,031 (67.9)	1,229 (67.4)	142 (45.2)	185 (86.0)	< .001
Former	2,143 (28.9)	542 (29.7)	148 (47.1)	22 (10.2)	
Current	230 (3.1)	52 (2.9)	24 (7.6)	8 (3.7)	
Race, No. (%)					
White	6,971 (94.2)	1,719 (94.3)	299 (95.2)	208 (96.7)	< .001
Black	174 (2.3)	36 (2.0)	10 (3.2)	4 (1.9)	
Hispanic	234 (3.2)	66 (3.6)	5 (1.6)	3 (1.4)	
Other	25 (0.3)	2 (0.1)	0	0	
WTC arrival time, No. (%)					
Morning of 9/11	1,129 (15.3)	366 (20.1)	52 (16.6)	37 (17.2)	< .001
Afternoon on 9/11–9/12	5,322 (71.9)	1,295 (71.0)	223 (71.0)	168 (78.1)	
9/13 to 9/24	953 (12.9)	162 (8.9)	39 (12.4)	10 (4.7)	
Pre-9/11 spirometry					
FEV_1, L[b]	4.43 ± 0.68[d]	4.38 ± 0.69[e]	3.94 ± 0.74[f]	4.32 ± 0.69[g]	< .001
FEV_1 % predicted[b]	105.9 ± 13.3[d]	104.3 ± 13.7[e]	95.2 ± 15.4[f]	103.3 ± 14.2[g]	< .001
FEV_1/FVC[b]	0.85 ± 0.05[d]	0.85 ± 0.05[e]	0.78 ± 0.07[e,f]	0.84 ± 0.05[g]	< .001
Post-9/11 spirometry					
FEV_1, L[b,c]	4.05 ± 0.65	3.96 ± 0.65	3.46 ± 0.73	3.92 ± 0.70	< .001
FEV_1 % predicted[b,c]	97.8 ± 12.9	95.4 ± 13.5	85.2 ± 15.3	94.4 ± 14.4	< .001
FEV_1/FVC[b,c]	0.84 ± 0.05	0.84 ± 0.05	0.74 ± 0.07	0.83 ± 0.06	< .001
Post-9/11 FEV_1 slope, mL/y[b]	−35.1 ± 30.8	−37.8 ± 32.4	−47.5 ± 36.3	−41.1 ± 37.0	< .001
Blood eosinophil concentration					
Pre-9/11 cells/μL[b]	154 ± 109[h]	162 ± 117[i]	186 ± 144[j]	153 ± 104[k]	< .001
Post-9/11 cells/μL[b,c]	184 ± 126[l]	194 ± 136[m]	231 ± 175[n]	198 ± 132	< .001

BD = bronchodilator; PFT = pulmonary function test; WTC = World Trade Center.
[a]ANOVA or χ^2 test comparing values in first three columns.
[b]Mean ± SD.
[c]Value on first post-9/11 monitoring examination.
[d]N = 6,836.
[e]N = 1,686.
[f]N = 285.
[g]N = 209.
[h]N = 3,295.
[i]N = 857.
[j]N = 151.
[k]N = 109.
[l]N = 7,388.
[m]N = 1,815.
[n]N = 314.

overlap subgroup had a lower pre-BD FEV_1 % predicted, lower pre-BD FEV_1/FVC ratio, and higher RV/TLC ratio than any other diagnostic category (Table 2). BD response was similar in patients with asthma/COPD overlap and isolated-asthma (22.6 ± 13.3% vs 19.9 ± 12.8% increase in FEV_1, respectively; $P = .09$).

Both the pre-9/11 and first post-9/11 FEV_1 % predicted in each subgroup were on average ≥ 80% on monitoring

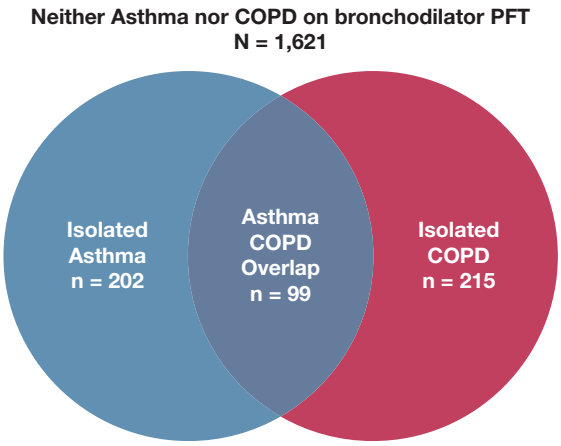

Figure 2 – *Asthma/COPD overlap in WTC-exposed firefighters who had a BD-PFT. The Venn diagram demonstrates abnormalities on BD-PFTs obtained via the WTC treatment program. Isolated-asthma was diagnosed in 202 individuals who had FEV_1 BD response of > 12% and 200 mL. Isolated-COPD was diagnosed in 215 individuals who had a post-BD FEV_1/FVC ratio < 0.70. Asthma/COPD overlap was diagnosed in 99 who had both an FEV_1 BD response > 12% and 200 mL, and an FEV_1/FVC ratio < 0.70. The remainder of the study population (n = 1,621) did not have a BD response or airflow limitation. See Figure 1 legend for expansion of abbreviations.*

PFTs but were lowest in those who went on to develop asthma/COPD overlap (Fig 3A). The FEV_1/FVC ratio on the first post-9/11 monitoring PFT was also lowest in this subgroup (Fig 3B). The annual post-9/11 FEV_1 loss in individuals with asthma/COPD overlap was similar to that of the COPD subgroup (47.6 mL/y [95% CI, 43.5-51.6] and 47.2 mL/y [95% CI, 44.7-49.6], respectively), and greater than the rate of FEV_1 loss in those with isolated-asthma (43.4 mL/y; 95% CI, 40.7-46.2) or neither outcome (36.8 mL/y; 95% CI, 35.9-37.6).

Risk Factors for Asthma/COPD Overlap

Univariable analyses showed that the incidence of asthma/COPD overlap was elevated in participants with post-9/11 eosinophil concentration ≥ 300 cells/μL (HR, 1.69; 95% CI, 1.00-2.81; $P < .05$) (Fig 4A), those with a history of smoking (HR, 1.67; 95% CI, 1.11-2.50; $P = .02$) (Fig 4B), and those experiencing post-9/11-accelerated FEV_1 decline (HR, 2.05; 95% CI, 1.22-3.43; $P = .006$) (Fig 4C). In multivariable marginal Cox regression models for multiple events, asthma/COPD overlap was predicted by eosinophil concentration ≥ 300 cells/μL (Table 3). Eosinophil concentration was not significantly associated with isolated-asthma or isolated-COPD. When isolated-asthma and asthma/COPD overlap were compared directly, asthma/COPD overlap was still associated with elevated eosinophils (Table 4). Results were similar if analyses were restricted to those who had eosinophils measured < 15 months following 9/11 (data not shown). A unique risk factor for isolated-asthma was high-intensity WTC exposure, and for isolated-COPD, it was ever-smoking. Post-9/11-accelerated FEV_1 decline was associated with all three outcomes. The observed associations did not change when eosinophil concentration was assessed as a continuous variable (data not shown).

To confirm that elevated post-9/11 eosinophil concentration and accelerated FEV_1 decline were associated with incident asthma/COPD overlap, a sensitivity analysis was conducted excluding patients with a pre-exposure PFT that showed a FEV_1/FVC ratio < 0.7 (n = 69). First post-9/11 eosinophil concentration ≥ 300 cells/μL and accelerated FEV_1 decline both remained significant predictors of asthma/COPD overlap (HR, 1.67 [95% CI, 1.03-2.71], $P = .03$; and HR, 2.15 [95% CI, 1.35-3.43], $P = .001$, respectively). To assess if pre-exposure blood eosinophil levels were indicative of a predisposition to asthma/COPD overlap, another sensitivity analysis was performed by using pre-9/11 eosinophil concentration in place of the post-9/11 measurement. The subgroup of participants who had had a pre-9/11 blood draw

TABLE 2] Bronchodilator PFT Results

Variable	Asthma/COPD Overlap	Isolated-Asthma	Isolated-COPD	Neither Diagnosis
Pre-BD FEV_1 % predicted	67.3 ± 14.8	80.9 ± 13.5[a]	82.3 ± 15.2[a]	96.9 ± 13.2[a]
Post-BD FEV_1 % predicted	81.3 ± 14.5	96.2 ± 13.7[a]	85.9 ± 15.0[a]	100.5 ± 13.5[a]
Pre-BD FVC % predicted	93.3 ± 15.8	87.1 ± 13.9[a]	101.2 ± 15.1[a]	98.3 ± 12.9[a]
Post-BD FVC % predicted	101.8 ± 14.0	96.0 ± 13.3[a]	103.4 ± 15.1	98.5 ± 12.9[a]
Pre-BD FEV_1/FVC	0.56 ± 0.08	0.73 ± 0.07[a]	0.62 ± 0.07[a]	0.77 ± 0.05[a]
Post-BD FEV_1/FVC	0.62 ± 0.07	0.78 ± 0.05[a]	0.64 ± 0.06[a]	0.80 ± 0.05[a]
Pre-BD RV/TLC	0.40 ± 0.10	0.33 ± 0.09[a]	0.33 ± 0.08[a]	0.28 ± 0.07[a]

Data are expressed as mean ± SD. RV = residual volume; TLC = total lung capacity. See Table 1 legend for expansion of other abbreviations.
[a]$P < .05$ vs asthma/COPD overlap subgroup.

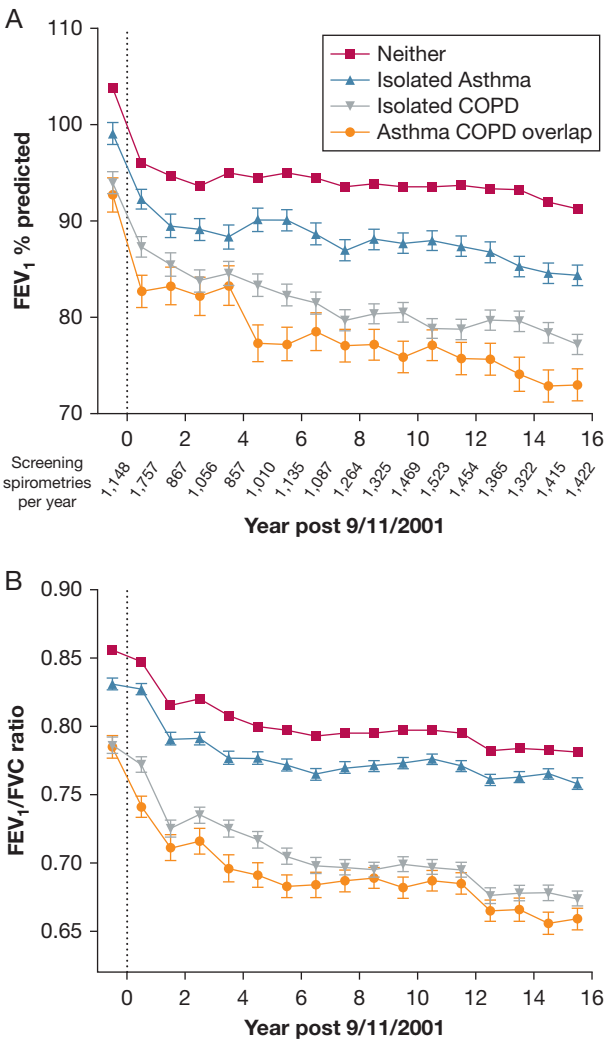

Figure 3 – *A-B, Lung function over time. A, Mean ± SEM (SEM not shown if it is smaller than the size of the symbol) FEV_1 % predicted in each year between 9/11/2000 and 9/10/2017 in the asthma/COPD overlap (orange), isolated-COPD (gray), isolated-asthma (blue), and asthma-free and COPD-free (red) groups. The vertical line at 0 represents 9/11/2001. The number of spirometries per year is shown below the x-axis. B, Mean FEV_1/FVC ratio in the aforementioned groups in each year, adjusted for race, height, and age, using the same number of spirometries per year as shown in panel A.*

(n = 1,008) had baseline characteristics and lung function similar to those of the full study population (data not shown). We found that pre-9/11 eosinophil concentration ≥ 300 cells/μL was also associated with the outcome (HR, 1.42; 95% CI, 1.22-1.66; $P < .001$). Change in eosinophil concentration from pre-9/11 to post-9/11 was not associated with asthma/COPD overlap (data not shown).

To gain further insight into the immunologic pathways associated with isolated-asthma, isolated-COPD, and asthma/COPD overlap, we examined serum T-helper cell type 1, T-helper cell type 17 (T_h17), and T-helper cell type 2 (T_h2) biomarkers obtained within 6 months of 9/11. A multivariable marginal Cox regression analysis for multiple events in the serum biomarker subpopulation (n = 215) found that higher early post-9/11 IgE was associated with incident asthma/COPD overlap, but this result was not significant after adjustment for multiple comparisons (Table 5). We found that elevated IL-4 predicted asthma/COPD overlap and elevated IL-21 predicted both isolated-asthma and isolated-COPD; elevated IFN-γ was a protective factor for isolated-asthma and isolated-COPD. Early post-9/11 levels of IL-5, IL-13, IL-17, IL-23, and IL-6 were not associated with any of the three mutually exclusive outcomes (data not shown).

Discussion

The WTC-exposed FDNY firefighter population is a cohort comprising previously healthy male subjects. Importantly, asthma documented during pre-employment medical evaluation precludes employment as a FDNY firefighter. Those who develop reactive airways disease during their career are removed from active duty[17]; therefore, the prevalence of pre-9/11 asthma in this cohort was low. The massive irritant exposure at the WTC site resulted in an acute drop in lung function, with rescue/recovery workers going on to experience air trapping, as well as fixed and reversible airflow obstruction.[2-4] In the present study, we observed that elevated early post-9/11 blood eosinophil concentration predicted irritant-associated asthma/COPD overlap but not isolated-asthma or isolated-COPD. A sensitivity analysis noted that pre-911 elevated eosinophils were a risk factor for asthma/COPD overlap. This finding suggests a pre-WTC exposure predisposition to irritant-associated fixed and reversible airway injury. Although we found some overlapping biomarkers of these outcomes, the observation that there are unique biomarkers of vulnerability to asthma/COPD overlap, isolated-asthma, and isolated-COPD suggests the potential for different pathologic processes for these three diagnoses; this topic could be explored in future studies.

The FDNY WTC-exposed cohort has advantages for investigating irritant-associated airways disease. Data from a centralized post-WTC medical treatment program enabled explicit diagnostic criteria for incident isolated-asthma, isolated-COPD, and asthma/COPD overlap. Pre-9/11 lung function and blood data were available for a large subset of the cohort, enabling assessment of early indicators of susceptibility to

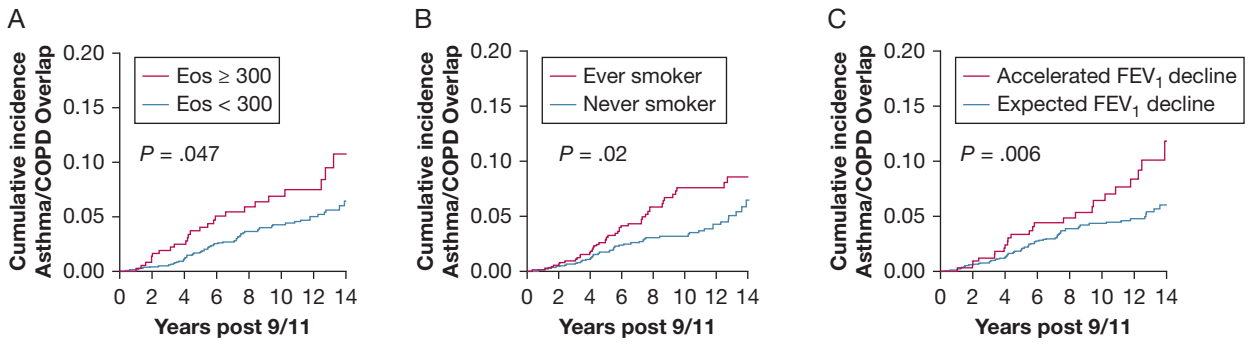

Figure 4 – *A-C, Cumulative incidence of asthma/COPD overlap in WTC-exposed firefighters who had a BD PFT. A, Cumulative incidence of asthma/COPD overlap in participants with blood EOS concentration ≥ 300 cells/μL (red) and < 300 cells/μL on first post-9/11 medical monitoring examination (blue). The level of significance shown in each panel was determined by using the log-rank test. B, Cumulative incidence in those who reported ever smoking (red) and never smoking (blue). C, Cumulative incidence in participants who had an accelerated rate of post-9/11 FEV_1 decline > 64 mL/y (red) and those with expected FEV_1 decline ≤ 64 mL/y (blue). EOS = eosinophil. See Figure 1 legend for expansion of other abbreviations.*

subsequent airway injury. Our observation that pre-exposure eosinophil concentration was associated with later asthma/COPD overlap suggests patient-intrinsic vulnerability to the damaging effects of WTC dust exposure. How much the exposure itself contributed to the presentation is limited because not every assessment was performed pre-exposure.

Compared with those who developed isolated-asthma or isolated-COPD, patients with asthma/COPD overlap had a lower post-exposure FEV_1 and FEV_1/FVC ratio. An investigation in a cohort without WTC exposure found that low lung function in childhood was a risk factor for subsequent asthma/COPD overlap,[18] and thus our observed associations between early lung function measurements and this outcome may be evidence of similar biological mechanism(s). Both the asthma/COPD overlap and isolated-COPD subgroups have progressive airway injury, with greater post-9/11 FEV_1 rates of decline than individuals with isolated-asthma or neither diagnosis. The asthma/COPD overlap subgroup also experienced more air trapping, shown by higher RV/TLC at the time of BD-PFT. This finding is consistent with previous investigation of asthma/COPD overlap in never-smokers[19] and could be evidence of the severity of small airways dysfunction associated with WTC exposure.[20]

Eosinophils and IgE are two T_h2 mediators that have been extensively studied as risk factors for asthma, COPD, and asthma/COPD overlap.[12,21-25] In the present investigation, serum IgE was associated with asthma/COPD overlap but did not achieve significance after Bonferroni adjustment for multiple comparisons. We did observe a significant association between serum levels of the T_h2 cytokine IL-4 and this outcome. IL-4 may be a biomarker on the causal pathway to irritant-associated asthma/COPD overlap because inhibiting it with dupilumab reduced asthma severity in non-WTC-exposed patients with or without high eosinophil

TABLE 3] Marginal Cox Regression Models Predicting Isolated-Asthma, Isolated-COPD, and Asthma/COPD Overlap

	Asthma/COPD Overlap vs Neither			Isolated-Asthma vs Neither			Isolated-COPD vs Neither		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Eosinophils ≥ 300 cells/μL[a]	1.85	1.16-2.95	.009	0.93	0.63-1.36	.69	1.16	0.82-1.64	.39
Accelerated FEV_1 decline	2.17	1.40-3.35	< .001	2.12	1.54-2.91	< .001	2.18	1.59-2.99	< .001
Ever-smoker	0.92	0.58-1.44	.70	0.77	0.56-1.05	.09	1.60	1.18-2.17	.003
WTC exposure morning of 9/11	1.40	0.84-2.32	.19	1.58	1.14-2.20	.006	0.86	0.59-1.26	.44

The total N value was 2,124 due to missing covariates. Data were adjusted for age, race, BMI, and first post-9/11 FEV_1/FVC measurement. HR = hazard ratio. See Table 1 legend for expansion of other abbreviation.
[a]First post-9/11 measurement.

TABLE 4] Marginal Cox Regression Models Predicting Isolated-Asthma, Isolated-COPD, and Asthma/COPD Overlap

Variable	Asthma/COPD Overlap vs Isolated-Asthma			Asthma/COPD Overlap vs Isolated-COPD		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Eosinophils ≥ 300 cells/μL[a]	2.00	1.11-3.62	.02	1.60	0.89-2.85	.12
Accelerated FEV_1 decline	1.02	0.60-1.74	.94	0.99	0.60-1.65	.98
Ever-smoker	1.19	0.69-2.05	.52	0.57	0.34-0.98	.04
WTC exposure morning of 9/11	0.88	0.49-1.61	.68	1.62	0.88-3.01	.12

The total N value was 2,124 due to missing covariates. Data were adjusted for age, race, BMI, and first post-9/11 FEV_1/FVC measurement. See Table 1 and 3 legends for expansion of abbreviations.
[a]First post-9/11 measurement.

levels.[26,27] Further investigation is required to assess the T_h2 pathways that are associated with FEV_1 decline, airflow limitation, and BD response following an intense irritant exposure.

The incident asthma observed in the present study is a variant of irritant-induced asthma.[28] The fact that it was associated with high-intensity WTC exposure but not eosinophil concentration suggests that airway reactivity in this cohort is a form of noneosinophilic asthma.[29] IFN-γ was a protective biomarker for this condition and also for isolated-COPD. High IFN-γ is associated with low IL-4 in modulation of pulmonary lymphocyte-mediated innate immunity.[30] Furthermore, asthma is associated with blunted IFN-γ response.[31,32]

The balance between T_h2 and T_h17 cytokines in airway inflammation is under active investigation.[33-35] IL-21, which was found to significantly predict isolated-asthma and isolated-COPD in the present cohort, is a component of the T_h17 pathway that is produced by innate lymphoid cells which regulate airway inflammation.[36] Elevated levels are associated with airway inflammation in mouse models and humans.[37-39] The data from the WTC-exposed FDNY cohort are consistent with a T_h2 and T_h17 response predicting airway remodeling and reactivity. These data support further investigation of the innate T_h17 response to pulmonary irritants.

In univariable analyses, we found that in addition to high eosinophil concentration and accelerated FEV_1 decline, ever-smoking was associated with asthma/COPD overlap. After adjusting for confounders, such as post-9/11 lung function, smoking was a unique risk factor for isolated-COPD but not isolated-asthma or asthma/COPD overlap. Therefore, the relationship between smoking and asthma/COPD overlap in this cohort was confounded by the other covariates. High WTC exposure level was not associated with isolated-COPD or asthma/COPD overlap, which suggests that an intense but brief irritant exposure did not increase risk of airway remodeling. In this cohort, isolated-COPD was not associated with eosinophil levels. In a population with smoking-related COPD, however, elevated blood

TABLE 5] Marginal Cox Regression Models Predicting Isolated-Asthma, Isolated-COPD, and Asthma/COPD Overlap in the Subpopulation With Serum Drawn Between 9/11/2001 and 3/10/2002

Variable	Asthma/COPD Overlap vs Neither			Isolated-Asthma vs Neither			Isolated-COPD vs Neither		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
IgE[a]	2.31	1.14-4.67	.02[b]	1.21	0.92-1.58	.16	1.14	0.81-1.62	.45
IFN-γ[a]	0.42	0.22-0.81	.01[b]	0.48	0.32-0.70	< .001	0.45	0.28-0.70	< .001
IL-21[a]	1.33	0.89-1.98	.17	1.73	1.27-2.35	< .001	2.06	1.31-3.23	.002
IL-4 substituted for IL-21 in marginal Cox regression model									
IL-4[a]	1.51	1.17-1.95	.002	1.68	1.08-2.61	.02[b]	1.35	0.96-1.91	.08

The total N value was 215. Data were adjusted for age, race, BMI, smoking status, WTC exposure level, and first post-9/11 FEV_1/FVC. IFN = interferon. See Table 1 and 3 legends for expansion of other abbreviations.
[a]One $\log_2$ increase (doubling) of cytokine concentration.
[b]A *P* value of .0024 was considered significant after Bonferroni correction.

eosinophil concentration was a biomarker of increased exacerbation.[40] The variability of eosinophil effect reported in the literature may be related to the proportion of the study cohorts with an asthma component.[41,42]

There are several limitations to this investigation. The FDNY firefighters are overwhelmingly white, male, and experienced a massive irritant exposure, potentially limiting generalizability of these findings; however, most findings from the FDNY cohort have been replicated in other WTC-exposed cohorts. Our definitions of isolated asthma, asthma/COPD overlap, and isolated COPD depend on results from the most recent BD-PFT. It is possible that those with isolated COPD, defined as FEV_1/FVC < 0.7 and no BD response in this study, have asthma/COPD overlap because we did not proceed to methacholine challenge testing in the subgroup. Similarly, those with asthma/COPD overlap, defined as FEV_1/FVC < 0.7 and a BD response, may not have persistent FEV_1/FVC < 0.7 with permanent airway remodeling. A third limitation may be the use of eosinophils ≥ 300 cells/μL or < 300 cells/μL in our analyses. We modeled post-9/11 eosinophils as a continuous variable and still observed a significant association with asthma/COPD overlap. This method suggests that cut-point selection did not drive the analyses. Lastly, this study was vulnerable to selection bias. The study population with clinically indicated BD-PFT was systematically different from those without BD-PFT, with more intense WTC exposure, higher eosinophil levels, and post-WTC exposure lower lung function. This outcome precludes assessment of rates of asthma/COPD overlap in the entire cohort because undiagnosed cases are likely. Nevertheless, analyses within the BD-PFT population provide a valid assessment of risk factors for specific diagnoses within a symptomatic subgroup.

Conclusions

The data from the FDNY WTC Health Program are a valuable resource for understanding irritant-associated airways disease in a previously healthy population. High eosinophil concentrations, uniquely associated with asthma/COPD overlap in this population, may reflect biological pathways that predispose one to exaggerated inflammation and/or poor counterregulatory responses to inflammation, leading to reversible and fixed airflow obstruction. There may be potential for early interventions that involve targeting specific inflammatory pathways in an attempt to improve lung function outcomes.

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Author contributions: M. D. W. had full access to all of the data in the study and agrees 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. M. D. W. conceived of the study and designed it in conjunction with C. L., R. Z.-O., C. B. H., and D. J. P.; and M. D. W., A. S., B. P., R. Z.-O., and T. S. analyzed and interpreted the data. A. S., M. D. W., and C. L. drafted the first manuscript, with critical revisions from B. P., R. Z.-O., C. B. H., D. J. P., M. P. W., T. S., H. W. C., A. N., and K. I. B. All authors approved the final manuscript.

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