


## RESEARCH ARTICLE

# Serum Th-2 cytokines and FEV<sub>1</sub> decline in WTC-exposed firefighters: A 19-year longitudinal study

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## Abstract

**Background:** Accelerated-FEV<sub>1</sub>-decline, defined as rate of decline in FEV<sub>1</sub> > 64 ml/year, is a risk factor for asthma and chronic obstructive pulmonary disease in World Trade Center (WTC)-exposed firefighters. Accelerated-FEV<sub>1</sub>-decline in this cohort is associated with elevated blood eosinophil concentrations, a mediator of Th-2 response. We hypothesized that an association exists between Th-2 biomarkers and FEV<sub>1</sub> decline rate in those with accelerated-FEV<sub>1</sub>-decline.

**Methods:** Serum was drawn from Fire Department of the City of New York (FDNY) firefighters 1–6 months (early) (N = 816) and 12–13 years (late) (N = 983) after 9/11/2001. Th-2 biomarkers IL-4, IL-13, and IL-5 were assayed by multiplex Luminex. Individual FEV<sub>1</sub> decline rates were calculated using spirometric measurements taken: (1) between 9/11/2001 and 9/10/2020 for the early biomarker group and (2) between late measurement date and 9/10/2020 for the late biomarker group. Associations of early and late Th-2 biomarkers with subsequent FEV<sub>1</sub> decline rates were analyzed using multivariable linear regression controlling for demographics, smoking status, and other potential confounders.

**Results:** In WTC-exposed firefighters with accelerated-FEV<sub>1</sub>-decline, IL-4, IL-13, and IL-5 measured 1–6 months post-9/11/2001 were associated with greater FEV<sub>1</sub> decline ml/year between 9/11/2001 and 9/10/2020 (−2.9 ± 1.4 ml/year per IL-4 doubling; −8.4 ± 1.2 ml/year per IL-13 doubling; −7.9 ± 1.3 ml/year per IL-5 doubling). Among late measured Th-2 biomarkers, only IL-4 was associated with subsequent FEV<sub>1</sub> decline rate (−4.0 ± 1.6 ml/year per IL-4 doubling).

**Conclusions:** In WTC-exposed firefighters with accelerated-FEV<sub>1</sub>-decline, elevated serum IL-4 measured both 1–6 months and 12–13 years after 9/11 is associated with greater FEV<sub>1</sub> decline/year. Drugs targeting the IL-4 pathway may improve lung function in this high-risk subgroup.

## KEYWORDS

cohort studies, FEV<sub>1</sub> slope, firefighting, Th-2 biomarkers, World Trade Center

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## 1 | INTRODUCTION

The World Trade Center (WTC) collapse on September 11, 2001 (9/11) released extremely high concentrations of dust and products of combustion into the air in lower Manhattan, causing lung injury in Fire Department of the City of New York (FDNY) rescue and recovery workers.<sup>1</sup> Twelve percent of WTC-exposed firefighters developed a rate of decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) that was more than twice the average rate of FEV<sub>1</sub> decline of the cohort, >64 ml/year decline, defined as accelerated-FEV<sub>1</sub>-decline in previous investigations.<sup>2,3</sup> We observed that higher blood eosinophil concentrations, cells that mediate T-helper 2 (Th-2) immunity, were associated with accelerated-FEV<sub>1</sub>-decline in this population after controlling for covariates, in addition to being associated with wheeze and airflow obstruction in other WTC-exposed cohorts.<sup>2,4</sup> Individuals in the accelerated-FEV<sub>1</sub>-decline subpopulation were more than four times as likely to have had incident airflow limitation as those who had expected age-related FEV<sub>1</sub> decline.<sup>2</sup> Accelerated-FEV<sub>1</sub>-decline also increased our patients' risk for asthma and asthma/chronic obstructive pulmonary disease (COPD) overlap syndrome by twofold,<sup>5</sup> and is associated with increased mortality in non-WTC-exposed individuals with smoking-related COPD.<sup>6</sup>

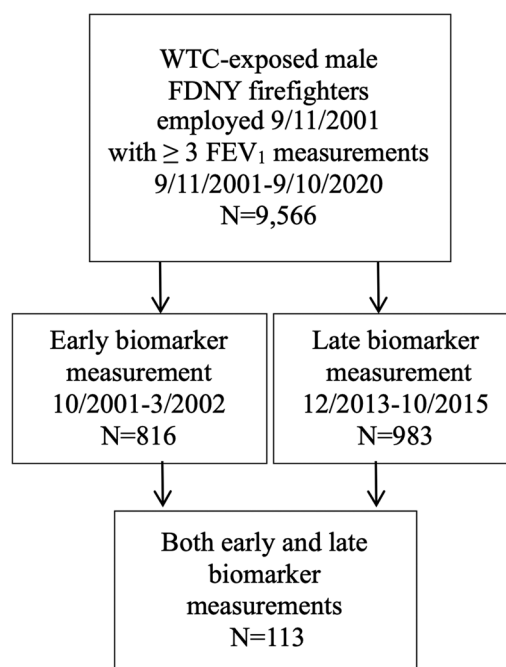
Inhaled corticosteroid and long-acting beta agonist (ICS/LABA) combination therapy is a standard therapy for asthma and COPD with frequent exacerbations.<sup>7–10</sup> As time post-9/11 has increased, ICS/LABA has been less effective in controlling WTC exposure-associated respiratory symptoms.<sup>11</sup> The goal of the FDNY WTC Health Program's biomarker discovery program is to improve the prediction of disease risk and identification of inflammatory pathways to provide new therapeutic targets in those who are not responding to ICS/LABA treatment.

Elevated levels of eosinophils and of Th-2 biomarkers IL-4 and IgE measured within 6 months of 9/11 are risk factors for asthma/COPD overlap in WTC-exposed firefighters.<sup>5</sup> Elevated IL-4 is also a risk factor for WTC exposure-associated asthma.<sup>5</sup> Conversely, higher levels of IFN- $\gamma$ , a Th-1 cytokine, was associated with reduced risk of asthma and asthma/COPD overlap in WTC-exposed firefighters.<sup>5</sup> Studies in populations with uncontrolled persistent asthma have shown that the monoclonal antibody dupilumab binds and inhibits the IL-4/IL-13 receptor, reducing asthma exacerbations, and improving asthma symptoms and FEV<sub>1</sub>.<sup>12–14</sup> In the current study, we hypothesized that an association exists between serum Th-2 biomarkers and FEV<sub>1</sub> decline rate in WTC-exposed firefighters with accelerated-FEV<sub>1</sub>-decline.

## 2 | METHODS

### 2.1 | Study population

The source population included 9566 male firefighters who were actively employed by FDNY on 9/11, who first arrived to work at



**FIGURE 1** Flow diagram. Source population of World Trade Center (WTC)-exposed Fire Department of the City of New York (FDNY) male firefighters who were actively employed on 9/11/2001 (9/11) and received  $\geq 3$  pulmonary function tests measuring forced expiratory volume in 1 s (FEV<sub>1</sub>) between 9/11 and 9/10/2020, and final study population including only those who had serum Th-2 biomarkers measured during an “early” and/or “late” post-9/11 time period

the WTC site between 9/11 and 9/24/2001, and who had  $\geq 3$  FEV<sub>1</sub> measurements between 9/11/2001 and 9/10/2020 (Figure 1). The final study population was restricted to those who had serum Th-2 biomarkers measured at either or both of the following time intervals: 1–6 months and 12–13 years post-9/11 ( $N = 1686$ ). Participants provided written informed consent, and the Albert Einstein College of Medicine Institutional Review Board approved this study.

### 2.2 | Baseline characteristics

We obtained demographic data from the FDNY employee database. Participants' height, weight, self-reported smoking status, and time of initial arrival at the WTC site were assessed during routine medical monitoring examinations. Those who consistently self-reported no cigarette smoking were classified as never-smokers.

Serum biomarker concentrations were measured from blood drawn over two intervals: the first was between 1 and 6 months after 9/11, and the second took place 12–13 years post-9/11. Serum was stored at  $-80^{\circ}\text{C}$ . IL-4, IL-13, IL-5, IFN- $\gamma$ , and TNF- $\alpha$  were assayed with EMD Milipore HSTCMAG28SPMX21.

## 2.3 | ICS/LABA treatment

Medication data were available via the FDNY electronic medical record and the FDNY WTC Health Program claims database. Participants in the late blood draw group were classified as having had ICS/LABA treatment if they had initiated the treatment before the late blood draw date.

## 2.4 | Outcomes

FEV<sub>1</sub> measurements were obtained from spirometric data collected during the FDNY medical monitoring examinations, as described in our previous studies.<sup>1–3</sup> Individual rates of FEV<sub>1</sub> decline, and the corresponding standard error measurements, were estimated for each participant using linear regression analyses examining the effect of follow-up time in years on FEV<sub>1</sub> (ml).<sup>2</sup> Rates of FEV<sub>1</sub> decline were calculated in two ways: (1) using participants' first post-9/11 FEV<sub>1</sub> measurement and all subsequent measurements through 9/10/2020 (overall FEV<sub>1</sub> decline rate), and, (2) for participants with a late serum measurements, using participants' late blood draw date and all subsequent measurements through 9/10/2020 (late FEV<sub>1</sub> decline rate). Individuals were classified as having accelerated-FEV<sub>1</sub>-decline if they experienced >64 ml/year decline in FEV<sub>1</sub>.<sup>2,3</sup>

## 2.5 | Statistical analyses

Characteristics of the source population and the final study population were assessed as proportions and means (SD). We estimated intraclass correlations between early and late biomarker concentrations in participants who had had serum drawn during both time intervals ( $N = 113$ ) using average measures from linear mixed-effects models with random effects. We then performed multivariable linear regression analyses to examine associations of early and late serum biomarker measurements with overall and late rates of FEV<sub>1</sub> decline, respectively, using the standard errors of the individual FEV<sub>1</sub> decline rate measurements for weighted least squares regression adjustment. Analyses in the early and late serum biomarker groups were stratified by FEV<sub>1</sub> decline status (accelerated-FEV<sub>1</sub>-decline and FEV<sub>1</sub> decline <64 ml/year), measured using participants' overall and late FEV<sub>1</sub> decline rates, respectively. A sensitivity analysis repeated these analyses using the data of participants in the late biomarker group who had not previously initiated ICS/LABA therapy ( $N = 228/299$  [76%] in the accelerated-FEV<sub>1</sub>-decline and  $N = 478/649$  [74%] in the FEV<sub>1</sub> decline ≤64 ml/year subgroups).

Each biomarker was assessed separately, and all multivariable models controlled for age on 9/11/2001, race, smoking (ever vs. never), WTC exposure level, height, and FEV<sub>1</sub>% predicted at time of blood draw. Biomarker concentrations were log<sub>2</sub>-transformed to improve skewness and kurtosis. All data analyses were performed using SAS version 9.4.

## 3 | RESULTS

The study population consisted of 1686 firefighters with early serum biomarkers measured between 10/2001 and 3/2002 ( $N = 816$ ) and/or late serum biomarkers measured between 12/2013 and 10/2015 ( $N = 983$ ); 113 individuals had biomarkers measured at both times. The median first post-9/11 blood draw date was 12/4/2001 (interquartile range: 11/14/2001 to 1/3/2002). The median second post-9/11 blood draw date was 9/23/2014 (interquartile range: 3/27/2014 to 12/14/2014). Compared with the source population, the population with early serum biomarker measurements was similar in age, race distribution, WTC exposure profile, FEV<sub>1</sub>% predicted at first post-9/11 monitoring (baseline) exam, and had similar FEV<sub>1</sub> decline rate (ml/year) over longitudinal follow-up. There were, however, a smaller proportion of ever-smokers. The population with late serum biomarker measurements was similar to the source population in age, race distribution, smoking status, and WTC exposure profile, but had a lower baseline FEV<sub>1</sub>% predicted and greater overall FEV<sub>1</sub> decline rate (Table 1).

We examined the longitudinal constancy of serum biomarker concentrations by estimating the intraclass correlations between early and late biomarkers in the 113 individuals with measurements at both times. The early and late measurements of the Th-2 biomarkers IL-5, IL-13 and IL-4 were correlated (IL-5 intraclass correlation coefficient [ICC]: 0.527,  $p < 0.001$ ; IL-13 ICC: 0.568,  $p < 0.001$ ; and IL-4 ICC: 0.468,  $p < 0.001$ ; Table 2). There was also correlation between early and late levels of IFN- $\gamma$ , a Th-1 cytokine (ICC: 0.802,  $p < 0.001$ ). A different pattern emerged for TNF- $\alpha$ , a cytokine that mediates acute inflammation. There was no significant correlation between early and late TNF- $\alpha$  concentrations (ICC: 0.209;  $p = 0.104$ ).

We then estimated the associations between early serum biomarker concentrations and overall FEV<sub>1</sub> decline rates in 117 individuals in the early measurement group with accelerated-FEV<sub>1</sub>-decline (>64 ml/year decline in FEV<sub>1</sub> from 9/11/2001 to 9/10/2020). IL-5, IL-13, and IL-4 concentrations were significantly associated with greater post-9/11 FEV<sub>1</sub> decline ( $-7.9 \pm 1.3$  ml/year per doubling of IL-5,  $p < 0.001$ ;  $-8.4 \pm 1.2$  ml/year per doubling of IL-13,  $p < 0.001$ ; and  $-2.9 \pm 1.4$  ml/year per doubling of IL-4,  $p = 0.04$ ) controlling for age, race, WTC exposure level, smoking status, height, and first post-9/11 FEV<sub>1</sub> percent predicted (Table 3). IFN- $\gamma$  and TNF- $\alpha$ , on the contrary, were both significantly associated with less post-9/11 FEV<sub>1</sub> decline ( $13.9 \pm 2.3$  ml/year [i.e., reduced FEV<sub>1</sub> decline] per doubling of IFN- $\gamma$ ,  $p < 0.001$  and  $16.7 \pm 4.1$  ml/year per doubling of TNF- $\alpha$ ,  $p < 0.001$ ) in this subgroup. In the subgroup of 699 firefighters with FEV<sub>1</sub> decline ≤64 ml/year between 9/11/2001 and 9/10/2020, only IL-5 was associated with greater FEV<sub>1</sub> decline ( $-1.3 \pm 0.5$  ml/year per doubling of IL-5,  $p = 0.008$ ; Table 4).

Given the correlation between early and late Th-2 biomarker concentrations, we also assessed the associations between late biomarker concentrations and late FEV<sub>1</sub> decline rate. In 274 participants who experienced accelerated-FEV<sub>1</sub>-decline after the date of their late serum biomarker measurement (defined as having >64 ml/year decline in FEV<sub>1</sub> from date of late measurement to 9/10/2020), only

**TABLE 1** Cohort characteristics

	Biomarkers 10/2001 to 3/2002 N = 816	Biomarkers 12/2013 to 10/2015 N = 983	Source population N = 9566
Age on 9/11	41.4 ± 7.5	42.0 ± 7.8	40.2 ± 7.4
Race, n (%)			
White	780 (95.6)	904 (92.0)	9012 (94.2)
African American	12 (1.5)	39 (4.0)	223 (2.3)
Hispanic	23 (2.8)	36 (3.7)	304 (3.2)
Other	1 (0.1)	4 (0.4)	27 (0.3)
Smoking status, n (%)			
Never	680 (83.3)	615 (62.6)	6406 (67.0)
Ever	136 (16.7)	368 (37.4)	3160 (33.0)
World Trade Center arrival time, n (%)			
Morning of 9/11	130 (15.9)	174 (17.7)	1560 (16.3)
Afternoon of 9/11 to 9/12	626 (76.7)	697 (70.9)	6849 (71.6)
9/13/2001 or later	60 (7.4)	112 (11.4)	1157 (12.1)
FEV <sub>1</sub> % predicted <sup>a</sup>	98.6 ± 14.5	97.2 ± 14.6	97.0 ± 13.7
FEV <sub>1</sub> decline ml/year <sup>b</sup>	38.4 ± 26.6	36.1 ± 23.4	37.3 ± 28.9

<sup>a</sup>First post-9/11 measurement.<sup>b</sup>Between 9/11/2001 and 9/10/2020.**TABLE 2** Intraclass correlations between early and late serum biomarkers in individuals with measurement at both time points<sup>a</sup>

Serum cytokine	ICC <sup>b</sup>	95% Confidence interval	p value
IL-4	0.468	0.226, 0.629	<0.001
IL-5	0.527	0.318, 0.672	<0.001
IL-13	0.568	0.375, 0.701	<0.001
IFN-γ	0.802	0.705, 0.867	<0.001
TNF-α	0.209	-0.140, 0.451	0.104

Abbreviation: ICC, intraclass correlation coefficient.

<sup>a</sup>N = 113.<sup>b</sup>Two-way random effects model average measure.

IL-4 was associated with subsequent FEV<sub>1</sub> decline ( $-4.0 \pm 1.6$  ml/year per doubling of IL-4,  $p = 0.01$ ; Table 5). There was no association between late IL-5, IL-13, IFN-γ, or TNF-α concentration and late FEV<sub>1</sub> decline rate in these individuals. In the 611 participants with late FEV<sub>1</sub> decline  $\leq 64$  ml/year, we did not observe associations between late IL-5, IL-13, IL-4, IFN-γ, or TNF-α concentrations and late FEV<sub>1</sub> decline rate (Table 6).

Sensitivity analyses conducted in the subset of the late biomarker measurement population who had not received ICS/LABA treatment yielded similar results to those shown above; higher IL-4 concentration was associated with a larger FEV<sub>1</sub> decline

( $-3.3 \pm 1.5$  ml/year per doubling of IL-4,  $p = 0.03$ ), only in participants with accelerated-FEV<sub>1</sub>-decline ( $N = 228$ ).

## 4 | DISCUSSION

A subset of WTC-exposed rescue/recovery workers have accelerated-FEV<sub>1</sub>-decline, a strong risk factor for asthma, COPD and asthma/COPD overlap syndrome.<sup>2,5</sup> Unless effective therapy can improve lung function trajectories in the accelerated-FEV<sub>1</sub>-decline subgroup, many will progress to COPD-related impairment.<sup>2</sup> Accelerated-FEV<sub>1</sub>-decline has also been associated with increased mortality in non-WTC-exposed individuals with smoking-related COPD.<sup>6</sup> Cigarette smoking, heterozygosity for alpha-1-antitrypsin deficiency, and elevated blood eosinophil concentrations are all risk factors for accelerated-FEV<sub>1</sub>-decline in WTC-exposed firefighters.<sup>2,3,15</sup> Prolonged longitudinal follow-up is needed to identify biomarkers and define phenotypes to improve therapy for individuals with accelerated-FEV<sub>1</sub>-decline who are not responding to standard treatment. In this investigation, we found that greater concentrations of the serum Th-2 biomarkers IL-4, IL-13, and IL-5 measured soon after WTC exposure were risk factors for greater annual FEV<sub>1</sub> decline in the subgroup with post-9/11 accelerated-FEV<sub>1</sub>-decline (9/11/2001 to 9/10/2020), while greater concentration of IFN-γ, a Th-1 cytokine, was associated with a slower rate of FEV<sub>1</sub> decline.

**TABLE 3** Multivariable linear regression models examining associations between early serum biomarker concentrations and subsequent FEV1 decline (ml/year) in those with accelerated-FEV1-decline<sup>a</sup>

	Unstandardized coefficients <sup>b</sup>		Standardized coefficients <sup>b</sup>	
	$\beta$	SE	$\beta$	p value
Doubling IL-4 <sup>c</sup>	-2.88	1.38	-0.15	0.039
Doubling IL-5 <sup>c</sup>	-7.94	1.32	-0.38	<0.001
Doubling IL-13 <sup>c</sup>	-8.42	1.17	-0.45	<0.001
Doubling IFN- $\gamma$ <sup>c</sup>	13.9	2.3	0.45	<0.001
Doubling TNF- $\alpha$ <sup>c</sup>	16.7	4.1	0.26	<0.001

Abbreviation: WTC, World Trade Center.

<sup>a</sup>N = 117.

<sup>b</sup>Controlling for age, smoking status, race, WTC exposure level, height, and FEV<sub>1</sub>% predicted at time of biomarker measurement in weighted least squares regression using 1/SE of individual FEV<sub>1</sub> decline rates.

<sup>c</sup>The number of biomarker concentration doubling from the 10th to 90th percentile: 3.5 for IL-4, 2.8 for IL-5, 3.2 for IL-13, 1.8 for IFN- $\gamma$ , and 2.0 for TNF- $\alpha$ .

**TABLE 4** Multivariable linear regression models examining associations between early serum biomarker concentrations and subsequent FEV1 decline (ml/year) in those with  $\leq 64$  ml/year FEV1-decline<sup>a</sup>

	Unstandardized coefficients <sup>b</sup>		Standardized coefficients <sup>b</sup>	
	$\beta$	SE	$\beta$	p value
Doubling IL-4 <sup>c</sup>	0.04	0.28	0.006	0.877
Doubling IL-5 <sup>c</sup>	-1.34	0.50	-0.10	0.008
Doubling IL-13 <sup>c</sup>	0.17	0.43	0.014	0.690
Doubling IFN- $\gamma$ <sup>c</sup>	-0.53	0.66	-0.03	0.422
Doubling TNF- $\alpha$ <sup>c</sup>	-0.09	1.03	-0.003	0.932

Abbreviation: WTC, World Trade Center.

<sup>a</sup>N = 699.

<sup>b</sup>Controlling for age, smoking status, race, WTC exposure level, height, and FEV<sub>1</sub>% predicted at time of biomarker measurement in weighted least squares regression using 1/SE of individual FEV<sub>1</sub> decline rates.

<sup>c</sup>The number of biomarker concentration doubling from the 10th to 90th percentile: 3.5 for IL-4, 2.8 for IL-5, 3.2 for IL-13, 1.8 for IFN- $\gamma$ , and 2.0 for TNF- $\alpha$ .

**TABLE 5** Multivariable linear regression models examining associations between late serum biomarker concentrations and subsequent FEV1 decline (ml/year) in those with accelerated-FEV1-decline<sup>a</sup>

	Unstandardized coefficients <sup>b</sup>		Standardized coefficients <sup>b</sup>	
	$\beta$	SE	$\beta$	p value
Doubling IL-4 <sup>c</sup>	-4.00	1.58	-0.16	0.01
Doubling IL-5 <sup>c</sup>	0.02	1.02	0.001	0.98
Doubling IL-13 <sup>c</sup>	0.41	0.83	0.03	0.62
Doubling IFN- $\gamma$ <sup>c</sup>	-2.33	1.78	-0.08	0.191
Doubling TNF- $\alpha$ <sup>c</sup>	-2.25	2.13	-0.07	0.291

Abbreviation: WTC, World Trade Center.

<sup>a</sup>N = 274 due to missing covariates.

<sup>b</sup>Controlling for age, smoking status, race, WTC exposure level, height, and FEV<sub>1</sub>% predicted at time of biomarker measurement in weighted least squares regression using 1/SE of individual FEV<sub>1</sub> decline rates.

<sup>c</sup>The number of biomarker concentration doubling from the 10th to 90th percentile: 2.5 for IL-4, 4.5 for IL-5, 6 for IL-13, 2.5 for IFN- $\gamma$ , and 1.8 for TNF- $\alpha$ .

	Unstandardized coefficients <sup>b</sup>		Standardized coefficients <sup>b</sup>	
	$\beta$	SE	$\beta$	p value
Doubling IL-4 <sup>c</sup>	-0.27	1.08	-0.01	0.807
Doubling IL-5 <sup>c</sup>	-0.38	0.65	-0.02	0.559
Doubling IL-13 <sup>c</sup>	-0.25	0.56	-0.02	0.660
Doubling IFN- $\gamma$ <sup>c</sup>	-0.67	1.03	-0.03	0.515
Doubling TNF- $\alpha$ <sup>c</sup>	-0.61	1.77	-0.01	0.729

Abbreviation: WTC, World Trade Center.

<sup>a</sup>N = 611 due to missing covariates.

<sup>b</sup>Controlling for age, smoking status, race, WTC exposure level, height, and FEV<sub>1</sub>% predicted at time of biomarker measurement in weighted least squares regression using 1/SE of individual FEV<sub>1</sub> decline rates.

<sup>c</sup>The number of biomarker concentration doubling from the 10th to 90th percentile: 2.5 for IL-4, 4.5 for IL-5, 6 for IL-13, 2.5 for IFN- $\gamma$ , and 1.8 for TNF- $\alpha$ .

**TABLE 6** Multivariable linear regression models examining associations between late serum biomarker concentrations and subsequent FEV<sub>1</sub> decline (ml/year) in those with  $\leq 64$  ml/year FEV<sub>1</sub> decline<sup>a</sup>

Surprisingly, TNF- $\alpha$ , a marker of acute inflammation,<sup>16</sup> was also protective against FEV<sub>1</sub> decline in this subgroup. Finally, we found that IL-4 concentration measured from serum drawn 12–13 years after WTC exposure was also associated with greater FEV<sub>1</sub> decline rate in those who experienced accelerated-FEV<sub>1</sub>-decline between the later blood draw date and 9/10/2020.

Individuals' early and late serum IL-4, IL-13, IL-5, and IFN- $\gamma$  concentrations, measured during two time periods over 10 years apart, were correlated; however, early and late measurements of TNF- $\alpha$ , a cytokine marking acute inflammation,<sup>16</sup> were not significantly correlated. The relative stability of Th-1 and Th-2 biomarkers is consistent with individuals having characteristic set points for T-cell-mediated innate or adaptive inflammation that persists over longitudinal follow-up. Similarly, in WTC-exposed firefighters with non-resolving chronic rhinosinusitis, blood eosinophil levels were consistently elevated throughout longitudinal follow-up.<sup>17</sup> In our cohort and in other WTC-exposed individuals, elevated eosinophil levels were associated with FEV<sub>1</sub> decline, airflow obstruction, and wheezing.<sup>2,4</sup> The association between persistently elevated Th-2 biomarkers and greater FEV<sub>1</sub> decline in those with accelerated-FEV<sub>1</sub>-decline suggests an intrinsic predisposition to Th-2 inflammation, which, in the context of an acute irritant injury, produces non-resolving inflammation and end organ damage.<sup>18</sup>

Members of the accelerated decline subgroup likely suffer from irritant-induced occupational asthma, caused by injury to the airway epithelium from WTC dust and products of combustion.<sup>5,19</sup> The Th-2 innate response is induced by injured epithelium releasing alarmins such as IL-33 or thymic stromal lymphopoietin (TSLP), which lead to Th-2 cytokine production by Group 2 innate lymphoid cells (ILC2s) in the lung.<sup>20–22</sup> Conversely, IFN- $\gamma$  inhibits ILC2 function,<sup>23</sup> and TNF- $\alpha$  induces the RelB, an inhibitor of ILC2.<sup>24,25</sup> The associations of multiple Th-2 cytokines measured soon after WTC exposure with FEV<sub>1</sub> decline rate likely represent an acute inflammatory response to dust and products of combustion at the WTC site. The persistence of the association of IL-4 with subsequent FEV<sub>1</sub> decline, even when measured 12–13 years after WTC exposure, is consistent with IL-4

mediating chronic post-injury inflammation. Prolonged alteration of IL-4 concentration in serum could be a result of "trained immunity," a form of innate immune memory produced by covalent histone modification in lung ILC2 cells in patients with severe asthma.<sup>26</sup> Notably, ILC2 cells are steroid-resistant, which may partly explain why inhaled steroids fail to control respiratory symptoms in many WTC-exposed firefighters.<sup>11,27–29</sup> Future research should assess associations of accelerated-FEV<sub>1</sub>-decline with upstream mediators of chronic airway inflammation that modulate ILC2 activity such as TSLP and IL-33.

There are several limitations to this study. Serum biomarkers were available for only a subset of the WTC-exposed firefighter cohort, raising the potential of selection bias; however, the study populations are similar to the source population, and samples were drawn during routine monitoring exams, thereby reducing this potential bias. Atopy is likely underrepresented in this population, as asthma at time of pre-employment medical evaluation precludes work as a FDNY firefighter, but unmeasured confounding could still be present and would particularly be of concern in the late biomarker measurement analyses. By the time of the late blood draw, some WTC-exposed firefighters had received ICS/LABA therapy that could have altered serum cytokine levels. A sensitivity analysis excluding individuals who initiated ICS/LABA treatment before time of late blood draw, however, did not alter the association between IL-4 and subsequent FEV<sub>1</sub> decline. Lastly, this investigation did not examine other potential risk factors such as heterozygosity for alpha-1-antitrypsin deficiency.<sup>15</sup> Despite these limitations, the FDNY WTC Health Program is a valuable resource for understanding irritant-induced conditions such as accelerated-FEV<sub>1</sub>-decline in an occupational setting where there is otherwise little available data. Even with the unique aspects of the FDNY WTC-exposed cohort, findings in this population have been replicated in other WTC-exposed cohorts.<sup>30–34</sup>

A strength of our study was that individual rates of FEV<sub>1</sub> decline were calculated using spirometric measurements taken



after participants' blood draw dates, reducing the potential for "reverse causation." While there is no evidence that greater FEV<sub>1</sub> decline rate is associated with atopy commonly found in allergic asthma, allergen-induced adaptive immunity cannot be excluded.

In summary, our longitudinal biomarker data suggest that accelerated-FEV<sub>1</sub>-decline patients are biologically different in one or more Th-2 pathways. Accelerated-FEV<sub>1</sub>-decline patients are likely predisposed to exaggerated inflammation and/or poor counter-regulatory responses to inflammation. Targeting Th-2 inflammatory pathway(s) for intervention may yield more effective therapies. Studies with IL-4/IL-13 blocking drugs such as dupilumab are needed to assess whether targeting elevated IL-4 improves FEV<sub>1</sub> trajectories in those with accelerated-FEV<sub>1</sub>-decline.<sup>12,13</sup>

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## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

## DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

## AUTHOR CONTRIBUTIONS

*Conception or design of the work:* Michael D. Weiden, Rachel Zeig-Owens, David G. Goldfarb, and Barbara Putman. *Acquisition, analysis, and interpretation of data:* Michael D. Weiden, David G. Goldfarb, Ankura Singh, Barbara Putman, Rachel Zeig-Owens, Theresa Schwartz, C. B. H., David J. Prezant. *Drafting the work or revising it critically for important intellectual content:* Michael D. Weiden, Ankura Singh, Rachel Zeig-Owens, Hillel W. Cohen, David G. Goldfarb, David J. Prezant. *Final approval of the version to be published and agreement to be accountable for all aspects of the work:* Michael D. Weiden.

## ETHICS APPROVAL AND INFORMED CONSENT

The Albert Einstein College of Medicine Institutional Review Board approved this study (IRB #2019-10309). All participants provided written informed consent.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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