ORIGINAL RESEARCH

Visit-to-Visit FEV_1 Variation and Mortality in New York City Fire Department Rescue and Recovery Workers Exposed to World Trade Center Collapse–Related Dust

Kaat-Renée Deforce[1], Lies Lahousse[1,2], David G. Goldfarb[3,4,5], David J. Prezant[3,4,5], and Michael D. Weiden[3,6]

[1]Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium; [2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands; [3]The Bureau of Health Services, The FDNY World Trade Center Health Program, The Fire Department of New York City, Brooklyn, New York; [4]Department of Medicine, Montefiore Medical Center, Bronx, New York; [5]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York; and [6]Pulmonary, Critical Care, and Sleep Medicine Division, Department of Medicine and Department of Environmental Medicine, New York University School of Medicine, New York, New York

ORCID ID: 0000-0002-3494-4363 (L.L.).

Abstract

Rationale: Forced expiratory volume in 1 second (FEV_1) and its longitudinal change are mortality risk factors. Visit-to-visit FEV_1 variation is a risk factor for death in cystic fibrosis but has not been studied in other cohorts.

Objectives: We sought to assess whether longitudinal visit-to-visit FEV_1 variation is a mortality risk factor in rescue and recovery workers in the Fire Department of New York who were exposed to dust related to the collapse of the World Trade Center on September 11, 2001 (9/11/2001).

Methods: Linear mixed-effects regression of all post-9/11/2001 FEV_1 measurements defined the time effect on longitudinal FEV_1 decline (FEV_1 slope) and its standard error (visit-to-visit FEV_1 variation). Cox proportional hazards and logistic models adjusted for age and smoking assessed the association between FEV_1-related risk factors and mortality. Receiver operating characteristic area under the curve (AUC) assessed predictive model performance.

Results: Among 11,745 workers with three or more FEV_1 measurements, 575 (4.9%) died. When all FEV_1-related risk factors were combined, each 5-ml/yr increase in visit-to-visit FEV_1 variation increased mortality 2.1-fold (hazard ratio [HR] = 2.14; 95% confidence interval [CI] = 1.84–2.48); each 10% predicted reduction in the last longitudinal FEV_1 increased mortality 15% (HR = 1.15; 95% CI, 1.09–1.21), but each 10-ml/yr longitudinal FEV_1 decline was not associated with mortality (HR = 1.04; 95% CI, 0.99–1.10). The receiver operating characteristic AUC of a fully adjusted multivariable cumulative mortality model was 0.82 (95% CI, 0.80–0.84); for unadjusted visit-to-visit FEV_1 variation, the AUC was 0.80 (95% CI, 0.78–0.82); for last longitudinal FEV_1, the AUC was 0.61 (95% CI, 0.59–0.64); and for longitudinal FEV_1 decline, the AUC was 0.58 (95% CI, 0.56–0.61). In the ratio of participants with high exposure/total number of participants (1,988/11,745; 16.9%), among patients with high exposure, defined as arrival at the World Trade Center site before noon on 9/11/2001, the risk of high visit-to-visit FEV_1 variation (top quartile, $\geq$10.35 ml/yr) increased 25% (odds ratio = 1.25; 95% CI, 1.12–1.40).

Conclusions: Visit-to-visit FEV_1 variation is a mortality risk factor in rescue and recovery workers in the Fire Department of New York City, with greater accuracy for predicting cumulative mortality than either last longitudinal FEV_1 or longitudinal FEV_1 decline. Further investigation in other cohorts is needed to assess the generalizability of this rarely studied mortality risk factor.

Keywords: FEV_1; mortality; longitudinal monitoring; mortality prediction

(Received in original form January 22, 2025; accepted in final form April 25, 2025)

Supported by National Institute for Occupational Safety and Health grants U01 OH011682, U01 OH011480, and U01 OH011302 and contracts 200-2017-93326, 200-2017-93426, 75D301-22-R-72142, and 75D301-22-R-72244.

Author Contributions: Full access to all the data in the study and responsibility for the integrity of the data and the accuracy of the data analysis: D.J.P. and M.D.W. Study concept and design: M.D.W., L.L., and K.-R.D. Acquisition, analysis, or interpretation of data: K.-R.D., D.G.G., D.J.P., and M.D.W. Drafting of the manuscript: K.-R.D., L.L., D.J.P., and M.D.W. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: D.G.G. and M.D.W. Obtained funding: D.J.P. Administrative, technical, or material support: D.J.P. and M.D.W. Study supervision: D.J.P. and M.D.W.

Ann Am Thorac Soc Vol 22, No 9, pp 1343–1350, Sep 2025

DOI: 10.1513/AnnalsATS.202501-093OC
Internet address: www.atsjournals.org

The collapse of two 100-story buildings in the World Trade Center complex (WTC) on September 11, 2001 (9/11/2001), produced a massive dust cloud, overwhelming the lung's defenses with deposition of large particles in the lower airways (1, 2). Elevated serum inflammatory cytokine levels were associated with development of forced expiratory volume in 1 second (FEV_1) falling below the lower limit of normal (3). Dust from the WTC collapse that was added to alveolar macrophages *in vitro* induced inflammatory cytokine production like that observed in serum (4). Manifestations of airway injury related to the dust from the WTC collapse included acute FEV_1 decline (5) and incident obstructive airway disease (6), as well as bronchial wall thickening and emphysema on computed tomography (CT) scans (7). After the acute FEV_1 decline, longitudinal FEV_1 decline stabilized in most workers, but 12.7% had accelerated FEV_1 decline postexposure, defined by a loss of >64 ml/yr, and 8.2% had increased FEV_1 after the acute post-WTC decline (8). Accelerated FEV_1 decline is a manifestation of airway injury with increased incidence of asthma, chronic obstructive pulmonary disease (COPD), asthma–COPD overlap syndrome, and death (9, 10).

Rescue/recovery workers who arrived before noon on 9/11/2001 were enveloped by the collapse-related dust cloud and suffered the highest level of dust exposure, a risk factor for airway injury (6) and cardiovascular disease (11). Visit-to-visit FEV_1 variation is associated with lung transplant and death in patients with cystic fibrosis (12). The association between visit-to-visit FEV_1 variation and mortality is poorly described in other cohorts.

Notably, a single measurement of FEV_1 is a biomarker of health in both the Fire Department of New York City (FDNY) occupational cohort and the National Health and Nutrition Examination Survey (or, NHANES) III community-based cohort (13). Each liter reduction in baseline FEV_1 was associated with a 2.3-fold greater risk for all-cause mortality and a 3.1-fold increase in heart disease–related mortality (10). An FEV_1 <80% predicted with an FEV_1/forced vital capacity (FVC) ratio ≥70%, preserved ratio impaired spirometry (PRISm), is associated with increased mortality (14, 15) and progression to COPD (16). The intensive longitudinal follow-up of the closed FDNY cohort with WTC dust exposure provides a unique opportunity to explore poorly described FEV_1 related manifestations of airway injury and to assess whether visit-to-visit FEV_1 variation is a risk factor for death. The aim of the present investigation is to evaluate the validity of visit-to-visit FEV_1 variation, last longitudinal FEV_1, and longitudinal FEV_1 decline for mortality prediction in WTC dust–exposed FDNY rescue/recovery workers.

Methods

Study Population

The source population for the primary analytic cohort included 12,314 WTC dust–exposed FDNY rescue/recovery workers who were actively employed by the FDNY on 9/11/2001 and were alive on 9/12/2001. Participants who did not have three or more pulmonary function test (PFT) results between 9/12/2001 and 12/31/2023, with high-quality (Grade A or B) FEV_1 measurements, were excluded ($n = 569$), resulting in an analytic cohort of 11,745 (Figure 1). There were 575 (4.9%) deaths recorded in the analytic cohort from 9/12/2001 to 12/31/2023 (Table 1). FDNY participants provided written informed consent, and the study was approved by the Montefiore Medical Center and Albert Einstein College of Medicine Institutional Review Board (approval number 07–09–320).

Study Design

This cohort study evaluated the association between lung function, as measured by various FEV_1-related metrics, and mortality. The primary exposure metrics included visit-to-visit FEV_1 variation, longitudinal FEV_1 decline, and last longitudinal FEV_1.

PFT

Prebronchodilator (pre-BD) spirometry measured FEV_1 following a protocol described elsewhere (5). Spirometry data were included if at least two acceptable measures with an American Thoracic Society grade of A or B were available. FEV_1 percent predicted values were calculated by dividing the observed FEV_1 measurements by the expected values on the basis of sex, height, and age, using the Global Lung Function Initiative race-neutral reference equations (17). Longitudinal FEV_1 decline and visit-to-visit FEV_1 variation data were derived from 153,288 medical monitoring spirometries obtained during the period of 9/12/2001–12/31/2023, using linear mixed-effects models. Clinically indicated spirometry data were not included in the analysis.

Mortality Ascertainment

Mortality data for the FDNY cohort were ascertained through FDNY WTC records (9/12/2001 through 12/31/2023).

Other Cohort Characteristics

In the FDNY cohort, demographic and cardiometabolic data were acquired from the FDNY WTC Health Program database. Smoking history data were collected through self-administered surveys completed during periodic medical evaluations. Participants were classified as ever-smokers if they reported a history of smoking on at least one monitoring questionnaire.

Statistical Analysis

We used descriptive statistics to summarize demographic, exposure, and lung function variables. Continuous variables were reported as means and standard deviations or medians with interquartile ranges, whereas categorical variables were presented as counts and percentages.

We used a linear mixed-effects modeling approach in SAS to estimate individual-specific intercepts and slopes for FEV_1 over time. First, the dataset was prepared by calculating the time elapsed in years from the earliest recorded date for each subject. We applied PROC MIXED to model FEV_1 as a function of the time variable. The model included both fixed and random effects, with random intercepts and slopes specified for each participant to account for

Correspondence and requests for reprints should be addressed to Michael Weiden, M.D., Pulmonary, Critical Care, and Sleep Medicine Division, Department of Medicine and Department of Environmental Medicine, New York University School of Medicine, New York, NY 10016. E-mail: michael.weiden@nyulangone.org.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

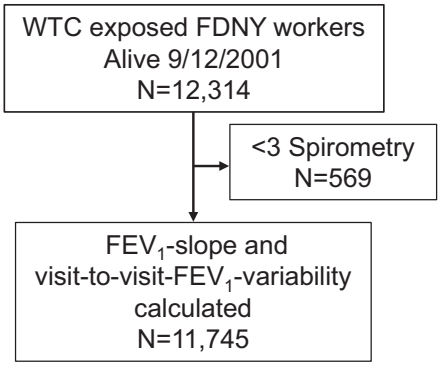

Figure 1. Study population of FDNY rescue and recovery workers. The source population consisted of 12,314 FDNY rescue/recovery workers who were employed by the FDNY on 9/11/2001, were present at the WTC site between 9/11/2001 and 7/24/2002, and were alive on 9/12/2001. A total of 569 individuals with fewer than three spirometry tests during the same period were excluded with a final study population of 11,745. FDNY = Fire Department of New York City; FEV_1 = forced expiratory volume in 1 second; WTC = World Trade Center complex.

subject-specific variation. Following the mixed-effects modeling, the fixed and random effects estimates were extracted and combined using data-processing steps. These combined estimates included subject-specific intercepts and slopes, representing the individual-level baseline FEV_1 and the rate of FEV_1 decline over time. Additionally, an overall standard error for the combined estimates was calculated as the square root of the sum of squared standard errors for the fixed and random effects. This approach provided precise estimates of individual-specific FEV_1 intercepts and slopes, enabling a detailed analysis of trends in FEV_1 trajectory over time.

We used Cox proportional hazards models to estimate the mortality hazard associated with FEV_1 metrics, adjusted for age at last PFT and smoking history. Follow-up time started at last FEV_1 measurement and ended at death or on 12/31/2023, whichever was earlier. We evaluated FEV_1-related metrics together in a single Cox model. We performed a sensitivity analysis on the participants (n = 1,641) with last longitudinal FEV_1 <80% predicted, to assess the impact of PRISm on mortality in this cohort. PRISm was defined as a last longitudinal FEV_1/FVC ratio of ≥70%.

Logistic regression models assessed the association between FEV_1-related metrics and cumulative mortality for the period of 9/12/2001 through 12/31/2023. We evaluated predictive performance using receiver operating characteristic (ROC) curves. Model calibration was analyzed by comparing observed and predicted mortality across deciles of risk. We used multivariable logistic regression, with visit-to-visit FEV_1 variation equal to or greater than the top quartile as the outcome (≥10.3 ml/yr), to assess the relationship of high FEV_1 variation with arrival time to the WTC before noon on 9/11/2001 (high exposure), smoking, and age. The multivariable logistic model also contained the first medical monitoring FEV_1/FVC ratio <70% and cardiometabolic risk factors, including systolic blood pressure, BMI, and glucose levels as covariates. Database management and statistical analyses were performed using SAS, Version 9.4 (SAS Institute Inc.); SPSS, Version 29 (IBM Corporation); and GraphPad Prism, Version 9 (GraphPad Software Inc.).

Results

Cohort Characteristics

The FDNY cohort had a mean age of 39.3 years (SD = 7.8) on 9/11/2001 and were predominantly male (96.6%) and White (87.5%); 36.4% were ever-smokers, and 16.9% had high exposure to the WTC dust, defined as arrival at the WTC site before noon on 9/11/2001. The cohort had normal lung function, 101.0 ± 14.7 FEV_1% predicted at their first post-9/11 PFT. The average rate of FEV_1 decline was −36.2 ml/yr (SD = 15.6). As expected with airway injury produced by massive dust exposure at the WTC collapse, the proportion of cohort members with pre-BD FEV_1 <80% increased from 6.6% on first longitudinal FEV_1 to 14% on last longitudinal FEV_1. Similarly, a pre-BD screening FEV_1/FVC ratio <70% increased from 2.8% on first longitudinal FEV_1/FVC ratio to 9.9% on last longitudinal FEV_1/FVC ratio. The median visit-to-visit FEV_1 variation was 8.96 ml/yr, and the top quartile of FEV_1 variation was ≥10.3 ml/yr (Table 1).

The cohort had intensive longitudinal lung function measurements with 153,288 FEV_1 measurements in the period of 9/12/2001–12/31/2023, resulting in 13.0 ± 4.1 measurements per person. Obstructive airway disease treated with inhaled corticosteroids and long-acting β-agonists for more than 2 years was common (n = 2,209; 18.8% of the cohort). Of the 2,519 cohort members referred to a single hospital pulmonary function laboratory for BD PFTs, 354 (14.1%) had a post-BD FEV_1/FVC ratio of <70. Interstitial lung diseases, including sarcoidosis and pulmonary fibrosis, were rare (0.7% and 0.6%, respectively). In this healthy worker cohort, 444 (3.8%) had fasting blood glucose ⩾120 mg/dl, and 849 (7.2%) had a systolic blood pressure ⩾140 mm Hg. Alternately 4,047 (34.5%) had a BMI ⩾30. The cohort was 59.0 ± 8.5 years old on their last PFT and suffered 575 deaths over 190,384 person-years of follow-up from their third PFT until 12/31/2023. There were 26,617 person-years of follow-up from their last PFT until death or 12/31/2023.

Mortality Hazard Associated with FEV_1-Related Risk Factors

We performed a time-to-event analysis with follow-up time starting after the last PFT, resulting in a crude mortality rate of 21.6 per 1,000 person-years. Visit-to-visit FEV_1 variation, last longitudinal FEV_1, and longitudinal FEV_1 decline were all significantly associated with mortality when added as single variables to an adjusted Cox model (Table 2). Surprisingly, when all three variables are added to the same Cox model, longitudinal FEV_1 decline per 10 ml/yr was no longer associated with mortality (hazard ratio [HR] = 1.04; 95% confidence interval [CI] = 0.99–1.10). In contrast, each 5-ml/yr increase in visit-to-visit FEV_1 variation increased mortality hazard over twofold (HR = 2.14; 95% CI, 1.84–2.48), and each 10% reduction in the last longitudinal FEV_1% predicted increased mortality hazard by 15% (HR = 1.15; 95% CI, 1.09–1.21). In the subgroup with last longitudinal FEV_1% predicted of <80%, PRISm (defined

Table 1. Cohort characteristics

Variable	Cohort Data
Demographics	
Age on 9/11/2001, mean ± SD	39.3 ± 7.8
Sex, male, *n* (%)	11,366 (96.8)
Race, White, *n* (%)	10,273 (87.5)
Smoking, ever, *n* (%)	4,280 (36.4)
Smoking on first exam	
Never	8,391 (71.4)
Former	1,772 (15.1)
Current	1,582 (13.5)
High WTC exposure, *n* (%)	1,988 (16.9)
Lung function	
Number of PFTs per person, mean ± SD	13.0 ± 4.1
Number of FEV_1 measurements	153,288
FEV_1 slope, ml/yr, mean ± SD	−36.2 ± 15.6
Visit-to-visit FEV_1 variation, ml/yr, median (IQR)	8.96 (8.23–10.35)
First FEV_1 % predicted, mean ± SD	101.0 ± 14.7
First FEV_1 <80%, *n* (%)	774 (6.6)
Last FEV_1 % predicted, mean ± SD	96.6 ± 16.4
Last FEV_1 <80% predicted, *n* (%)	1,641 (14.0)
First FEV_1/FVC, mean ± SD	83.4 ± 5.8
First FEV_1/FVC < 70%, *n* (%)	336 (2.8)
Last FEV_1/FVC, mean ± SD	77.5 ± 6.1
Last FEV_1/FVC < 70%, *n* (%)	1,162 (9.9)
Lung disease, *n* (%)	
ICS/LABA treatment ⩾2 yr	2,209 (18.8)
Post-BD FEV_1/FVC <70*	354/2,519 (14.1)
Pulmonary fibrosis†	80 (0.7)
Sarcoidosis‡	70 (0.6)
Cardiovascular risk factors at first monitoring exam	
Blood glucose, mean ± SD	93.3 ± 21.6
Blood glucose ⩾120 mg/dl, *n* (%)	444(3.8)
SBP, mean ± SD	119 ± 13.3
SBP ⩾140 mm Hg, *n* (%)	849 (7.2)
BMI, mean ± SD	29.1 ± 4.3
BMI ⩾30, *n* (%)	4,047 (34.5)
Longitudinal follow-up	
Deaths, *n* (%)	575 (4.9)
Age at last PFT, mean ± SD	59.0 ± 8.5
Person-years since third PFT	190,384
Person-years since last PFT	26,617

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β-agonist; PFT = pulmonary function test; SD = standard deviation; WTC = World Trade Center complex.
N = 11,745. Values are presented as mean ± SD or as *n* (%), unless otherwise indicated.
*Referral BD PFT in 2,519 cohort members.
†Cleven and colleagues, 2024 (34).
‡Hena and colleagues, 2018 (36).

as FEV_1/FVC ratio ⩾70%) increased the mortality hazard by 95% (HR = 1.95; 95% CI, 1.31–2.92). Similar to the whole cohort, longitudinal FEV_1 decline was not associated with mortality (HR = 1.04; 95% CI, 0.96–1.12), but each 5-ml/yr increase in visit-to-visit FEV_1 variation increased the mortality hazard by 93% (HR = 1.93; 95% CI, 1.40–2.65), and each 10% reduction in the last longitudinal FEV_1% predicted increased mortality hazard by 25% (HR = 1.25; 95% CI, 1.08–1.45).

Predictive Model Performance

Because logistic mortality models estimate probability of death at the end of follow-up, they are more useful in death prediction than time-to-event survival analysis. We performed cumulative mortality analysis with follow-up starting after the third PFT, resulting in a crude mortality rate of 3 per 1,000 person-years. The lower crude mortality rate in the cumulative mortality analyses compared with the time-to-event analysis is likely related to immortal time bias produced by the age difference between 9/11/2001 and the age at last longitudinal FEV_1 (39.3 ± 7.8 yr vs. 59.0 ± 8.5 yr). As a result, age at last-longitudinal-FEV_1 and longitudinal-FEV_1 is used in the cumulative mortality models. An additional advantage of predicting the probability of death is the ability to compare expected mortality with observed mortality to test model performance using a receiver operating characteristic area under the curve (ROC-AUC). A ROC-AUC of 1 demonstrates perfect concordance between expected and observed mortality, whereas an AUC of 0.5 indicates no predictive validity (Figure 2).

Visit-to-visit FEV_1 variation as a single variable (unadjusted risk factor) had an AUC of 0.80 (95% CI, 0.78–0.82). Compared with other unadjusted risk factors of mortality, visit-to-visit FEV_1 variation emerged as the one with the best predictive performance compared with other FEV_1-related mortality risk factors, with AUC values ranging from 0.61 to 0.53 (Figure 2). The full predictive model incorporating visit-to-visit FEV_1 variation, last longitudinal FEV_1, longitudinal FEV_1 decline, and other well-defined mortality risk factors of age and smoking history had an AUC of 0.82 (95% CI, 0.80–0.84); the predictive model without longitudinal FEV_1 decline was not significantly different from the full model, with an AUC of 0.82 (95% CI, 0.80–0.84). The multivariable predictive model missing visit-to-visit FEV_1 variation had an AUC of 0.66 (95% CI, 0.64–0.68), which was significantly lower than the AUC of visit-to-visit FEV_1 variation as an unadjusted risk factor (AUC = 0.80; 95% CI, 0.78–0.82).

We performed a calibration analysis comparing the expected mortality produced by the full model with the observed mortality separating the cohort into deciles of risk. The top 10% of risk in the full predictive model had an expected mortality of 23.6% and an observed mortality of 23.7%. For the next decile of risk, the expected mortality is 7.7% and the observed mortality is 9.6%. Conversely, the bottom 10% of risk has an expected mortality of 0.82% and an observed mortality of 0.94%. Similarly, when unadjusted visit-to-visit FEV_1 variation was used as a single variable predicting cumulative mortality, the top 10% of risk had an expected mortality of 22.5% and an observed mortality of 22.4%. The bottom 10% of risk had an expected mortality of 1.5% and an observed

Table 2. Survival hazard associated with FEV_1-related risk factors

FEV_1-Related Risk Factor	HR	95% CI		*P* Value
		Lower Limit	Upper Limit	
Risk factors in three separate Cox models*				
Visit-to-visit FEV_1 variation per 5 ml/yr	2.20	1.90	2.55	<0.001
Last longitudinal FEV_1 per 10% decline	1.17	1.11	1.22	<0.001
Longitudinal FEV_1 decline per 10 ml/yr	1.10	1.05	1.15	<0.001
Risk factors in one Cox model*				
Visit-to-visit FEV_1 variation per 5 ml/yr	2.16	1.86	2.51	<0.001
Last longitudinal FEV_1 per 10% decline	1.14	1.09	1.20	<0.001
Longitudinal FEV_1 decline per 10 ml/yr	1.04	0.99	1.10	0.128
Risk factors in those with last longitudinal FEV_1 <80% predicted†				
Visit-to-visit FEV_1 variation per 5 ml/yr	1.927	1.401	2.65	<0.001
Last longitudinal FEV_1 per 10% decline	1.253	1.083	1.45	0.002
Longitudinal FEV_1 decline per 10 ml/yr	1.037	0.961	1.119	0.352
Last longitudinal FEV_1/FVC ratio ≥70% (PRISm)	1.953	1.307	2.924	0.001

Definition of abbreviations: CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; PRISm = preserved ratio impaired spirometry.
*Cox models adjusted for age at last PFT and smoking.
†*N* = 1,641, with 146 deaths.

mortality of 0.7%. A linear regression of predicted/observed data demonstrates an R^2 of 0.99 for the full model and an R^2 of 0.98 when unadjusted visit-to-visit FEV_1 variation was used to predict cumulative mortality.

Baseline Covariates Associated with Subsequent Visit-to-Visit FEV_1 Variation

We used multivariable logistic regression to assess the association between covariates measured at the beginning of longitudinal follow-up and subsequent high visit-to-visit FEV_1 variation, defined as variation equal to or greater than the top quartile (Figure 3), with all covariates added to a single model to adjust for collinearity. The odds of high visit-to-visit FEV_1 variation increased 1.7-fold in those with an FEV_1/FVC ratio of <70%; increased 30% with increasing age per 10 years; increased 30% in former smokers and 33% in current smokers; increased 66% with increasing glucose per 10 mg/dl; increased 25% in those with high exposure to WTC dust versus intermediate and low exposure; increased 21% with increasing systolic blood pressure per 10 mm Hg; and increased 13% with increasing BMI per 5 U. This suggests that exposure to dust, smoking, and cardiometabolic risk factors are independently associated with subsequent high visit-to-visit FEV_1 variation.

Discussion

Intensive follow-up of the FDNY WTC dust–exposed cohort, with 13 longitudinal PFTs per person over 22 years and complete death data, provides an exceptional opportunity to characterize FEV_1–related mortality risk factors. Recently, Todd and colleagues (12) reported that visit-to-visit FEV_1 variation is a risk factor for death or lung transplantation in cystic fibrosis. We now report that visit-to-visit FEV_1 variation is strongly associated with mortality in this previously healthy cohort that suffered massive exposure to dust and products of combustion from the 9/11/2001 attack on the WTC. Visit-to-visit FEV_1 variation has a

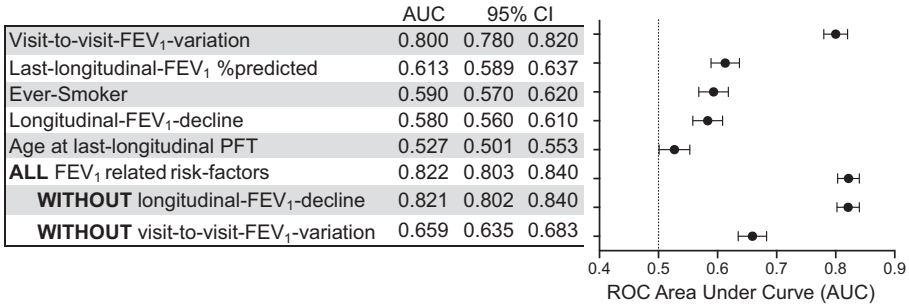

Figure 2. Logistic models assessed performance of FEV_1-related and epidemiologic covariates as risk factors for mortality. Unadjusted visit-to-visit FEV_1 variation had a higher ROC-AUC than that of all other unadjusted mortality risk factors. Shown are the ROC-AUCs for three multivariable logistic models. Model 1 included age, smoking, visit-to-visit FEV_1 variation, last longitudinal FEV_1, and longitudinal FEV_1 decline as covariates. Model 2 has longitudinal FEV_1 decline removed from Model 1. Model 3 has visit-to-visit FEV_1 variation removed from Model 1. The ROC-AUCs of Models 1 and 2 are not significantly different. Model 3 has a lower ROC-AUC than unadjusted visit-to-visit FEV_1 variation. AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ROC = receiver operating characteristic.

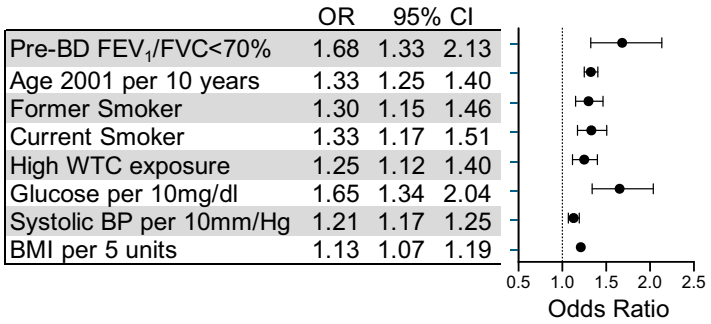

Figure 3. Association of covariates measured on first medical monitoring exam with visit-to-visit FEV_1 variation equal to or greater than the top quartile as the outcome. All covariates combined in a single logistic model to account for collinearity. The odds ratios and 95% confidence intervals are shown. BD = bronchodilator; BMI = body mass index; BP = blood pressure; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; OR = odds ratio; WTC = World Trade Center complex.

higher AUC compared with last longitudinal FEV_1 and longitudinal FEV_1 decline. Unadjusted visit-to-visit FEV_1 variation also has a higher predictive accuracy for death in this cohort than an individual's age or smoking status. Removing visit-to-visit FEV_1 variation from a multivariable mortality prediction model markedly decreases the predictive accuracy (the AUC) of mortality prediction, whereas removing longitudinal FEV_1 decline does not significantly change the predictive accuracy of the mortality model's performance. The strength of visit-to-visit FEV_1 variation as a mortality risk factor in this low mortality cohort is remarkable.

One of the characteristics of WTC dust–related airway injury is a dose–response relationship with more pathology in those who were caught in the dust cloud on the morning of 9/11/2001 (high WTC exposure) when compared with those who arrived after noon on 9/11/2001. High WTC exposure is associated with 25% increased odds of being in the top quartile of visit-to-visit FEV_1 variation, suggesting that this FEV_1-related mortality risk factor is, in part, due to intense WTC dust exposure produced by being enveloped in the dust cloud. Cigarette smoking and baseline airflow obstruction, defined by a pre-BD FEV_1/FVC ratio of $<$70%, are independently associated with increased odds of 30% and 68%, respectively, of being in the top quartile of visit-to-visit FEV_1 variability. Further research is required to better understand the pathogenesis of visit-to-visit FEV_1-variation as a manifestation of airway injury.

Results from time-to-event Cox survival models demonstrate visit-to-visit FEV_1 variation, last longitudinal FEV_1, and longitudinal FEV_1 decline are all significantly associated with mortality when added as single FEV_1-related risk factors to Cox models adjusted for age at last PFT and smoking history. Each 5-ml/yr increase in visit-to-visit variation is associated with a twofold increase in mortality. Each 10% decrease in last longitudinal FEV_1 is associated with a 15% increase in mortality, and each 10-ml/yr further decline in FEV_1 is associated with a 10% increase in mortality. Strikingly, when longitudinal FEV_1 decline is combined with last longitudinal FEV_1 and visit-to-visit FEV_1 variation, longitudinal FEV_1 decline is no longer significantly associated with mortality, suggesting that visit-to-visit FEV_1 variation and last longitudinal FEV_1 are both collinear with longitudinal FEV_1 decline and more informative than longitudinal FEV_1 decline. This finding requires independent replication in other longitudinal cohorts.

Because visit-to-visit FEV_1 variation is typically interpreted as measurement error, the present analysis used mixed-effects linear models, which account for random effects and repeated measurement correlation structure. This report used 153,288 FEV_1 measurements (13.0 ± 4.1 per person) over 22 years. Therefore, we obtained measurements approximately every 2 years in a population with a decline of -36.2 ± 15.6 ml/yr. High intervisit variation in spirometry has been reported for healthy individuals and for those with established COPD (16). The definition of "visit-to-visit FEV_1 variation" is one of two components of the FEV_1 trajectory derived from our linear mixed-effects model that yield intervisit variation when combined. A high visit-to-visit FEV_1 variation reflects fluctuations in lung function with different patterns over time. Future investigations using more advanced modeling are needed to identify which specific patterns of FEV_1 variation are associated with mortality.

Cardiovascular biomarkers predict susceptibility to lung injury in WTC dust–exposed firefighters (18). There is a complex relationship between WTC dust exposure, lung function, cardiovascular risk factors, and cardiovascular mortality (10, 11, 19). We now report that the top quartile of visit-to-visit FEV_1 variation is significantly correlated with numerous cardiometabolic risk factors, including BMI, systolic blood pressure, and blood sugar (Figure 3). Prior studies have shown that low cross-sectional FEV_1 is associated with cardiovascular mortality and morbidity in community-based cohorts, with and without diabetes, that were not exposed to WTC dust (20–22). While the mortality risk associated with visit-to-visit FEV_1 variation is poorly defined, the association of visit-to-visit systolic blood pressure variation has been reported in both community-based and hypertensive cohorts (23–27). Future research is required to define the relationship between visit-to-visit FEV_1 variation and visit-to-visit systolic blood pressure variation.

There are several reasons to conclude that visit-to-visit FEV_1 variation is a pathophysiologically relevant individual characteristic and not just measurement error. These include *1*) a twofold increase in mortality hazard for each 5-ml/yr visit-to-visit FEV_1 variation increase, *2*) the high predictive validity for mortality prediction in cumulative mortality analysis, and *3*) an analogy to visit-to-visit blood pressure variation as a mortality risk factor. Ultimately, the validity and generalizability of visit-to-visit FEV_1 variation as a mortality risk factor requires replication in multiple different cohorts. Visit-to-visit FEV_1 variation also occurs in children with well-controlled asthma (28). This FEV_1-related risk factor, however, has not been used as an outcome in intervention studies.

This study has several strengths. The FDNY WTC health program is a closed cohort with little longitudinal dropout and intensive follow-up over the past 22 years. The cohort has been characterized by over 120 peer-reviewed publications (29) covering a broad range of disease states related to obstructive airway disease caused by WTC

dust–related airway injury, including changes in FEV_1 trajectory (5, 30, 31), variable and fixed obstructive airway disease (6, 8–10), upper airway disease (32, 33), pulmonary fibrosis (34), sarcoidosis (35, 36), and cardiovascular disease risk factors (11, 18, 19) as risk factors for airway disease. We now add increased visit-to-visit FEV_1 variation and PRISm to the mortality risk factors associated with WTC-dust exposure.

There are however significant limitations to the present investigation. The FDNY cohort has unique exposure to extremely high levels of dust and products of combustion. It is a healthy worker cohort that comprises predominantly white males and has a lower mortality when compared with the general population (13). There was no attempt to present a causal analysis to better understand the associations reported in this analysis. The generalizability of the observations from this cohort requires replication in independent cohorts. The screening spirometries used in the medical monitoring program did not have a post-BD measurement reducing the specificity of the FEV_1/FVC ratio. Interstitial lung diseases, however, are rare in this cohort (Table 1). Clinically indicated chest CT in 4,277 WTC dust–exposed firefighters had a high prevalence of bronchial wall thickening, emphysema, and air trapping (7). Additionally in CT scans from 6,655 workers, only 80 patients had pulmonary fibrosis (34) and only 74 firefighters had post-9/11 biopsy-confirmed sarcoidosis after abnormal imaging (36). Of the 2,519 members of this cohort who were referred to a single hospital-based pulmonary function laboratory, only 14.1% had a post-BD FEV_1/FVC ratio of <70%. Fixed and/or variable airflow obstruction diagnosed using BD–PFT and/or a methacholine challenge test provided indication for prolonged treatment with inhaled corticosteroids and long-acting β-agonists in 18.8% of the cohort. Pseudorestrictive physiology, now called PRISm, was common soon after 9/11/2001 (6), but 8.2% of the cohort had improved FEV_1 after a steep trans-9/11 FEV_1 decline (8) with conversion of the PRISm physiology to standard airflow obstruction. An FEV_1/FVC ratio of <70% on screening spirometry increased from 2.8% on first post-9/11/2001 exam to 9.9% on last longitudinal spirometry. PRISm on last longitudinal spirometry is associated with a nearly twofold increase in mortality. Finally, respiratory diseases accounted for only 28/475 (6%) of the total deaths (10). Heart disease and cancer mortality are the predominant disease-specific mortality categories associated with lung function decline. This extensive phenotyping of the FDNY WTC–exposed cohort suggests that low FEV_1 on screening spirometries obtained in the medical monitoring program predominately represent obstructive airway disease and not interstitial lung disease.

In summary, we report a rarely studied association between visit-to-visit FEV_1 variation and mortality in a cohort that suffered airway injury after a massive dust exposure from the WTC collapse. Like systolic blood pressure variation, visit-to-visit FEV_1 variation may be a pathophysiologically important patient characteristic that increases susceptibility to death. Further investigation is required to assess whether FEV_1 variation and blood pressure variation have a common cause. If so, one could hypothesize that chronic inflammation was the common link between blood pressure variation, lung function variation, and increased susceptibility to death. Given the unique aspects of the FDNY WTC cohort, the current observations need to be replicated independently in other cohorts to test the generalizability of the association between visit-to-visit FEV_1 variation and mortality. If visit-to-visit FEV_1 variation is a risk factor for poor outcome in community cohorts and disease-specific cohorts, such as soldiers returning from Iraq and Afghanistan (37, 38), then future treatment studies could collect data on FEV_1 variation as a prespecified outcome. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Rom WN, Weiden M, Garcia R, Yie TA, Vathesatogkit P, Tse DB, *et al.* Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med* 2002;166: 797–800.

2 Fireman EM, Lerman Y, Ganor E, Greif J, Fireman-Shoresh S, Lioy PJ, *et al.* Induced sputum assessment in New York City firefighters exposed to World Trade Center dust. *Environ Health Perspect* 2004; 112:1564–1569.

3 Nolan A, Naveed B, Comfort AL, Ferrier N, Hall CB, Kwon S, *et al.* Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust. *Chest* 2012;142:412–418.

4 Weiden MD, Naveed B, Kwon S, Segal LN, Cho SJ, Tsukiji J, *et al.* Comparison of WTC dust size on macrophage inflammatory cytokine release *in vivo* and *in vitro*. *PLoS One* 2012;7:e40016.

5 Aldrich TK, Gustave J, Hall CB, Cohen HW, Webber MP, Zeig-Owens R, *et al.* Lung function in rescue workers at the World Trade Center after 7 years. *New Engl J Med* 2010;362:1263–1272.

6 Weiden MD, Ferrier N, Nolan A, Rom WN, Comfort A, Gustave J, *et al.* Obstructive airways disease with air trapping among firefighters exposed to World Trade Center dust. *Chest* 2010;137:566–574.

7 Liu C, Putman B, Singh A, Zeig-Owens R, Hall CB, Schwartz T, *et al.* Abnormalities on chest computed tomography and lung function following an intense dust exposure: a 17-year longitudinal study. *Int J Environ Res Public Health* 2019;16:1655.

8 Zeig-Owens R, Singh A, Aldrich TK, Hall CB, Schwartz T, Webber MP, *et al.* Blood leukocyte concentrations, FEV_1 decline, and airflow limitation: a 15-year longitudinal study of WTC-exposed firefighters. *Ann Am Thorac Soc* 2018;15:173–183.

9 Singh A, Liu C, Putman B, Zeig-Owens R, Hall CB, Schwartz T, *et al.* Predictors of asthma/COPD overlap in FDNY firefighters with World Trade Center dust exposure: a longitudinal study. *Chest* 2018;154: 1301–1310.

10 Goldfarb DG, Hall CB, Choi J, Zeig-Owens R, Cohen H, Cannon M, *et al.* Association of lung function decline with all-cause and cancer-cause mortality after World Trade Center dust exposure. *Ann Am Thorac Soc* 2023;20:1136–1143.

11 Cohen HW, Zeig-Owens R, Joe C, Hall CB, Webber MP, Weiden MD, *et al.* Long-term cardiovascular disease risk among firefighters after the World Trade Center disaster. *JAMA Netw Open* 2019;2:e199775.

12 Todd JV, Morgan WJ, Szczesniak RD, Ostrenga JS, O'Connell OJ, Cromwell EA, *et al.* Forced expiratory volume in 1 second variation predicts lung transplant or mortality in people with cystic fibrosis in the United States. *Ann Am Thorac Soc* 2024;21:1416–1420.

13 Cannon MF, Goldfarb DG, Zeig-Owens RA, Hall CB, Choi J, Cohen HW, *et al.* Normal lung function and mortality in World Trade Center responders and NHANES III participants. *Am J Respir Crit Care Med* 2024;209:1229–1237.

14 Wijnant SRA, De Roos E, Kavousi M, Stricker BH, Terzikhan N, Lahousse L, *et al.* Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J* 2020;55:1901217.

15 Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, *et al.*; COPDGene Investigators. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene study. *Am J Respir Crit Care Med* 2018;198:1397–1405.

16 Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111–122.
17 Bhakta NR, Bime C, Kaminsky DA, McCormack MC, Thakur N, Stanojevic S, *et al.* Race and ethnicity in pulmonary function test interpretation: an official American Thoracic Society statement. *Am J Respir Crit Care Med* 2023;207:978–995.
18 Weiden MD, Naveed B, Kwon S, Cho SJ, Comfort AL, Prezant DJ, *et al.* Cardiovascular biomarkers predict susceptibility to lung injury in World Trade Center dust-exposed firefighters. *Eur Respir J* 2013;41: 1023–1030.
19 Naveed B, Weiden MD, Kwon S, Gracely EJ, Comfort AL, Ferrier N, *et al.* Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med* 2012;185: 392–399.
20 Duong M, Islam S, Rangarajan S, Leong D, Kurmi O, Teo K, *et al.*; PURE investigators. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV_1 (PURE): an international, community-based cohort study. *Lancet Glob Health* 2019;7:e613–e623.
21 Huang N, Tang C, Li S, Ma W, Zhai X, Liu K, *et al.* Association of lung function with the risk of cardiovascular diseases and all-cause mortality in patients with diabetes: results from NHANES III 1988-1994. *Front Cardiovasc Med* 2022;9:976817.
22 Court T, Capkova N, Pająk A, Malyutina S, Tamosiunas A, Bobák M, *et al.* All-cause and cardiovascular mortality in relation to lung function in the full range of distribution across four Eastern European cohorts. *Sci Rep* 2022;12:12959.
23 Dai L, Song L, Li X, Yang Y, Zheng X, Wu Y, *et al.* Association of visit-to-visit blood pressure variation with the risk of all-cause mortality and cardiovascular events in general population. *J Clin Hypertens (Greenwich)* 2018;20:280–288.
24 Yano Y, Reis JP, Lewis CE, Sidney S, Pletcher MJ, Bibbins-Domingo K, *et al.* Association of blood pressure patterns in young adulthood with cardiovascular disease and mortality in middle age. *JAMA Cardiol* 2020;5:382–389.
25 de Havenon A, Delic A, Yaghi S, Wong KH, Majersik JJ, Stulberg E, *et al.* Midlife blood pressure variation and risk of all-cause mortality and cardiovascular events during extended follow-up. *Am J Hypertens* 2021;34:1269–1275.
26 Liu M, Chen X, Zhang S, Lin J, Wang L, Liao X, *et al.* Assessment of visit-to-visit blood pressure variability in adults with optimal blood pressure: a new player in the evaluation of residual cardiovascular risk? *J Am Heart Assoc* 2022;11:e022716.
27 Gupta A, Whiteley WN, Godec T, Rostamian S, Ariti C, Mackay J, *et al.*; ASCOT-10 Investigators. Legacy benefits of blood pressure treatment on cardiovascular events are primarily mediated by improved blood pressure variation: the ASCOT trial. *Eur Heart J* 2024;45:1159–1169.
28 Filipow N, Turner S, Petsky HL, Chang AB, Frischer T, Szefler S, *et al.* Variation in forced expiratory volume in 1 s in children with symptomatically well-controlled asthma. *Thorax* 202414;79:1145–1150.
29 Cleven KL, Rosenzvit C, Nolan A, Zeig-Owens R, Kwon S, Weiden MD, *et al.* Twenty-year reflection on the impact of World Trade Center exposure on pulmonary outcomes in Fire Department of the City of New York (FDNY) rescue and recovery workers. *Lung* 2021;199:569–578.
30 Banauch GI, Brantly M, Izbicki G, Hall C, Shanske A, Chavko R, *et al.* Accelerated spirometric decline in New York City firefighters with α_1-antitrypsin deficiency. *Chest* 2010;138:1116–1124.
31 Banauch GI, Hall C, Weiden M, Cohen HW, Aldrich TK, Christodoulou V, *et al.* Pulmonary function after exposure to the World Trade Center collapse in the New York City Fire Department. *Am J Respir Crit Care Med* 2006;174:312–319.
32 Kwon S, Putman B, Weakley J, Hall CB, Zeig-Owens R, Schwartz T, *et al.* Blood eosinophils and World Trade Center exposure predict surgery in chronic rhinosinusitis. A 13.5-year longitudinal study. *Ann Am Thorac Soc* 2016;13:1253–1261.
33 Putman B, Zeig-Owens R, Singh A, Hall CB, Schwartz T, Webber MP, *et al.* Risk factors for post-9/11 chronic rhinosinusitis in Fire Department of the City of New York workers. *Occup Environ Med* 2018;75:884–889.
34 Cleven KL, Zeig-Owens R, Mueller AK, Vaeth B, Hall CB, Choi J, *et al.* Interstitial lung disease and progressive pulmonary fibrosis: a World Trade Center cohort 20-year longitudinal study. *Lung* 2024;202: 257–267.
35 Izbicki G, Chavko R, Banauch GI, Weiden MD, Berger KI, Aldrich TK, *et al.* World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest* 2007; 131:1414–1423.
36 Hena KM, Yip J, Jaber N, Goldfarb D, Fullam K, Cleven K, *et al.*; FDNY Sarcoidosis Clinical Research Group. Clinical course of sarcoidosis in World Trade Center-exposed firefighters. *Chest* 2018;153:114–123.
37 King MS, Eisenberg R, Newman JH, Tolle JJ, Harrell FE Jr, Nian H, *et al.* Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med* 2011;365:222–230.
38 Saers J, Andersson L, Janson C, Sundh J. Respiratory symptoms, lung function, and fraction of exhaled nitric oxide before and after assignment in a desert environment-a cohort study. *Respir Med* 2021; 189:106643.