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RESEARCH

World Trade Center-Associated Respiratory Effects

Worsened longitudinal visit-to-visit-FEV_1-variation and mortality in WTC exposed FDNY workers: a 23-year landmark analysis

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Abstract

Introduction The World Trade Center (WTC) collapse produced an inhalation disaster. Body Mass index (BMI) is a risk-factor for WTC-related lung injury. Visit-to-visit-forced-expiratory-volume-at-one-second-variation (FEV_1-variation) is a mortality risk-factor in WTC-exposed Fire Department of New York (FDNY) workers. We hypothesized: worsened-FEV_1-variation with greater time post-9/11/2001 will be a mortality risk-factor associated with cross sectional BMI and longitudinal weight-variation.

Methods Annual WTC-monitoring measured lung function and weight. FEV_1-variation was quantified as individual-specific coefficient of variation (CV) and FEV_1-slope-SEM, among 9410 WTC-exposed workers who were alive at the 1/1/2019 Landmark and had ≥ 3 FEV_1-measurments early (9/12/2001 through 12/31/2009) and later (1/1/2010 through 12/31/2018). Weight-variation quantified as individual-specific weight-CV 9/12/2001 through 12/31/2018. Worsened-FEV_1-variation was defined as later/early FEV_1-variation ratio > 1. The outcome was all-cause mortality 1/1/2019 through 12/31/23. Cox regression assessed the 5-year mortality risk of Worsened-FEV_1-variation. Logistic regression assessed covariates associated with worsened-FEV_1-variation.

Results Fourty-seven percent (4459/9410) of WTC-exposed FDNY-workers experienced worsened-FEV_1-variation. an exposure that was associated with 40% greater 5-year mortality risk (HR = 1.40; 95% CI 1.07, 1.89) in a Cox model adjusted for landmark, age, FEV_1, BMI, weight-variation, and smoking. Similarly, Worsened-FEV_1-variation defined by FEV_1-slope-SEM was a mortality risk factor (HR = 1.39; 95% CI 1.05, 1.83). Each 5 kg/m^2 increase in BMI and each 5%CV increased weight-variation was associated with 18% and 17% greater odds of worsened-FEV_1-variation (OR = 1.18; 95% CI 1.06, 1.27 and OR = 1.17; 95% CI 1.07, 1.27 respectively).

Interpretation Worsened-FEV_1-variation with greater time post-9/11/2001 is a mortality risk-factor associated with obesity and weight-variation. The association of Worsened-FEV_1-variation and weight-variation may reflect concurrent metabolic and pulmonary instability that increase vulnerability to death.

Keywords Mortality · FEV1 variation trajectory · Body Mass Index Trajectory · World Trade Center Exposure

Introduction

Terrorists attacked the World Trade Center (WTC) on September 11, 2001 (9/11) producing a particulate matter (WTC-PM) inhalation disaster. Fire Department of the City of New York (FDNY) rescue/recovery workers experienced markedly different exposure levels based on arrival time. Workers who arrived before noon on 9/11 (High-WTC-exposure) were enveloped in a dense dust cloud with extraordinarily high $PM_{2.5}$ concentrations in the mg/m^3 range [1]. The intensity of this exposure overwhelmed normal upper-airway filtration mechanisms, allowing highly inflammatory super-coarse particles to penetrate the lower airways [2]. The dust was highly alkaline (pH 9.0–11.0) causing acute chemical injury to aerodigestive mucosa [3]. Those arriving after day 3 were intermittently but chronically exposed to resuspended WTC-PM. The combination of early arrival and prolonged exposure during rescue/

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recovery put workers at highest risk for non-resolving upper airway inflammation [4]. Initially adequate respiratory protection was rarely worn enhancing WTC-PM dust exposure exacerbating respiratory symptoms [5].

The FDNY WTC-medical monitoring program performed physical exams approximately every 12–18 months. Exams included spirometry, height, and weight. Because of ongoing medical treatment for WTC-related illnesses, there has been minimal longitudinal drop out [6–8]. Exposure and outcome metrics recorded by the FDNY WTC Health Program provide a rich longitudinal dataset ideal for investigating the pathophysiology of WTC-related lung injury. High-WTC-exposure increased the risk of lower respiratory tract injury [9] with incident asthma, COPD, and asthma-COPD overlap [10, 11] and cardiovascular diseases [12, 13]. Cardiometabolic risk factors, particularly body mass index (BMI), are well defined risk-factors for WTC related lung injury defined as incident FEV_1 below the lower limit of normal [14].

As the cohort has aged, mortality risk factors have become a research focus. We have observed that both lower cross-sectional FEV_1 and steeper FEV_1-decline are mortality risk factors in this cohort [15, 16]. Recently, we reported visit-to-visit-FEV_1 variation (FEV_1-variation) is another FEV_1 related mortality risk-factor [17]. We further observed that high WTC exposure and components of metabolic syndrome, including high baseline BMI, were associated with increased odds of high (top quartile) FEV_1-variation. In the current investigation, we test whether FEV_1 variation changes with increasing time since WTC exposure. We hypothesize that worsened-FEV_1-variation over time since 9/11 will be associated with BMI and weight variation and will represent an additional mortality risk factor.

Methods

Study population

The source population consisted of 11,474 WTC exposed FDNY rescue/recovery workers [17]. WTC exposed workers received medical monitoring examinations every 12–18 months. Worker signed informed consent; Montefiore Medical Center/Albert Einstein College of Medicine IRB approval (#07-09-320).

Data collection

Data was maintained in the FDNY WTC Health Program Data Center. WTC-monitoring exams include FEV_1, weight and height measurements. Mortality data for the FDNY cohort were ascertained through FDNY WTC records (9/12/2001-12/31/2023).

Spirometry

Screening spirometry without bronchodilator was performed according to contemporaneous ATS criteria: only high-quality, grade A/B measurements, were included (7). The cohort completed 113,628 WTC-monitoring exams 9/12/2001-12/31/2018 (12.1 ± 2.2 exams per person) with 111,231 (97.9%) being grade A/B. FEV_1 percent predicted values used race neutral GLI Global reference equations [18].

Study design

We conducted a Landmark mortality analysis of WTC-exposed FDNY rescue/recovery workers who were alive 1/1/2019 (Fig. 1), providing common start and equal follow-up times to reduce immortal time bias [19]. To assess FEV_1-variability trajectory, exposure was divided into two prespecified 9-year intervals; early (9/12/2001–12/31/2009) and later (1/12010–12/31/2018). Because estimation of

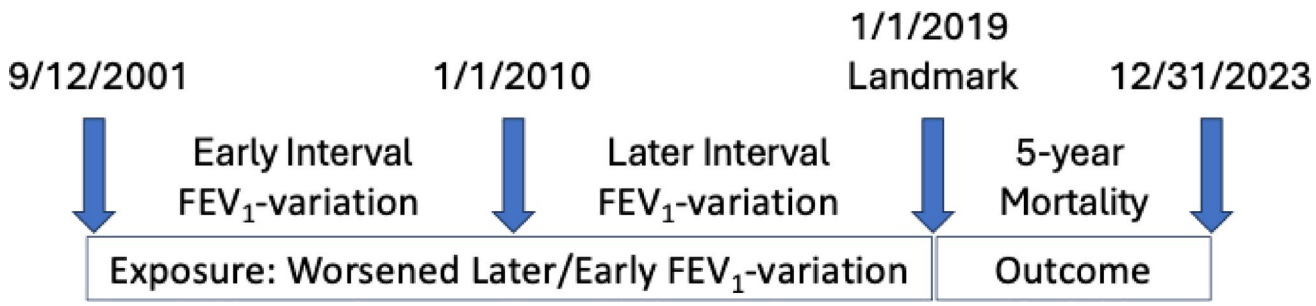


Fig. 1 Landmark analysis study design. A 1/1/2019 landmark analysis of $N=9410$ workers who were alive 12/31/2018 provided common start and equal follow-up times to reduce immortal time bias. Early/later FEV_1-variation change was the exposure and 5-year post-1/1/2019 mortality the outcome. Early-Interval FEV_1-variation was derived from $N=47,410$ FEV_1 measurements (5.0 ± 1.4 per person). Later-Interval FEV_1-variation was derived from $N=63,784$ FEV_1 measurements (6.4 ± 1.7 per person)

within-person variation by linear regression requires more than three measurements, the analytic cohort of $N=9410$ needed ≥3 FEV_1 measurements both early and later. The primary exposure was greater FEV_1-variation between early and later 9-year intervals, the outcome was 5-year all-cause mortality 1/1/2019-12/31/2023 (Fig. 1). Secondary exposures were landmark-BMI and longitudinal weight-variation (2001–2018). Covariates were landmark-FEV_1. Prespecified confounders were smoking (ever/never) and landmark-age. The study followed STROBE guidelines.

Statistical analysis

Visit-to-visit variation has been defined by both coefficient of variation (CV) and standard error of the slope (slope-SEM) derived from linear regression [17, 20–22]. We calculated both FEV_1-CV and FEV_1-slope-SEM. Doubling of FEV_1-variation was used because log_2 transformation improved FEV_1variation kurtosis (61.2 ± 0.05 to 5.8 ± 0.05 for FEV_1-slope-SEM and 11.5 ± 0.05 to 1.4 ± 0.05 for FEV_1-CV). Categorical Worsened-FEV_1-variation was defined as ratio > 1 of later-FEV_1-variation/early-FEV_1-variation. Continuous FEV_1-variation change was defined as log_2 of the later-FEV_1-variation/early-FEV_1-variation ratio. Logistic regression assessed worker characteristics associated with worsened-FEV_1-variation. The association between worsened-FEV_1-variation and all-cause mortality was modeled using Cox regression with equal person-time at risk for all study participants. There were no interactions between worsened-FEV_1-variation and age ($p=0.48$) or weight variation ($p=0.98$) but there was interaction between continuous worsening-FEV_1-variation and ICS/LABA treatment ($p=0.029$).

Five sensitivity analyses evaluated the robustness of the association between worsened-FEV_1-variation and mortality: (1) Modeling FEV_1-variation as defined by either FEV_1-CV or FEV_1-slope-SEM. (2) Assessing worsened-FEV_1-variation in subgroup ($N=6434$) without known pulmonary abnormalities. (3) Assessing worsened-FEV_1-variation in subgroup ($N=2935$) with need for ICS/LABA treatment, having accelerated-FEV_1-decline or landmark FEV_1<80%. (4) Assessing worsening-FEV_1-variation as a continuous exposure. (5) Evaluating exposure dose response by categorizing FEV_1-variation into tertiles of FEV_1-CV or FEV_1 Slope-SEM. Data analysis was performed using SPSS.v30 and Prism.v10.

Results

Cohort characteristics and FEV_1-variation

The analytic cohort $N=9410$ suffered 207 deaths over 46,487 person years yielding 4.45 deaths/1000 person years (Fig. 1). There were 111,231 FEV_1 measurements (11.8 ± 2.2 measurements per person) 9/12/2001–12/31/2018.

Mean FEV_1-variation was 5.87 ± 3.80 CV% in the early interval and 5.51 ± 3.22 CV% in the later interval, corresponding to a mean decrease in variation (improvement) between the two intervals of 0.36 ± 4.4 CV% (paired t test). Between 10th -90th percentile, early-to-later changes in FEV_1-variation ranged from a 4.85 CV% decrease (improvement) to a 3.96 CV% increase (worsened), an 8.8 CV% interdecile range. FEV_1-CV was not associated with FEV_1 measurements per person (β = 0.009 ± 0.016% per FEV_1 measurement $p=0.55$).

We categorized individuals according to change in FEV_1-variation: 4459 (47.4%) demonstrated worsened-variation and 4951 (52.6%) improvement (Table 1). Workers with worsened-FEV_1-variation experienced 122 post-landmark deaths (2.73%, 5.5/1000 person-years) while workers with improved-FEV_1-variation experienced 85 post-landmark deaths (1.73%, 3.5/1000 person-years) (Table 1).

Despite having lower (better) FEV_1-variation in the early interval, the worsened-FEV_1-variation stratum had delayed FEV_1-variation increase. Early, FEV_1-variation was 3.39 CV% lower in the worsened-FEV_1-variation stratum than in the improved-FEV_1-variation stratum (95% CI = − 3.53 to − 3.26). The worsened stratum suffered a delayed increase from early to the later (Δ = 2.73 ± 3.07 CV% 95% CI = 2.64–2.82) (Table 1). Later, FEV_1-variation was 2.49 CV% higher in the worsened-FEV_1-variation stratum than in the improved-FEV_1-variation stratum (95% CI = 2.36–2.61).

First-post-9/11 (baseline) characteristics associated with worsened-FEV_1-variation.

We next assessed the association of worsened-FEV_1-variation with first post-9/11 risk factors. Compared with workers whose FEV_1-variation improved, workers suffering worsened-FEV_1-variation were slightly older (0.40 years 95% CI = 0.10–0.71) and had higher baseline-BMI and Landmark-BMI (0.56 kg/m^2, 95% CI = 0.41–0.72; and 0.78 kg/m^2 95% CI = 0.58–0.98; respectively). Compared with workers with BMI < 30, workers with BMI ≥ 30, BMI ≤ 35 had 21% greater odds of worsened-FEV_1-variation (95% CI = 1.11–1.33) and workers with BMI > 35 had 42% higher odds of worsened-FEV_1-variation (95% CI = 1.20–1.68). Workers with worsened-FEV_1-variation had lower baseline FEV_1 (− 3.5% predicted lower; 95% CI = − 4.0 to − 2.9), but

Table 1 Characteristics of workers in Worsened- and Improve-FEV1-variation strata

Variable	FEV_1-variation Strata		Unadjusted difference or (95% CI)*
	Worsened ¶ *N*=4459 (47.4%)	Improved *N*=4951 (52.6%)	
Longitudinal FEV_1-variation			
Early FEV_1-variation ml/year ‖	4.08±2.05	7.48±4.27	− 3.39 (− 3.53, − 3.26)
Later FEV_1-variation ml/year††	6.82±3.71	4.33±2.08	2.49 (2.36, 2.61)
Later minus early FEV_1-variation	2.73±3.07	− 3.15±3.50	5.88 (5.75, 6.01)
Demographics			
Age on 9/11/2001	39.0±7.6	38.6±7.6	0.40 (0.095, 0.71)
Ever smoker**	1572 (35.2%)	1682 (33.9%)	1.2 (− 0.6, 3.2)
First post 9/11 -BMI §<30	2840 (63.7%)	3401 (68.7%)	Reference
First post 9/11 -BMI≥30, <35	1293 (29%)	1275 (25.8%)	1.21 (1.11,1.33)
First post 9/11 BMI≥35	324 (7.3%)	274 (5.5%)	1.42 (1.20,1.68)
First post 9/11 BMI kg/m^2	29.3±4.0	28.7±3.7	0.56 (0.41, 0.72)
BMI kg/m^2 Closest to 1/1/2019	30.9±5.1	30.1±4.6	0.78 (0.58, 0.98)
Weight-slope lbs/year†	0.61±1.4	0.52±1.3	0.083 (0.028,0.14)
Weight-variation CV%‡	4.55±2.56	4.35±2.32	0.20 (0.10, 0.30)
FEV_1 related risk-factors			
First post 9/11 FEV_1%predicted	99.8±13.1	103.3±15.6	− 3.5(− 4.0,− 2.9)
FEV_1-slope ml/year 2001–2018	− 37.0±22.0	− 32.9±23.5	− 4.1 (− 5.1, − 3.2)
First post 9/11 FEV_1/FVC<70%	105 (2.3%)	116 (2.3%)	0.00 (− 0.01,0.01)
FEV_1% Closest to 1/1/2019	95.7±15.4	99.7±14.8	− 4.0 (− 4.6, − 3.4)
Mortality			
Alive 12/31/2018	4337 (97.3%)	4866 (98.3%)	Reference
Died 1/1/2019-12/31/2023	122 (2.73%)	85 (1.73%)	OR=1.61 (1.22, 2.13)
Mortality Rate/1000-person years*	5.5	3.5	RR=1.61 (1.22, 2.13)

¶Worsened-FEV_1-variation as a categorical variable was defined as ratio>1 of later-FEV_1-variation/early-FEV_1-variation. ‖ Forced expiratory volumes at one second variation in the interval 9/12/2001-12/31/2009 †† Forced expiratory volumes at one second variation of the interval 1/1/2010-12/31/2018 *Unadjusted odds or rate ratio>1 represents greater risk with Worsened-FEV_1-variation. †Weight change (mean time effect on weight) and ‡Weight-variation (standard error of the mean time effect). ** Reported current or former smoking on any of the 113,606 medical monitoring exams 9/12/2001–1/1/2019. § Body Mass Index kg/m^2

the prevalence of baseline FEV_1/FVC ratio<70% was not different.

Worsened-FEV_1-variation predictors: multivariable models.

Adjusted logistic regression showed similar results as crude odds ratios (Fig. 2). Each 10-year increase in age was associated with 8% higher odds of worsened-FEV_1-variation (95% CI=1.02–1.14) and each 10% predicted lower baseline FEV_1 was associated with 18% higher odds of worsened-FEV_1-variation (95% CI=1.14–1.21). Each 5 kg/m^2 increase in baseline BMI is associated with18% higher odds of worsened-FEV_1-variation (95% CI=1.12–1.24).

We next evaluated if longitudinal risk factors were associated with worsened-FEV_1-variation. The interdecile range for FEV_1-slope was from −66.3 to −8.2 ml/year; weight-variation ranged 2.12–7.49 CV% and weight-change ranged from 0.92 lbs./year weight loss to 2.30 lbs./year weight gain. Compared to improved-FEV_1-variation, worsened-FEV_1-variation had greater weight-variation (Δ=0.20 CV%; 95% CI=0.10–0.30) and more weight gain (Δ=0.083 lbs/year; 95% CI=0.028–0.14) (Table 1). Each 5 CV% increase in weight-variation was associated with 17% higher odds of worsened-FEV_1-variation (95% CI=1.07–1.27) but weight gain (Fig. 2 bottom rows) was not significantly associated with the odds of worsened-FEV_1-variation (OR=1.03; 95% CI=0.99–1.06). In linear regression, each 5% increase in weight-CV was associated with a 0.47±0.93%, $p<0.001$ increase of longitudinal FEV_1-CV change .

FEV_1-variation trajectory and mortality hazard.

Like the unadjusted rate ratio (RR=1.61; 95% CI=1.22–2.13 Table 1), a crude Cox model demonstrated 60% higher mortality hazard associated with Worsened-FEV_1-variation (95% CI=1.21–2.11 Fig. 3A), Worsened-FEV_1-CV increased 5-year mortality hazard 40% (95% CI=1.07–1.89) and Worsened-FEV_1-slope-SEM increased 5-year mortality hazard 39% (95% CI=1.05–1.83 Fig. 3A bottom row) in separate fully adjusted cox models.

Findings were consistent across all sensitivity analyses Fig. 3B and C. To test if FEV_1-variation is a mortality risk factor in workers without lung function abnormalities we developed a restricted subgroup (*N*=6434 Fig. 3B) that excluded workers treated for Asthma/COPD with ICS/

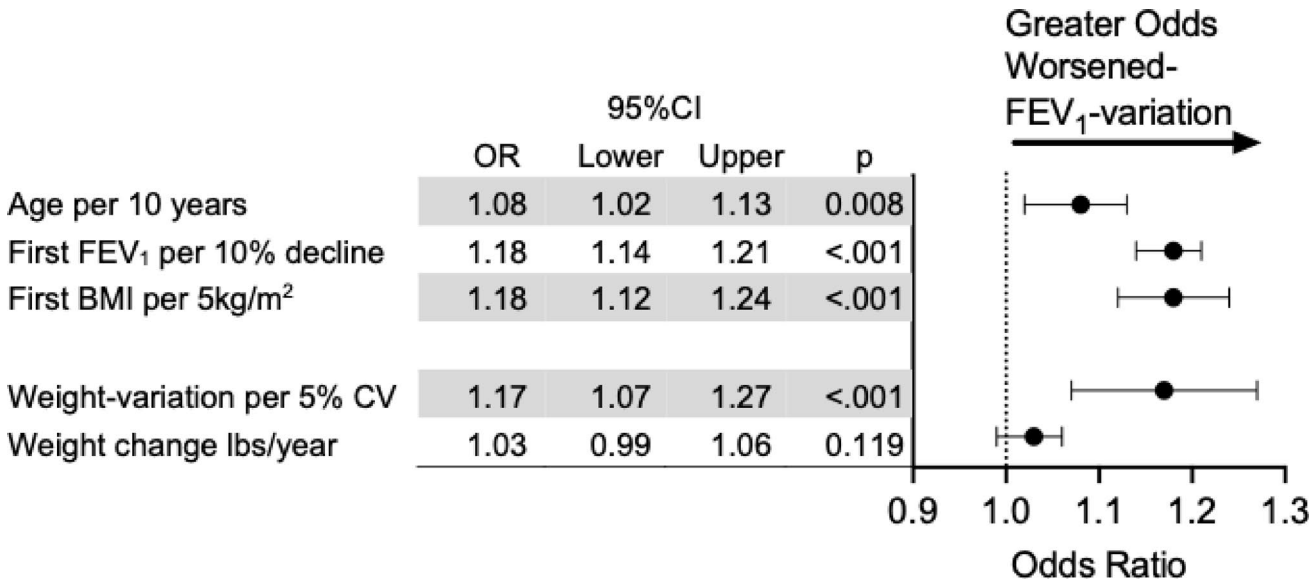


Fig. 2 Two multivariable logistic regressions with worsened-FEV_1-variation as the outcome. Upper three rows, cross-sectional variables. Older age at study entry, lower first-post-9/11-FEV_1 and greater first-post-9/11-BMI are associated with increased odds of worsened-FEV_1-variation (OR 1.08 per 10 years; 95% CI 1.02–1.14, OR 1.18 per 10% predicted decline, 95% CI 1.14–1.21, OR 1.18 per 5 kg/m^2; 95% CI 1.12–1.24, respectively). Lower two rows show an independent model with longitudinal variables. Visit-to-visit weight-variation is associated with increased odds of worsened-FEV_1-variation but weight change is not associated with worsened-FEV_1-variation (OR = 1.17 per 5 CV%; 95% CI = 1.07–1.27 and OR1.03 lbs/year; 95% CI 0.99–1.06, respectively)

LABA for 2 or more years (N = 1854), workers with accelerated-FEV_1-decline (N = 1164) and workers with landmark FVC < 80% (N = 1406). In this restricted subgroup, FEV_1-variation as a continuous variable is a mortality risk factor (HR = 1.29 per CV doubling; 95% CI = 1.07–1.55). Surprisingly FEV_1-variation was not a mortality risk factor (HR = 0.97 95% CI = 0.82–1.16) in the subgroup (N = 2935 Fig. 3C) enriched for lung function abnormalities.

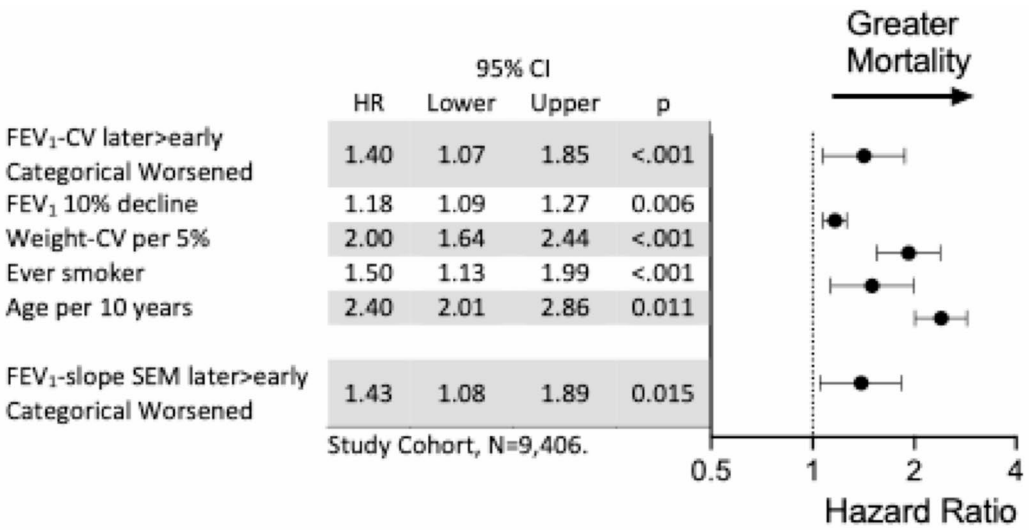
We observed a trend toward interaction between worsened FEV1-variation and early ICS/LABA treatment (p = 0.098), and a significant interaction when worsening-FEV1-variation was modeled continuously (p = 0.029), suggesting effect modification of the association between improved-FEV_1-variation and mortality by ICS/LABA treatment. To determine whether effect modification was a direct ICS/LABA treatment effect, we performed multivariable logistic regression and found no association between early ICS/LABA treatment and improved-FEV_1-variation (OR = 0.91, 95% CI 0.80–1.04; p = 0.165) after adjustment for age, smoking status, BMI, first post-9/11-FEV_1, and early FEV_1-slope suggesting ICS/LABA does not appear to directly improve the variation phenotype.

To better characterize the dose–response relationship between change in FEV_1 variation and mortality, we categorized change in both FEV_1-CV and FEV_1 slope-SEM into tertiles representing worsened, stable, and improved variation. Mean (SD) %CV visit-to-visit-FEV_1-variation increased 3.68 ± 3.23% in the worsened stratum, decreased 0.20 ± 0.73% in the stable stratum, and decreased 4.55 ± 3.74% in the improved stratum. Compared with stable FEV_1-CV (Fig. 4A), worsened FEV_1-CV was associated with a 49% increased mortality hazard (HR = 1.49, 95% CI 1.06–2.09; p = 0.021), whereas improved FEV_1-CV was not associated with mortality (HR = 1.14, 95% CI 0.79–1.65; p = 0.472). Similarly, when visit-to-visit-FEV_1-variation was defined by SEM-slope, variation increased 17.7 ± 24.8 mL/year in the worsened stratum, declined 6.4 ± 4.4 mL/year in the stable stratum, and declined 37.7 ± 30.9 mL/year in the improved stratum. Compared with stable FEV_1 slope-SEM (Fig. 4B), worsened FEV_1 slope-SEM was associated with a 50% increased mortality hazard (HR = 1.50, 95% CI 1.08–2.09; p = 0.016), whereas improved FEV_1 slope-SEM was not associated with mortality (HR = 1.03, 95% CI 0.72–1.47; p = 0.869).

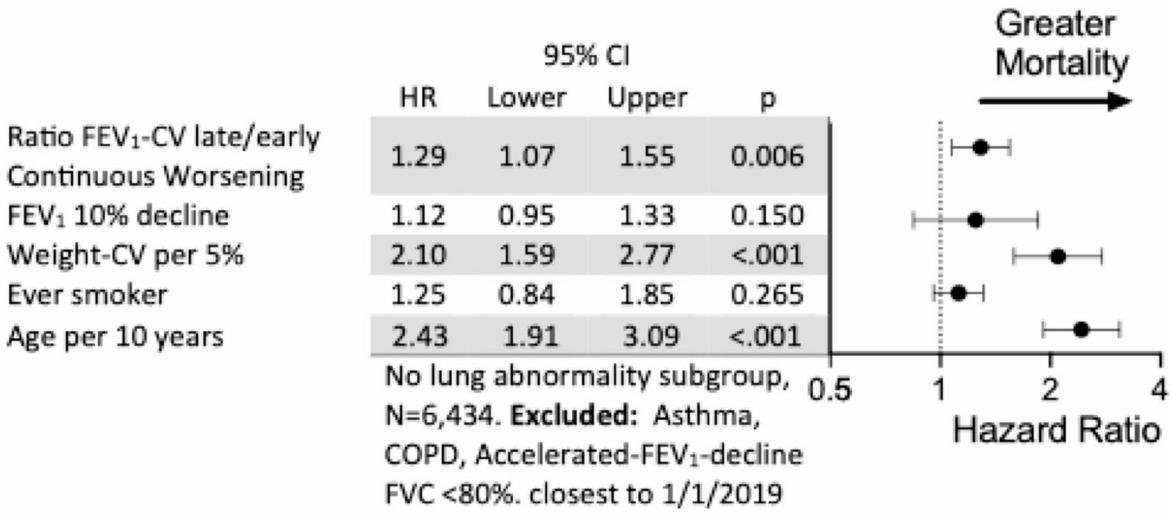
Discussion

The trajectory of visit-to-visit FEV_1-variation (FEV_1-variation) over time following WTC exposure was heterogeneous. Approximately half of WTC-exposed FDNY workers experienced worsened-FEV_1-variation, defined by increased variation from the pre-January 1, 2010 to post-January 1, 2010 exposure windows. Pulmonary function instability emerging nine years after WTC exposure was associated with increased mortality risk and co-occurred

A.


95% CI
HR Lower Upper p
FEV1-CV later>early Categorical Worsened 1.40 1.07 1.85 <.001
FEV1 10% decline 1.18 1.09 1.27 0.006
Weight-CV per 5% 2.00 1.64 2.44 <.001
Ever smoker 1.50 1.13 1.99 <.001
Age per 10 years 2.40 2.01 2.86 0.011
FEV1-slope SEM later>early Categorical Worsened 1.43 1.08 1.89 0.015
Study Cohort, N=9,406.
Greater Mortality
0.5 1 2 4
Hazard Ratio

B.


95% CI
HR Lower Upper p
Ratio FEV1-CV late/early Continuous Worsening 1.29 1.07 1.55 0.006
FEV1 10% decline 1.12 0.95 1.33 0.150
Weight-CV per 5% 2.10 1.59 2.77 <.001
Ever smoker 1.25 0.84 1.85 0.265
Age per 10 years 2.43 1.91 3.09 <.001
No lung abnormality subgroup, N=6,434. Excluded: Asthma, COPD, Accelerated-FEV1-decline FVC <80%. closest to 1/1/2019
Greater Mortality
0.5 1 2 4
Hazard Ratio

C.

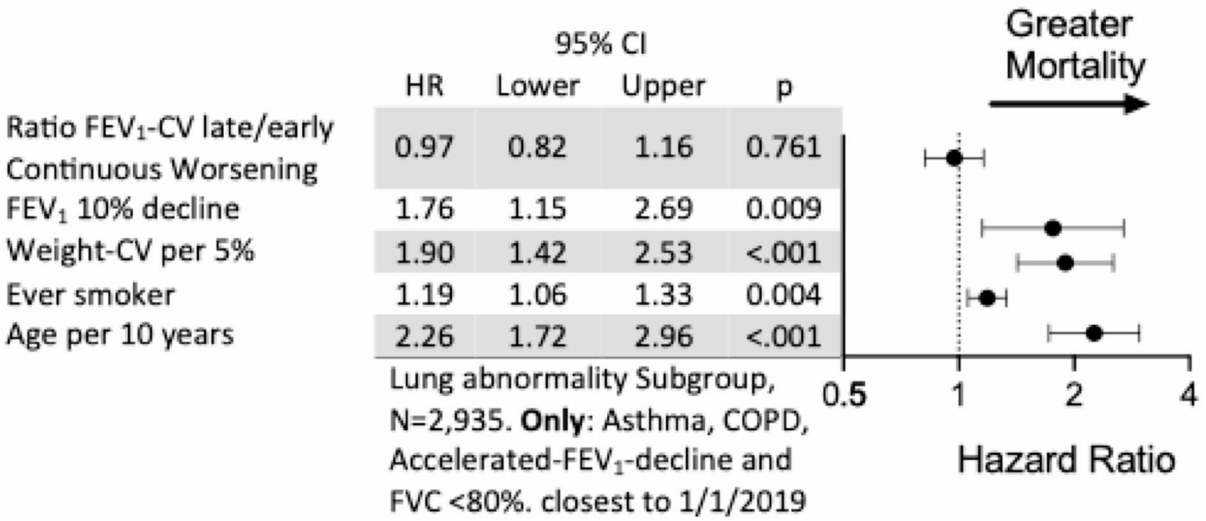

95% CI
HR Lower Upper p
Ratio FEV1-CV late/early Continuous Worsening 0.97 0.82 1.16 0.761
FEV1 10% decline 1.76 1.15 2.69 0.009
Weight-CV per 5% 1.90 1.42 2.53 <.001
Ever smoker 1.19 1.06 1.33 0.004
Age per 10 years 2.26 1.72 2.96 <.001
Lung abnormality Subgroup, N=2,935. Only: Asthma, COPD, Accelerated-FEV1-decline and FVC <80%. closest to 1/1/2019
Greater Mortality
0.5 1 2 4
Hazard Ratio

Fig. 3 Mortality hazard of longitudinal change in FEV_1-visit-to-visit variation. Panel **A** Top row, the categorical variable Worsened-FEV_1-CV as time post 9/11 increases is a mortality risk-factor (HR = 1.40; 95% CI 1.07–1.89). Bottom row, Worsened-FEV_1-slope-SEM is also a mortality risk factor (HR = 1.39; 95% CI 1.05–1.83) when substituted for Worsened-FEV_1-CV in an independent cox model. Both cox models adjusted for cross-sectional FEV_1 per 10% predicted decrement closest to but before 1/1/2019, longitudinal weight variation, smoking, and age. Panel **B** The continuous variable Worsening-FEV_1-CV (log_2 ratio late/early FEV_1-variation) is a mortality risk-factor (HR = 1.29; 95% CI 1.07–1.55 per doubling of early/late ratio) in a restricted subgroup (N = 6434) without lung function abnormalities. This subgroup excluded participants with asthma and/or COPD, accelerated-FEV_1-decline, vital capacity < 80% predicted closest to but preceding the 1/1/2019 landmark. Panel **C** Worsening-FEV_1-CV is not mortality risk-factor (HR = 0.97; 95% CI 0.82–1.16) in a restricted subgroup (N = 2935) enriched of lung function abnormities. The subgroup only included participants with asthma or COPD or accelerated-FEV_1-decline or vital capacity < 80% predicted closest to but preceding the 1/1/2019 landmark

with baseline obesity, greater visit-to-visit weight-variation (weight-variation), and steeper FEV_1 decline. Despite their collinearity, worsened-FEV_1-variation, weight-variation, and landmark adiposity remained independent predictors of mortality. The heterogeneity of the trajectory of FEV_1-variation parallels the heterogeneity of trajectory of respiratory symptoms after initiation of ICS/LABA treatment for asthma and or COPD [23, 24]. Multi-system instability, reflected by increased FEV_1-variation, adiposity, and weight-variation, may reduce physiologic reserve, and increase vulnerability to adverse health outcomes, including higher all-cause mortality. Further research is needed to determine whether instability in other treatable metabolic syndrome trait(s) are also associated with worsened-FEV_1-variation.

The association between FEV_1-variation and mortality is robust. In prior work we measured FEV_1 variation using a model-based estimate of FEV_1-slope standard error of the mean (FEV_1-slope-SEM) [17], whereas this study used coefficient of variation, a common measure of visit-to-visit fluctuation in cardio-metabolic risk factors [20, 21, 22], as the primary exposure and FEV_1-slope-SEM in sensitivity analysis. Each definition of visit-to-visit variation has advantages and disadvantages. FEV_1-CV does not use the number of FEV_1 measurements in its derivation but does not separate variation due to individuals' average FEV_1-slope from visit-to visit-variation. FEV_1-slope-SEM explicitly separates variation due to longitudinal decline in FEV_1 from visit-to-visit variation around the average but uses the number of FEV_1 measurements per person in its derivation so can be biased by differences in the number of longitudinal FEV_1 measurements per person. The association of worsened-FEV_1-variation with mortality is replicated using both FEV_1-CV and FEV_1-slope-SEM definitions of FEV_1-variation. In a sensitivity analysis excluding workers with asthma and or COPD [23, 24], accelerated-FEV_1-decline [10, 16] and low vital capacity (FVC < 80% predicted), we observed worsened-FEV_1-variation remained significantly associated with mortality.

In a second sensitivity analysis of workers enriched for pulmonary abnormalities, worsened-FEV_1-variation was not significantly associated with mortality. We observed the association between worsened FEV_1 variation and mortality was absent among ICS/LABA treated workers but remained significant in ICS/LABA untreated workers, demonstrating effect modification. However, ICS/LABA therapy was not associated with improvement in FEV_1 variation in multivariable logistic regression using improved FEV_1-variation as the outcome. These findings do not support a simple mechanism in which ICS/LABA reduces mortality through improvement in FEV_1 variation. Absence, in this cohort, of an association between worsened-FEV_1-variation and mortality in asthma and/or COPD patients requiring prolonged ICS/LABA treatment argues against these diseases being the predominant explanation for the association between worsened-FEV_1-variation and mortality. Further research is needed to determine whether the observed effect modification reflects a direct treatment effect or residual confounding by indication, whereby ICS/LABA treatment identifies a subgroup with underlying immunologic or clinical characteristics associated with both treatment initiation and reduced mortality risk.

We also investigated the dose response to change in FEV_1-variation dividing the cohort into worsened, stable, and improved strata. Compared to stable-FEV_1-variation over time, worsened-FEV_1-variation has significantly greater mortality in both FEV_1-slope-SEM and FEV_1-CV definitions of FEV_1-variation. There is, however, no difference in mortality between stable and improved-FEV_1-variation stratum demonstrating the most severely impacted 33% is driving the mortality risk. Although continuous exposures often provide greater statistical efficiency, this was not observed in our analyses. For both the CV and slope-SEM definitions, continuous worsening in FEV_1 variation showed lower precision and weaker mortality discrimination than the dichotomous definition. These findings suggest that the relationship between worsening-FEV_1-variation and mortality may not be linear across the full distribution of FEV1-variation change. This pattern is consistent with a threshold effect and may explain why the dichotomous exposure demonstrated greater precision than the continuous exposure.

Worsened-FEV_1-variation could reflect progressive airway instability driven by recurrent systemic inflammation associated with metabolic syndrome [25, 26]. To test this possibility, we assessed the association of worsened-FEV_1-variation with both early obesity and with longitudinal weight-variation [22]. Both baseline obesity and greater

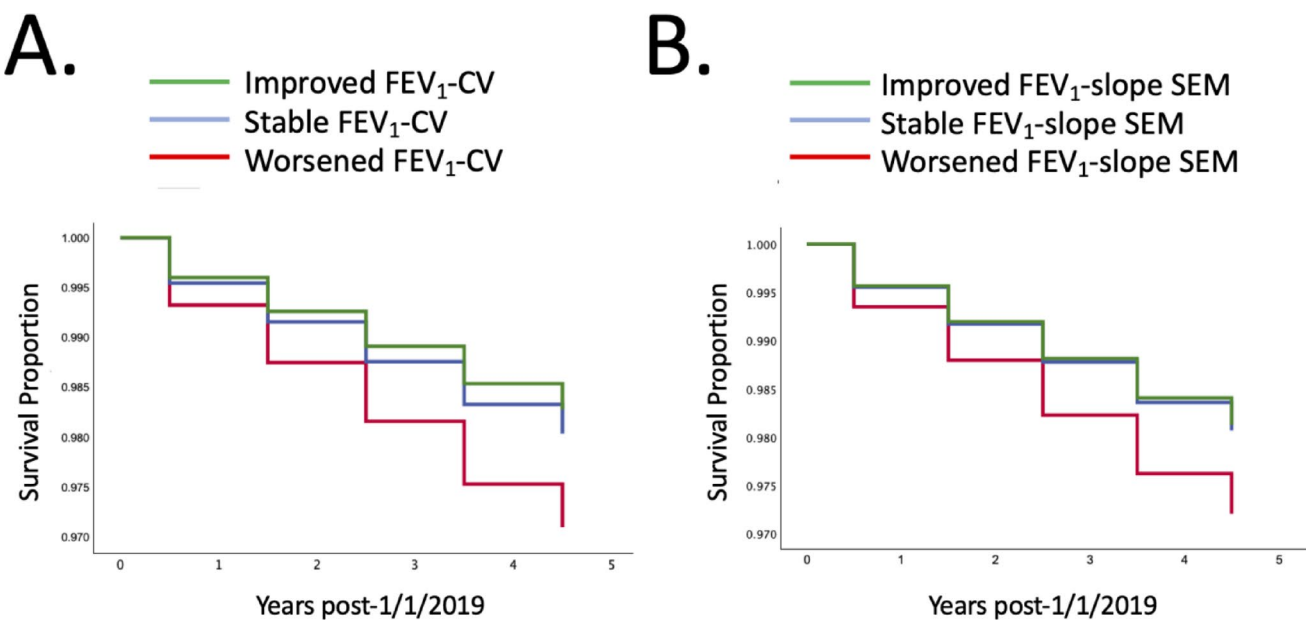


Fig. 4 Mortality hazard of longitudinal change in categorical tertials (1) Improved (Green). (2) Stable (Blue) and (3) Worsened FEV_1-visit-to-visit variation (Red). Panel **A** Compared to stable-CV, worsened-CV had a 49% increased mortality (HR = 1.49, 95% CI = 1.06–2.09 $p = 0.021$) but improved FEV_1-CV was not significantly different from stable-FEV_1-CV (HR = 1.14, 95% CI = 0.79–1.65 $p = 0.472$) Panel **B** Compared to stable FEV_1-slope SEM worsened FEV_1-slope-SEM has a 50% increased mortality (HR = 1.50 95% CI = 1.08–2.09 $p = 0.016$) but improved FEV_1-slope-SEM was not significantly different from stable-FEV_1-slope-SEM (HR = 1.03, 95% CI = 0.72–1.47, $p = 0.869$)

longitudinal weight-variation were associated with greater odds of worsened-FEV_1-variation. Despite being correlated, worsened-FEV_1-variation and longitudinal weight-variation do not interact and remain significant mortality risk-factors when combined in a fully adjusted cox mortality model. Pulmonary and metabolic instability each carry prognostic information beyond their shared correlation. The associations between worsened-FEV_1-variation, greater adiposity, and increased 5-year all-cause mortality suggests that rising FEV_1-variation reflects underlying multisystem pathophysiologic processes that increase susceptibility to death. Further research is needed to test if additional components of metabolic syndrome are risk-factors for worsened-FEV_1-variation.

This analysis has limitations. Requiring three spirometries in two 9-year exposure windows likely introduced survivor bias but this is a healthy worker cohort with low mortality from 9/12/2001 to the landmark date [15, 16]. Unmeasured confounders associated with both worsened-FEV_1-variation and mortality may bias mortality models. The categorical exposure worsened-FEV_1-variation is necessarily arbitrary, but the continuous exposure of later FEV_1-variation is also a mortality risk suggesting little information is lost by stratification. Finally, given the unique nature of WTC-exposure in this healthy worker cohort, these observations require replication in independent occupational, community and disease specific cohorts.

In conclusion, FEV_1-variation is an understudied mortality risk-factor reflecting biologically important end-organ instability analogous to blood-pressure and/or weight-variation [20–22]. We interpret FEV_1 variation not as measurement noise but as a physiologic signal reflecting instability of pulmonary function, analogous to variability in blood pressure or body weight. Measures of longitudinal risk-factor instability contribute prognostic information beyond what is contained in cross-sectional and risk factor-slope measurements. An integrated systems approach that explicitly models risk-factor variability as an exposure may improve risk stratification in longitudinal cohorts. Regular assessment of FEV_1-variability may identify workers at increased risk, allowing early interventions to limit disease progression and improve health outcomes. Further research with analytic approaches capable of incorporating time-dependent covariates like BMI is needed [27]. Replication of this analysis in other cohorts is required to better understand longitudinal change in FEV_1-variation as a mortality risk-factor [28–31].

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Data availability The data that support the findings of this study may be available upon request to , David J. Prezant.

Declarations

Competing interests The authors declare no competing interests.

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