A. OVERALL COVER PAGE

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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Specific Aim 1. To assess the impact of ICS/LABA treatment on FEV1 trajectory by estimating FEV1 slope before and after treatment, using treated patients as their own controls.

Specific Aim 2. To identify rescue/recovery worker characteristics that predicts favorable response to ICS/LABA treatment in the full cohort, in order to detect untreated individuals who are most likely to benefit from the treatment.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

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Abstract of the final report of 1U01OH011682-01A1 NIOSH/CDC Treatment Response of WTC Related Airway Injury

Rescue/recovery work at the World Trade Center (WTC) disaster site caused a decline in lung function in Fire Department of the City of New York (FDNY) firefighters. Over 15 years of post-exposure follow-up, 1 in 8 WTC- exposed firefighters experienced accelerated FEV1 decline, a FEV1 loss greater than 64 ml/year. Accelerated FEV1 decline is associated with chronic obstructive pulmonary disease (COPD) and asthma. Despite the high burden of respiratory diseases there are no evidence-based indications for inhaled corticosteroid (ICS) combined with long- acting beta-agonist (LABA) treatment in patients whose only defining characteristic is accelerated FEV1 decline. Only 35% of WTC-exposed FDNY firefighters with accelerated FEV1 decline have been treated with ICS/LABA. If the rapid rate of FEV1 loss in the accelerated FEV1 decline population is not reduced, patients with accelerated FEV1 decline will likely develop COPD, the fourth leading cause of death in the United States. Determining if ICS/LABA treatment is effective in blunting FEV1 decline in these patients would have important implications not only for WTC-exposed cohorts, but also for other workplace respiratory disease surveillance. In preliminary analyses, we found that ICS/ LABA use is associated with worse lung function and reduced quality of life. This observation is consistent with selection by indication bias, whereby sicker individuals are the ones who are treated. To mitigate the effects of this bias, we used treated patients as their own controls, examining FEV1 trajectory prior to and after initiation of ICS/LABA therapy. After ICS/LABA initiation, FEV1 trajectory improved by 9.9±1.1 ml/year (mean±SEM). This grant will explore heterogeneity in ICS/LABA response. The current multi- center collaboration aims to estimate how many in the untreated accelerated decline group have a pretreatment phenotype predictive of significant ICS/LABA benefit. This proposal tests the overall hypothesis that ICS/LABA treatment improves FEV1 trajectory in accelerated FEV1 decline patients, and that specific patient characteristics, including elevated blood eosinophils, will be associated with a favorable response to ICS/LABA treatment. Specific Aim 1 demonstrated ICS/LABA-treatment did not improve FEV1 slope patients as their own controls, Specific Aim 2 found Th2 cytokines and IgA measured soon after WTC exposure predicted poor outcomes. Further accelerated FEV1 decline is a significant risk factor for all cause and cancer caused mortality. Since FEV1 is not a modifiable risk factor for death, we will focus on the effect of poorly controlled CVD risk factors on survival in the accelerated-FEV1-decline subgroup to set the stage for future efforts to improve CVD risk factor control at a stage were lung function remains normal. Our long-range goal is to identify cohort members at greatest risk of death because of lung function decline, so that focused case management can effectively treat hypertension, hyperglycemia, and dyslipidemia thereby improving survival

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Association of Lung Function Decline with All-cause and Cancer-cause Mortality after World Trade Center Dust Exposure

Rationale: In numerous cohorts, lung function decline is associated with all-cause and cardiovascular-cause mortality but the association between forced expiratory volume in one second (FEV1) decline and cancer-cause mortality, particularly after occupational/environmental exposure(s), is unclear. Exposure to dust/smoke from the World Trade Center (WTC) disaster caused inflammation and lung injury in Fire Department of the City of New York (FDNY) rescue/recovery workers. In addition, prior research found that over 10% of the cohort experienced greater than twice the age-related decline in FEV1 (≥64 mL/year). Objective: To evaluate the association of longitudinal lung function with all-cause and cancer- cause mortality after exposure to the WTC disaster.

Methods: We conducted a prospective cohort study using longitudinal pre-bronchodilator FEV1 data for 12,264 WTC-exposed FDNY firefighters and emergency medical service (EMS) providers. All-cause and cancer-cause mortality were ascertained using National Death Index data from 9/12/2001-12/31/2021. Joint longitudinal survival models evaluated the association of baseline FEV1 and change in FEV1 from baseline with all-cause and cancer-cause mortality adjusted for age, race/ethnicity, height, smoking, work assignment (firefighter vs. EMS providers) and WTC exposure.

Results: By 12/31/2021, 607/12,264 (4.9%) of the cohort had died (crude rate=259.5/100,000 person-years) and 190/12,264 (1.5%) had died from cancer (crude rate=81.2/100,000 person- years). Baseline FEV1 was ≥80% predicted in 10,970/12,264 (89.4%); final FEV1 was ≥80% in 9,996 (81.5%). Lower FEV1 at baseline was associated with greater risk for all-cause mortality (hazard ratio [HR] per liter=2.32; 95% CI=1.98-2.72) and cancer-cause mortality (HR per liter=1.99; 95% CI=1.49-2.66). Longitudinally, each 100 mL/year decline in FEV_1 was associated with an 11% increase in all-cause mortality (HR=1.11; 95% CI=1.06-1.15) and a 7% increase in cancer-cause mortality (HR=1.07; 95% CI=1.00-1.15). Compared with FEV_1 decline <64 mL/year, those with FEV_1 decline ≥64 mL/year had higher all-cause (HR=2.91; 95% CI=2.37-3.56) and cancer-cause mortality (HR=2.68; 95% CI=1.90-3.79).

Conclusions: Baseline FEV_1 and longitudinal FEV_1 decline are associated with increased risk of all-cause and cancer-cause mortality in a previously healthy occupational cohort, the majority of whom had normal lung function, after intense exposure to dust/smoke. Further investigation is needed to define pathways by which lung function impacts mortality after an irritant exposure.

World Trade Center (WTC) exposure was followed by lung injury with an immediate decline in forced expiratory volume in one second (FEV_1) among rescue/recovery workers.[1] Lung function stabilized for most but some exposed workers continued to decline ≥64 mL/year (accelerated- FEV_1-decline) or double the expected age-related decline of 32 mL/year.[2] Post-exposure accelerated-FEV_1-decline is associated with chronic inflammation and, in other studies, increased the hazard of incident chronic obstructive pulmonary disease (COPD) and asthma.[3] Cancer incidence is elevated in WTC-exposed cohorts but cancer-cause mortality is reduced when compared with the general population,[4,5] possibly related to aggressive case ascertainment, close case management during treatment and the healthy worker effect. The association of baseline lung function and change in lung function over time with all-cause and cause-specific mortality in WTC cohorts has not been defined.

Increased all-cause mortality among those with impaired lung function and accelerated lung function decline has been found in the general population and other occupational cohorts.[6-12] Sircar and colleagues found a dose-response trend when evaluating the association between FEV_1 decline and mortality among coal miners using selected cut-points of <30 mL/y, 30-90 mL/y, and >90 mL/y. Marott *et al.* observed individuals who developed COPD later in adulthood had a greater risk of mortality when compared with those who never developed COPD or those who developed COPD in early adulthood.[8] In other studies, FEV_1 decline was associated with lung cancer mortality but the association between lung function decline and mortality from other cancers is unclear.[7,14]

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The Fire Department of the City of New York (FDNY) WTC Health Program has collected extensive longitudinal data over the 2 decades following the terrorist attack and building collapse on 9/11/2001 that have been an invaluable resource for studying latent health effects of exposure to WTC dust and smoke such as pulmonary and cardiovascular diseases and cancer.[15,16] Few studies, if any, have explored the association between lung function and mortality in a cohort with normal baseline lung function and none have examined this association in a WTC-exposed cohort. The primary objective of this study was to evaluate the association between lung function at baseline and changes over time using longitudinal measurements, with all-cause and cancer-cause mortality as outcomes in an occupational cohort with normal baseline lung function and WTC exposure – an exposure with a well- established association to lung injury.[17] Importantly, the extensive longitudinal data available on this cohort were needed to investigate whether either baseline FEV_1, or changes in FEV_1 over time, or both are independently associated with all-cause and cause-specific mortality.

Methods

Study population

The source population included firefighter and emergency medical service (EMS) providers who were actively employed by the FDNY as of 9/11/2001 and responded to the WTC site between 9/11/2001 and 7/24/2002. Ethno-racial groups other than white, Black, and Hispanic were excluded from analyses due to small numbers (n=77 participants). Participants without pulmonary function testing (PFT) were excluded (n=38). All participants provided informed written consent. The final study population included 12,264 participants (supplemental Figure 1). The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Approved this study

Pulmonary Function Testing (PFT): Spirometry

Participants had longitudinal medical monitoring including pre-bronchodilator spirometry to assess lung function. The FDNY protocol is described elsewhere;[1,18] briefly, calibration techniques were consistent throughout follow-up[19] and only high-quality grades of 'A' and 'B' were included in the current evaluation. FEV_1 was used for all analyses due to its reproducibility and since it is most commonly used in longitudinal analyses.[20] We included only the later of two exams separated by <9 months to reduce the potentially exaggerated influence on FEV_1 decline of exams measured close together. PFTs that met the above criteria and were conducted between 9/11/2001 and 12/31/2021 (end of study), were included in the study. Percent predicted of normative values for FEV_1 was calculated based on race-, sex-, and age-based prediction equations from the National Health and Nutrition Examination Survey (NHANES III).[21]

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Mortality Ascertainment

Dates and causes of death were ascertained via linkages to the National Death Index (NDI) through 12/31/2021. Causes of death from International Classification of Diseases (ICD)- -10 were classified in conformity with the National Institute of Occupational Safety and Health (NIOSH) major death categories.[22,23] Outcomes were all-cause mortality, and mortality from cancer ("cancer-cause mortality", NIOSH categories 2-10). Additionally, deaths from diseases of the heart (NIOSH category 16) and from respiratory system diseases (NIOSH category 18) were analyzed.

Other cohort characteristics

Demographic data including age as of 9/11/2001, sex, height, and race/ethnicity were acquired from the FDNY employee database. Smoking behaviors were obtained via self-administered surveys conducted at periodic medical evaluations.

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Those who consistently reported never- smoking were classified accordingly. Since few participants continued to smoke after WTC exposure, current and former smokers were classified as “ever smokers” in all analyses. Initial time of arrival at the WTC disaster site is a measure of exposure intensity.[24]

Statistical Methods

Cohort characteristics were evaluated as counts/proportions and means/standard deviations, as appropriate. For all analyses, baseline lung function was defined as the initial PFT measurement after 9/11/2001. Joint longitudinal survival modelling was employed to assess the association between baseline FEV_1 and rate of change of FEV_1 with mortality.[25-30] The longitudinal and time-to-event sub-models were linked using a random-effects shared-parameter models framework assuming that the risk of event at a given time depends on the longitudinal response predicted at that time. For longitudinal FEV_1 measurements and survival time, we used a linear mixed-effects model with a random intercept and a random slope (over time) and a piecewise exponential proportional hazards model with the longitudinal process of FEV_1, respectively, sharing the same random effects. Time zero was at a participant’s baseline PFT. In addition, we decomposed the longitudinal FEV_1 response as baseline FEV_1 and change in FEV_1 over time and assessed their associations with survival outcomes. Model equations can be found in the supplemental section. Joint modeling allows us to evaluate the time-varying covariates on the risk of death while accounting for individual heterogeneity in both longitudinal and survival sub- models and provides efficient estimates with reduced bias.[25-31]

In the primary analysis, the survival outcome was all-cause mortality. Piecewise exponential proportional hazards models were fit using 7 distinct intervals such that the number of deaths were partitioned equally for each period. Follow-up began at the time of participants’ baseline PFT and ended at the earliest of death or the end of the follow-up period for the study (i.e., 12/31/2021). Except for the last exam, in the longitudinal sub-model person- time accrual for each repeated measure was computed as the difference (in years) between successive PFTs. For the final exam, person-time was calculated as the difference between the final PFT in the study period and the end of follow-up (i.e., death or 12/31/2021). The primary analysis controlled for age, race/ethnicity, smoking, height, work assignment (EMS/firefighter) as of 9/11/2001, and WTC arrival time. Adjusted cumulative mortality plots were created using results from the joint longitudinal survival model. Seven curves were plotted for FEV_1 decliners in the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles.

In secondary analyses, the associations between baseline FEV_1 and FEV_1 trajectories with cancer-, heart disease-, and respiratory-causes of death were estimated. Two sensitivity analyses were conducted: 1) removing PFT measurements within three years of the end of the follow-up for an individual to eliminate the potential bias incurred from reverse-causality (i.e., removing measurements that possibly were after the onset of impaired lung function caused by incident cancer or other serious disease); 2) requiring at least three PFT measurements to assess the extent to which selection bias affected results in the full models.

In an additional analysis, rates of change in FEV_1 were estimated for each participant using linear regression. While for the primary analysis all PFT measurements were included, for this additional analysis only participants with at least three FEV_1 measurements were included to improve precision of estimates of rates of change and to be consistent with previous WTC research evaluating pulmonary function decline.[2,3] Rates of decline were then stratified by participants that had accelerated lung function decline, defined as ≥64 mL/year, double the age-related decline observed in our prior WTC-related research.[2,3] Piecewise exponential survival models controlling for age on 9/11race/ethnicity, sex, smoking, and WTC arrival time were used to estimate mortality hazard ratios (HR) of participants with ≥64 mL/year decline compared to the rest of the cohort.

Results

Cohort characteristics

The study population included 12,264 WTC-exposed firefighters and EMS providers who were actively employed on 9/11/2001. Cohort characteristics are presented in Table 1. There were more firefighters (n=10,301) than EMS providers (n=1,963). The mean age of the cohort was 39.7 years (SD=7.8) on 9/11/2001. Most participants were never smokers (63.8%).

By 12/31/2021, 607/12,264 (4.9%) of the cohort had died with a crude death rate 259.5/100,000 person-years and 190/12,264 (1.5%) died of cancer with a crude death rate of 81.2/100,000 person-years. Crude mortality over the follow-up period was lower in firefighters than in EMS providers (4.5% vs 7.4%). Of 607 total deaths included in the analyses, 190/607 (31.3%) were cancer related. There were 131 (21.6%) heart disease-, and 30 (4.9%) respiratory- causes of death.

Most of the cohort had normal lung function on their initial PFT (Table 2), with FEV_1 percent predicted ≥80% in 10,970/12,264 (89.4%) and FEV_1/FVC ≥70% in 11,751 (97.6%). The median FEV_1 rate of change was 34.7 mL/year loss (IQR=22.1-49.5 mL/year loss). At the time of the participants' last PFT, the proportion of the cohort with FEV_1 percent predicted ≥80% and FEV_1/FVC ≥70% had substantially decreased (Table 2). On average 19.1 (SD=2.6) years elapsed from participants' first PFT to the end of follow-up. The median (IQR) of years elapsed from last PFT to end of follow-up was 1.3 (0.6-3.0) and 1.9 (0.8-4.1) for non-deceased and deceased participants, respectively.

Joint Longitudinal Survival Models

Lung Function and all-cause mortality. Participants contributed 233,931 person-years of follow-up. Baseline lung function was associated with a 2.3-fold increase in all-cause mortality per 1-liter lower FEV_1 (Figure 1A). A 100 mL/year longitudinal decline in lung function from baseline was independently associated with 11% increased mortality (Figure 1B). In the longitudinal sub-model, the 50^{th} percentile of FEV_1 slope was a 35 mL/y decline, the 5^{th} percentile of FEV_1 slope was a 1 mL/y decline and the 95^{th} percentile of FEV_1 slope was 84 mL/y decline (Figure 2). Cumulative all-cause mortality increased with greater rates of decline in longitudinal FEV_1 across the range.

Lung Function and cause-specific mortality. As with the findings for all-cause mortality, baseline FEV_1 was associated with a 1.99-fold increased hazard for cancer-cause mortality per 1-liter lower FEV_1 (Figure 1A). Similarly, each 100 mL/year decline in longitudinal FEV_1 was associated with a 7% increase in cancer-cause mortality (Figure 1B). Each 1-liter lower for baseline FEV_1 was associated with a 3.1- and 5.7-fold increase in heart disease- and respiratory- disease mortality, respectively. Every 100 mL/year longitudinal decline in lung function was associated with 10% increased mortality for heart-disease and 26% increased mortality for respiratory-disease (Figure 1B).

Sensitivity analyses evaluating removing PFT measurements within three years of the end of the follow-up period and requiring at least three PFT measurements yielded similar results to the main models (supplemental table E1).

Mortality by accelerated lung function decline. We observed 1,244 participants (10.1%) who declined by at least 64 mL/year (accelerated FEV_1-decline). The crude all-cause cumulative mortality for those with FEV_1 decline <64 mL/year was 3.2%, and 11.3% for those with accelerated-FEV_1-decline. Multivariable analyses adjusted for age on 9/11, race/ethnicity, sex, smoking (ever vs. never), and WTC initial arrival time demonstrated that compared with expected-FEV_1-decline, accelerated-FEV_1-decline was associated with a 2.9-fold increase in all- cause mortality (Figure 4). Accelerated-FEV_1-decline was also associated with a 2.7-fold increase in cancer-cause, a 2.6-fold increase in heart disease-cause, and 4.7-fold increase in respiratory-cause mortality. Small numbers of deaths over the first 20-years post exposure limited the power to observe statistical significance of the association for many specific cancer types.

Discussion

Longitudinal data over twenty years provide a unique resource for assessing the association of lung function with all-cause and cause specific mortality. Similar to longitudinal studies without WTC-exposure and using different modeling

techniques,[6,8] this prospective cohort study of 12,264 WTC-exposed FDNY responders found that greater FEV_1 decline is associated with increased all-cause, heart disease-cause and respiratory disease-cause mortality. This investigation also revealed a significant association of FEV_1 decline and cancer-cause mortality, findings that are even more important given this cohort's normal baseline lung function and low-mortality rates.[32] It is plausible that prior studies analyzing pulmonary function and mortality, longitudinally, were unable to observe associations with long latency outcomes like cancer-cause mortality due to relatively few years of follow-up. The joint longitudinal survival model used in the current study enabled us to evaluate the independent contributions of first post-WTC-exposure baseline FEV_1 and FEV_1 decline with mortality. Interestingly, baseline FEV_1 was strongly associated with mortality even though only 10.5% of the cohort had relatively abnormal lung function (a baseline post-WTC <80% predicted). Further analyses are needed to assess if pre-WTC exposure FEV_1 is also associated with mortality.

Longitudinal lung function is well-characterized in this cohort with an average of 11 FEV_1 measurements. We observed a 2-fold greater risk of death from all causes per 1-liter lower FEV_1 at baseline and an 11% elevated hazard per 100 mL/year decline in FEV_1, after controlling for age, race/ethnicity, height, smoking, arrival time at the WTC site, and work assignment. We have previously shown that accelerated-FEV_1-decline (i.e., FEV_1 loss of more than 64 mL/year) is associated with incident respiratory diseases such as COPD, asthma and asthma/COPD overlap syndrome.[2,3] The current study demonstrates that accelerated-FEV_1-decline is associated with a greater than 2.5-fold increased risk for cancer-, heart disease- and respiratory-cause mortality; a magnitude of risk similar to that seen in the primary analysis. These findings demonstrate that both baseline FEV_1 and FEV_1 decline are important independent risk factors for all-cause and cause-specific mortality.

There are several biologically plausible explanations for the association between lung function and mortality from diseases in multiple organ systems. WTC-related lung injury is associated with inflammatory biomarkers in serum obtained even years after 9/11/2001.[3,33] There is extensive evidence that individuals with chronic inflammation[34-36] have worse disease prognosis. Systemic chronic inflammation produced by physical inactivity, poor diet, environmental and industrial toxicants, and psychological stress can lead to lung disease, heart disease and cancer that result in most of the world's disability and mortality.[37] Among patients with COPD, Eickhoff et al found significant impairment of vasodilation and a possible increased risk of cardiovascular disease due to airflow obstruction and systemic inflammation.[38] Further, a recent study demonstrated exposure to WTC dust increases clonal hematopoiesis.[39] This is defined by the outgrowth of hematopoietic stem cells with somatic mutations of growth- inhibiting genes, including DMNT3A and TET2. Myeloid stem cells with these somatic mutations expand and then develop into inflammatory monocytes. Risk factors for clonal hematopoiesis include old age and cigarette smoking. DNMT3A and TET2 mutations were also the most common mutations in large population studies of patients with COPD, heart disease and cancer.[34,35,40,41] The investigation of this cohort may have implications to other environmental/occupational cohorts such as studies of the respiratory health effects of airborne hazards after burn pit exposures in the Southwest Asia Theater of Military Operations.[42]

While we cannot fully determine the mechanistic association between lung function and mortality, these findings are notable for many reasons and could provide a rationale for pharmacologic and lifestyle interventions among participants with accelerated-FEV_1-decline. Previously, we showed treatment with inhaled corticosteroids and long-acting beta agonists (ICS/LABA) did not slow lung function decline in most patients in this cohort and did not improve respiratory symptoms if started after 2010.[43,44] The accelerated-FEV_1-decline phenotype and its association with increased mortality, even in patients with normal lung function, is concerning and could meet the definition of pre-COPD, arguing for monitoring and the development of improved therapies that could then allow for early intervention.[8]

This study has distinctive strengths over prior work evaluating the association between lung function and mortality. First, our study featured a large sample size, excellent cohort retention, and repeated measurements for twenty years of follow-up, something lacking in prior studies examining the association between lung function and mortality. Second,

FDNY has excellent mortality capture. Complete demographic data including social security number were used for NDI linkages. Death data were also validated by independent FDNY records. Third, our study featured rigorous quality assurance, standardization, and consistency for spirometry testing procedures. Since spirometry is effort dependent, a standardized process is paramount when studying outcomes longitudinally. Fourth, the joint longitudinal survival methodology accounted for dependencies between the longitudinal exposure process (lung function) and the time-to-event outcome process (death). By modeling the two concurrently, bias is reduced. Specifically, a given set of covariates at each time interval is used to predict mortality such that the exposure precedes the outcome. While all longitudinal FEV_1 measurements are used in the model, future FEV_1 values are not used to predict an underlying biological process which leads to death. Further, joint modeling also preserves temporality by allowing each repeated FEV_1 measurement in the longitudinal model to predict mortality at each respective time interval, thereby reducing biases produced by informative censoring.[45] This method enables estimation of the association between FEV_1 trajectories and survival, and allows modeling of baseline FEV_1 and rate of change in FEV_1 over time (FEV_1 slope) in the prediction of survival. Finally, the consistent results we obtained regarding the known associations with heart and respiratory disease mortality,[6,8] shown in other studies to be associated with lung function, lends strength to the validity of our methods.

There are some limitations to this work. First, we were underpowered to detect an association between lung function decline and mortality for specific cancer types or other less common causes of death. Continued follow-up will be important for future work. Second, unmeasured confounding, particularly related to continued workplace exposures among firefighters and EMS providers that remained active in the years following 9/11/2001, could not be discounted. We believe, however, that this bias was likely to be minimal across differing lung function trajectories. Third, we cannot fully rule out informative missingness in the pulmonary function data. However, the short amount of average time elapsed from the last PFT to end of follow-up (<2 years) demonstrates that it would have not introduced substantial bias. Further, the potential for missingness may bias towards the null as the deceased had on average slightly longer time between last PFT and end of follow-up (i.e., death date) suggesting that any additional measurements would have shown worse lung function. Finally, a sensitivity analysis after removing PFT measurements within three years of the end of the follow-up period, found a similar effect, reducing the potential bias incurred from reverse-causality.

In summary, this study provides evidence that lung function decline is associated with all-cause mortality and cancer-cause mortality, after controlling for important confounders. We found that both baseline FEV_1 and change in FEV_1 over time are associated with all-cause, cancer-cause mortality and mortality from heart and lung disease. Systemic inflammation affecting the respiratory and cardiovascular systems as well as poor cancer control produced by WTC-associated clonal hematopoiesis is a possible mechanism that contributes to all-cause and cause specific mortality. While aspects of the WTC exposure are unique, our study design could benefit the monitoring of other cohorts with occupational/environmental exposures.[13,42,46] Further research can test the hypothesis that chronic inflammation is a common cause for loss of lung function and increased mortality rates.

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Table 1: Selected cohort characteristics

Variable		Overall N=12,264	Firefighters N=10,301	EMS N=1,963
Age on 9/11/2001 mean (SD)		39.7 (7.8)	40.4 (7.4)	35.9 (8.6)
PFT exams mean (SD)		11.2 (4.1)	11.1 (3.9)	12.0 (5.2)
Post-9/11 Follow-up years mean (SD)		19.1 (2.6)	19.1 (2.6)	18.9 (2.5)
Race/ethnicity n (%)				
	White	10756 (87.7%)	9701 (94.2%)	1055 (53.7%)
	Black	696 (5.7%)	268 (2.6%)	428 (21.8%)
	Hispanic	812 (6.6%)	332 (3.2%)	480 (24.5%)
Sex n (%)				
	Male	11862 (96.7%)	10277 (99.8%)	1585 (80.7%)
	Female	402 (3.3%)	24 (0.2%)	378 (19.3%)
Smoking status n (%)				
	Never	7819 (63.8%)	6804 (66.1%)	1015 (51.7%)
	Current/Former	4445 (36.2%)	3497 (33.9%)	948 (48.3%)
WTC exposure n (%)				
	9/11 AM	2076 (16.9%)	1672 (16.2%)	404 (20.6%)
	9/11 PM	6028 (49.2%)	5444 (52.8%)	584 (29.8%)
	9/11 PM-9/12	2050 (16.7%)	1794 (17.4%)	256 (13.0%)
	9/13-9/24	1793 (14.6%)	1264 (12.3%)	529 (26.9%)
	9/25-site close	275 (2.2%)	87 (0.8%)	188 (9.6%)
	Unknown	42 (0.3%)	40 (0.4%)	2 (0.1%)

Abbreviations: EMS, Emergency Medical Service providers; PFT, Pulmonary Function Test

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Table 2: Longitudinal Lung Function

	First PFT*		Last PFT*	
		FEV_1 in mL		**FEV_1 in mL**
Strata of FEV_1 % predicted	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**
0-59	79 (0.6)	1892 (436.2)	309 (2.5)	1718 (403.5)
60-69	204 (1.7)	2585 (367.2)	502 (4.1)	2344 (361.7)
70-79	1011 (8.2)	3067 (387.8)	1457 (11.9)	2719 (387.1)
80-89	2606 (21.3)	3497 (432.1)	2823 (23.0)	3106 (438.0)
90-99	3652 (29.8)	3884 (451.7)	3391 (27.7)	3431 (466.7)
100-109	2822 (23.0)	4231 (503.8)	2422 (19.8)	3731 (489.0)
110-119	1307 (10.7)	4609 (566.6)	1023 (8.3)	3973 (561.0)
120-140	583 (4.8)	5030 (667.0)	337 (2.8)	4187 (641.4)
FEV_1/FVC <70%‡	288 (2.4)		1,142 (9.3)	
FEV_1 % predicted by vital status	**N**	**Mean (SD)**		**Mean (SD)**
Deceased	607	90.5 (16.1)		84.9 (17.9)
Alive	11,657	96.2 (13.6)		92.3 (14.8)

Abbreviations: FEV_1, one-second forced expiratory volume; FVC, Forced Vital Capacity; PFT, Pulmonary Function Test (Spirometry); SD, standard deviation

*262 participants had one PFT and thus contributed to both the first and last measurement calculations

‡12,039 and 12,249 participants had valid PFTs for their first and final visits, respectively

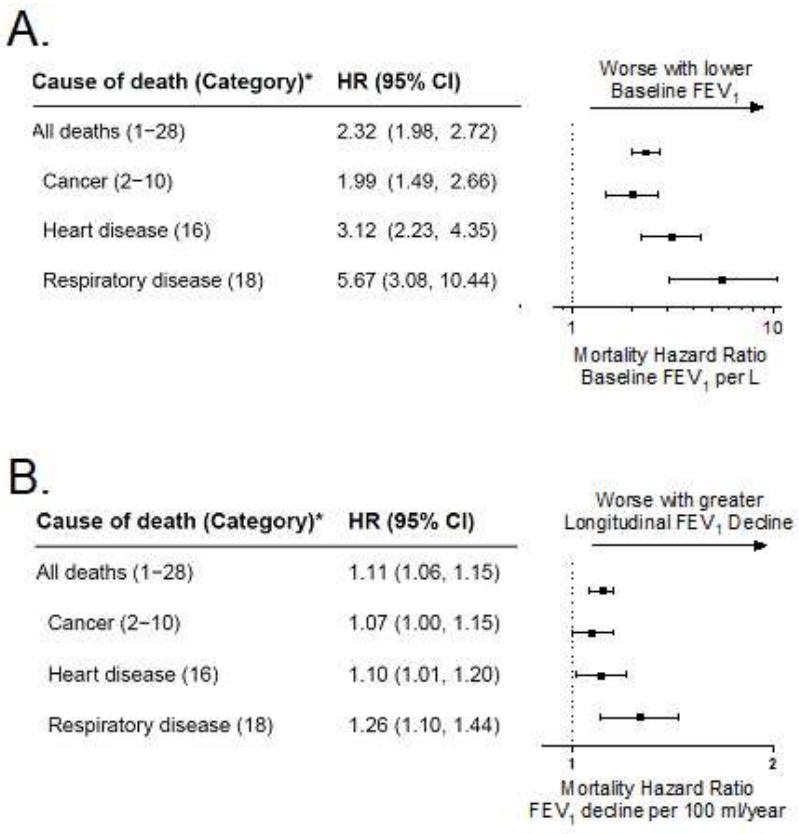

Figure 1: Joint Longitudinal survival models evaluating the association between baseline FEV1 in panel A and longitudinal change from baseline and mortality in Panel B. Abbreviations: FEV1, one-second forced expiratory volume; HR, hazard ratio; Models control for age on 9/11, race/ethnicity, height, smoking (ever vs. never), work assignment on 9/11 (firefighters vs. Emergency Medical Service [EMS] providers), and WTC initial arrival time. *Category corresponds with NIOSH LTAS major categories22

B.2 (B2.pdf)

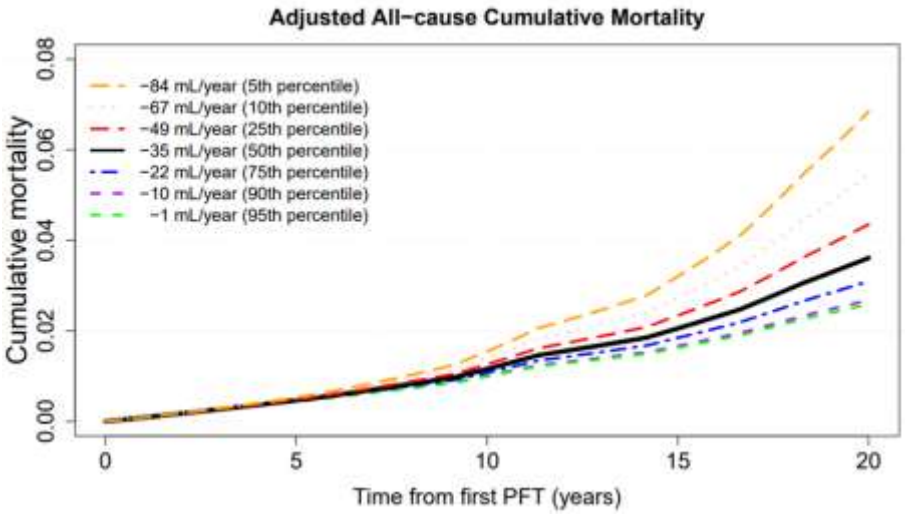

Figure 2: Results from Joint Longitudinal Survival models for WTC-exposed FDNY responders evaluating lung function decline and all-cause mortality. Seven curves correspond with results from cumulative mortality plots for FEV1 decliners in the 5th (orange), 10th (pink), 25th (red), 50th (black), and 75th (blue), 90th (purple), and 95th (green) percentiles. Model controls for age on 9/11 (centered at 40), race (centered at white), smoking (centered at never), work assignment on 9/11 (centered at firefighters), height (centered at 180 centimeters) and WTC arrival time (centered at initial arrival between 9/13/2001-7/25/2002). Abbreviations: FEV1, one-second forced expiratory volume, PFT, Pulmonary Function Test (Spirometry)

Cause of death (Category)*	FEV_1 Decline <64 mL/y n=10,457 n (%)	≥64 mL/y n=1,244 n (%)	HR (95% CI)
All deaths (1–28)	332 (3.17)	140 (11.25)	2.91 (2.37, 3.56)
Cancer (2–10)	116 (1.11)	48 (3.86)	2.68 (1.90, 3.79)
Heart disease (16)	68 (0.65)	26 (2.09)	2.59 (1.63, 4.12)
Respiratory disease (18)	15 (0.14)	13 (1.05)	4.74 (2.20, 10.24)

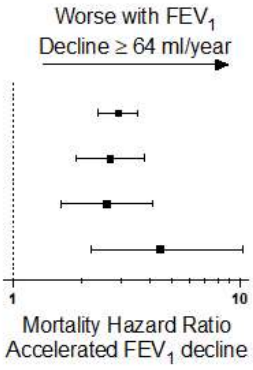

Figure 3: Accelerated lung function decline and mortality by cause of death. Accelerated lung function decline is defined as an individual with greater than or equal to 64 mL losses in FEV1 per year; n=563 participants contributed 2 or fewer PFTs and thus were not included in the analysis to improve precision of slope (rate of change) estimates. Crude death proportions are presented. Piecewise exponential survival models control for age on 9/11, race/ethnicity, sex, arrival at the WTC site, and smoking. The top 3 cancer causes of death were cancers of the digestive organs (category 3; n=61), the hematopoietic/lymphatic system (category 10; n=25), and the respiratory system (category 4; n=23); *Category corresponds with NIOSH LTAS major categories

B.2 (B2.pdf)

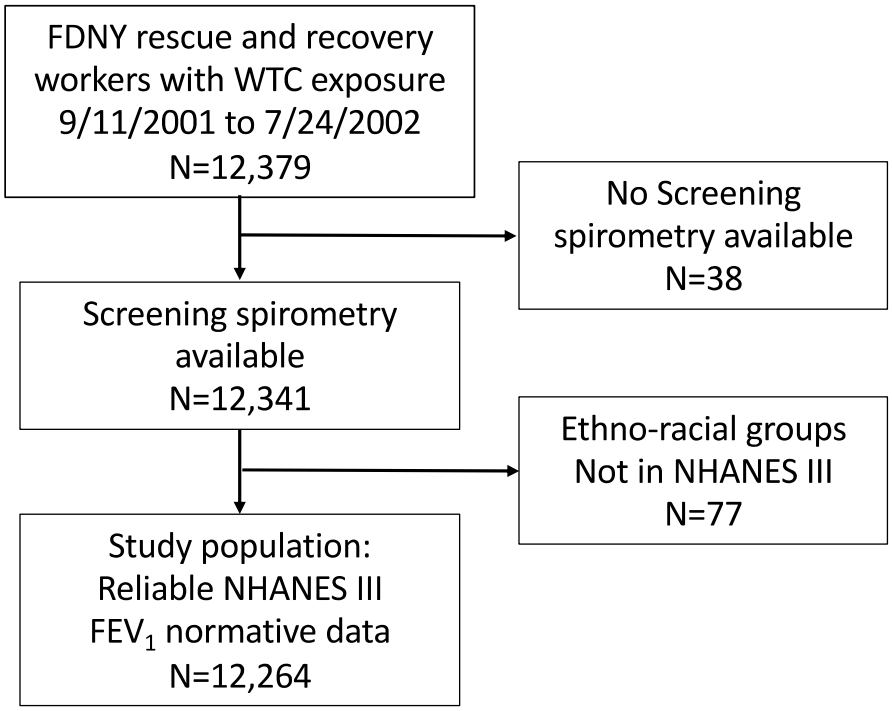

Figure S1 – FDNY rescue and recovery workers who participated in the FEV_1 and mortality study. Shown is the source population of 12,379 FDNY rescue and recovery workers who were employed by the FDNY on 9/11/2001, present at the WTC site between 9/11/2001 and 7/24/2002 and consented to research. The final study population of 12,267 included those with at least one routine monitoring PFTs taken between 9/11/2001 and 12/31/2021 reliable NHANES III normative data (i.e., white, Black, and Hispanic race/ethnicity).

B.2 (B2.pdf)

Table S1: Sensitivity analyses

	Cause of Death	First FEV_1 (95% CI) (per 1 L lower)	Mortality Hazard Ratio (95% CI) FEV_1 slope (per 100 mL/year decline)
Sensitivity analysis #1	All-cause	2.13 (1.80, 2.53)	1.09 (1.04, 1.13)
	Cancer	1.88 (1.39, 2.53)	1.03 (0.96, 1.11)
Sensitivity analysis #2	All-cause	2.06 (1.71, 2.48)	1.15 (1.10, 1.19)
	Cancer	1.84 (1.34, 2.54)	1.07 (1.00, 1.16)

Sensitivity analyses: 1) removing PFT measurements within three years of the end of the follow-up period to eliminate the potential bias incurred from reverse-causality (i.e., onset of cancer causes impaired lung function); 2) requiring at least three PFT measurements to assess the extent which selection bias affected results in the full models.

*Models control for age on 9/11, race/ethnicity, height, smoking (ever vs. never) work assignment on 9/11 (firefighters vs. Emergency Medical Service [EMS] providers) and WTC initial arrival time.

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C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Putman B, Lahousse L, Zeig-Owens R, Singh A, Hall CB, Liu Y, Schwartz T, Goldfarb D, Webber MP, Prezant DJ, Weiden MD. Low serum IgA and airway injury in World Trade Center-exposed firefighters: a 17-year longitudinal study. Thorax. 2019 December;74(12):1182-1184. PubMed PMID: 31611340; DOI: 10.1136/thoraxjnl-2019-213715.
N/A: Not NIH Funded	Putman B, Lahousse L, Singh A, Zeig-Owens R, Hall CB, Fazzari MJ, Schwartz T, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Dyspnea and Inhaled Corticosteroid and Long-acting β-Agonist Therapy in an Occupational Cohort: A Longitudinal Study. Annals of the American Thoracic Society. 2020 June;17(6):770-773. PubMed PMID: 32068437; PubMed Central PMCID: PMC7470248; DOI: 10.1513/AnnalsATS.201910-794RL.
N/A: Not NIH Funded	Putman B, Lahousse L, Goldfarb DG, Zeig-Owens R, Schwartz T, Singh A, Vaeth B, Hall CB, Lancet EA, Webber MP, Cohen HW, Prezant DJ, Weiden MD. Factors Predicting Treatment of World Trade Center-Related Lung Injury: A Longitudinal Cohort Study. International journal of environmental research and public health. 2020 December 4;17(23). PubMed PMID: 33291671; PubMed Central PMCID: PMC7730939; DOI: 10.3390/ijerph17239056.
N/A: Not NIH Funded	Weiden MD, Zeig-Owens R, Singh A, Schwartz T, Liu Y, Vaeth B, Nolan A, Cleven KL, Hurwitz K, Beecher S, Prezant DJ. Pre-COVID-19 lung function and other risk factors for severe COVID-19 in first responders. ERJ open research. 2021 January;7(1). PubMed PMID: 33527077; PubMed Central PMCID: PMC7607970; DOI: 10.1183/23120541.00610-2020.
N/A: Not NIH Funded	Goldfarb DG, Colbeth HL, Skerker M, Webber MP, Prezant DJ, Dasaro CR, Todd AC, Kristjansson D, Li J, Brackbill RM, Farfel MR, Cone JE, Yung J, Kahn AR, Qiao B, Schymura MJ, Boffetta P, Hall CB, Zeig-Owens R. Impact of healthcare services on thyroid cancer incidence among World Trade Center-exposed rescue and recovery workers. American journal of industrial medicine. 2021 October;64(10):861-872. PubMed PMID: 34275137; PubMed Central PMCID: PMC8796202; DOI: 10.1002/ajim.23277.
N/A: Not NIH Funded	Goldfarb DG, Putman B, Lahousse L, Zeig-Owens R, Vaeth BM, Schwartz T, Hall CB, Prezant DJ, Weiden MD. Lung function decline before and after treatment of World Trade Center associated obstructive airways disease with inhaled corticosteroids and long-acting beta agonists. American journal of industrial medicine. 2021 October;64(10):853-860. PubMed PMID: 34254700; PubMed Central PMCID: PMC9292780; DOI: 10.1002/ajim.23272.
N/A: Not NIH Funded	Weiden MD, Singh A, Goldfarb DG, Putman B, Zeig-Owens R, Schwartz T, Cohen HW, Prezant DJ. Serum Th-2 cytokines and FEV(1) decline in WTC-exposed firefighters: A 19-year longitudinal study. American journal of industrial medicine. 2021 October;64(10):845-852. PubMed PMID: 34288008; PubMed Central PMCID: PMC9290799; DOI: 10.1002/ajim.23276.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
WEIDEM01	Y	Weiden, Michael D.	BS,MS,MD	PD/PI	2.1	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

I am a pulmonary physician who investigates the causes and consequences of non-resolving inflammation in the lung. I also care for WTC exposed FDNY rescue and recovery workers with upper and lower airway injury. This clinical experience informs my research. My research in turn informs my clinical care. We observed a large proportion of previously untreated patients have accelerated-FEV1-decline defined a more than 64ml/year FEV1 decline, twice the average FEV1 decline in the cohort that increases the risk for COPD is a significant risk factor for death (Goldfarb et al., 2023). Treatment with ICS/LABA, standard of care for both asthma and COPD does not improve FEV1-decline (Goldfarb et al., 2021) or respiratory symptoms (Putman et al., 2020). We have observed several serum biomarkers expressed within six months of exposure can be risk factors for poor outcome He have also reported that low IgA, a mediator of mucosal immunity is a risk factor for poor outcome (Putman et al., 2019) and elevated Th2 cytokines are associated with FEV1 decline (Weiden et al., 2021).

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

NOTHING TO REPORT

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT
No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE
Not Applicable
G.11 PROGRAM INCOME
Not Applicable
G.12 F&A COSTS
Not Applicable

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

The observation that standard of care treatment of airway injury with inhaled steroids and long-acting beta agonist does not alter FEV1 decline or respiratory symptoms we are exploring the effect of poorly controlled CVD risk factors on survival in the accelerated-FEV1-decline subgroup. This will set the stage for future efforts to improve CVD risk factor control at a stage were lung function remains normal. Our long-range goal is to identify cohort members at greatest risk of death because of lung function decline, so that focused case management can effectively treat hypertension, hyperglycemia, and dyslipidemia thereby improving survival.