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RESEARCH ARTICLE

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Lung function decline before and after treatment of World Trade Center associated obstructive airways disease with inhaled corticosteroids and long-acting beta agonists

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Abstract

Background: Greater than average loss of one-second forced expiratory volume (FEV_1) is a risk factor for asthma, chronic obstructive pulmonary disease (COPD), and asthma/COPD overlap syndrome in World Trade Center (WTC)-exposed firefighters. Inhaled corticosteroids and long-acting beta agonists (ICS/LABA) are used to treat obstructive airways disease but their impact on FEV_1-trajectory in this population is unknown.

Methods: The study population included WTC-exposed male firefighters who were treated with ICS/LABA for 2 years or longer (with initiation before 2015), had at least two FEV_1 measurements before ICS/LABA initiation and two FEV_1 measurements posttreatment between September 11, 2001 and September 10, 2019. Linear mixed-effects models were used to estimate FEV_1-slope pre- and post-treatment.

Results: During follow-up, 1023 WTC-exposed firefighters were treated with ICS/LABA for 2 years or longer. When comparing intervals 6 years before and 6 years after treatment, participants had an 18.7 ml/year (95% confidence interval [CI]: 11.3–26.1) improvement in FEV_1-slope after adjustment for baseline FEV_1, race, height, WTC exposure, weight change, blood eosinophil concentration, and smoking

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status. After stratification by median date of ICS/LABA initiation (January 14, 2010), earlier ICS/LABA-initiators had a 32.5 ml/year (95% CI: 19.5–45.5) improvement in slope but later ICS/LABA-initiators had a nonsignificant FEV_1-slope improvement (7.9 ml/year, 95% CI: −0.5 to 17.2).

Conclusions: WTC-exposed firefighters treated with ICS/LABA had improved FEV_1 slope after initiation, particularly among those who started earlier. Treatment was, however, not associated with FEV_1-slope improvement if started after the median initiation date (1/14/2010), likely because onset of disease began before treatment initiation. Research on alternative treatments is needed for patients with greater than average FEV_1-decline who have not responded to ICS/LABA.

KEYWORDS

FEV_1-slope, ICS/LABA, treatment effect

1 | INTRODUCTION

On September 11, 2001 (9/11), the collapse of the World Trade Center (WTC) towers produced a massive exposure to dust and combustion products resulting in lung injury in Fire Department of the City of New York (FDNY) rescue and recovery workers. There was an acute and persistent decline in lung function,[1] particularly one-second forced expiratory volume (FEV_1), with 12% of the population developing accelerated-FEV_1-decline, defined as greater than 64 ml/year loss during follow-up, more than double the cohort average.[2] WTC-exposed cohorts had an increased incidence of obstructive airways disease (OAD) with air-trapping and airway reactivity.[3–7] Specifically, high-intensity WTC exposure and respiratory symptoms such as cough, shortness of breath, and wheeze that developed in this population shortly after 9/11 were associated with accelerated decline in lung function and early diagnoses of OAD.[8–10]

Greater than average FEV_1-decline is a strong risk factor for chronic obstructive pulmonary disease (COPD), asthma and asthma/COPD overlap syndrome in WTC-exposed individuals.[2,3] Cigarette smoking is associated with excess FEV_1-decline and OAD[11] but many never smokers who were exposed to the WTC have these manifestations of lung injury.[12] FEV_1-decline is associated with excess mortality in smoking-related COPD in non-WTC exposed populations.[13] Randomized placebo-controlled clinical trials of ICS/LABA in COPD patients demonstrated an 8–16 ml/year improvement of FEV_1-slope with treatment.[14,15] The impact of ICS/LABA on FEV_1-slope in WTC-related lung injury is unknown. In observational pharmacological research, it is advantageous to compare outcomes within a participant before and after initiation of therapy to reduce the potential for selection by indication bias. Thus, in our present study we compared FEV_1-slopes among WTC-exposed participants before and after initiation of ICS/LABA to evaluate the impact of treatment. Specifically, our aim was to assess the extent to which ICS/LABA treatment alters FEV_1-slope among patients with WTC-related lung injury and further, if the time of initiation is associated with response to therapy.

2 | METHODS

2.1 | Study population

The source population included 10,106 WTC-exposed male firefighters who were actively employed by FDNY on 9/11, consented to physical health research, and had at least one medical monitoring exam. Since the FDNY WTC-exposed firefighter cohort was less than 1% female, women were not included in the source population for this study. Other inclusion criteria were that participants record at least two pulmonary function tests (PFT) before and two after initiation of ICS/LABA and could not be missing exams for more than four consecutive years at any point during the follow-up period, resulting in a final study population of 1023 WTC-exposed firefighters. A full flow of participants can be found in Figure 1.

2.2 | Study measures

Demographic, anthropometric, smoking, WTC exposure, blood eosinophil concentration and spirometry data were retrieved from the FDNY employee database or were assessed during routine medical monitoring exams. WTC-exposure was defined by initial arrival time of work at the WTC site (morning of 9/11; afternoon of 9/11–9/12; 9/13 or later). Smoking status was recorded at each exam and was defined as never, former, or current. Spirometry measurements included FEV_1, absolute, in ml, and as a percentage of NHANES normative equations.[16] All PFTs were used for screening and did not use a bronchodilator. PFTs for this study spanned from October 2001 to September 2019. From the beginning of follow-up through mid-2002, the FDNY used Portascreen spirometers (S&M Instruments), and from mid-2002 through the end of follow-up used EasyOne spirometers (NDD Medical Technologies) as part of monitoring exams which included quality grading in accordance with the American Thoracic Society guidelines.[17] Only "A" and "B" quality grades were used in this study.[17] The Albert Einstein College of Medicine Institutional Review Board approved this study (IRB #2019-10309).

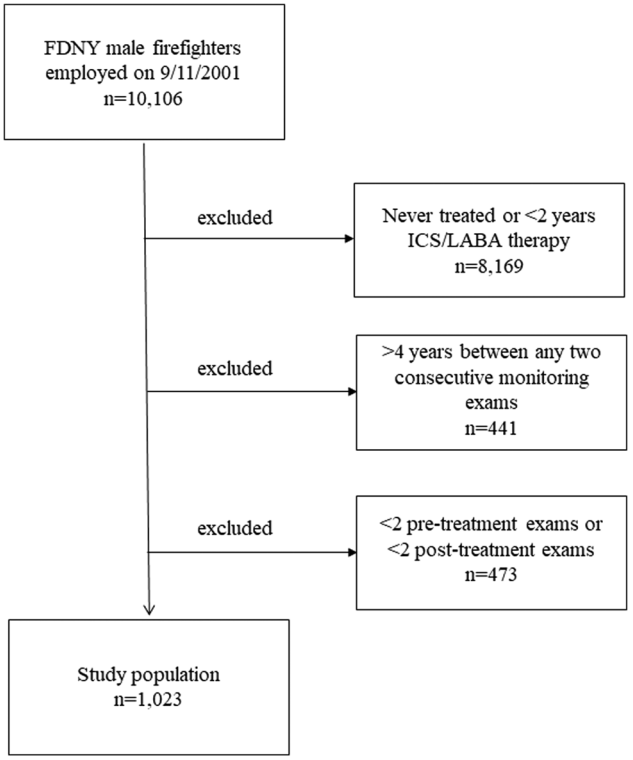

FIGURE 1 Flow of participants. FDNY, Fire Department of the City of New York; ICS/LABA, inhaled corticosteroid with long-acting beta agonists

2.3 | Treatment data

Medication data were obtained from the FDNY electronic medical record (EMR) and the WTC Health Program (WTCHP) claims database. Deidentified EMRs were screened for drug names of ICS/LABA containing medications and the sentence abstracts were reviewed by a trained clinician to determine the first date of ICS/LABA treatment, defining the date of initiation. Date of initiation was defined as the earlier of first prescription billed in the claims database and first physician note in the EMR. Similarly, the last date of ICS/LABA treatment was defined as the most recent date in the claims data and EMR, or September 10, 2017, if the note/claim occurred after. This date (September 10, 2017) was chosen to allow those participants who initiated ICS/LABA later adequate time and measurements to elicit a response to therapy longitudinally. The duration of ICS/LABA treatment was computed as the difference between the last date of ICS/LABA treatment and date of initiation. These analyses were restricted to participants who were treated with ICS/LABA for at least 2 years.

2.4 | Statistical analysis

First, univariate statistics were calculated for the overall and excluded populations. Age was calculated on 9/11, and other time-varying characteristics such as weight, smoking status, blood eosinophil concentration and FEV_1, on participants' first exam after 9/11. Descriptive statistics were assessed as proportions for categorical variables and means (standard deviations) for most continuous variables; differences between the analytic and excluded populations were evaluated using χ^2 tests for association and student *t*-tests, respectively. Since blood eosinophil concentration was non-normally distributed, median and IQR were reported, and differences were evaluated using the Mann–Whitney U test.

To allow comparable follow-up for all participants both pre- and post-ICS/LABA initiation, for the primary analysis the follow-up period was truncated to 6 years before and 6 years after ICS/LABA initiation. Thirty-nine participants who had only one pre- or one postinitiation exam, following truncation were not analyzed in the primary analyses. Linear mixed-effects models were used to compute absolute slopes, over the entire follow-up period and, separately, before and after ICS/LABA initiation, using a piecewise spline model. All covariates were included as fixed effects and intercepts as random effects to account for heterogeneity across study participants and correlations of repeated measurements. Intra-individual variability for FEV_1 measurements, both overall, as well as before and after treatment were calculated using an intercept-only linear mixed-effects model variance components. Models including random slopes for pre- and postinitiation time periods were also considered, however, AIC goodness of fit statistics demonstrated a poorer fit when compared to the random intercept-only, model. Additionally, random slope models are sensitive to outlier values and thus, was not presented in the current study. Additional details regarding linear mixed-effects models have been detailed previously.[11,18]

Three models were evaluated: (1) without potential confounders; (2) controlling for FEV_1 at first exam in the follow-up period (baseline), race, age at ICS/LABA initiation, and height; (3) controlling for the time-fixed covariates in Model 2, plus WTC arrival time (date of first arrival at the WTC site), and the following time-varying confounders: weight, smoking status at each exam, and blood eosinophil concentration at time of ICS/LABA initiation. Confounders for final models were selected, a priori. Most confounders (i.e., age at initiation, blood eosinophil concentration, race, time of arrival at WTC site, height, and smoking status) were nonmissing data points. Exams with missing weights (n = 873 exams, 10.5%) were assumed to be missing at random, since measurements are usually recorded as part of medical monitoring examinations, immediately before spirometry is conducted. Therefore, it was assumed that weights were not differentially missing for any specific groups of participants or periods of time. For Model 3, complete case analyses were conducted.

We then calculated the median date of ICS/LABA initiation for the entire cohort and created a binary variable according to whether they initiated before or after this date. Then, we tested for interaction between a period of initiation (1 if initiated before the median; 0 after the median) and follow-up time. Subsequently, multivariable regression analyses were stratified by the period of ICS/LABA initiation. Additional characteristics for these groups were assessed on a univariate level. Age was calculated both at first exam in the follow-up period and at the time of initiation. All other time-varying factors were reported at the time of initiation or in the exam immediately preceding it. Crude slopes for FEV_1 (absolute) and weight were calculated over the entire follow-up period.

TABLE 1 Cohort characteristics

Group characteristic[a]	Study population[b] 1023	Excluded population[c] 9083
Age[b]	40.5 (6.4)	40.3 (7.5)
Race *n* (%)		
White	973 (95.1)	8,529 (93.9)
African American	11 (1.1)	239 (2.6)
Other	39 (3.8)	315 (3.5)
Smoking status *n* (%)[c]		
Never[d]	726 (71.0)	6,728 (74.1)
Former	150 (14.7)	1,302 (14.3)
Current	147 (14.4)	1,053 (11.6)
World Trade Center arrival time *n* (%)		
Morning of 9/11	188 (18.4)	1,469 (16.2)
Afternoon of 9/11–9/12	746 (72.9)	6,455 (71.1)
9/13 or later	89 (8.7)	1,159 (12.8)
Height (cm)	177.3 (6.4)	177.2 (6.4)
Weight (lbs)	201.4 (26.2)	199.7 (27.7)
FEV_1 (ml)[e]	3,842.8 (613.2)	4,012.8 (686.6)
FEV_1 (% predicted)[e]	92.6 (13.0)	97.2 (13.8)
FEV_1 (mL)[c]	4,226.9 (667.5)	4,425.3 (704.8)
FEV_1 (% predicted)[c]	100.9 (14.0)	105.8 (13.9)
Eosinophils/μL blood median(Q1, Q3)[c,f]	177.0 (113.0, 256.0)	156.0 (102.0, 236.0)

Abbreviation: FEV_1, one-second forced expiratory volume.

[a]Mean (*SD*) unless stated otherwise.

[b]On Sep 11, 2001.

[c]At first post-9/11 medical monitoring exam.

[d]*n* = 1 person in excluded population with unknown smoking status.

[e]At last spirometry exam before Sep 11, 2001; data were available for 965/1023 (94.3) in the study population and 8449/9083 (93.0%) in the excluded population.

[f]Eosinophil data available for 910 (89.0%) participants in study population and 7998 (88.1%) in excluded population.

In a sensitivity analysis, the following was extended to all exams beyond those 6 years before and after initiation. Analyses for linear mixed-effects models were conducted using PROC MIXED in SAS v9.4 (SAS Institute, Inc.; https://www.sas.com).

3 | RESULTS

From September 11, 2001 to September 10, 2019, we analyzed 8281 annual medical monitoring exams among 1023 participants who were treated with ICS/LABA for more than 2 years and had at least two FEV_1 measurements before and after the time they initiated treatment. Compared with the excluded population, the study population had a similar age distribution on 9/11, ethno-racial makeup, smoking history, WTC exposure profile, height, and weight. The study population had a significantly lower absolute FEV_1, FEV_1% predicted, and higher blood eosinophil concentrations at first post-9/11 monitoring exam when compared with the excluded population (Table 1). We observed a −35.4 ml/year (95% confidence interval [CI]: −35.9 to −34.9) change in FEV_1 among all individuals excluded from the study because they were not treated with ICS/LABA.

We assessed FEV_1-slope before and after ICS/LABA initiation using linear mixed-effects models (Table 2). In Model 1, with no potential confounders, the average FEV_1 slope was −55.2 ml/year before ICS/LABA initiation and −33.5 ml/year after treatment yielding a 21.7 ml/year (95% CI: 14.1–29.3) improvement over time (Table 2; Model 1). The average FEV_1-slope was −55.2 ml/year before ICS/LABA initiation and −33.3 ml/year after treatment yielding a 21.9 ml/year (95% CI: 14.4–29.4) improvement in slope after adjusting for FEV_1 at the beginning of the follow-up period, race, age at initiation and height (Table 2; Model 2). The average FEV_1-slope was −52.0 ml/year before ICS/LABA initiation and −33.3 ml/year after treatment yielding an 18.7 ml/year (95% CI: 11.3–26.1) improvement in slope in the model controlling for FEV_1 at the beginning of the follow-up period, race, age at initiation, WTC arrival time, height, blood eosinophil concentration, and smoking (Table 2; Model 3). In a sensitivity analysis using all longitudinal FEV_1 data, the FEV_1 slope improved by 10.3 ml/year (95% CI: 7.3–13.3) in the model with no covariates.

The median date of initiation was January 14, 2010 and thus earlier ICS/LABA initiation was defined as January 18, 2002–January 14, 2010 and later ICS/LABA initiation was defined as January 15, 2010–September 9, 2015. We observed a significant interaction between follow-up time and period of initiation (earlier vs. later) in each of the mixed-effects models ($p < 0.01$ for interaction term) presented in Table 2. We therefore stratified by the time period of ICS/LABA initiation to better understand the nature of this interaction. Groups that initiated on or before that date were classified as earlier initiators, and those who initiated after were classified as later initiators. (Table 3). We observed a 34.5 ml/year (95% CI: 21.9–47.2) improvement among earlier initiators and a 12.6 ml/year improvement (95% CI: 3.0–22.2) among later initiators in the model that included no covariates. When adding race, height, age at initiation, and FEV_1 at the beginning of the follow-up period to the model, we observed a 35.2 ml/year (95% CI: 22.6–47.9) improvement among earlier initiators and a 12.6 ml/year improvement (95% CI: 3.2–22.1) among later initiators. When controlling for all time-independent and time-dependent covariates, we observed a 32.5 ml/year (95% CI: 19.5–45.5) improvement among earlier initiators and a nonsignificant 7.9 ml/year improvement (95% CI: −1.0 to 16.8) among later initiators. In the sensitivity analysis using all longitudinal FEV_1 data, earlier initiators had a 32.5 ml/year improvement (95% CI: 15.8–32.9) while later initiators a nonsignificant 4.8 ml/year improvement (95% CI: −1.8 to 11.3) in an unadjusted model.

TABLE 2 Linear mixed-effects model evaluating FEV_1 slope ml/year before and after ICS/LABA initiation $n = 984$

	Pre-initiation FEV_1 slope	Post-initiation FEV_1 slope	Δ FEV_1 slope
Model 1 (no covariates)	−55.2 (−60.0 to −50.4)	−33.5 (−37.9 to −29.0)	21.7 (14.1–29.3)
Model 2[a]	−55.2 (−60.0 to −50.3)	−33.3 (−37.7 to −28.9)	21.9 (14.4–29.4)
Model 3[b]	−52.0 (−56.9 to −47.2)	−33.3 (−37.5 to −29.1)	18.7 (11.3–26.1)

Note: All estimates presented in ml/year (95% CI).

Abbreviations: CI, confidence interval; FEV_1, one-second forced expiratory volume; ICS/LABA, inhaled corticosteroid with long-acting beta agonists; WTC, World Trade Center.

[a]Covariates include FEV_1 at the beginning of the follow-up period, race, age at ICS/LABA initiation, and height.

[b]Covariates include FEV_1 at the beginning of the follow-up period, race, age at ICS/LABA initiation, height, WTC arrival time, weight change, blood eosinophil concentration at time of initiation, and smoking status.

TABLE 3 Linear mixed-effects model stratified by period of ICS/LABA initiation: Earlier initiation (Jan 18, 2002–Jan 14, 2010) and later initiation (Jan 15, 2010–Sep 9, 2015)

Model 1 (no covariates)			
	Pre-initiation FEV_1 slope	**Post-initiation FEV_1 slope**	**Δ FEV_1 slope**
Earlier	−62.6 (−71.1 to −54.1)	−28.1 (−34.6 to −21.6)	34.5 (21.9–47.2)
Later	−50.5 (−56.2 to −44.8)	−37.9 (−44.0 to −31.7)	12.6 (3.0–22.2)
Model 2[a]	**Pre-initiation FEV_1 slope**	**Post-initiation FEV_1 slope**	**Δ FEV_1 slope**
Earlier	−62.9 (−71.5 to −54.3)	−27.7 (−34.1 to −21.2)	35.2 (22.6–47.9)
Later	−50.3 (−56.0 to −44.6)	−37.7 (−43.7 to −31.7)	12.6 (3.2–22.1)
Model 3[b]	**Pre-initiation FEV_1 slope**	**Post-initiation FEV_1 slope**	**Δ FEV_1 slope**
Earlier	−59.5 (−68.6 and −50.5)	−27.1 (−33.3 to −20.8)	32.5 (19.5–45.5)
Later	−46.9 (−52.4 and −41.4)	−38.9 (−44.6 to −33.2)	7.9 (−1.0 to 16.8)

Note: Estimates presented in ml/year (95% CI).

Abbreviations: CI, confidence interval; FEV_1, one-second forced expiratory volume; ICS/LABA, inhaled corticosteroid with long-acting beta agonists; WTC, World Trade Center.

[a]Covariates include FEV_1 at beginning of follow-up period, race, age at ICS/LABA initiation, and height.

[b]Covariates include FEV_1 at beginning of follow-up period, race, age at ICS/LABA initiation, height, WTC arrival time, weight change, blood eosinophil concentration at time of initiation, and smoking status.

We then examined differences between the time strata to assess for confounding. The groups had a similar number of exams and overall follow-up time. They also had similar age distributions on 9/11, smoking rates, and WTC exposure (Table 4). At exams on, or immediately preceding treatment, earlier initiators had slightly higher average eosinophils when compared with late initiators (157 and 150 μl/year, respectively). At initiation, later initiators weighed slightly more than earlier initiators.

Finally, we assessed if FEV_1 variability changed after ICS/LABA initiation. In the entire study group, 22.3% of all variability in FEV_1 could be attributed to intra-individual variability in Model 1. Before treatment, there was 17.1% intraindividual variability and after starting ICS/LABA variability declined to 13.2%. A similar trend was observed for earlier and later initiators, as well (Table 5).

4 | DISCUSSION

The dust and smoke exposure produced by the collapse of the WTC towers on September 11, 2001 resulted in obstructive airways diseases which are frequently treated with ICS/LABA.[2,3,7,10] After the original insult, WTC-exposed cohorts have been followed longitudinally for almost two decades. The data used in this study allowed for analysis of treatment efficacy by measuring FEV_1-slope before and after ICS/LABA initiation to determine if the trajectory changed after initiation; using the same patient population for both periods reduces the potential for selection by indication bias. This provided a unique opportunity to observe the impact of ICS/LABA treatment on FEV_1 trajectory over durations much longer than those used in randomized drug trials.[14,15] One systematic review highlighted the importance of long periods of longitudinal follow-up when analyzing

TABLE 4 Univariate characteristics by period of inhaled corticosteroid/long-acting beta agonist (ICS/LABA) initiation

Group characteristic[a]	Earlier initiation Jan 18, 2002–Jan 14, 2010 *n* = 511	Later initiation Jan 15, 2010–Sep 9, 2015 *n* = 512
Years from Sep 11, 2001 to initiation	5.3 (1.9)	10.9 (1.6)
Years of follow-up	9.2 (1.6)	9.9 (1.2)
Total exams median (Q1, Q3)	7 (6, 8)	9 (7, 10)
Pre-initiation exams median (Q1, Q3)	3 (2, 3)	4 (3, 5)
Post-initiation exams median (Q1, Q3)	4 (3, 5)	5 (4, 5)
Age (years) on Sep 11, 2001	41.4 (6.6)	39.6 (6.2)
Smoking status		
Never	337 (66.0)	352 (68.8)
Former	126 (24.7)	142 (27.7)
Current	48 (9.4)	18 (3.5)
Arrival time at WTC		
Morning of 9/11	93 (18.2)	95 (18.6)
Afternoon of 9/11–9/12	370 (72.4)	376 (73.4)
9/13 or later	48 (9.4)	41 (8.0)
Eosinophils/μl[b]	157.0 (94.0–243.0)	150.0 (98.5–228.0)
Δ FEV_1 ml/year[c]	−43.5 (−47.5 to −39.6)	−44.0 (−47.4 to −40.5)
FEV_1 (% predicted) at baseline[d]	90.3 (13.2)	92.3 (11.6)
FEV_1 (% predicted) at initiation[b]	87.6 (13.6)	89.9 (12.6)
Weight lbs[b]	207.4 (31.8)	211.3 (29.3)
Δ Weight lbs/year[c]	0.7 (0.5, 0.9)	0.2 (0.0, 0.4)

Abbreviations: FEV_1, one-second forced expiratory volume; ICS/LABA, inhaled corticosteroid with long-acting beta agonists; *SD*, standard deviation; WTC, World Trade Center.

[a]Mean (*SD*) unless stated otherwise.

[b]Measured on date of ICS/LABA initiation or exam immediately preceding initiation.

[c]Unadjusted slope and 95% confidence interval using all exams within 6 years of ICS/LABA initiation.

[d]At first exam in follow-up period.

TABLE 5 Interindividual variability for repeated FEV_1 measurements

Period of initiation	Pre-initiation	Post-initiation	Overall
Overall	17.2	13.4	22.7
Earlier	20.2	12.2	22.1
Later	15.7	15.0	24.0

Note: All estimates are expressed as percentages; intra-individual variability for FEV_1 measurements, both overall, as well as before and after treatment were calculated using an intercept-only linear mixed-effects model variance components; earlier period spans from Jan 18, 2002 to Jan 14, 2010 and later period spans from Jan 15, 2010 to Sep 9, 2015.

Abbreviation: FEV_1, one-second forced expiratory volume.

ICS-containing drugs as the greatest rates of FEV_1 improvement are most often found within the first year after initiation.[19] When using data from all patients, we observed a 21.7 ml/year FEV_1-slope improvement following ICS/LABA treatment in crude models and an 18.7 ml/year improvement when controlling for confounders including smoking, eosinophils, and weight change. These results are similar to the 8–16 ml/year improvement in FEV_1-slope observed in the context of randomized placebo-controlled trials of ICS/LABA in moderate COPD patients from the general population.[14,15]

This study featured a rich data set that allowed for adjustment of multiple confounders, which did not alter the observed associations from crude models. The relatively short, well-defined exposure in a previously healthy group of rescue/recovery workers is a benefit of studying WTC exposed cohorts. Our stratified analysis revealed that FEV_1-slope improved over 34.5 ml/year if ICS/LABA treatment was started soon after exposure while FEV_1-slope did not change significantly among participants that initiated ICS/LABA treatment after January 14, 2010. The results for FEV_1-slope are consistent with failure to resolve respiratory symptoms if ICS/LABA treatment is started long after exposure.[10] ICS/LABA was initiated at the time patients presented to pulmonologists for evaluation of respiratory symptoms but it is likely that the onset of disease began before presentation for treatment. These data, however, were not directly retrievable from the electronic medical record. Improvement in FEV_1-slope after earlier ICS/LABA initiation is attenuated when controlling for potential causes of destructive lung inflammation, smoking, and blood eosinophil concentration.[20] This is consistent with the hypothesis that ICS/LABA treatment is more effective in blunting destructive pulmonary inflammation if started soon after lung injury.

An alternate hypothesis consistent with the data is that distinct lung injury endotypes with different latencies occurred after WTC exposure. The short-latency endotype(s) have greater FEV_1-decline postinjury but are effectively treated with ICS/LABA improving the FEV_1 trajectory and respiratory symptoms.[10] The long latency endotype(s) have intrinsic risks for FEV_1 decline and are ICS/LABA unresponsive. Support for this theory is the observation that post-treatment FEV_1-slope is worse if treatment is started long after WTC exposure. Additional support that these are distinct endotypes comes from an observation in previous work which demonstrated changing predictors of ICS/LABA treatment as time from WTC exposure increases.[10,21] These two hypotheses, however, are not mutually exclusive. Further research is needed to define the balance between patient intrinsic risk for FEV_1 decline and timing of treatment

initiation in determining risk for further lung injury with ICS/LABA treatment.

Another explanation for longitudinal attenuation of the association between ICS/LABA initiation and FEV_1-slope is a maturation effect. We, therefore, truncated FEV_1 measurements to the 12 years surrounding ICS/LABA initiation to provide comparable follow-up in the stratified analysis. Secular alteration of FEV_1 variability might contribute to FEV_1-slope changes over time. Specifically, we observed considerable inter-individual variability in FEV_1 measurements that were greater in the earlier initiation stratum than the later stratum. It is possible that symptoms like WTC cough increased FEV_1 variability initially but as cough improved with time, variability declined.[22–24] Spirometry was quality assured[1] and this study used only exams with A and B quality grades. This reduces the likelihood that changes in FEV_1-slope are a technical artifact. Further research is needed to determine if FEV_1 variability is an important outcome measure.

This study includes a predominately male cohort of previously healthy firefighters which may limit the generalizability of our findings. Nevertheless, many discoveries in the FDNY cohort have been replicated in other WTC exposed populations.[5,6,24–26] Another limitation was that we could not fully determine the degree to which regression to the mean or selection by indication biases, which were produced by the different endotypes, may have accounted for the diminished effect between ICS/LABA initiation and change in FEV_1-slope. We observed a precipitous decline in lung function among WTC-exposed firefighters shortly after 9/11 followed by continued failure to recover.[11] Among participants who were excluded from the present study, we found a longitudinal decline of 35 mL/year, overall. This observation among those that were excluded coheres with normal age-related decline. Continued study of the overall cohort, including those not prescribed ICS/LABA, will be pivotal going forward. Additionally, this study did not assess the impact of other therapies such as long-acting muscarinic antagonists (LAMA) since it was approved for asthma late in the overall follow-up period.[27] Thus, LAMA was not consistently used to treat patients for this study and may have only impacted a minority of study participants that initiated therapy in the later period. Finally, this study did not measure adherence to medication and therefore a longitudinal decline in adherence could have contributed to the observed effects. We have, however, not observed a decline in ICS/LABA pharmacy refills over time in this cohort.

In conclusion, this investigation emphasizes the importance of longitudinal follow-up and systematic data collection during annual medical monitoring of WTC-exposed cohorts. Our finding that ICS/LABA initiation more than eight years post-WTC exposure does not significantly improve FEV_1-slope suggests treatments other than ICS/LABA are needed to limit the negative sequela associated with accelerated-FEV_1-decline.[2,3] Further investigation of LAMA and new biologic therapies may be warranted in patients unresponsive to ICS/LABA.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DISCLOSURE BY AJIM EDITOR OF RECORD

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

AUTHOR CONTRIBUTIONS

Conception or design of the work: Michael D. Weiden, Rachel Zeig-Owens, David G. Goldfarb, and Barbara Putman. The acquisition, analysis, and interpretation of data: Michael D. Weiden, David G. Goldfarb, Barbara Putman, Rachel Zeig-Owens, Theresa Schwartz, Charles B. Hall, and David J. Prezant. Drafting the work or revising it critically for important intellectual content: Michael D. Weiden, Rachel Zeig-Owens, David G. Goldfarb, and David J. Prezant. Final approval of the version to be published and agreement to be accountable for all aspects of the work: Michael D. Weiden.

DATA AVAILABILITY STATEMENT

Data that support the findings of the study may be obtained from the corresponding author (MDW) upon reasonable request in accordance with the study's official Data Sharing Plan.

ETHICS APPROVAL AND INFORMED CONSENT

The Albert Einstein College of Medicine Institutional Review Board approved this study (IRB #2019-10309). Informed consent was obtained from all participants.

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