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Association of quantitative CT lung density measurements and lung function decline in World Trade Center workers

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Abstract

Background: Occupational exposures at the WTC site after 11 September 2001 have been associated with presumably inflammatory chronic lower airway diseases.

Aims: In this study, we describe the trajectories of expiratory air flow decline, identify subgroups with adverse progression, and investigate the association of those trajectories with quantitative computed tomography (QCT) imaging measurement of increased and decreased lung density.

Methods: We examined the trajectories of expiratory air flow decline in a group of 1,321 former WTC workers and volunteers with at least three periodic spirometries, and using QCT-measured low (LAV%, −950 HU) and high (HAV%, from −600 to −250 HU) attenuation volume percent. We calculated the individual regression line slopes for first-second forced expiratory volume (FEV_1slope), identified subjects with rapidly declining ("accelerated decliners") and increasing ("improved"), and compared them to subjects with "intermediate" (0 to −66.5 mL/year) FEV_1slope. We then used multinomial logistic regression to model those three trajectories, and the two lung attenuation metrics.

Results: The mean longitudinal FEV_1 slopes for the entire study population, and its intermediate, decliner, and improved subgroups were, respectively, −40.4, −34.3, −106.5, and 37.6 mL/year. In unadjusted and adjusted analyses, LAV% and HAV%

Abbreviations: BDR, bronchodilator response; HAV%, high attenuation volume percent; HU, Hounsfield units; ICOERD, international classification of computed tomography for occupational and environmental respiratory diseases; LAV%, low attenuation volume percent; QCT, quantitative computed tomography; WTC, World Trade Center.

were both associated with "accelerated decliner" status (OR_{adj}, 95% CI 2.37, 1.41–3.97, and 1.77, 1.08–2.89, respectively), compared to the intermediate decline.

Conclusions: Longitudinal FEV_1 decline in this cohort, known to be associated with QCT proximal airway inflammation metric, is also associated with QCT indicators of increased and decreased lung density. The improved FEV_1 trajectory did not seem to be associated with lung density metrics.

KEYWORDS

CT–lung, helical computed tomography, imaging of the chest, inhalation injury, lung function decline, lung function trajectories, multivariate analysis of prognostic factors, occupational respiratory diseases, World Trade Center-related lung disease

1 | INTRODUCTION

Occupational exposures at the World Trade Center (WTC) disaster site in 2001-2002 have been associated with a variety of adverse health effects,[1] including chronic lower airway diseases.[1,2] The predominant spirometric abnormality has been a nonspecific reduced forced vital capacity (FVC) patterns,[3,4] and findings of airflow obstruction, bronchodilator response, or airway hyperresponsiveness are less frequent.[1,4] We previously reported on mostly mild chest computed tomography (CT) parenchymal findings (eg, interstitial abnormalities and emphysema).[5] Quantitative chest computed tomography (QCT) measurements[6] can help to characterize the presumed inflammatory changes underlying those heterogeneous WTC-related lower airway disorders and lung function changes, even if mild. Although post-WTC longitudinal follow-up of lung function among workers in the WTC occupational cohorts have suggested a normal age-related mean expiratory flow decline,[7-9] that average hides widely divergent longitudinal lung function trajectories.[9] We hypothesized that both increased (eg, from early interstitial lung disease) and decreased (eg, from early emphysema) lung density markers could help to explain the adverse lung function trajectories in a cohort under long-term health surveillance. In this study, we used longitudinal spirometry data to examine those trajectories, and the association of QCT metrics of increased and decreased lung density with accelerated FEV_1 decline among WTC rescue and recovery workers.

2 | METHODS

2.1 | Subjects and clinical data acquisition

All subjects were members of the WTC General Responders Cohort (GRC) and participated in the screening, surveillance, and clinical programs of the WTC Clinical Center of Excellence at Mount Sinai Medical Center (New York, NY). They were also part of the subcohort (n = 1,641) evaluated by the WTC Pulmonary Evaluation Unit (WTC PEU), who underwent chest CT scanning between 2003 and 2012, as part of their diagnostic evaluation. Details on subject recruitment, eligibility criteria, and screening and surveillance protocols have been previously reported.[10] In brief, participants were all workers and volunteers who performed rescue, recovery, and service restoration duties at the WTC disaster site from 11 September 2001 to June 2002. This open cohort includes all occupational groups deployed at the WTC disaster site.[11] Beginning in July 2002, all subjects underwent a baseline screening evaluation, which included questionnaires on respiratory and other symptoms, pre-WTC- and WTC-related occupational exposures, physical examination (including height and weight), laboratory testing, and spirometry. Subsequent ("monitoring") health surveillance visits included a similar evaluation at 12- to 18-month intervals, and clinical services were offered for individualized diagnostic and treatment services.[1,2]

2.2 | CT imaging procedures

All CT studies were obtained at Mount Sinai Hospital, in General Electric® or Siemens® multidetector row chest CT scanners. Chest CT studies were performed using an institutional clinical protocol[12] with a radiation dose at 120 kVp, and a mean of 146 (SD 69) mAs, with subjects in the supine position, noise correction, and routine periodic scanner calibration. CT scans were obtained from the lung apices to the bases in a single breath hold at maximum inspiration, and we excluded those with section thicknesses exceeding 1.5 mm, contrast administration, or respiratory or motion artifacts. All deidentified and coded chest CT images were stored and cataloged during the past 5 years in the WTC PEU Chest CT Image Archive (ClinicalTrials.gov identifier NCT03295279).[5]

2.3 | Inclusion criteria and QCT systems

Inclusion into this study required that the WTC workers had (1) at least three screening and surveillance spirometries, (2) adequate quality study for QCT measurements of their lung parenchyma performed with the Simba system (http://www.via.cornell.edu/simba/simba),[13] and (3) complete data for all covariates of interest. None of the chest CT was obtained for investigation of acute processes (infections, congestive heart failure, etc.). For this study, we selected the first adequate quality and available chest CT scan on each subject. For descriptive purposes, and as previously reported,[5] each study was also read by research radiologists using the International Classification of High-resolution Computed Tomography for Occupational and Environmental Respiratory Diseases (ICOERD)[14] to classify and grade dichotomously and/or semiquantitatively eight main types of abnormalities.

2.4 | Spirometry

Spirometries were performed using a single device, the EasyOne® portable flow device (ndd Medizintechnik AG, Zurich, Switzerland). Bronchodilator response (BDR) was assessed at least once in the majority of subjects (most often at their baseline visit) by repeating spirometry 15 minutes after administration of 180 mcg of albuterol via metered dose inhaler and disposable spacer. Predicted values for spirometric measurements were calculated for all subjects' acceptable tests, based on reference equations from the third National Health and Nutrition Examination Survey (NHANES III),[15] and all testing, quality assurance, ventilatory impairment pattern definitions, and interpretative approaches followed American Thoracic Society recommendations.[16-18] We selected spirometries for this study if they had a computer quality grade of A or B, or C if at least five trials had been obtained.[18]

2.5 | Measurements

We defined *a priori*, modeled, and plotted the three types of longitudinal post-WTC FEV_1 trajectories (see below, under Statistical Analysis). For the multinomial logistic regression model (see below) with the three trajectories of longitudinal FEV_1 as outcomes, we used as main predictors the two QCT-measured lung density indicators. For low parenchymal density (radiological attenuation), suggestive of emphysema, we used low attenuation volume percent at −950 HU (LAV%, also known as EI950). Categorization was necessary given the variable distribution, using a cut point of 2.5%, based on previously published findings in a nonsmoking healthy multiethnic population.[19] For high lung parenchymal density, which could suggest interstitial disease changes, we used high attenuation volume percent from −600 to −250 HU (HAV%). Although a study in smokers used a cut point of 10%[20] for HAV%, we felt that using the top decile (6.25%) as the cut point for our study was more appropriate, and equally necessary given the variable distribution.

2.6 | Statistical analysis

We used linear regression to calculate the slope of FEV_1 (FEV_1slope) on each of 1,321 subjects who had a minimum of three periodic measurements.[21] We then estimated the average group decline, and its standard deviation, to classify FEV_1slopes into three trajectories defined as follows: accelerated FEV_1 decline ("accelerated decliner") by an FEV_1 slope<−66.5 mL/year (ie, exceeding the group mean + 0.5 SD), excessive FEV_1 gain ("improved") by an FEV_1slope > 0 mL/year, and intermediate FEV_1 decline ("intermediate decliner") by an FEV_1slope between 0 and −66.5 ml/year (ie, between 0 and the group mean + 0.5 SD). We also estimated the root mean squared error (RMSE) as an indicator of group FEV_1 variability.[9]

Descriptive statistics included means and standard deviations (SDs), and medians and interquartile ranges (IQR) for normally and non-normally distributed continuous variables, respectively; counts and proportions were used for categorical variables. Unadjusted bivariate analyses included *t*-test, chi-squared test, or Wilcoxon rank test as appropriate. We employed, moreover, standardized differences (StD)[22] for the descriptive comparisons of the ICOERD findings with the outcomes (FEV_1 trajectories) and main predictors (QCT lung density indicators), with a StD > 0.2 suggesting a potentially important difference.

Covariates included in all multivariable models were age on 11 September 2001, sex, height, ethnicity/race (Latino, non-Latino White, and non-Latino other races), body mass index (BMI) at first evaluation and individual BMI trajectories by linear regression (BMI slope, in kg/m^2/year), FEV_1 percent predicted at baseline, evidence of bronchodilator response at any visit (BDRany, dichotomous), smoking status (never, former and current smokers), and smoking intensity (in pack-years) at the baseline examination. Occupational WTC exposure indicators included WTC arrival within 48 hours (dichotomous), and WTC exposure duration (in days, or per 100-day units).[1,9] A subject was considered a never smoker if (s)he had smoked less than 20 packs of cigarettes (or 12 oz. of tobacco) in a lifetime, or less than 1 cigarette/day (or 1 cigar/week) for 1 year. A minimum of 12 months without tobacco use was required to deem a subject a former smoker. In the model with QCT predictors, we included scanner manufacturer and slice thickness (in mm) to adjust for potentially important CT scan technical differences.

We first used linear mixed random effects modeling to plot the above described longitudinal FEV_1 trajectories. Mean absolute FEV_1 was estimated for each 1-year period between 2001 and 2015 (the actual follow-up year was rounded). In this multivariable model, age on 11 September 2001, BMI slope, height, sex, ethnicity/race, and bronchodilator response (BDRany) were included as fixed effects, centering the first three at the mean values for the cohort. Random intercepts accounted for between-subject variability, and repeated measures correlations accounted for intra-subject variability.

In order to estimate the effect of increased and decreased lung density on longitudinal FEV_1 trajectories after 11 September 2001, we employed multinomial logistic regression for the fully specified multivariable analysis of the association between QCT lung density indicators and the categorical outcome of FEV_1 trajectories ("accelerated decline," "intermediate decline," and "improved lung function"). We excluded multicollinearity by the variance inflation factor method and tested for interactions. In this analysis, we used multiple imputation (MI) with full conditional specification to account for missing QCT measurements. Results of complete case and imputed analyses were similar, the observed effects had the same direction and statistical significance, so we only report the latter. Model performance was assessed by means of the c statistic. A two-sided p value less than 0.05 defined statistical significance. The SAS program, version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

3 | RESULTS

Figure 1 shows the study flow chart. Table 1 shows that the study population consisted of 1,321 subjects who had at least three technically acceptable spirometries, with a total, median, and IQR per subject of 7,446, 6, and 4–7 studies, respectively, between July 2002 and June 2016. The mean age on 11 September 2001 was 42.1 (SD 9) years, and more than 80% were both male, and either overweight or obese (mean BMI 29.2 SD 4.9 kg/m^2). The mean longitudinal FEV_1slope for all subjects was −40.4 mL/year (SD = 52.2 mL/year, RMSE = 0.17 mL/year). Figure 2 displays the trajectories in absolute FEV_1 from 2002 to 2016, as revealed by the linear mixed random effects model. The mean longitudinal FEV_1 slopes for the intermediate decline (n = 876, 66.3%), accelerated decline (n = 280, 21.2%), and improved FEV_1 (n = 165, 12.5%) subgroups were, respectively, -34.3 (SD = 16.9, RMSE = 0.15) ml/year, −106.5 (SD 47.1, RMSE 0.21) ml/year, and 37.6 (SD 55.2, RMSE 0.21) ml/year. The observed differences with the intermediate decline subgroup in mean FEV_1 at the last follow-up visit were significant for both the improved (0.26 l, $P = 0.004$) and the accelerated decline (−0.44 l, $P < 0.0001$) subgroups.

In order to examine the association of increased and decreased lung density with the aforementioned post-WTC FEV_1 trajectories, we selected the first available chest CT scan with those measurements, obtained a median of 7.09 (IQR 5.75–8.61) years after 11 September 2001. Unadjusted comparisons to the

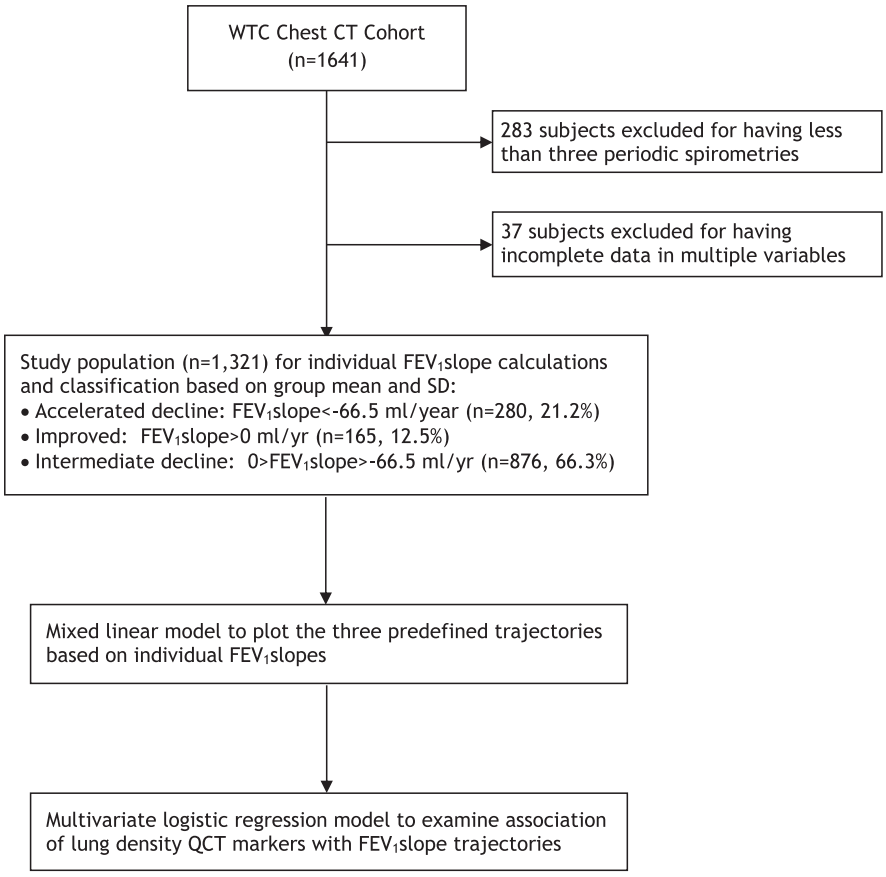

FIGURE 1 Study flowchart

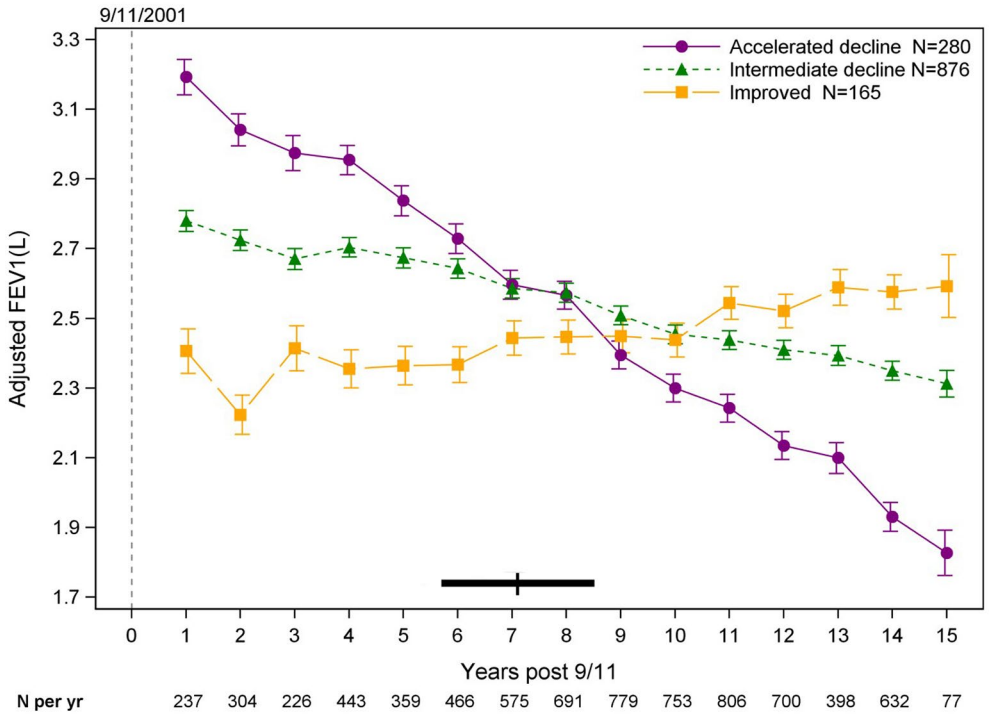

FIGURE 2 Post-11 September 2001 grouped longitudinal FEV_1 trajectories, in 1321 former nonfirefighting WTC workers. Yearly mean FEV_1 in liters from 2002 to 2016, adjusted for WTC occupational exposure (arrival within 48 hours of the disaster), age on 11 September 2001, sex, height, ethnicity/race, BMI slope, baseline smoking status, and BDRany. The three post-11 September 2001 FEV_1 trajectories are: accelerated decline (purple circle, solid line), intermediate decline (green triangle, short dash), and improved FEV_1 (yellow square, long dash). Error bars show the standard error of the mean. Numbers below the x-axis represent the sample size at each time point. The dotted vertical line represents 11 September 2001. For reference, selected chest CT scans were obtained a median of 7.09 (IQR 5.75-8.61) years after 11 September 2001 (illustrated by the thick bar above horizontal time line).

intermediate decliners (Table 1) showed that the "accelerated decliners" were significantly more likely to have higher categorical LAV% and HAV% ($P < 0.001$, and $P = 0.009$, respectively), to be male, taller, non-Latino/White and ever smoker, to gain weight over time, and to have higher baseline FEV_1% predicted, BDRany, and shorter WTC exposure duration. Compared with the intermediate decliners, the improved FEV_1 subjects were more likely to have high LAV% ($P = 0.039$), to be male, younger, and taller, have higher BMI at baseline and to lose weight on follow-up. They also had a lower baseline FEV_1% predicted, were more likely to have BDRany, to have arrived early at the WTC disaster site, and to have had a shorter WTC exposure duration. As expected, the mostly subtle radiological findings associated with high HAV% were linear and ground glass opacities, inhomogeneous attenuation, and honeycombing, while high LAV% was mainly associated with emphysema, but also with the presence of any well rounded or large opacities (Table OS1). We found no unadjusted (Table OS1) or adjusted[23] (data not presented) association between the visual radiologic abnormalities and the lung function trajectories.

As emphysema and interstitial lung disease both share some associated causal factors (eg, tobacco and occupational exposures) and can coexist[24,25] we checked for overlap between the two QCT predictors (ie, confirmed their independence). Only one study subject with both emphysema and inhomogeneous attenuation had both high HAV% and high LAV% as defined, so the two predictors were essentially independent from each other. Table 2 shows the results of the multinomial logistic regression analysis of lung density measures and lung function trajectories in 1,321 subjects. In this analysis both categorical LAV% and HAV% were significantly associated with accelerated FEV_1 decline (OR_{adj}, 95% CI 2.37, 1.41–3.97, and 1.77, 1.08–2.89, respectively), but not with improved FEV_1.

4 | DISCUSSION

In this study, we extend our previous assessment[9] of the rate of FEV_1 decline in a diverse group of former WTC workers[11] over a longer period of time. We also demonstrated the association of accelerated FEV_1 decline with QCT-measured decreased (LAV%) and increased (HAV%) lung density metrics. The subgroup with abnormal lung function gain or improvement, which had an inconsistent association with proximal airway wall thickness in our previous study,[9] failed to demonstrate a significant association with either LAV% or HAV% in this study.

The recently described[9,26] divergent long-term FEV_1 trajectories in the WTC worker and volunteer cohorts motivated

TABLE 1 Patient characteristics and unadjusted comparisons of decliners and improved versus intermediate decline group.

	Total n = 1321	Intermediate decline n = 876	Accelerated decline n = 280		Improved n = 165	
	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	P^a	N (%) or Mean ± SD	P^b
HAV% > 6.25%	102 (10.2)	54 (8.3)	32 (14.3)	**0.009**	16 (12.0)	0.174
HAV%#	2.8 (2.3, 4.0)	2.8 (2.3, 3.9)	2.7 (2.2, 4.0)	0.448	3.0 (2.3, 4.5)	0.169
LAV% > 2.5%	96 (9.6)	44 (6.8)	36 (16.1)	**<0.001**	16 (12.0)	**0.039**
LAV%#	0.1 (0.01, 0.6)	0.07 (0.01, 0.6)	0.1 (0.00, 0.9)	0.187	0.04 (0.00, 0.7)	0.583
Age (years)	42.1 ± 9.0	42.2 ± 9.0	43.2 ± 9.1	0.117	39.9 ± 8.5	**0.002**
Male sex	1082 (81.9)	685 (78.2)	250 (89.3)	**<0.001**	147 (89.1)	**0.001**
Ethnicity/race				**<0.001**		0.137
Latino	461 (34.9)	338 (38.6)	68 (24.3)		55 (33.3)	
Non-Latino/White	690 (52.2)	426 (48.6)	184 (65.7)		80 (48.5)	
Non-Latino/Other	170 (12.9)	112 (12.8)	28 (10.0)		30 (18.2)	
Smoking Status				**0.048**		0.231
Never	709(53.7)	486 (55.5)	132 (47.1)		91 (55.2)	
Former	371(28.1)	233 (26.6)	86 (30.7)		52 (31.5)	
Current	241(18.2)	157 (17.9)	62 (22.1)		22 (13.3)	
Height (cm)	171.5 ± 9.8	170.5 ± 9.9	173.8 ± 8.8	**<0.001**	173.2 ± 10.4	**0.001**
Baseline BMI (kg/m^2)	29.2 ± 4.9	28.9 ± 4.8	29.5 ± 5.3	0.107	30.2 ± 4.9	**0.002**
BMI slope (kg/m^2/year)	0.1 ± 0.4	0.1 ± 0.3	0.2 ± 0.4	**<0.001**	−0.1 ± 0.5	**<0.001**
FEV_1% predicted	87.1 ± 17.0	87.9 ± 16.0	91.5 ± 16.3	**0.001**	75.7 ± 18.6	**<0.001**
BDRany	296 (22.4)	165 (18.8)	71 (25.4)	**0.018**	60 (36.4)	**<0.001**
WTC arrival < 48 hours	688 (52.1)	438 (50)	148 (52.9)	0.405	102 (61.8)	**0.005**
WTC exposure (days)	92.4 ± 73.2	96.7 ± 74.8	85.2 ± 69.2	**0.023**	81.5 ± 69.8	**0.016**
Scanner manufacturer				0.142		0.112
Siemens (S)	328 (32.7)	198 (30.6)	80 (35.9)		50 (37.6)	
General Electric (GE)	676 (67.3)	450 (69.4)	143 (64.1)		83 (62.4)	
Slice thickness (mm)	1.1 ± 0.16	1.1 ± 0.16	1.1 ± 0.14	0.213	1.1 ± 0.19	0.667

Statistically significant differences are bolded.

[a]*P*-value for 2-sample comparisons between the accelerated and intermediate decline groups.

[b]*P*-value for 2-sample comparisons between the improved and intermediate decline groups.

[#]Medians (IQR) reported due to skewed distributions.

an examination of QCT metrics and lung function decline. We previously established that wall area percent, a QCT metric of proximal airway inflammation, is associated with accelerated FEV_1 decline.[9] We hypothesized that changes in lung density, which QCT may help to identify at early stages, could also be associated with the diverging trajectories (accelerated decline and improvement). Chronic parenchymal lung diseases associated with decreased (eg, emphysema), and increased (eg, interstitial lung diseases) lung density usually have a long latency after inciting exposures, and the included CT studies were obtained a median of 7.1 years after 11 September 2001. Our previous findings on systematic and semiquantitative readings of the CT scans, noted the prevalence of usually mild emphysema and interstitial lung disease in about 10% of this cohort, respectively.[5] Because the findings were so mild, we hypothesized that QCT density metrics corresponding to those abnormalities could be used to quantify their extent more precisely, and to assess whether they were significantly associated with adverse functional outcomes, even if quantitatively mild. Our findings would suggest that they are, that further follow-up is warranted, and that QCT can play a role in longitudinal respiratory surveillance of this cohort.

Extending our previous study[9] to delineate better the longitudinal FEV_1 trajectories, further suggests that the improved function group may have experienced the earliest and deepest lung function decrease (i.e., they were the "rapid accelerated decliners" after the WTC exposures), but also has demonstrated recovery toward higher pre-WTC FEV_1 levels,

TABLE 2 Comparisons QCT lung density metrics (LAV% and HAV%) between the accelerated decliner (n = 280) and the improved (n = 165) versus intermediate decliner (n = 876) subgroups, respectively

	All subjects (n = 1321)	
	Accelerated decline (n = 280)	Improved (n = 165)
	OR_{adj} (95% CI)	OR_{adj} (95% CI)
LAV% (>2.5% vs. ≤2.5%)	**2.37 (1.41, 3.97)**	1.76 (0.91, 3.41)
HAV% (>6.25% vs. ≤6.25%)	**1.77 (1.08, 2.89)**	1.55 (0.83, 2.93)
FEV_1 percent predicted	**1.03 (1.02, 1.04)**	**0.96 (0.95, 0.97)**
BDRany (yes vs. no)	**2.05 (1.42, 2.96)**	**1.56 (1.02, 2.40)**
BMIslope (0.2 kg/m^2/year unit)	**1.29 (1.18, 1.40)**	**0.80 (0.71, 0.89)**
Baseline BMI (kg/m^2)	**1.04 (1.01, 1.07)**	1.03 (0.99, 1.07)
Sex (male vs. female)	1.42 (0.85, 2.36)	**2.69 (1.39, 5.22)**
Height (cm)	**1.03 (1.01, 1.06)**	0.99 (0.96, 1.01)
Age on 11 September 2001 (10-year unit)	1.11 (0.93, 1.33)	**0.57 (0.45, 0.72)**
WTC arrival < 48 hours (yes vs. no)	1.09 (0.80, 1.48)	1.17 (0.79, 1.74)
WTC exposure (100-day unit)	0.82 (0.67, 1.01)	0.81 (0.63, 1.05)
Smoking status		
Current versus Never	1.29 (0.88, 1.90)	0.70 (0.40, 1.21)
Former versus Never	1.17 (0.83, 1.65)	1.33 (0.86, 2.04)
Ethnicity/race		
Latino versus Non-Latino/White	0.72 (0.50, 1.05)	0.92 (0.58, 1.45)
Non-Latino/Other versus White	0.77 (0.48, 1.24)	1.12 (0.67, 1.90)
Scanner manufacturer (GE vs. S)	0.99 (0.68, 1.45)	1.29 (0.76, 2.19)
Slice thickness (mm)	1.31 (0.43, 3.99)	0.75 (0.17, 3.27)

Note: Significant associations are bolded.

as suggested by a WTC firefighters' study.[26] The latter can be accounted by a calculated difference in pre-WTC predicted FEV_1 of 190 mL in favor of the improved, compared to the intermediate decline subjects (data not presented). The latter is in turn expected, given the sex and height differences between the subgroups (Table 2). The accelerated decline subgroup had a similarly higher pre-WTC predicted FEV_1 than the intermediate group, which also further underscores the severity of their longitudinal functional loss. Although our models suggested several important predictive factors of those divergent trajectories, further characterization and follow-up are warranted.

The value of the QCT emphysema measurement (LAV%) has been extensively used in studies of smokers and COPD (reviewed in [27]). The QCT high lung density (HAV%) metric, moreover, has been used less often, mainly in the investigation of interstitial disease changes with COPD,[20] and adverse effects on lung function in pulmonary fibrosis patients,[28] or of cigarette smoking.[29] Aside from studies with a predominance of smokers, HAV% in subjects from the Framingham Heart Study,[30] was also modestly predictive of lung volume loss. The interstitial abnormalities measured by HAV% may be reversible. Our findings, and those of previous studies, support the longitudinal and quantitative investigation of increased and decreased lung density in occupationally exposed cohorts like that of the WTC responders.

The pathogenesis of both COPD and interstitial fibrosis[31,32] is thought to share trajectories marked by a series of pulmonary tissue injuries, including those caused by environmental toxicants, such as tobacco, occupational vapors, dust, and gases, as well as dysregulated aging,[20,33,34] developmental, and other factors. The factors that determine the diverging pathophysiologic paths between the two, however, remain to be elucidated. While both diseases can indeed coexist,[24,25] we found no substantial evidence of overlap of their respective QCT markers in our study group. While there is thus far no conclusively documented evidence of association of WTC-related exposures with the causation of either COPD or interstitial fibrosis in the WTC cohorts, our models included both tobacco smoking and WTC occupational exposure variables as covariates and not main predictors in the models. Properly designed studies are needed to elucidate their potential causative roles.

The strengths of this study relate to the richness of the patient population, the amount of data available for important covariates, the availability of extensive, and detailed imaging data, unique in WTC cohort studies. This study also has some limitations. We did not assess the effect of pre-WTC occupational exposures,[5] the effect of smoking after the baseline examination, or of smoking intensity. Periodic cross-sectional assessments of smoking status in this cohort, moreover, suggest steadily decreasing cross-sectional current smoking rates.[3] Our study subjects underwent chest CT scanning for a variety of reasons, often not inclusive of abnormal lung function (eg, investigation of nodules, atelectatic densities, etc.). This represents an inevitable selection bias that allowed us, however, to obtain QCT measurements. We measured the indicators of lung density on CTs performed 7.1 years after 11 September 2001, at a time when the three FEV_1 trajectories were already clearly established (Figure 1). Our observations in this and our previous study on the divergent FEV_1 trajectories[9] were similar to those reported in the WTC firefighters' cohort,[26] where the overall longitudinal FEV_1 decline was −32 mL/year, versus −40.4 mL/year in our cohort. Preliminary data on the Mount Sinai WTC General Responders Cohort (n = 15,753), that includes our cohort, indicate a longitudinal FEV_1 decline of −33.2 mL/year,[4] which further supports our *a priori* trajectory classifications. We chose FEV_1 for this study, because of its reliability and

repeatability, particularly in the setting of large screening and surveillance spirometry programs. All WTC occupational studies with spirometry data have shown nonobstructive low FVC as the largely predominant spirometric impairment,[3,4] and thus essentially parallel trajectories of FEV_1 and FVC.[7] Future studies should examine, however, the differential effect of our and other QCT markers in subgroups of patients. We lacked comparison QCT imaging data from a well-defined control group of occupationally and WTC unexposed, totally asymptomatic subjects, with normal spirometry and chest radiograph, but we believe that our selection of QCT lung density metrics cut off criteria were adequate for these analyses. We used retrospective chest CT imaging data, which were subject to slight variations in protocols over time. However, most studies were performed in a very small number of scanners, at a single location, and with an intended technical consistency. In addition, quality control was exerted to exclude CT scan studies that did not meet technical standards for quantitative imaging analyses and, as a result, our models did not suggest significant effects of scanner brand and study slice thickness.

As the potential for the development of chronic lung diseases looms on this cohort,[35,36] this and our previous studies[1,5,9] underscore the need for surveillance and suggest the potential role of both qualitative and quantitative chest CT in the ongoing evaluation of lung function changes and disease transitions in this cohort.

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CONFLICT OF INTEREST

The authors had no other relevant financial conflict of interest disclosure to make. The contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the CDCP/NIOSH. The funding agencies had no role in the study design, in the collection, analysis, or interpretation of the data, in the writing of the report, or in the decision to submit this article for publication.

AUTHOR CONTRIBUTIONS

de la Hoz, Estépar, and Celedón designed and oversaw the study and selected analytical strategies. Liu, Antoniak, Jeon, Weber, and Doucette performed all statistical analyses. Reeves performed the QCT measurements and Xu participated in the radiological readings (ICOERD data). All authors contributed to writing, reviewed and revised the drafts, and approved the final manuscript. de la Hoz had full access to all the data in the study and had final responsibility for the decision to submit for publication.

ETHICS STATEMENT

The study was conducted in accordance with the guidelines for human studies of the amended Declaration of Helsinki. The Mount Sinai Program for the Protection of Human Subjects (HS12-00925) reviewed and approved the study protocol.

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REFERENCES

1. de la Hoz RE, Shohet MR, Chasan R, et al. Occupational toxicant inhalation injury: the World Trade Center (WTC) experience. *Int Arch Occup Environ Health*. 2008;81(4):479-485.
2. de la Hoz RE. Occupational asthma and lower airway disease in former World Trade Center workers and volunteers. *Curr Allergy Asthma Rep*. 2010;10(4):287-294.
3. Weber J, Reeves AP, Doucette JT, et al. Quantitative CT evidence of airway inflammation in World Trade Center workers and volunteers with low FVC spirometric pattern. *Lung*. 2020;198(3):555-563.

4. de la Hoz RE, Shapiro M, Nolan A, Celedón JC, Szeinuk J, Lucchini RG. Association of low FVC spirometric pattern with WTC occupational exposures. *Respir Med*. 2020;170:106058.
5. de la Hoz RE, Weber J, Xu D, et al. Chest CT scan findings in World Trade Center workers. *Arch Environ Occup Health*. 2019;74(5):263-270.
6. San José Estépar R, Reilly JJ, Silverman EK, Washko GR. Three-dimensional airway measurements and algorithms. *Proc Am Thorac Soc*. 2008;5(9):905-909.
7. Skloot GS, Schechter CB, Herbert R, et al. Longitudinal assessment of spirometry in the World Trade Center Medical Monitoring Program. *Chest*. 2009;135(2):492-498 (Erratum in Chest 2009; 135(4):1114.
8. Aldrich TK, Gustave J, Hall CB, et al. Lung function in rescue workers at the World Trade Center after 7 years. *N Engl J Med*. 2010;362(14):1263-1272.
9. de la Hoz RE, Liu X, Doucette JT, et al. Increased airway wall thickness is associated with adverse longitudinal first-second forced expiratory volume trajectories of former World Trade Center workers. *Lung*. 2018;196(4):481-489.
10. Wisnivesky JP, Teitelbaum S, Todd AC, et al. Persistence of multiple illnesses in September 11 rescue workers. *Lancet*. 2011;378(9794):888-897.
11. Woskie SR, Kim H, Freund A, et al. World Trade Center disaster: assessment of responder occupations, work locations, and job tasks. *Am J Ind Med*. 2011;54(9):681-695.
12. Mendelson DS, Roggeveen M, Levin SM, Herbert R, de la Hoz RE. Air trapping detected on end-expiratory high-resolution computed tomography in symptomatic World Trade Center rescue and recovery workers. *J Occup Environ Med*. 2007;49(8):840-845.
13. Lee J, Reeves AP, Fotin SV, Apananosovich TV, Yankelevitz DF. Human airway measurement from CT Images. In: *SPIE International Symposium on Medical Imaging* (February 2008). Vol 6915. Bellingham, WA: SPIE; 2008:691518.
14. Suganuma N, Kusaka Y, Hering KG, et al. Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. *J Occup Health*. 2009;51(3):210-222.
15. Hankinson JL, Odencratz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.
16. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152(3):1107-1136.
17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
18. Enright PL, Skloot GS, Cox-Ganser JM, Udasin IG, Herbert R. Quality of spirometry performed by 13,599 participants in the World Trade Center Worker and Volunteer Medical Screening Program. *Respir Care*. 2010;55(3):303-309.
19. Hoffman EA, Ahmed FS, Baumhauer H, et al. Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample - The MESA Lung Study. *Ann Am Thorac Soc*. 2014;11(6):898-907.
20. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med*. 2011;364(10):897-906.
21. Wang ML, Avashia BH, Petsonk EL. Interpreting longitudinal spirometry: weight gain and other factors affecting the recognition of excessive FEV_1 decline. *Am J Ind Med*. 2009;52(10):782-789.
22. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Statistics - Simulation Computation*. 2009;38(6):1228-1234.
23. de la Hoz RE, Antoniak K, Liu X, Doucette JT, Weber J, Jeon Y. Chronic parenchymal lung disease radiological abnormalities and declining longitudinal FEV_1 trajectory in WTC workers and volunteers [Abstract]. *Am J Respir Crit Care Med*. 2019;199(IC):A1862.
24. Wiggins J, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. *Respir Med*. 1990;84(5):365-369.
25. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J*. 2005;26(4):586-593.
26. Zeig-Owens R, Singh A, Aldrich TK, et al. Blood leukocyte concentrations, FEV_1 decline, and airflow limitation - a 15-year longitudinal study of World Trade Center-exposed firefighters. *Ann Am Thorac Soc*. 2018;15(2):173-183.
27. Litmanovich D, Boiselle PM, Bankier AA. CT of pulmonary emphysema-current status, challenges, and future directions. *Eur Radiol*. 2009;19(3):537-551.
28. Ash SY, Harmouche R, Vallejo DL, et al. Densitometric and local histogram based analysis of computed tomography images in patients with idiopathic pulmonary fibrosis. *Respir Res*. 2017;18(1):45.
29. Lederer DJ, Enright PL, Kawut SM, et al. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med*. 2009;180(5):407-414.
30. Kliment CR, Araki T, Doyle TJ, et al. A comparison of visual and quantitative methods to identify interstitial lung abnormalities. *BMC Pulm Med*. 2015;15:134.
31. Agusti A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1248-1256.
32. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet*. 2011;378(9807):1949-1961.
33. Faner R, Rojas M, MacNee W, Agustí A. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2012;186(4):306-313.
34. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene study. *Acad Radiol*. 2010;17(1):48-53.
35. Guidotti TL, Prezant DJ, de la Hoz RE, Miller A. The evolving spectrum of pulmonary disease in responders to the World Trade Center tragedy. *Am J Ind Med*. 2011;54(9):649-660.
36. Szeinuk J, Padilla ML, de la Hoz RE. Potential for diffuse parenchymal lung disease after exposures at World Trade Center Disaster site. *Mount Sinai J Med*. 2008;75(2):101-107.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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