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Original Research

Quantitative CT metrics of injury patterns among WTC workers on different longitudinal FEV_1 trajectory groups

Zitong Zhang [a], Raúl San José Estépar [b], John T. Doucette [a], Jonathan Weber [c], James C. Ross [b], Juan C. Celedón [d], Rafael E. de la Hoz [a,e,*]

[a] Department of Environmental Medicine, New York, NY, USA
[b] Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA
[c] DeMatteis Cardiovascular Institute, St. Francis Hospital & Heart Center, Roslyn, NY, USA
[d] Division of Pediatric Pulmonary Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA, USA
[e] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

Introduction: We have demonstrated diverging FEV_1 trajectories in WTC workers on longitudinal health surveillance. We performed a cohort study to investigate the association of those FEV_1 trajectories with novel QCT markers of subtle lung parenchymal injury.

Methods: We included WTC responders with CT scans with quantitative measurements (all as percentage of the CT-measured lung volume) of five different metrics: normal parenchyma (Norm%), high attenuation normal parenchyma (NormHA%), interstitial lung abnormality features (ILAV%), honeycombing pattern (HcV%), and emphysema. We used linear regression to calculate each subject's FEV_1 slope and classified them into three distinct trajectories: 1) accelerated decline (ACCEL): < -62.5 mL/year; 2) normal decline (NORM): 0 to -30 ml/year, baseline FEV_1%predicted$>70\%$ and no significant dyspnea; 3) improved: >0 mL/year.

Results: Among 446 participants, 211 had ACCEL, 142 NORM, and 93 improved FEV_1 trajectory. On chest CTs at an average of 7.5 years after 11-September-2001 and compared to the NORM subgroup, ACCEL and improved trajectory subgroups both had less normal lung tissue (Norm%), with ACCEL having more emphysema, and improved participants higher ILAV% and NormHA%. The values of HcV% were very low and not significantly different across groups. ACCEL had a significantly higher all-cause mortality.

Conclusion: In this occupational cohort on longitudinal surveillance, accelerated lung function decline appears primarily associated with emphysema and airway disease, while lung function improvement is associated with subtle quantitative CT findings suggestive of interstitial inflammatory processes. The latter appeared largely nonprogressive at the time, as honeycombing was very infrequent and not different across trajectory subgroups.

1. Introduction

Many responders who worked at the World Trade Center (WTC) after the September 11, 2001 attacks were exposed to a poorly characterized [1,2] mix of airborne toxicants during rescue and recovery efforts. These exposures have been associated with several chronic airway diseases [3–7], and longitudinal health and lung function surveillance continues for these occupational cohorts [8]. While studies have consistently reported an average age-related expiratory flow rate decline in the WTC occupational cohorts [9,10], more detailed analyses have revealed diverging trajectories [11,12], with a subset of participants experiencing clearly accelerated FEV_1 decline, while another subset demonstrates an unexpected improvement over time [11]. In order to characterize the structural differences that may underlie these distinct functional trajectories, we have utilized quantitative computed tomography (QCT), a well-established research tool that provides an ever-growing array of measurements of airway and lung parenchymal [13] and other structures within the chest.

* Corresponding author. Division of Occupational and Environmental Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, WTC HP CCE Box 1059, New York, NY, 10029, USA.
E-mail addresses: Zitong.Zhang@mssm.edu (Z. Zhang), rsanjose@bwh.harvard.edu (R. San José Estépar), John.Doucette@mssm.edu (J.T. Doucette), Jonathan.Weber@icahn.mssm.edu (J. Weber), jross@bwh.harvard.edu (J.C. Ross), Juan.Celedon@chp.edu (J.C. Celedón), Rafael.delaHoz@mssm.edu (R.E. de la Hoz).

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We have previously demonstrated QCT changes suggestive of airway inflammatory processes in our cohort of WTC rescue and recovery workers [14,15]. Further, we have shown that proximal airway inflammation, as assessed by wall area percent (WAP), was associated with diverging longitudinal expiratory flow decline [16] in WTC workers. In a longer-term study, we investigated well-established QCT markers of low and high attenuation volume percent, respectively LAV% and HAV% and suggestive of emphysema and interstitial lung disease, both indicative of more chronic destructive parenchymal disease processes. We found that LAV% was associated with accelerated FEV_1 decline, but not with FEV_1 improvement. There was no association of HAV% with either of the diverging FEV_1 trajectories. The improved FEV_1 subgroup, which had the lowest baseline predicted FEV_1, had no association with either LAV% or HAV%. While the value of LAV% has been extensively documented in studies of smokers and COPD (reviewed in Ref. [17]), HAV% has been used less often. Among participants in the Framingham Heart Study, HAV% was only modestly predictive of lung volume loss [18], possibly because some of the interstitial abnormalities quantified by HAV% may be reversible and not necessarily indicative of progressive pulmonary fibrosis. The need for more precise markers of chronic lung parenchymal injury, not exclusively based on lung densitometry, was clear.

To allow a more precise assessment of lung tissue characteristics and subtle forms of injury that may not be visible on standard CT imaging, we examined a group of novel, deep learning driven QCT lung parenchyma texture metrics [19–21] in WTC responders, hypothesizing that they would be differentially associated with our previously defined FEV_1 trajectory groups.

2. Methods

2.1. Study participants and procedures

The current study included 446 members of the WTC Chest CT Imaging Cohort [22,23]. Study participants were general responders, who performed rescue, recovery, and service restoration duties at the WTC disaster site from 11 September 2001 to 30 June 2002 [24], and have participated in the screening, surveillance, and clinical programs of the WTC Clinical Center of Excellence at Mount Sinai Medical Center in New York. As part of their diagnostic evaluation, participants had chest CT scanning and met the following criteria for inclusion in this study: (1) having at least three adequate quality screening and surveillance spirometries, (2) adequate quality imaging study for the QCT measurements under study, and (3) complete data for all covariates of interest. No chest CT scan was obtained for investigation of acute processes (infections, congestive heart failure, pulmonary embolism, etc.). For the current analysis, we selected the first adequate quality and available chest CT scan on each subject. The latest clinical follow up data were available until December 2025, and included, when appropriate, all-cause mortality, as reported to the National Death Index (NDI) or internally to the WTC Health Program, with approximate or exact date, but a few cases required chart review. This study was approved by the Mount Sinai Program for Protection of Human Subjects (Study 12-00925).

2.2. Spirometry and CT imaging procedures

Since inception of the screening and surveillance program, spirometry has been performed using a single device, the EasyOne® portable flow device (ndd Medizintechnik AG, Zurich, Switzerland). We have selected spirometry records with a forced exhalatory volume of at least 6 s and reproducibility grade = A or B, or C if at least 5 trials had been obtained [14]. We calculated predicted values of first-second expiratory volume (FEV_1) with reference equations from the third phase of the National Health and Nutrition Examination Survey (NHANES III) [25].

All chest CT studies were obtained at Mount Sinai Hospital, on General Electric® or Siemens® multidetector row chest CT scanners, as previously described [22,26].

2.3. Measurements

Our main predictors were QCT markers of parenchymal integrity and injury, measured as percentage of the CT-measured lung volume with those characteristics. Each voxel in the lung region was classified according to five distinct and mutually exclusive patterns, namely: (1) normal parenchyma (Norm%), representing regions of lung tissue with completely normal attenuation; (2) high attenuation normal parenchyma (NormHA%) [19], a method that combines densitometry with machine learning to detect high attenuation changes in visually normal appearing lung; (3) interstitial lung abnormality volume (ILAV%) [20], capturing early interstitial changes suggestive of clinical or subclinical fibrotic processes; and (4) honeycombing volume percent (HcV%), indicating regions with characteristic cystic airspace patterns consistent with more advanced fibrotic remodeling. Lastly (5) emphysema scores were derived by combining measures of centrilobular emphysema (CLE) and paraseptal emphysema (PSE), which reflect different morphological subtypes of emphysematous parenchymal destruction. Total lung volume was measured from each subject's chest CT image to derive the proportion of lung volume with the previously listed QCT markers, and to estimate the percentage of the predicted measurement based on the individual's age, gender and height using a race-neutral prediction equation [27]. We compared those quantitative CT-based metrics among the three longitudinal FEV_1 trajectory groups (described below). The Chest Imaging Platform QCT system (http://www.chestimagingplatform.org/) was utilized for all imaging measurements. The Chest Imaging Platform is an open source and well-validated system that has been used in many large studies [28].

Our outcome of interest was longitudinal FEV_1 trajectory. As in previous work [11], we used linear regression to calculate the individual trajectory slope of FEV_1 (FEV_1slope) on each study participant who had a minimum of three acceptable quality spirometries. We then estimated the average group decline, to classify FEV_1slopes into three distinct trajectories defined as follows: (1) accelerated FEV_1 decliner (ACCEL) when FEV_1slope<-62.5 mL/year; (2) FEV_1 improver when FEV_1slope>0 mL/year; (3) the reference normal FEV_1 decline group (NORM) was defined by (a) an FEV_1slope between 0 and -30 mL/year; (b) no records of clinically significant dyspnea on the modified Medical Research Council (mMRC) scale [29]; (c) a pre-bronchodilator FEV_1 percent predicted ([100*pre-bronchodilator FEV_1]/predicted FEV_1) $\geq$ 70% at the baseline visit.

Among the potential confounders considered for model adjustment, we selected the subjects' age on 11-September-2001, sex, height, ethnicity/race (classified as Latino/any race, or non-Latino/White,/Black, or/other), body mass index (BMI) and smoking status (never and ever smokers) at their baseline examination, and an indicator of WTC exposure intensity, namely arrival within 48 h of the disaster.

2.4. Statistical analysis

Continuous variables are described as mean with standard deviation (SD) or median with interquartile range (IQR), and categorical variables as counts and proportions, as appropriate. To evaluate for selection bias and the potential impact of missing data, we used standardized differences (StD) [30] to compare the characteristics of the WTC Chest CT cohort members included and excluded from this study, with values of 0.2, 0.5, and 0.8 representing small, medium, and large differences, respectively. Multinomial logistic regression was used to evaluate the association between each CT-based metric and the FEV_1 longitudinal trajectory groups. Separate models were constructed for each metric, with the three-level lung function trajectory as the outcome, to estimate the relative odds of observing each lung trajectory per unit increase in the metric, using the normal decline (NORM) group as the reference.

Interaction terms between covariates were tested in the models. Model fitness was assessed using the Akaike Information Criterion (AIC), and comparable AIC values across models indicated similar overall model performance regardless of the specific CT-based metric used. 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. We followed the STROBE guidelines for manuscript preparation [31].

3. Results

Fig. 1 shows the study flowchart with the process to select the three well defined comparison groups. Spirometry data from July 2002 to December 2019 were available. Of the 446 selected study participants, 211 had accelerated longitudinal FEV_1 decline (ACCEL), 142 had normal FEV_1 decline (NORM), and 93 demonstrated FEV_1 improvement. For the longitudinal analysis of their lung function trajectories, participants were followed for a mean (SD) of 10.7 (4) years, each contributing an average of 5.2 (2) acceptable quality spirometry measurements. The average spirometry follow up time was slightly longer for NORM (14.1 years), than for ACCEL and improver groups (12.6 and 12.5 years, respectively). Chest CT scans were obtained at an average of 7.5 (SD 2) years after 11 September 2001, with no difference by trajectory subgroup (data not shown).

Table 1 shows the characteristics of the study population and the three trajectory subgroups. Their mean age on 11 September 2001 was 41.4 (8.8) years, with a predominance of male sex (88%) and non-Latino White ethnicity/race (57%), followed by Latino ethnicity (23%) and non-Latino Black race (10%). Nearly half of our subjects (49%) reported a history of having ever smoked cigarettes, and 51.8% arrived at the WTC site within 48 h of the disaster. Compared to subjects from the WTC Chest CT Imaging Archive cohort who were excluded from this study, those included had a small difference (standardized difference 0.21) in male gender predominance (Table OS1).

Compared to participants in the NORM group, those in both the ACCEL and improver groups were older and had higher baseline BMI and a higher proportion of ever-smokers. The percent predicted total lung volumes were similar for subjects in the NORM (82.2%) and ACCEL (83.2%) groups, while the improver group exhibited the smallest lung volumes (75.9%).

Table 1 also shows the mean value of quantitative CT-derived lung metrics among trajectory groups. Participants in the normal decline group had a higher mean proportion of normal lung parenchyma (Norm %, 81.8%, SD 15.9%) than those in the accelerated decliner (77.6%, SD 17.8%) and improver groups (74.2% SD 20%). Participants in the improver group had significantly higher proportion of high attenuation normal parenchyma (NormHA%, 11.7%, SD 15.1%) than both the accelerated decliner (7.0%, SD 10.3%) and normal decliner (6.9%, SD 11.4%) groups. Participants in the improver group also had higher interstitial lung abnormality volume percent (ILAV%, 5.8%, SD 6.7%) than both the normal (3.9%, SD 5.2%) and the accelerated decline (5.1%, SD 7%) groups. Conversely, the highest emphysema scores, a combination of CLE and PSE scores, were observed in the accelerated decline group (6.0%, SD 6.3%), compared with both the normal (4.0%, SD 3.8%) and the improver (4.8%, SD 4.2%) groups. Honeycombing volume (HcV%) percent measurements were, on the other hand, quite low and very similar across all three groups. As of December 2025, the all-cause mortality was significantly higher among the accelerated decliner trajectory group compared to all others. The significance of that association persisted after adjustment for age (data not shown).

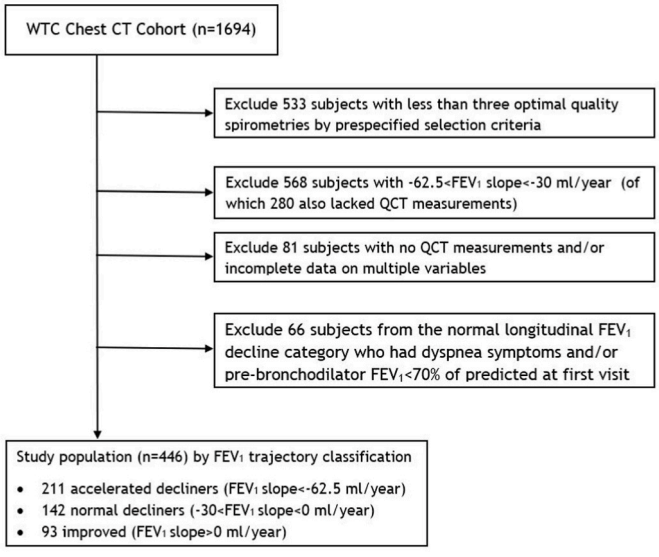

Fig. 1. Study flowchart.

Table 2 shows the odds of observing different lung function trajectories with each unit increase in different QCT metrics. Compared with a normal longitudinal FEV_1 decline, each unit increase in Norm% scores was associated with significantly lower odds of an accelerated decline (OR_{adj} = 0.986, 95% CI 0.972, 1.000) or an improved trajectory (OR_{adj} = 0.977, 95% CI 0.962, 0.993). Further, each unit increase in NormHA% and ILAV% was associated with significantly higher odds of an improved trajectory compared with a normal decline (for NormHA%, OR_{adj} = 1.03, 95% CI 1.006, 1.051; for ILAV%, OR_{adj} = 1.05, 95% CI 1.005, 1.058). In addition, each unit increase in the emphysema score was associated with a significantly higher odds of observing an accelerated decline compared with a normal decline (OR_{adj} = 1.07, CI 1.014, 1.137) FEV_1 trajectory. We did not observe significant differences among the three lung function trajectory groups in honeycombing ILAV % scores. There were no significant interaction effects in the logistic regression models. In a *post hoc* analysis we observed that all the QCT metrics of an intermediate FEV_1 decline trajectory group (-62.5 ml/yr $<$ FEV_1 slope $<$ -30 ml/year, n = 288) lay between those of ACCEL and NORM, except for NormHA%, which seemed equal to that of ACCEL (data not shown).

4. Discussion

In this study of WTC rescue and recovery workers and volunteers, there were significant differences in quantitative CT imaging-assessed lung parenchymal texture between groups with different longitudinal FEV_1 trajectory. The highest proportion of normal lung parenchyma (Norm%) was observed in subjects with no reported significant dyspnea and a normal longitudinal FEV_1 trajectory, suggesting relatively preserved lung architecture. Lower Norm% scores and higher emphysema scores were associated with accelerated FEV_1 decline, which confirms our previous finding using lung attenuation volume% (LAV%), a densitometric QCT measurement of emphysema [11]. Lower Norm% and higher NormHA% and ILAV% scores were interestingly associated with the FEV_1 improvement trajectory, perhaps reflecting functional recovery from still somewhat active lung interstitial inflammation or remodeling perhaps following an early injury phase.

Despite suspected risk [32,33], no study has thus far demonstrated clinical, radiological and functional evidence of increased incidence of interstitial lung disease and abnormalities among WTC rescue and recovery workers and volunteers [23,34–36]. The studies may have been limited by poor relevant exposure assessment and thereby classification, and insufficiently long follow up time to account for latency [33] but also lack of adequate subgroup analyses. Using novel QCT lung texture metrics [19–21], our findings suggest that the diverging longitudinal FEV_1 trajectory groups have different associated predominant lung parenchymal disease processes. Accelerated decline in a subgroup of these workers is associated primarily with emphysema, a key pathophysiological component of chronic obstructive pulmonary disease (COPD), and not with interstitial lung disease abnormalities and disease.

Table 1
Characteristics of 446 WTC responders with functional and QCT imaging data, classified according to longitudinal FEV_1 trajectory: normal decline, accelerated decline, and improved.

	General (n = 446)		Normal decline (n = 142, 31.8%)		Accelerated decline (n = 211, 47.3%)		Improved (n = 93, 20.9%)	
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %
Age at 9/11/2001 (yr)	41.44	8.80	39.82	8.22	43.10	9.06	40.13	8.46
Height (cm)	173.00	9.16	170.52	9.53	174.48	8.13	173.40	10.02
BMI (kg/m^2)	29.38	4.69	28.84	4.67	29.59	4.66	29.74	4.76
Male gender	393	88.12	171	82.61	197	93.36	80	86.02
Ethnicity/race								
Non-Latino/Black	43	9.64	14	9.86	17	8.06	12	12.90
Latino/any race	102	22.87	47	33.10	36	17.05	19	20.43
Non-Latino/White	253	56.73	65	45.77	139	65.88	49	52.69
Other/Unknown	48	10.76	16	11.27	19	9.00	13	13.98
Ever smoking status	216	48.98	55	38.73	118	56.73	43	47.25
WTC arrival<48 h	229	51.81	75	52.82	104	49.76	50	54.95
Interval between 911 and CT test (yr)	7.52	1.95	7.38	1.73	7.70	1.97	7.29	2.20
Whole lung volume (L)[a]	5.13	1.39	5.01	1.33	5.34	1.37	4.84	1.44
TLC predicted[a]	6.29	0.93	6.05	1.00	6.42	0.81	6.36	1.03
Lung Volume%pred[a]	81.42	20.52	82.23	20.31	83.24	20.55	75.86	20.02
QCT metrics[b]								
Norm%	78.22	17.89	81.83	15.87	77.58	17.80	74.15	20.03
NormHA%	7.94	11.92	6.87	11.41	7.02	10.32	11.65	15.08
ILAV%	4.87	6.43	3.86	5.17	5.13	7.00	5.80	6.70
HcV%	0.40	1.65	0.26	0.29	0.54	2.38	0.31	0.26
Emphysema	5.11	5.23	4.01	3.77	5.99	6.25	4.78	4.17
CLE	2.32	2.87	1.72	2.06	2.81	3.49	2.11	2.09
PSE	2.79	2.67	2.29	2.02	3.18	3.08	2.67	2.40
All-cause mortality	42	9.11	2	1.27	36	17.06	4	4.30

[a] QCT measured total lung volume as a percent of the predicted total lung capacity (TLC) value based on age, height, and gender [27].
[b] QCT measurements of lung parenchymal texture, all expressed as proportion of the QCT measured total lung volume. Norm%: completely normal lung parenchyma; NormHA%: visually normal lung parenchyma with measurable high attenuation; ILAV%: interstitial lung abnormalities or disease; HcV%: honeycombing; emphysema: areas with what appeared as centrilobular (CLE) or paraseptal (PSE) emphysema.

Table 2
Adjusted odds of observing accelerated decline or improved longitudinal FEV_1 trajectory with each unit increase in the lung texture parenchymal QCT metrics[b], with the normal decline subgroup as reference. The multinomial logistic regression model was adjusted for age on 9/11/2001, gender, BMI, baseline smoking status, and WTC arrival within 48 h.

QCT metrics[b]	Adjusted odds ratio for FEV_{1t} trajectory groups (OR_{adj}, 95% CI)	
	Accelerated decline vs normal decline	Improved vs normal decline
Norm%	0.986 (0.972, 1.000)[a]	0.977 (0.962, 0.993)[a]
NormHA%	1.003 (0.982, 1.024)	1.028 (1.006, 1.051)[a]
ILAV%	1.035 (0.994, 1.078)	1.050 (1.005, 1.058)[a]
HcV%	1.823 (0.831, 4.001)	1.596 (0.701, 3.633)
Emphysema	1.073 (1.014, 1.137)[a]	1.050 (0.981, 1.124)

[a] p-value<0.05.
[b] QCT measurements of lung parenchymal texture, all expressed as proportion of the QCT measured total lung volume. Norm%: completely normal lung parenchyma; NormHA%: visually normal lung parenchyma with measurable high attenuation; ILAV%: interstitial lung abnormalities or disease; HcV%: honeycombing; emphysema: areas with what appeared as centrilobular (CLE) or paraseptal (PSE) emphysema.

Conversely, the subgroup that showed evidence of lung function improvement (unexpected for their age) exhibited subtle QCT patterns suggestive of interstitial lung abnormalities, including increased high attenuation in normal-appearing lung (NormHA%), a pattern previously associated with inflammatory processes [19] and interstitial lung abnormalities. This suggests a parenchymal pattern of perhaps reversible interstitial inflammation, and in turn may explain why more global assessments of high attenuation volume percent (HAV%) have been relatively unrewarding in research studies of this [11] and other cohorts [18]. One possible explanation is that HAV% identifies a mix of progressive (fibrotic) and reversible interstitial inflammatory disease [37]. Finally, the scanty evidence so far of progressive pulmonary interstitial fibrosis in any of our subgroups, as measured by quantitative (such as HcV% in this study), semiquantitative [22] or qualitative studies [34] further suggests a pattern associated with improvement, and support the recommendation for systematic follow up and risk stratification [38,39] that may be applicable to surveillance settings such as ours.

Our study has substantial strengths, including access to a well-characterized cohort of WTC responders with long-term follow-up and repeated spirometry measurements (minimum of 3, average 5), allowing robust classification of lung function trajectories [40]. The study also presented evidence of the relevance of our FEV_1 trajectory groups by showing a clear difference in mortality among them. Moreover, we were able to capture subtle and diverse patterns of lung injury using novel validated quantitative CT imaging metrics, which can provide more detailed insight into lung structure and texture, and thus enhance our ability to detect and compare underlying differences across lung function trajectories.

We acknowledge several study limitations. First, we had a relatively small sample size due to the need to have complete and adequate quality imaging and functional data, as well as strict *a priori* definitions of the trajectory groups, in part to reduce the potential impact of the previously reported high coefficients of variation of the QCT metrics. Second, the novel and promising QCT metrics that we deployed (Norm%, NormHA%, ILAV% and HcV%) have been utilized in relatively small studies and will benefit from further validation. QCT remains largely a research tool, with many factors still limiting its clinical use, such as sensitivity to highly variable chest imaging equipment and protocols, and lack of clinically established and validated diagnostic cutoffs. Third, we used surveillance spirometry. Despite widespread lack of recognition, similar technical limitations and challenges are common in most large-scale respiratory epidemiology studies, and we applied well-specified and specific quality criteria for spirometry selection into this study, which are consistent with our previous ones and with accepted guidelines. Fourth, selection bias is possible in any observational study, though there were no differences between eligible subjects who were and were not included in the current analysis. Lastly, there are limitations and proposed alternatives to linear regression-based methods to

describe lung function trajectories [41], but investigations in our cohort continue to suggest its value.

In summary, our results support the value of QCT-based lung metrics to detect subtle but significant structural differences among WTC responders with diverging longitudinal lung function trajectories. Study participants with differing FEV_1 trajectories showed distinct patterns in QCT-derived lung texture metrics. Accelerated decliners in this occupational cohort with plummeting cross-sectional current smoking rates [7,14] had more emphysema and less normal lung tissue, while the improver group showed increased NormHA% and ILAV%, possibly reflecting post-injury interstitial inflammation, and less normal lung tissue. Our findings underscore the structural and functional differences among the subgroups of WTC responders and support the use of quantitative imaging and longitudinal functional trending to improve our understanding of long-term pulmonary outcomes in a cohort on long-term respiratory health surveillance.

CRediT authorship contribution statement

Zitong Zhang: Formal analysis, Methodology, Writing – original draft. **Raúl San José Estépar:** Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **John T. Doucette:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Jonathan Weber:** Data curation, Formal analysis, Methodology, Writing – review & editing. **James C. Ross:** Methodology, Writing – review & editing. **Juan C. Celedón:** Conceptualization, Methodology, Writing – review & editing. **Rafael E. de la Hoz:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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