

Cluster Analysis of World Trade Center Related Lower Airway Diseases

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Abstract: Introduction: Cluster analysis can classify without *a priori* assumptions the heterogeneous chronic lower airway diseases found in former workers at the World Trade Center (WTC) disaster site. Methods: We selected the first available chest computed tomography scan with quantitative computed tomography measurements on 311 former WTC workers with complete clinical, and spirometric data from their closest surveillance visit. We performed a nonhierarchical iterative algorithm K-prototype cluster analysis, using gap measure. Results: A five-cluster solution was most satisfactory. Cluster 5 had the healthiest individuals. In cluster 4, smoking was most prevalent and intense but there was scant evidence of respiratory disease. Cluster 3 had symptomatic subjects with reduced forced vital capacity impairment (low FVC). Clusters 1 and 2 had less dyspneic subjects, but more functional and quantitative computed tomography evidence of chronic obstructive pulmonary disease (COPD) in cluster 1, or low FVC in cluster 2. Clusters 1 and 4 had the highest proportion of rapid first-second forced expiratory volume decliners. Conclusions: Cluster analysis confirms low FVC and COPD/pre-COPD as distinctive chronic lower airway disease phenotypes on long-term surveillance of the WTC workers.

Keywords: occupational lung disease, smoke inhalation injury, chronic obstructive pulmonary disease, World Trade Center Attack, 2001, longitudinal changes in lung function, spirometry

Among workers engaged in rescue and recovery efforts, occupational exposures to dust and fumes at the World Trade Center (WTC) disaster site have been associated with lower respiratory symptoms,¹ worse lung function² and accelerated longitudinal lung function decline trajectories,^{3,4} asthma⁵ and other chronic airway diseases,^{6–8} and both qualitative⁹ and quantitative^{4,8,10–12} abnormalities on computed tomography (CT) of the chest. Common co-existing morbidities, such as obesity, are linked to greater severity of WTC-related respiratory symptoms, airway disorders, and morbidity.^{13–19}

The heterogeneity of the WTC-related lower airway diseases (LAD) poses a challenge for research studies and clinical care. Although stringent case definitions have been used to address this issue

LEARNING OUTCOMES

After reading this article readers will be able to:

- Understand the value of cluster analysis in the clinical and pathophysiological characterization of heterogeneous airway disorders.
- Appraise the value of longitudinal surveillance and detailed objective clinical functional, and imaging evaluation in the characterization of adverse respiratory health effects from an exposure.

in clinical research studies,⁶ cluster analysis can be particularly helpful in classifying heterogeneous WTC-related chronic LAD²⁰ into groups without any *a priori* assumptions. To achieve this goal, cluster analysis examines multiple clinical, physiologic, and imaging characteristics, including novel quantitative chest CT (QCT) features.

Identifying categories or clusters of WTC-related chronic LAD could help us better study and understand their pathogenesis, which should ultimately lead to improved diagnosis and management. We sought to, first, identify clusters of WTC-related chronic LAD and then examine their association with longitudinal lung function trajectories^{4,10} as clinical outcomes, in a cohort of WTC workers with QCT imaging data.

METHODS

Subject Recruitment and Study Procedures

All study subjects were members of the Mount Sinai WTC General Responders' Cohort (GRC)²¹ who had chest CT images and

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This article has two online supplements.

Funding sources: This work was supported by cooperative agreement no. U01 OH010401 (specific aim 1, RED, PI; Y.J., JTD, RSI, and JCC co-Is, APR co-I in 2012-2016), and contract 200-2017-93325 (WTC General Responders Cohort Data Center) from the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH). The contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the CDC/NIOSH.

Interim results of this work were presented as an abstract at the 2021 International Congress of the European Respiratory Society (*Eur Respir J*. 2021;58(suppl 65):PA3350. doi: 10.1183/13993003.congress-2021.PA3350). We adhered to the STROBE guidelines for cross-sectional studies (see Supplementary Digital Content).

Conflict of interest: R.E.D. received honoraria from the European Respiratory Society. A.P.R. received royalty payment from Cornell Center for Technology Licensing for patents licensed to General Electric (GE), has stock options in, and is a member of the Scientific Advisory Board of HeartLung Technologies. R.S.J. has a contract to serve as Image Core for studies sponsored by Lung Biotechnology and Insmad, respectively, has a sponsored research agreement with Boehringer Ingelheim, receives consulting fees from Leuko Labs and Icahn School of Medicine at Mount Sinai, has three patents pending in the space of lung cancer risk assessment using machine learning technology, and is co-founder and stock holder of Quantitative Imaging Solutions. J.C.C. has received research materials (inhaled corticosteroids) from Merck, to provide medications free of cost to participants in a National Institutes of Health (NIH)-funded study, unrelated to the current work.

Authors' contributions: R.E.D., Y.J., and J.C.C. designed and oversaw the study and selected analytical strategies. A.P.R. and R.S.J. performed all quantitative computed tomography measurements. Y.J. and J.T.D. performed all statistical analyses. All authors contributed to writing, reviewed and revised the drafts, and approved the final manuscript.

Supplemental digital contents are available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.joem.org).

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DOI: 10.1097/JOM.0000000000003023

QCT data in the WTC Chest CT Imaging Archive⁹ and who also had complete clinical and spirometric data from the surveillance visit closest to the CT scan. The procedures conducted during the surveillance visits²² and the chest CT scanning procedures^{4,9} have been previously described in detail, and we selected the first available chest CT scan with QCT measurements. As in our previous studies, all QCT measurements were performed with the Chest Imaging Platform (<https://chestimagingplatform.org>) or the SIMBA Image Management and Analysis System (<http://www.via.cornell.edu/visionx/simba/>) by their respective developers (R.S.J. and A.P.R.).^{4,8,10–12}

We selected spirometries that met our quality selection requirement, namely, forced exhalatory time >6 seconds and overall spirometry (reproducibility) grades A, B, or (if at least five trials were available) C.^{2,8,23} As previously reported,²³ our spirometry program quality assurance included both daily inspiratory and expiratory volume calibration checks and weekly expiratory linearity checks.

For the cluster analysis, we examined 21 characteristics, including those in the following groups¹: self-reported demographic information such as age on September 11, 2001, sex, and ethnicity/race (grouped into Latino of any race, non-Latino White, and all other races)²; smoking status (never, former, and current) and intensity of smoking (in pack-years), as previously defined^{2,24,3}; self-reported indicators of occupational exposures at the WTC site, such as early arrival (within 48 hours) at the site²⁵ and cumulative exposure duration.^{2,6} From the periodic surveillance visit closest to the chest CT scan, we included the following⁴: clinically significant dyspnea (defined as a modified Medical Research Council score ≥ 2 [*“I walk slower than people of my same age on the level because of breathlessness, or have to stop for breath when walking at my own pace on the level”*]^{26,5}); spirometric pattern, classified as normal, low forced vital capacity (FVC < lower limit of normal, with normal ratio of first-second forced expiratory volume [FEV₁] to FVC, FEV₁/FVC), or obstructive (FEV₁/FVC < lower limit of normal).^{2,27} We also considered⁶ bronchodilator response (BDR) at any visit, most often the baseline, defined as an increase in either FEV₁ or FVC of at least 12% and 200 mL in response to inhaled albuterol administration^{7,10}; body mass index (BMI) in kilograms per square meter measured at the baseline visit⁸; weight gain (as indicated by longitudinal measured BMI trajectory (BMIslope) in kilograms per square meter per year¹⁰). Lastly, from the QCT data,⁹ total lung volume (TLV_{CT}), with calculated predicted values²⁸ and assessed by *z* scores,¹⁰ lung attenuation volume percent, either high (HAV% from -600 to -250 Hounsfield units [HU], with >10% as cut point) and low (LAV% less than -950 HU, low attenuation volume percent, with >2.5% as cut point),^{4,29} indirect distal airway measurements such as¹¹ end-expiratory air trapping at -856 HU (AT_{EXP}-856),^{8,29} and¹² mean expiratory:inspiratory lung density ratio (MLD_{EL}),⁸ and proximal airway metrics such as¹³ wall area percent (WAP) directly measured on the third generation of the right upper lobe,^{8,10,29} and¹⁴ Pi10, the average wall thickness of a hypothetical airway with a 10-mm luminal perimeter on CT.^{29,30}

As in previous studies of longitudinal lung function trajectories among participants in the Mount Sinai WTC GRC cohort,^{4,10} we conducted a secondary analysis of the FEV₁ trajectories for the resulting clusters. As in previous work,⁴ we estimated the longitudinal FEV₁slopes for each subject with at least 3 good quality (as defined previously) spirometries performed between July 2002 and December 2018, and used them to define the following three trajectories as follows: rapid FEV₁ decline (*“rapid decliner”*) by an FEV₁slope < -66.5 mL/y (ie, less than the group mean-0.5 SD), FEV₁ gain (*“gainer”*) by an FEV₁slope > 0 mL/y, and intermediate FEV₁ decline (*“intermediate decliner”*) by an FEV₁ slope between 0 and -66.5 mL/y (ie, between 0 and the group mean-0.5 SD).

The Mount Sinai Program for the Protection of Human Subjects approved this study (HS 12-00925). We adhered to the Strengthening the Reporting of Observational studies in Epidemiology guidelines for cross-sectional studies (see Supplementary Digital Content, <http://links.lww.com/JOM/B466>).

Statistical Analysis

Given our mix of continuous and categorical variables, we chose a nonhierarchical iterative method, the K-prototype clustering algorithm. This algorithm integrates the K-means, for continuous variables, and K-modes, for categorical variables, based on partitioning a set of subjects into homogeneous clusters.^{31–33} The K-prototype algorithm is available in the KCLUS procedure in SAS Viya (SAS Institute, Cary, NC), a cloud-enabled, in-memory analytics engine that provides quick, accurate, and reliable analytical insights. All continuous variable measurements were standardized using *z*-scores. The optimal number of clusters was determined by the first peak of the gap statistic³⁴ on the K-prototype clustering analysis. The gap measure is obtained by subtracting the logarithm of the within-cluster sum of squares error from the logarithm of its expectation for clustering solutions over a range of possible number of clusters. Differences between clusters were compared using Pearson χ^2 test or analysis of variance, as appropriate. For the secondary analysis comparing FEV₁ trajectory groups (rapid and intermediate decline, and gain) among the resulting clusters, we used Pearson χ^2 test. For the comparison of the subjects included versus those excluded from the study, we used standardized differences (StDs).³⁵ For dichotomous variables, average differences between proportions expressed in standard deviation units were calculated. For skewed distribution continuous variables (eg, smoking intensity and WTC exposure duration), we used a rank-based method to calculate StDs. For categorical variables with *k* levels (eg, ethnicity/race and smoking status), we used a multivariate Mahalanobis distance method to generalize the standardized difference metric to handle a multinomial sample. The StD values of 0.2 to 0.5 are generally considered small. For all other statistical tests, a *P* value < 0.05 was considered significant. All analyses were conducted in SAS Viya 3.5 and SAS version 9.4 (SAS Institute, Cary, NC). For graphical purposes, the results were displayed as a heat map, using Microsoft Office Excel version 365 (Microsoft Corporation, Redmond, WA), and conditional formatting with color scaling.

RESULTS

From the WTC Chest CT Imaging Archive cohort (N = 1630), 311 subjects had all QCT measurements, as well as complete clinical and spirometric data from the surveillance visit closest to the CT scan. None of the StDs in the comparison of variables between the subjects included in this study and those with incomplete or missing data and thus excluded (n = 1319, see Supplemental Digital Content, Table OS1, <http://links.lww.com/JOM/B467>) suggested an important difference in age, baseline BMI, smoking status, early WTC exposure arrival and cumulative duration, prevalence of dyspnea, or evidence of BDR. Included subjects' smoking intensity was slightly higher than among excluded subjects (7.8 [11.6] vs 6.3 [12.8] pack-years, StD = 0.22).

Table 1 summarizes the main characteristics of the 311 study participants included in the study and the results of the cluster analysis. Chest CT scans were performed 6.65 (SD = 1.87) years and nearest spirometries 6.43 (SD = 2.12) years after September 11, 2001. Consistent with the characteristics of the WTC General Responders Cohort,² the participants' mean age (SD) was 42.9 (8.5) years on September 11, 2001, most were male (approximately 84%) and nearly half (49.8%) arrived at the WTC disaster site within 48 hours (early).

The cluster analysis showed that two, three, and five clusters generated the highest gap statistic (1.21–1.26), but that a five-cluster solution seemed most satisfactory. Except for HAV%, all variables were significantly different among the five clusters (Table 1), which are displayed graphically in the heat map of Figure 1. Clusters 3 and 5 had a lower proportion of male participants (approximately 68% to approximately 72%) than that in other clusters (ranging from approximately 86% to approximately 95%). In all clusters, the mean baseline BMI was ≥ 27.7 kg/m², with cluster 3 having the highest mean value (31.3 kg/m²). On the other hand, cluster 3 was the only one with a slight

TABLE 1. Characteristics and Functional and QCT Findings of the Study Population (*n* = 311), Presented as Counts and Proportions, or Means and SDs

Variables	Pauci-Symptomatic With High Prevalence of Airflow Obstruction	Pauci-Symptomatic With Intermediate Prevalence of a Low FVC Pattern	Symptomatic With High Prevalence of a Low FVC Pattern	Nonsusceptible Smokers	Relatively Healthy Subjects	Total	<i>P</i>
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5		
<i>n</i>	29	82	40	86	74	311	
Age on 9/11/2001, yr	46.4 (10.3)	42.2 (8.8)	42.2 (7.4)	44.2 (7.2)	41.1 (9.0)	42.9 (8.5)	0.0241
Male sex	25 (86.2)	75 (91.5)	27 (67.5)	81 (94.2)	53 (71.6)	261 (83.9)	<0.0001
Ethnicity/race							
Non-Latino/White	20 (69.0)	53 (64.6)	8 (20.0)	77 (89.5)	8 (10.8)	166 (53.4)	<0.0001
Non-Latino/other races	3 (10.3)	16 (19.5)	6 (15)	9 (10.5)	6 (8.1)	40 (12.9)	
Latino/any race	6 (20.7)	13 (15.9)	26 (65.0)	0 (0)	60 (81.1)	105 (33.8)	
Height, cm	172.6 (7.7)	175.3 (9.6)	167.3 (8.5)	175.4 (8.7)	164.6 (9.4)	171.5 (10.1)	<0.0001
Baseline BMI, kg/m ²	27.7 (3.7)	28.7 (4.5)	31.3 (5.4)	28.8 (4.0)	28.3 (4.0)	28.9 (4.4)	0.0042
BMI slope, kg/m ² /yr	0.13 (0.26)	0.05 (0.29)	−0.02 (0.31)	0.13 (0.34)	0.18 (0.37)	0.10 (0.3)	0.0116
Smoking status							<0.0001
Never smoker	8 (27.6)	57 (69.5)	20 (50.0)	13 (15.1)	53 (71.6)	151 (48.6)	
Former smoker	13 (44.8)	15 (18.3)	13 (32.5)	43 (50.0)	7 (9.5)	91 (29.3)	
Current smoker	8 (27.6)	10 (12.2)	7 (17.5)	30 (34.9)	14 (18.9)	69 (22.2)	
Smoking intensity, pack-years	15.8 (16.4)	3.6 (7.1)	7.6 (11.0)	14.1 (12.6)	2.0 (5.8)	7.8 (11.6)	<0.0001
WTC arrival time ≤48 hr	11 (37.8)	79 (96.3)	30 (75.0)	26 (30.2)	9 (12.2)	155 (49.8)	<0.0001
WTC exposure duration, d	85.0 (68.3)	70.2 (64.9)	97.4 (82.1)	98.4 (75.7)	104.6 (72.5)	91.1 (73.2)	0.0313
Dyspnea mMRC ≥ 2	5 (17.2)	13 (15.9)	40 (100.0)	27 (31.4)	17 (23.0)	102 (32.8)	<0.0001
Lung function							
FEV ₁ %predicted	70.2 (17.4)	78.4 (15.0)	76.0 (12.5)	92.9 (11.3)	96.7 (16.5)	85.7 (17.2)	<0.0001
Spirometry pattern							<0.0001
Normal	7 (24.1)	24 (29.3)	6 (15.0)	80 (93.0)	65 (87.8)	182 (58.5)	
Low FVC	3 (10.3)	45 (54.9)	30 (75.0)	5 (5.8)	4 (5.4)	87 (28.0)	
Obstruction	19 (65.5)	13 (15.9)	4 (10.0)	1 (1.16)	5 (6.8)	42 (13.5)	
BDRany	23 (79.3)	25 (30.5)	17 (42.5)	10 (11.6)	6 (8.1)	81 (26.0)	<0.0001
QCT metrics							
TLV _{CT} z score	1.04 (0.83)	0.07 (0.77)	−0.063 (0.62)	0.78 (0.85)	−0.11 (0.78)	0.22 (0.94)	<0.0001
WAP	64.0 (6.6)	61.6 (8.0)	63.9 (7.8)	59.2 (7.4)	61.1 (6.4)	61.3 (7.5)	0.0031
AT _{Exp856}	22.3 (17.6)	4.7 (7.0)	3.0 (6.0)	6.6 (7.2)	7.4 (9.0)	7.3 (10.2)	<0.0001
MLD _{EI}	88.1 (4.4)	81.0 (5.9)	81.5 (7.0)	81.9 (6.1)	83.9 (5.7)	82.7 (6.3)	<0.0001
PI _{I0}	2.75 (0.16)	2.72 (0.15)	2.67 (0.12)	2.76 (0.015)	2.69 (0.12)	2.72 (0.14)	0.004
LAV% > 2.5%	21 (72.4)	3 (3.7)	0	8 (9.3)	7 (9.5)	39 (12.5)	<0.0001
HAV% > 10%	1 (3.5)	3 (3.7)	5 (12.5)	5 (5.8)	5 (6.8)	19 (6.1)	0.3885

AT_{Exp856}, end-expiratory air trapping at -856 HU; BDRany, bronchodilator response at any visit; FVC, forced vital capacity; HAV%, high attenuation volume percent; LAV%, low attenuation volume percent; mMRC, modified Medical Research Council; PI_{I0}, average wall thickness of a hypothetical airway with a 10-mm luminal perimeter on CT; TLV_{CT}, total lung volume by chest CT; MLD_{EI}, mean expiratory:inspiratory lung density ratio; WAP, wall area percent.

weight loss instead of weight gain over time. Regarding smoking status, former and current smoking were most frequent in clusters 1 (72.4%) and 4 (84.9%) and least so in clusters 2 (30.5%) and 5 (28.4%). Consistent with such smoking status, clusters 1 (15.8 pack-years) and 4 (14.1 pack-years) had the highest smoking intensity, while clusters 2 (3.6 pack-years) and 5 (2.0 pack-years) had the lowest smoking intensity. While early arrival to the WTC disaster site was most commonly reported among subjects in clusters 2 (96.3%) and 3 (72.4%),² subjects in cluster 3, 4, and 5 had longer cumulative WTC occupational exposure than those in clusters 1 and 2. With regard to spirometric patterns, airflow obstruction was most common in cluster 1 (65.5% of subjects), and a low FVC pattern prevailed in clusters 2 and 3 (54.9% and 75% of subjects, respectively). Conversely, a normal spirometry largely predominated in subjects in cluster 4 and 5 (93% and 87.8%, respectively), with relatively infrequent BDR (11.6 and 8%, respectively).

Based on the observed clinical, spirometric, and imaging characteristics, the five clusters could be defined as follows (Fig. 1):

1. Cluster 1—Pauci-symptomatic with high prevalence of airflow obstruction: slightly older age and including predominantly (approximately 69%) non-Hispanic White subjects; frequent former

and current smoking; relatively common late arrival at WTC site; low frequency of clinically significant dyspnea; lowest mean FEV₁%predicted with both airflow obstruction and bronchodilator responsiveness most commonly observed; high TLV_{CT}, WAP, AT₈₅₆, MLD_{EI}, and PI_{I0}; and lowest frequency of high HAV%. Most of these subjects were diagnosed clinically with COPD⁶ or pre-COPD.³⁶

2. Cluster 2—Pauci-symptomatic with intermediate prevalence of a low FVC pattern: predominantly never smoking, male and non-Latino subjects, most of whom arrived early at the WTC site; low frequency of dyspnea; slightly reduced mean FEV₁%predicted; and lowest HAV% without other positive QCT markers.
3. Cluster 3—Symptomatic with high prevalence of a low FVC pattern: highest proportion of women and Latinas(os); highest baseline BMI but no weight gain; dyspnea in all subjects with predominance of a low FVC pattern, slightly reduced mean FEV₁%predicted and relatively common bronchodilator responsiveness (second only that of subjects in cluster 1); frequent early arrival and longer stay at the WTC disaster site. Most subjects in this group were diagnosed clinically as having either chronic nonspecific bronchitis or asthma.^{6,7}

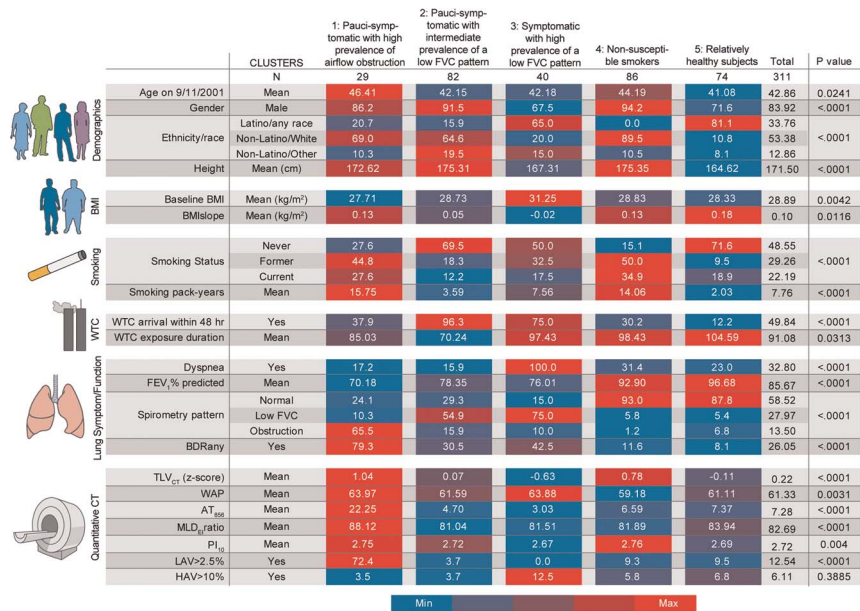


FIGURE 1. Cluster analysis with K-prototype of 311 WTC rescue and recovery workers from the WTC GRC and the WTC Chest CT Imaging Archive. With the exception of QCT measured HAV%, unadjusted analyses demonstrated statistically significant differences for all variables among the five clusters.

- 4. Cluster 4—Nonsusceptible smokers: slightly older and predominantly male non-Latino White subjects; highest proportion of former and current smokers; uncommon early arrival but high cumulative exposure to the WTC site; intermediate proportion of dyspnea with highest mean FEV₁%predicted and predominantly normal spirometry pattern with rarely observed bronchodilator responsiveness; high TLV_{CT} and highest Pi10.
- 5. Cluster 5—Relatively healthy subjects: slightly younger and predominantly never smoking Latino subjects with highest average weight gain; very infrequent early arrival but highest cumulative exposure to the WTC disaster site; dyspnea in a quarter of subjects; high mean FEV₁%predicted with very frequent normal spirometry pattern and very rare bronchodilator responsiveness; and average or fairly normal QCT markers.

Of note, 39.2% of the Non-Latino White subjects were Polish workers, almost all of them ever-smokers³⁷ and, not surprisingly, mostly in clusters 1 (31%, 9 of 29) or cluster 4 (54.8%, or 46 of 84). Lastly, we analyzed FEV₁ longitudinal trajectory groups as a clinical outcome for the five clusters (Table 2). For this longitudinal analysis, we had a mean of 5.0 (SD = 1.7) good quality spirometries in each of 256 of our subjects (82.3%). In this analysis, the highest proportion of subjects with rapid decline in FEV₁ was in cluster 1, while the highest proportion of subjects with intermediate decline in FEV₁ was in clusters 2 and 3. Although cluster 1 had the highest proportion of subjects with gain in FEV₁, this was based on a low count. Of note,

subjects in cluster 4, who had one of the highest mean FEV₁%predicted and predominance of normal spirometry, but also the highest Pi10, had a proportion of subjects with rapid decline in FEV₁ only second to that of subjects in cluster 1.

DISCUSSION

Cluster analysis confirms a low FVC pattern (clusters 2 and 3) and chronic airflow obstruction (suggestive or consistent with COPD, cluster 1)^{2,8,38} as distinctive chronic LAD phenotypes in WTC responders, while also supporting the presence of two distinct subgroups with unique clinical characteristics and longitudinal trajectories, seemingly nonsusceptible smokers in cluster 4 and relatively healthy subjects in cluster 5. Our analysis also illustrated the adverse cross-sectional and longitudinal lung function effects of tobacco smoking, obesity, and longitudinal weight gain trends.

Based on established diagnostic criteria, we previously noted the heterogeneity of the LAD among WTC responders,⁶ while most other studies have been based on symptom surveys,^{1,3,39} self-reported diagnoses,^{5,40} or single lung function measurements.^{41,42} In contrast, cluster analysis can integrate multiple variables, does not rely on *a priori* diagnostic assumptions and has been used to identify distinct phenotypes in heterogeneous diseases, such as asthma,^{43–45} COPD,⁴⁶ and obstructive sleep apnea.^{47,48} To our knowledge, cluster analysis has not been previously conducted in the WTC cohorts or in other inhalational disaster situations.

TABLE 2. First-Second Forced Expiratory Volume (FEV1) Trajectory Categories (Rapid and Intermediate Decliners, and Gainers) for 256 (82.3%) of the 311 Subjects in Each of the Five Clusters, Who Had at Least Three Good Quality Periodic Surveillance Spirometries Between 2002 and 2018

FEV ₁ Trajectory Group	Clusters					Total
	1	2	3	4	5	
Rapid decliners, n (%)	9 (39.1)	8 (11.6)	5 (14.7)	21 (30.9)	14 (22.6)	57 (22.3)
Intermediate, n (%)	9 (39.1)	55 (79.7)	25 (73.5)	39 (57.4)	44 (71.0)	172 (67.2)
Gainers, n (%)	5 (21.7)	6 (8.7)	4 (11.8)	8 (11.8)	4 (6.5)	27 (10.5)
Total	23 (9.0)	69 (27.0)	34 (13.3)	68 (26.6)	62 (24.2)	256

The functional and QCT characteristics of COPD predictably identified individuals that fit that disease phenotype in our population, as we demonstrated in a previous studies.⁸ Chronic obstructive pulmonary disease in these workers has been mild to moderate,³⁸ with close to a third of affected subjects being never smokers.³⁸ Our data in these workers with COPD thus far seem to suggest a predominance of the airway—over an emphysema-predominant subtype, as only 4% and 9.6%, respectively, had QCT evidence of emphysema, as indicated by low attenuation volume percent of $\geq 5\%$ and $\geq 2.5\%$, respectively,^{8,10} and half of the cases having functional features of asthma COPD overlap.³⁸

Low FVC (equivalent to a preserved ratio impaired spirometry)⁴⁹ has long been described as the most frequent abnormal spirometric pattern in the WTC occupational cohorts.^{1,2,6,50} This airway disease pattern is likely heterogeneous,⁴⁹ and 86.2% (75/87) of our subjects with it were in clusters 2 and 3. Unlike other cohorts (eg, COPDGen[®]), where subtypes of low FVC impairment have been recently identified,⁵¹ the WTC cohort was unselected for cigarette smoking. Our low FVC clusters 2 and 3 showed the strongest association² with early arrival at the WTC disaster site, when environmental exposures were likely highest.²⁵ Low FVC subjects in cluster 3 were more dyspneic, obese, and also showed slightly more restriction (based on TLV_{CT}), and QCT evidence of proximal airway inflammation (WAP), the latter most closely matching (as in our previous study⁸) that of COPD subjects. In contrast, cluster 2 subjects had the highest proportion of never smokers (similar to the relatively healthy subjects of cluster 5) and were less dyspneic. Importantly perhaps for our long-term surveillance, clusters 2 and 3 had lower proportions of subjects with rapid decline in lung function.

Our overall findings confirm some previously identified functional and imaging traits associated with accelerated lung function decline in the WTC cohort, such as BDR, WAP,¹⁰ and low attenuation volume percent.⁴ Consistent with our previous study,³⁷ Latinos (predominantly laborers) tended to be slightly younger, never smoking, and late arrivals at the disaster site and have less functional and imaging evidence of LAD (cluster 5). Of note, cluster 4 had a high proportion of subjects with rapid lung function decline (who may thus be at high risk for COPD) and Pi10 as the only significantly associated QCT marker. Given those results with cluster 4, Pi10, as well as other airway imaging metrics, deserve further investigation in the WTC cohort, as studies have shown its association with persistent chronic bronchitis,⁵² and possibly with more adverse but possibly preventable long-term functional outcomes. Cluster 4 also showed weight gain, and our previous studies had suggested the association of obesity¹² and weight gain¹⁰ with quantitative CT markers of airway inflammation, and accelerated longitudinal expiratory flow decline, respectively. While cluster 4 had the highest proportion of current and former smokers, our studies have shown the remarkable success of smoking cessation interventions in this cohort.^{2,8}

Our analysis benefited from an abundance of cross-sectional clinical, functional, and respiratory structural data and longitudinal functional trajectories to assess the potential adverse clinical impact of the identified clusters on respiratory health, in a population not selected for smoking as has been the case with other respiratory cohorts. Limitations, on the other hand, include the duration of the longitudinal follow-up, which may have limited the detection of more severe lung diseases, such as COPD and interstitial lung diseases. Surveillance is, however, ongoing, and should provide additional information in the future. Sample size may have been limiting for only one of 21 variables examined, but the number of cases of low FVC and subjects with apparently normal spirometries allowed cluster analysis to suggest underlying pathophysiological features and indicators to investigate further as the surveillance continues. We used a sample of complete data cases but our comparison of included versus excluded subjects suggests that our study sample of quite representative was the WTC Chest Imaging Archive cohort.

In conclusion, we identified five clusters of chronic lower respiratory disease in WTC responders, which have basic functional and QCT characteristics and clinical relevance for the treatment and longitudinal follow-up of this population. Although much has been published about the management of disease types, such as COPD and asthma, investigations like this shed light on the characteristics and evolution of other clusters such as our clusters 2, 3, and 4. Additional investigations are warranted of those subtypes, for further characterization of their clinical features, identification of additional QCT markers of early lung injury (and, possibly, repair), and longitudinal lung function trajectory.

ACKNOWLEDGMENTS

The authors thank all participants in this study and the staff of the Mount Sinai WTC Health Program Clinical Center of Excellence and the WTC General Responders Cohort Data Center. The authors also thank Jill K. Gregory, MFA, CMI, who contributed the illustration presented in Figure 1.

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