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ORIGINAL ARTICLE

Increased pulmonary artery diameter is associated with reduced FEV_1 in former World Trade Center workers

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Abstract

Rationale: Occupational exposures at the WTC site after September 11, 2001 have been associated with several presumably inflammatory lower airway diseases. Pulmonary arterial enlargement, as suggested by an increased ratio of the diameter of the pulmonary artery to the diameter of the aorta (PAAr) has been reported as a computed tomographic (CT) scan marker of adverse respiratory health outcomes, including WTC-related disease. In this study, we sought to utilize a novel quantitative CT (QCT) measurement of PAAr to test the hypothesis that an increased ratio is associated with FEV_1 below each subject's statistically determined lower limit of normal (FEV_1 < LLN).

Methods: In a group of 1,180 WTC workers and volunteers, we examined whether FEV_1 < LLN was associated with an increased QCT-measured PAAr, adjusting for previously identified important covariates.

Results: Unadjusted analyses showed a statistically significant association of FEV_1 < LLN with PAAr (35.3% vs 24.7%, $P = 0.0001$), as well as with height, body mass index, early arrival at the WTC disaster site, shorter WTC exposure duration, post-traumatic stress disorder checklist (PCL) score, wall area percent and evidence of bronchodilator response. The multivariate logistic regression model confirmed the association of FEV_1 < LLN with PAAr (OR 1.63, 95% CI 1.21, 2.20, $P = 0.0015$) and all the unadjusted associations, except for PCL score.

Conclusions: In WTC workers, FEV_1 < LLN is associated with elevated PAAr which, although likely multifactorial, may be related to distal vasculopathy, as has been hypothesized for chronic obstructive pulmonary disease.

KEYWORDS

2001, computer-assisted image processing, multidetector computed tomography, occupational medicine, pulmonary artery, smoke inhalation injury, spirometry, World Trade Center attack

1 | INTRODUCTION

Pulmonary arterial enlargement, as suggested by an increased ratio of the diameter of the pulmonary artery to the diameter of the aorta (PAAr) has been reported as a computed tomographic (CT) scan marker of adverse respiratory health outcomes, as a reflection of disease-related distal pulmonary vascular abnormalities. A study reported that increased

PAAr predicted severe exacerbations among chronic obstructive pulmonary disease patients.[1] A variety of chronic lower airway diseases has been associated with occupational exposures to dust, gases and fumes during the rescue, search and recovery efforts at the World Trade Center (WTC) disaster site in 2001-2002.[2,3] A recent case-control study among New York City firefighters reported that increased PAAr was an independent predictor of the reduction of first-second forced expiratory volume (FEV_1) below the individuals' lower limit lower of normal (FEV_1 < LLN), even after adjustment for WTC exposure, body mass index and age at the time of the CT.[4] Interestingly, an FEV_1 < LLN was in turn associated with serum biomarkers predictive of vasculopathy in that study.[4] Quantitative CT (QCT) measurements have emerged as powerful research tools in the non-invasive evaluation of the airway, pulmonary parenchymal and vascular and other thoracic structures, allowing further phenotypical characterization of a variety of lung diseases.[5]

In this study, we sought to utilize a novel QCT measurement of PAAr to test the hypothesis that an increased ratio is associated with FEV_1 < LLN in with a substantially larger group of similarly exposed WTC workers and volunteers, also adjusting for a larger number of very important predictors of adverse respiratory health effects in this patient group.[6]

2 | MATERIALS AND METHODS

2.1 | Subjects and clinical data acquisition

All subjects participated in the screening, surveillance and clinical programs of the World Trade Center (WTC) Clinical Center of Excellence at Mount Sinai Medical Center, in New York City, and were also part of the subcohort (n = 1,641) evaluated by the WTC Pulmonary Evaluation Unit (WTC PEU), who underwent chest computed tomography (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.[7] In brief, participants were all workers and volunteers who performed rescue, recovery and service restoration duties at the WTC disaster site from September 11, 2001 to June 2002. This cohort includes all occupational groups, except firefighters.[8] Beginning in July 2002, all subjects underwent a baseline screening evaluation, which included questionnaires on respiratory symptoms, pre-WTC- and WTC-related occupational exposures, 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.[2,9]

2.2 | CT imaging procedures

All CT studies were obtained at Mount Sinai in General Electric® or Siemens® multidetector row chest CT scanners. Chest CT studies were performed using a protocol[10,11] with a radiation dose at 120 kVp, and a mean of 146 (SD 69) mAs, and subjects in the supine position. CT scans were obtained from the lung apices to the bases in a single breath hold at maximum inspiration. All deidentified and coded chest CT images were stored and catalogued from 2012 to 2017 in the WTC PEU Chest CT Image Archive (ClinicalTrials.gov identifier NCT03295279).[11]

2.3 | Inclusion criteria and QCT systems

Inclusion into this study required that the WTC workers had (a) adequate quality study for quantitative chest CT scan (QCT) measurements of their pulmonary artery and aortic diameters, and wall area percent (WAP) performed with the Simba system (http://www.via.cornell.edu/simba/simba),[12,13] (b) at least two screening and surveillance spirometries and (c) complete data for all covariates of interest. After excluding 17 subjects with missing data on other variables, and imputing missing data for WAP (described in Statistical Analyses), a total of 1,180 subjects met inclusion criteria (Figure 1). None of the included subjects had interstitial lung disease, infectious or primary pulmonary neoplastic processes and other disorders. QCT measurements were performed blinded to any and all identifiers and clinical information.

2.4 | Spirometry

We selected the spirometry performed on the date closest to the date of the chest CT scan in which PAAr was measured by QCT (median interval 0.5 years). Spirometry was performed using the EasyOne® portable flow device (ndd, Zurich, Switzerland), selected for its accuracy and quality feedback.[14,15] Bronchodilator response (BDR) was assessed at least once (and most often at the baseline visit) by repeating spirometry 15 minutes after the administration of 180 mcg of albuterol via metered dose inhaler. BDR was defined as both a percent change ≥12% and an absolute increment ≥200 ml in either FEV_1 or the forced vital capacity (FVC) after bronchodilator administration. 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),[16] and all testing, quality assurance, ventilatory impairment pattern definitions and interpretative approaches followed American Thoracic Society recommendations.[17,18] Spirometries in this study were selected if deemed acceptable, and also had a

good quality grade (computer quality grade A or B or grade C with at least five trials).[18,19]

2.5 | Measurements

Our outcome of interest was the occurrence of an FEV_1 value below each subject's statistically determined lower limit of normal (FEV_1 < LLN). Our main dichotomous predictor was an increased PAAr, measured by QCT as previously described.[13] Briefly, pulmonary artery diameter was segmented and measured automatically in the axial plane between the heart and the artery bifurcation (instead of the traditional manual measurement at the level of the latter,[20] see Figure 2). The aortic diameter was determined at the level of the pulmonary artery bifurcation.

Covariates of interest included age on the date of the CT study, gender, height, race/ethnicity (grouped as Latino, non-Latino white and non-Latino of all other races), body mass index (BMI, expressed in kg/m^2) at baseline evaluation, evidence of bronchodilator response (BDR) at one or more visits, spirometric forced exhalatory time (FET, dichotomously, with a 6-second cutoff), QCT measurement of WAP, post-traumatic stress disorder checklist (PCL) score, diagnosis of obstructive sleep apnea by nocturnal polysomnography, baseline smoking status and WTC occupational exposure indicators.

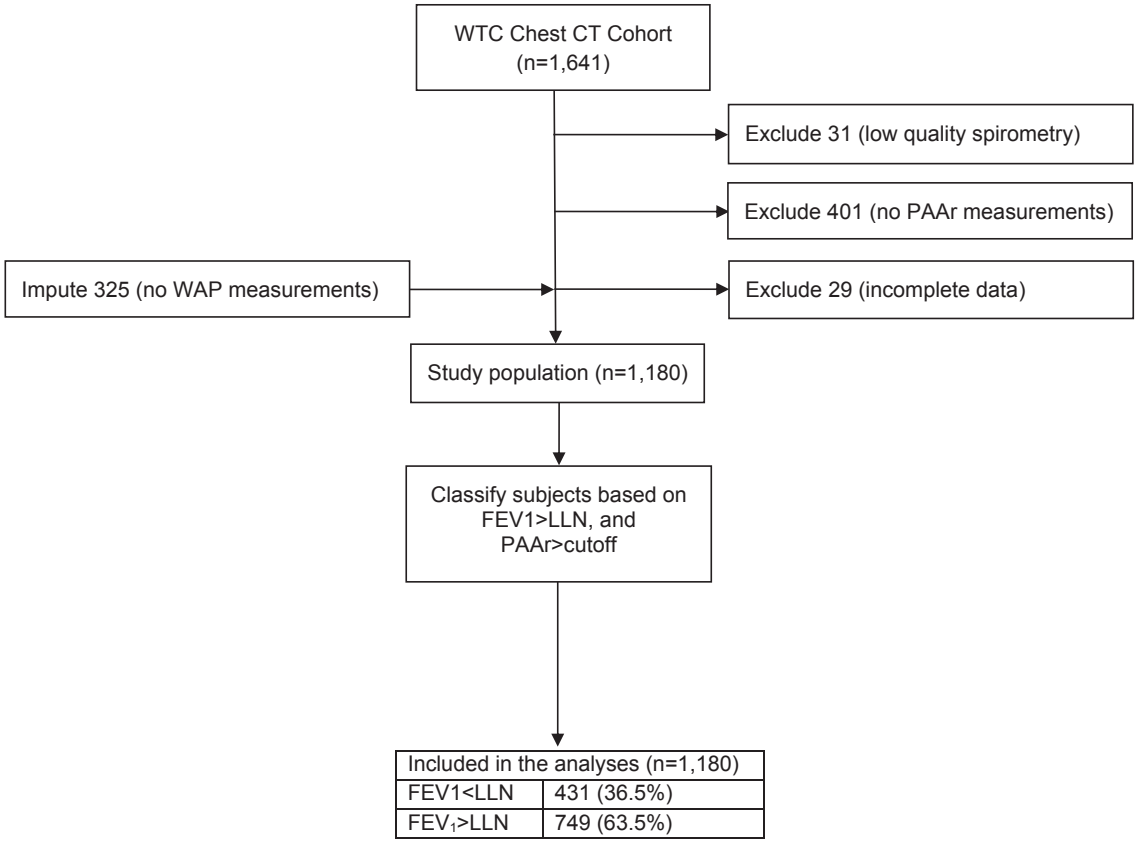

FIGURE 1 Study flow chart

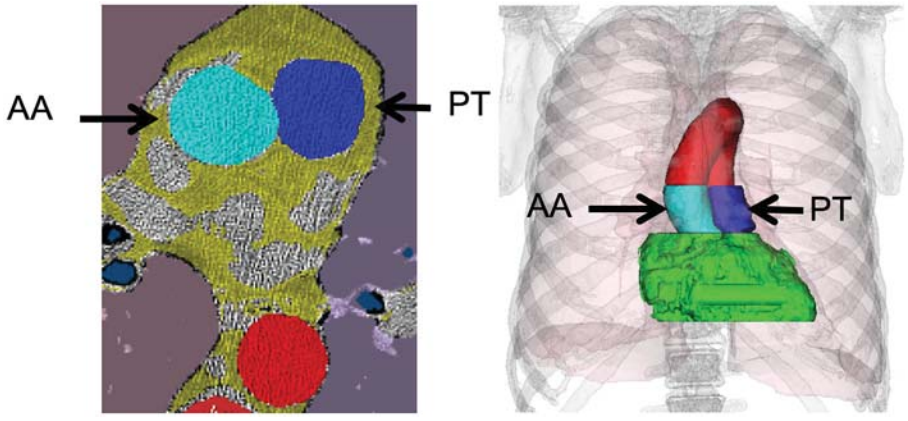

FIGURE 2 Pulmonary artery and aortic diameter are measured from a tridimensional volume, with the regions in dark and light blue indicating where the pulmonary trunk and the aorta measurements are made, respectively. To obtain a robust measure from the largest possible number of data points, the diameter is estimated from a 3D cylinder model matched to the blue pixels

Smoking status was assessed at the baseline examination. A subject was considered a lifetime non-smoker if (s)he had smoked less than 20 packs of cigarettes (or 12 oz. of tobacco) in their lifetime, or less than one 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.[21]

WTC occupational exposure relied on two self-reported dichotomous variables, assessed at the baseline examination: arrival at the WTC site within 48 hours of the terrorist attack, and cumulative WTC exposure duration exceeding 60 days.[2] For descriptive purposes, an occupational physician (RED) recoded, grouped and labelled occupations into the following six categories: (a) management, business, science, arts, service, sales or office occupations ("management/services"); (b) construction trades, maintenance and natural resources ("construction trades/maintenance"); (c) construction and demolition labourers, asbestos removers and building cleaners ("labourers/cleaners/asbestos removal")[22]; (d) production, transportation and material moving ("transportation"); (e) law enforcement specific and military ("law enforcement"); and (f) unemployed, retired or unknown ("unemployed/retired").

WAP was measured by QCT in the third bronchial generation of the right upper lobe,[5] using the Simba system.[12,23] The automated process starts with identification of the airways and their branch points on inspiratory scans. Airways can be followed out up to five generations, depending on the resolution of the images. Based primarily on density differences between the luminal air, airway wall and surrounding parenchyma, the airway lumen area (Ai), total airway area (Ao) and airway wall area (Aaw) are measured. These cross-sectional area measurements are averaged along the length of the bronchus. WAP is calculated as $(Ao - Ai)/Ao \times 100\%$, and was averaged over all measurable airways. An increase in WAP suggests airway wall thickening, in relation to the lumen, which is in turn suggestive of airway inflammatory changes.

Symptoms of chronic post-traumatic stress disorder were assessed with the PTSD Checklist (PCL) questionnaire, a validated scale,[24] where probable PTSD is defined by having a score equal to or greater than 44 points. This score has been used in a number of previous studies of the WTC[25] and other cohorts, and is strongly correlated with a clinical diagnosis of PTSD.[24] We also adjusted for a diagnosis of obstructive sleep apnea, in most cases by in-laboratory nocturnal polysomnogram.

For *post hoc* descriptive purposes, we classified subjects with $FEV_1 < LLN$ according to the presence or absence of evidence of lower airway disease (LAD), as follows: (a) LAD: both abnormal spirometry, revealing at any time either fixed or reversible obstruction, low FVC, or bronchodilator response, *and* reported shortness of breath with a score of three or more on the Medical Research Council breathlessness scale (MRC, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level")[26,27]; and (b) No LAD: normal or low FVC spirometry without associated significant breathlessness.

2.6 | Statistical analyses

Descriptive statistics included mean and standard deviation (SD), and median and interquartile ranges (IQR) for normally and non-normally distributed continuous variables, respectively, and counts and proportions for categorical variables. Unadjusted bivariate analyses included t test or Chi square test, as appropriate. We initially determined sex-specific PAAr cutoff values that maximized the Youden J index (sensitivity + specificity−1) in bivariate analyses with our outcome of interest, $FEV_1 < LLN$.[28] We then classified subjects dichotomously according to whether or not their PAAr exceeded their sex-specific cutoff value, and used a logistic regression model to estimate the odds of having a $FEV_1 < LLN$, adjusting for important covariates.[6] Although some of the predictors were correlated, significant multicollinearity was excluded by the variance inflation factor method. The discrimination of the logistic regression model was evaluated by means of the c statistic. After excluding 17 cases with more than 1 missing variable, WAP remained as the only variable with a considerable amount of missing data in the sample. We employed a multiple imputation (MI) procedure with monotone missing pattern method to account for missingness in our regression model. The results with the MI and the complete case data set were essentially identical, so only the former will be presented. The SAS program, version 9.4 (SAS Institute, Cary, NC), and a two-sided significance level of $\alpha = 0.05$ were used for all analyses.

3 | RESULTS

The study group consisted of 1,180 subjects. Subjects were predominantly (82.4%) male, with mean age at the time of the CT scan of 49.8 (SD 9.3) years (Table 1). The leading occupational categories of the study subjects were those of labourers/building cleaners and law enforcement, with a significantly higher proportion of the latter (26.9% vs 19.4%) having experienced our outcome of interest, $FEV_1 < LLN$. Subjects had their chest CT scan at a median of 7.5 (IQR 6-9) years after September 11, 2001. The spirometry closest to the chest CT scan was performed at a median of 0.54 (IQR 0.21-1.09) years either preceding (n = 394) or following (n = 786) the CT scan and a median of 7.6 (IQR 5.78-9.13) years after 11-September-2001. The sex-specific PAAr cutoff for our outcome of interest was determined to be 0.87 for men and 0.91

TABLE 1 Characteristics of the subjects in this study, unadjusted and adjusted analyses

	All subjects (n = 1180)		FEV_1 > LLN (n = 749)		FEV_1 < LLN (n = 431, 36.5%)						
	n or mean	% or SD	n or mean	% or SD	n or mean	% or SD	*P*	OR_{adj}	95%CI		*P*
Increased PAAr											
Yes	337	28.6	185	24.7	152	35.3	0.0001	1.63	1.21	2.20	0.0015
No	843	71.4	564	75.3	279	64.7		ref			
Sex											
Male	972	82.4	611	81.6	361	83.8	0.3433	ref			
Female	208	17.6	138	18.4	70	16.2		1.38	0.89	2.15	0.1537
Age (years)	49.8	9.34	49.8	9.43	49.8	9.20	0.9907	1.01	0.99	1.02	0.3973
Height (cm)	171.6	9.78	170.6	9.82	173.2	9.48	<0.0001	1.05	1.03	1.07	<0.0001
Race/Ethnicity											
Non-Latino White	630	53.4	409	54.6	221	51.3	0.2621	ref			
Non-Latino Non-White	139	11.8	80	10.7	59	13.7		1.41	0.92	2.15	0.1150
Latino	411	34.8	260	34.7	151	35.0		1.89	1.35	2.66	0.0002
Body mass index, kg/m^2	29.82	5.14	29.30	4.70	30.72	5.73	<0.0001	1.04	1.01	1.07	0.0077
Smoking status											
Never	627	53.1	400	53.4	227	52.7	0.9417	–	–	–	0.7619
Former	329	27.9	209	27.9	120	27.8		–	–	–	–
Current	224	19.0	140	18.7	84	19.5		–	–	–	–
Occupational category											
Management/ service	214	18.1	113	15.1	101	23.4	<0.0001	–	–	–	–
Construction trades/ maintenance	215	18.2	122	16.3	93	21.6		–	–	–	–
Labourer/cleaner/ asbestos removal	385	32.6	306	40.8	79	18.3		–	–	–	–
Transportation	69	5.9	36	4.8	33	7.7		–	–	–	–
Law enforcement/ military	261	22.1	145	19.4	116	26.9		–	–	–	–

(Continues)

TABLE 1 (Continued)

	All subjects (n = 1180)		FEV_1 > LLN (n = 749)		FEV_1 < LLN (n = 431, 36.5%)						
	n or mean	% or SD	n or mean	% or SD	n or mean	% or SD	*P*	OR_{adj}	95%CI		*P*
Unemployed/ retired/unknown	36	3.1	27	3.6	9	2.1		–	–	–	–
WTC arrival											
<48 hours	582	49.3	319	42.6	263	61.0	<0.0001	1.71	1.29	2.28	0.0002
>48 hours	598	50.7	430	57.4	168	39.0		ref			
WTC exposure duration											
<60 days	476	40.3	275	36.7	201	46.6	0.0008	1.44	1.09	1.90	0.0099
60+ days	704	59.7	474	63.3	230	53.4		ref			
Wall area percent (WAP)[b]	62.32	7.78	61.23	7.73	64.22	7.51	<0.0001	1.05[a]	1.02	1.08	0.0044
Sleep apnea											
Yes	479	40.6	308	41.1	171	39.7	0.6262	0.77	0.58	1.03	0.0794
No	701	59.4	441	58.9	260	60.3		ref			
Bronchodilator response (BDR)											
Yes	268	22.7	89	11.9	179	41.5	<0.0001	5.37	3.91	7.38	<0.0001
No	912	77.3	660	88.1	252	58.5		ref			
PTSD Checklist (PCL) score	44.4	19.13	45.5	18.85	42.6	19.48	0.0080	1.00	0.99	1.00	0.3107
FET ≥ 6 sec											
Yes	708	60.0	462	61.7	246	57.1	0.7799	0.78	0.59	1.03	0.0772
No	472	40.0	287	38.3	185	42.9		ref			

[a]Per each 5% units of WAP.
[b]Imputed.

for women. As expected, the prevalence of LAD was much higher among subjects with than those without FEV_1 < LLN (71.6% vs 20.1%). Figure 1 presents a study flow diagram, and Table 1 presents the comparison of the included and excluded subjects (n = 461 subjects). The two groups were very similar: the only statistically significant difference was that, compared to excluded subjects, included subjects were more likely to have been diagnosed with obstructive sleep apnea.

Table 1 shows the results of the analysis of the relation between PAAr (and other covariates of interest) and an FEV_1 < LLN. In the unadjusted analysis, subjects with an increased PAAr were significantly more likely to have an FEV_1 < LLN than those without an increase PAAr (35.3% vs 24.7%, $P = 0.0001$). In this unadjusted analysis, covariates significantly associated with an FEV_1 < LLN included height, BMI, early arrival at the WTC disaster site, shorter WTC exposure duration, PCL score, WAP and BDR. The multivariable logistic regression analysis adjusting for sex, race/ethnicity, WTC exposure and other covariates, PAAr was significantly associated with 1.63 increased odds of an FEV_1 < LLN (95% confidence interval for odds ratio = 1.21-2.20, $P = 0.0015$). The c statistic for this multivariable model was 0.76.

4 | DISCUSSION

We have demonstrated that pulmonary arterial enlargement, as indicated by the PAAr, is associated with an FEV_1 below the predicted lower limit of normal, even after adjustment for several known predictors of lung function,[6] such as bronchodilator hyperresponsiveness, wall area percent, baseline BMI, arrival at the WTC within 48 hours and shorter WTC occupational exposure duration, and smoking status.

A previous study of WTC firefighters of 34 cases with FEV_1%predicted within one standard deviation of the lowest observed (77%) at a subspecialty unit, and 63 control subjects, reported an association with an elevated PAAr (≥0.92).[4] Whereas PAAr was manually measured in that study, we utilized a highly accurate automated measurements[13] that can be readily deployed to a large imaging data set like ours. Moreover, we measured the PA diameter between the heart and the PA bifurcation, instead of the traditional manual measurement at the level of the latter[20]). This automated method was developed to make PAAr measurements perform more reliably on low-radiation dose chest CT scans, and thus be applicable to a diverse range of chest CT scan protocols. In further contrast to the previous study in WTC firefighters, we assessed the FEV_1 < LLN instead of FEV_1%predicted, as FEV_1 < LLN is a more informative and generalizable outcome.

The association between an elevated PAAr and an FEV_1 < LLN may be related to distal vasculopathy, as previously suggested,[4] and could be similar to what has been described in smokers with or without significant emphysema.[29] Although that could result from toxicant induced injury, as has been proposed for tobacco related chronic obstructive pulmonary disease,[30] another potential explanation is that increased PAAr reflects obesity[31] (with or without metabolic syndrome[32]) associated pulmonary hypertension, and a *post hoc* analysis showed that PAAr was significantly associated with obesity (data not shown). Our studies in this cohort have demonstrated the adverse effect of obesity and weight gain on longitudinal follow up,[6] the prevalence of obesity[33,34] and the metabolic syndrome is known to be substantial in this cohort,[35] and a case-control study among WTC firefighters demonstrated associations of metabolic syndrome biomarkers with adverse respiratory outcomes (FEV_1% less than predicted lower limit of normal).[36]

We selected a substantial number of important covariates and potential confounders. WAP is an indicator of proximal airway wall thickening, which can result from inflammatory changes, and be a common feature to the different WTC-related lower airway diseases,[2,9] and we previously demonstrated that WAP was significantly associated with adverse respiratory outcomes in this WTC occupational cohort.[6] To the extent that significant BDR also reflects bronchial inflammation, it would also be expected to be associated with adverse expiratory flow outcomes, and BDR has been associated with increased susceptibility to tobacco-smoke pulmonary toxicity.[37] The negative impact of obesity (more highly prevalent in the WTC occupational cohorts (more than 80%[33,34] than in the US population) on lung function[38] and pulmonary vasculature[31] is well known, and we previously demonstrated in this cohort that weight gain and loss were associated with accelerated expiratory flow decline or gain, respectively.[6] Although most research has focused on adverse effects of obesity on asthma,[39,40] our studies suggest that WTC-related inflammatory lower airway diseases are also similarly impacted by obesity.[6] Several studies have identified the association of early arrival at the WTC disaster site[2,41,42] with adverse respiratory health outcomes. Although a large study reported an association between prolonged exposure at the disaster site (defined as >90 days) and incident asthma,[42] our study suggests an inverse relation. One possible explanations for this finding could be the well-known markedly lower decreased dust levels a few days after the collapse of the WTC towers.[43] Another possible and not mutually exclusive explanation could be that subjects with adverse respiratory outcomes may have shortened their recovery work assignments at the disaster site. Sleep apnea is highly prevalent (and mostly untreated) in the WTC cohorts, and known to be associated with pulmonary hypertension. We found an unadjusted association of baseline smoking status with FEV_1 < LLN, but this variable was correlated with multiple covariates in our models, and was kept in the multivariable model for adjustment purposes.

The strengths of this study relate to the richness of the patient population, the amount of data available for covariates of interest, the availability of imaging data from the largest established WTC chest CT archive to date, and of a QCT tool that allows fast measurements in large imaging data sets of an increasingly recognized predictor of adverse health outcomes. This study also has some limitations. 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. Our study relied on retrospective chest CT imaging data, which were subject to variations in protocols over time. However, most studies were performed in a very small number of scanners at a single tertiary care institution, with an intended technical consistency, and quality control was exerted to exclude *a priori* studies that did not meet technical standards for QCT. We recently published the findings on systematic readings of the CT scans,[11] and noted the paucity of interstitial lung disease abnormalities. Indeed, the present study group did not include any subject with that type of disease. Despite the richness of our data and the good overall performance of our model, we lacked information on other factors that can relate to airway disease outcomes, like atopy, pre-WTC occupational exposures, smoking intensity, and smoking status after baseline, or on pulmonary vascular disease, such as metabolic syndrome components other than obesity.[32] Previous studies, however, have not suggested an association between atopy and WTC lower airway disease,[44] and occupational airway disease[45,46] and periodic cross-sectional assessments of smoking status in this cohort do not suggest increasing group smoking rates (data not presented).

In summary, our study demonstrates that PAAr is an independent predictor of adverse expiratory flow outcome, independently from several important and previously identified predictors of adverse respiratory outcomes in this and other patient populations. The findings also demonstrate the usefulness of QCT in the investigation and characterization of the different WTC-related lower airway diseases,[2,3] and the potential application of PAAr QCT measurement to future investigations of pulmonary vasculature in pulmonary diseases.

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CONFLICT OF INTEREST

The authors declare that they have no other conflicts of interest relevant to the contents of this article.

AUTHORS' CONTRIBUTIONS

RED, AN, RSJ and JCC designed and oversaw the study and selected analytical strategies. YJ, XL and JTD performed all statistical analyses. APR performed the QCT measurements. All authors contributed to writing, and reviewed and revised the draft and the final manuscript. RED, AN, RSJ and JCC are the guarantors of this article, and take responsibility for the integrity of the work as a whole, from inception to published article.

ETHICS STATEMENT

This study was reviewed and approved by the Mount Sinai Program for the Protection of Human Subjects (HS12-00925), and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Trial registration: ClinicalTrials.gov identifier NCT03295279.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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