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Increased Airway Wall Thickness is Associated with Adverse Longitudinal First–Second Forced Expiratory Volume Trajectories of 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. In this study, we describe the trajectories of expiratory air flow decline, identify subgroups with adverse progression, and investigate the association of a quantitative computed tomography (QCT) imaging measurement of airway wall thickness, and other risk factors for adverse progression.

Methods—We examined the trajectories of expiratory air flow decline in a group of 799 former WTC workers and volunteers with QCT-measured (with two independent systems) wall area percent (WAP) and at least 3 periodic spirometries. We calculated individual regression lines for first–second forced expiratory volume (FEV_1), identified subjects with rapidly declining and

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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increasing ("gainers"), and compared them to subjects with normal and "stable" FEV_1 decline. We used multivariate logistic regression to model decliner vs. stable trajectories.

Results—The mean longitudinal FEV_1slopes for the entire study population, and its stable, decliner, and gainer subgroups were, respectively, −35.8, −8, −157.6, and + 173.62 ml/year. WAP was associated with "decliner" status (OR_{adj} 1.08, 95% CI 1.02, 1.14, per 5% increment) compared to stable. Age, weight gain, baseline FEV_1 percent predicted, bronchodilator response, and pre-WTC occupational exposures were also significantly associated with accelerated FEV_1 decline. Analyses of gainers vs. stable subgroup showed WAP as a significant predictor in unadjusted but not consistently in adjusted analyses.

Conclusions—The apparent normal age-related rate of FEV_1 decline results from averaging widely divergent trajectories. WAP is significantly associated with accelerated air flow decline in WTC workers.

Keywords

Multidetector computed tomography; Smoke inhalation injury; Spirometry; World Trade Center Attack; 2001; Chronic bronchitis; Occupational disease

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]. Despite their heterogeneity, we have postulated that the latter have airway wall inflammation as their common denominator. Quantitative CT 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 [3]. Although longitudinal spirometric follow-up of the WTC occupational cohorts suggests a normal age-related expiratory flow decline [4, 5], this study sought to demonstrate and characterize subgroups with widely divergent, and more adverse respiratory health trajectories, and hypothesized that wall area percent (WAP), a quantitative CT marker of airway inflammation, is associated with those adverse outcomes.

Methods

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 part of the subcohort (n= 1641) 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. The study was approved by the Mount Sinai Program for the Protection of Human Subjects (HS12-00925). Details on subject recruitment, eligibility criteria, and screening and surveillance protocols have been previously reported [6]. 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 (Fig. 1). This cohort includes all occupational groups, except firefighters [7]. 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 [1, 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 [8] with a radiation dose at 120 kVp, and a mean of 146 (SD 69) mAs, with subjects in the supine position. CT scans were obtained from the lung apices to the bases in a single breath hold at maximum inspiration, with section thickness not exceeding 1.5 mm. 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) [9].

Inclusion Criteria and QCT Systems

Inclusion into this study required that the WTC workers had (1) adequate quality study for quantitative chest CT scan (QCT) measurements of their airways performed with the Simba system (http://www.via.cornell.edu/simba/simba) [10], (2) at least three screening and surveillance spirometries, and (3) complete data for all covariates of interest (this criterion alone excluded 90 subjects). A total of 799 subjects met those three criteria, and were thus included in this study. In order to confirm the consistency of our findings, we conducted the same analyses described herein using a second QCT system, the Chest Imaging Platform (CIP, formerly Airway Inspector, http://www.chestimagingplatform.org/), an open source and well-validated system that has been used in large studies [11]. We had CIP WAP measurements available on 455 subjects (described in Table S2) meeting the same three listed criteria. Both QCT measurements were performed independently, and blinded to each other, any identifier, and all clinical information. None of the included subjects had interstitial lung disease, infectious or neoplastic processes, and other disorders.

Spirometry

Spirometry was performed using the EasyOne® portable flow device (ndd, Zurich, Switzerland), selected for its accuracy, and quality feedback [12, 13]. Bronchodilator response (BDR) was assessed at least once (and most often at the baseline visit) by repeating spirometry 15 min after administration of 180 mcg of albuterol via metered dose inhaler. 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) [14], and all testing, quality assurance, ventilatory impairment pattern definitions, and interpretative approaches followed American Thoracic Society recommendations [15–17]. Spirometries in this study were selected if deemed acceptable, and more than 95% also had a good quality grade (computer quality grade A or B, or C if at least 5 trials had been obtained). Although airway obstructive impairment was defined by FEV_1/FVC below the lower limit of normal (LLN), post-bronchodilator

FEV_1/FVC ratio < 0.70 on at least two occasions [18, 19], defined chronic obstructive pulmonary disease (COPD).

Measurements

Our outcome of interest was the risk of having experienced accelerated air flow decline ("decliner" status), compared to normal baseline FEV_1 and age-related decline ("stable" status). The expiratory air flow indicator was the first–second forced expiratory volume (FEV_1). We used linear regression to calculate the slope of every patient's FEV_1 (FEV_1slope) over a minimum of 3 periodic measurements [20]. We first identified subjects ("stable" status) with FEV_1 above the lower limit of their predicted normal at their baseline visit, and a FEV_1slope, calculated from at least 3 subsequent visits, not exceeding a presumably and *a priori* determined "normal" age-related decline (or gain) of 25 ml/year. Our primary comparison was with those whose FEV_1 declined over the next two follow-up visits ("decliners"), defined by FEV_1 slope decrements of at least 4%/year from the baseline FEV_1 (regardless of whether the latter was above the subject's lower limit of normal at baseline). In a secondary analysis, we also compared the "stable" subgroup to those subjects who experienced accelerated FEV_1 gain ("gainers"), defined as a positive FEV_1slope from the first 3 spirometries exceeding 4%/year of their baseline FEV_1. We estimated the root mean squared error (RMSE) as an indicator of group FEV_1 fluctuation or variability.

Our main predictor of interest was airway wall area percent (WAP), measured by QCT in the 3rd bronchial generation of the right upper lobe [3], using the Simba system [10, 21]. 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. Wall area percentage (WAP) is calculated as (Ao − Ai)/Ao × 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.

Covariates of interest included age on September 11, 2001, gender, height, race/ethnicity (grouped as Latino, non-Latino white, and non-Latino of other races), body mass index (BMI, expressed in kg/m^2) at first evaluation, weight change on follow-up (BMIslope, in kg/m^2/year), baseline percent predicted FEV_1, evidence of bronchodilator response (BDR) at one or more visits, baseline smoking status (never, former and current smokers), and pre-WTC and WTC occupational exposure categories. BMIslope (kg/m^2/year) was calculated as the slope of the linear regression of each subject's BMI, over all visits available, and used as an indicator of longitudinal weight gain or decline.

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 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.

WTC occupational exposure relied on two self-reported variables: arrival at the WTC site within 48 h of the terrorist attack (dichotomous) and cumulative exposure duration (in days) [1]. Pre-WTC occupational exposures were assessed dichotomously as self-reported daily exposure, in the course of usual occupation before September 11, 2001, to any of the following list of 11 vapors, dust, gases, and fumes: asbestos, Cadmium, diesel and non-diesel exhaust, general, mineral, and silica/sand dust, wood dust, fiberglass, industrial cleaning solutions, and welding fumes. For descriptive purposes, an occupational physician (RED) recoded, grouped, and labeled occupations into the following 6 categories: (1) management, business, science, arts, service, sales, or office occupations ("management/services"); (2) construction trades, maintenance, and natural resources ("construction trades"); (3) construction and demolition laborers, asbestos handlers, and building cleaners ("laborers/cleaners") [22]; (4) production, transportation, and material moving ("transportation"); (5) law enforcement specific and military ("law enforcement"); and (6) unemployed, retired, or unknown ("unemployed/retired").

Statistical Analyses

Descriptive statistics included mean and standard deviation 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, χ^2 test, or Pearson correlation test, as appropriate. As mentioned before, linear regression was used to estimate the rate of change of FEV_1 and BMI, and to define subgroups for comparisons. We calculated the root mean squared error (RMSE) of the group linear regressions, as indicators of FEV_1 fluctuation or variability over time. Using the "stable" as the comparison group, we then used multivariate logistic regression to model decliner status vs. WAP, adjusting for the above-listed and described covariates. Logistic regression models were fitted to model the odds of being a decliner using a modified backward selection procedure, with a significance level of 0.2 to remain in the model. All unselected variables were subsequently added to the resulting model one at a time and retained in the model if they altered the β estimate for WAP by greater than 10%. The model was adjusted for baseline smoking status, even if non-significant. Although some of the predictors were correlated, multicollinearity was excluded by the variance inflation factor method. Model goodness of fit was assessed by means of the c statistic. The odds ratios for WAP and BMIslope were calculated per each 5%, and 0.2 kg/m^2/year units, respectively. Due to the small number of subjects meeting criteria to be in the gainer subgroup, and the number of variables under consideration, only unadjusted bivariate analyses were performed. 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.

Results

The study group consisted of 799 subjects. Subjects were predominantly male (81.7%), with mean age on September-11-2001 of 42.6 years (SD 8.8 years; Table 1). The most frequent occupations were laborers/building cleaners and law enforcement. Subjects had their baseline spirometry a median of 3.39 years (IQR 1.77–5.39 years) after 11-September-2001, and the interval between the first and third available spirometry for the entire group was a

median of 4.65 years (IQR 3.76, 5.72). The prevalence of baseline overweight and obesity were 47.9 and 34%, respectively. Table S1 presents the comparison of the included and excluded subjects.

The mean longitudinal FEV_1slopes (with RMSE) for the entire study population, and its stable (n= 103), decliner (n = 81), and gainer (n = 29) subgroups were, respectively, −35.8 (0.15), −8 (0.13), −157.6 (0.20), and + 173.6 (0.26) ml/year. For the entire group, we observed that WAP was correlated with baseline BMI (r = 0.243) and FEV_1%predicted (r= −0.208), and associated with evidence of BDR (all $p < 0.001$).

Table 1 shows and contrasts the characteristics of the decliner (n = 81) vs stable (n= 103) subgroups. Unadjusted analyses showed statistically significant associations of accelerated FEV_1 decline with WAP, age on 9/11/2001, BMIslope, baseline FEV_1%predicted, baseline smoking status, arrival at the WTC within 48 h of the terrorist attack, and BDR. The adjusted logistic regression model (Table 2) confirmed the association for WAP, age on 9/11/2001, BMIslope, baseline FEV_1% predicted, and BDR, but also for pre-WTC occupational exposures. The c statistic for the final model was 0.85. Except for age on 9/11/2001, and pre-WTC occupational exposures, we obtained remarkably similar results with the CIP platform QCT measurements, with significant adjusted associations for WAP, BMIslope, baseline FEV_1%predicted, and BDR (Table S3).

Table 1 also shows and contrasts the characteristics of the gainer (n= 29) vs stable (n= 103) subgroups. In unadjusted comparisons, accelerated FEV_1 gain was associated with baseline FEV_1%predicted, baseline smoking status, BDR, height, and early arrival at the WTC disaster site (Table 1). WAP was not associated with this trajectory in unadjusted or adjusted analyses with the Simba measurements. In contrast, with the CIP system there were both unadjusted and adjusted associations, but estimates were unstable due to a substantially smaller sample size (Table S4).

Discussion

We demonstrated a fairly normal average overall longitudinal FEV_1 decline in this group of exposed WTC workers (−35 ml/year). That finding belies widely divergent trajectories with subgroups with excessive air flow decline, as well as gain. We found that accelerated longitudinal FEV_1 decline in this WTC occupational cohort is predicted by quantitative CT measurement of bronchial wall area percent, after adjusting for significant predictors like bronchodilator response, age on September 11, 2001, weight gain/loss (as indicated by BMIslope), initial FEV_1%predicted, and pre-WTC occupational exposures.

We chose WAP as an indicator of proximal airway wall thickening, presumably as a result of inflammatory changes. This has been demonstrated in other studies of chronic airway diseases, including tobacco-[23, 24] and wood smoke-related COPD [25, 26]. In our classification of WTC-related airway disorders [1], a substantial proportion of cases does not meet established criteria for the diagnoses of asthma or COPD, but are instead diagnosed with non-specific chronic bronchitis or bronchiolitis, based on the presence of lower respiratory symptoms, non-specific lung function abnormalities, and/or chest CT imaging

evidence of end-expiratory air trapping [1, 2, 8]. Our findings suggest that WAP, possibly due to proximal bronchial inflammation and/or remodeling, is significantly associated with accelerated FEV_1 decline in this cohort.

The additional predictors of accelerated expiratory flow decline are not surprising. To the extent that significant BDR reflects bronchial inflammation, it is expected to be associated with accelerated expiratory flow decline, and BDR has been associated with increased susceptibility to tobacco-smoke pulmonary toxicity [27]. Indeed, WAP was associated with the presence of BDR in this study population ($p < 0.001$). On the other hand, data from the subgroup with accelerated expiratory flow gain suggest that BDR may be associated with improved function, presumably as a result of mitigation or resolution of toxicant-induced inflammation, pharmacologic treatment, both, or some other unrecognized factor. Further investigation is warranted of this heretofore underrecognized subgroup.

The negative impact of weight gain on longitudinal expiratory flow decline has been identified in community [28], and occupational cohort studies [29], with the effect ostensibly stronger among men [28] (the vastly predominant gender in the WTC occupational cohorts), and surpassing that of obesity at baseline [28]. Our finding confirms an earlier report on a similar cohort [4], but does not appear to have been examined in the firefighters' cohort [30], where obesity and overweight are more prevalent than in ours [31].

Several studies have identified the association of early arrival at the WTC disaster site [1, 32, 33] with adverse respiratory health outcomes, with the larger ones also describing a significant association for occupational WTC exposure duration [33]. As in our previous study [1], we found significant unadjusted association for early arrival, but not for prolonged exposure at the disaster site. In the adjusted model, however, early arrival fell short of statistical significance. We cannot exclude that a sample size limitation explained this finding. Similarly, we found an unadjusted association of baseline smoking status with abnormal expiratory flow decline or gain, but this variable was correlated with multiple covariates in our models, and was added as an adjusting but non-significant predictor to the final model.

We confirmed that overall longitudinal expiratory flow decline in this WTC occupational cohort is similar to what has been reported in other occupational cohorts [34]. It was noticeable, however, that our cohort had a larger fluctuation in longitudinal expiratory air flow trajectory [35] than has been reported in other occupational cohorts that, like ours, included exposed and symptomatic workers [36]. That finding motivated the investigation of the extremes of those trajectories in both directions. The secondary analyses of excessive expiratory flow increase (gainer subgroup) demonstrated unadjusted significant associations with FEV_1%predicted, baseline smoking status, bronchodilator response, height, and early arrival at the WTC, but the significantly reduced FEV_1%predicted at baseline of this subgroup appeared to be by far the strongest predictor. Gainers had a higher prevalence of current smoking (as of September-11-2001), and all ventilatory impairments, and also demonstrated the largest variability or fluctuation of their FEV_1 over time (Table 1).

The strengths of this study relate to the richness and diversity 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 the consistency of the findings using two different, independent, and blinded QCT measurement systems. 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. However, our subgroup case definitions served well the intended goal of identifying workers with adverse longitudinal lung function trajectory, as well as unexpected expiratory air flow gain. We used 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 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 [9], noted the paucity of interstitial lung disease features, and the group included in the present study did not include any subject with that type of disease. Despite the richness of our data, we lacked information on other factors that can relate to airway disease outcomes, like atopy, smoking status after baseline, and smoking intensity. Preliminary studies, however, have not suggested, an association between atopy and WTC lower airway disease [37], and occupational airway disease [38, 39], 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 the different expiratory flow trajectories followed by workers at the WTC disaster site, characterizes subgroups in need of further study, and supports a role for quantitative CT measurements in the investigation of the lower airway diseases observed in this cohort, and in occupational bronchitis [40–43] in general. The findings also provide supportive evidence for the bronchial inflammation that seems to underlie the different WTC-related lower airway diseases [1, 44], as has been recently emphasized for other dust-related occupational diseases [45], and underscores the often neglected importance of considering occupational and environmental exposures in any study of chronic inflammatory airway disorders [43].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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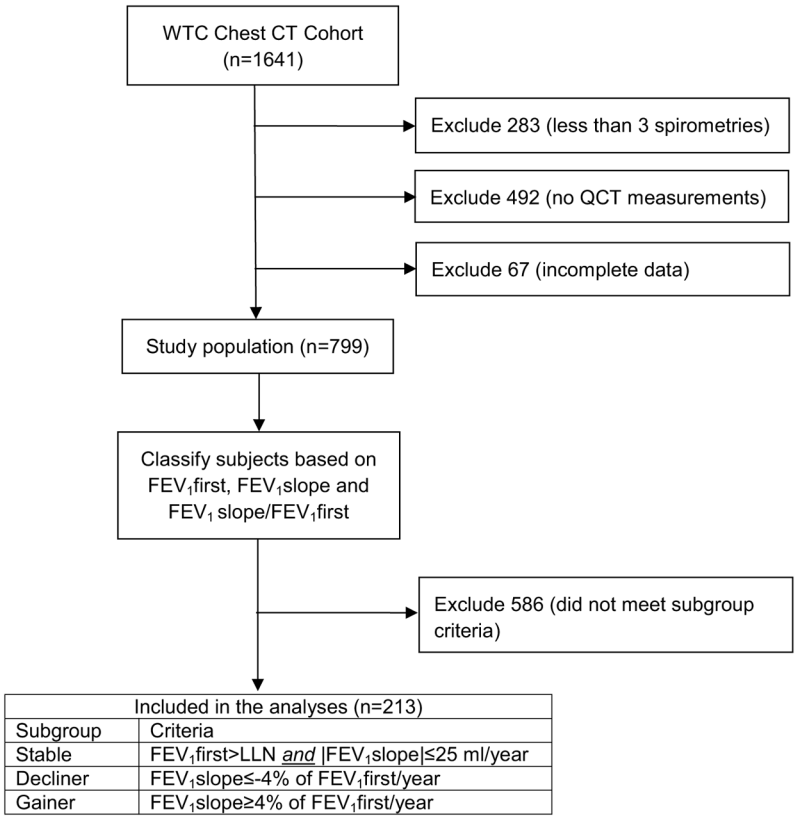

Included in the analyses (n=213)	
Subgroup	Criteria
Stable	FEV_1first>LLN *and* |FEV_1slope|≤25 ml/year
Decliner	FEV_1slope≤-4% of FEV_1first/year
Gainer	FEV_1slope≥4% of FEV_1first/year

Fig. 1.
Study flow chart

Table 1

Characteristics of the entire study group, and the stable, decliner, and gainer subgroups

	Entire group (n = 799)		**Stable (n = 103)**		**Decliner (n = 81)**			**Gainer (n = 29)**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p****	**Mean**	**SD**	***p****
FEV_1slope, *ml/year*	−35.7	0.15[a]	−7.8	0.15[a]	−157.6	0.2[a]	–	173.6	0.26[a]	–
Wall area percent	62.1	7.76	60.7	7.46	65.1	7.31	< **0.0001**	63.5	7.8	0.0824
Age, *years*	42.6	8.81	41.6	7.8	45.1	8.8	**0.0046**	41.0	8.3	0.7100
Height, *cm*	171.5	10.0	169.8	10.3	171.2	9.6	0.3392	175.1	8.5	**0.0119**
Baseline BMI, kg/m^2	28.96	4.76	28.85	4.35	29.74	4.79	0.1428	29.61	5.4	0.3738
BMIslope, $kg/m^2/year$	0.11	0.36	0.01	0.30	0.16	0.48	**0.0128**	−0.04	0.6	0.7020
Baseline FEV_1%predicted	87.1	16.9	95.6	11.7	82.3	17.1	< **0.0001**	56.6	15.6	< **0.0001**
WTC exposure duration, *days*	93.9	74.1	85.1	73.2	83.8	79.8	0.9059	88.5	78.3	0.8303
	n	%	n	%	n	%	*p*	n	%	*p*
Spirometry result										
Normal	483	60.5	89	86.4	44	54.3	–	2	6.9	–
Reduced FVC	233	29.2	11	10.7	25	30.9		12	41.4	
Obstruction	83	10.4	0	0	12	14.8		15	51.7	
COPD	44	5.5	0	0	9	11.1		6	20.7	
Occupation										
Management/services	141	17.6	15	14.6	22	27.2	–	8	27.6	–
Construction trades	150	18.8	16	16.0	17	21.0		7	24.1	
Laborers/cleaners	269	33.7	39	37.9	17	21.0		4	13.8	
Transportation	41	5.1	4	3.9	4	4.9		1	3.4	
Law enforcement	171	21.4	23	22.3	19	23.5		8	27.6	
Unemployed/retired	27	3.4	6	5.8	2	2.5		1	3.4	
Baseline smoking status										
Never	407	50.9	64	62.1	38	46.9		15	51.7	
Former	235	29.4	31	30.1	27	33.3	**0.0296**	6	20.7	**0.0146**
Current	157	19.7	8	7.8	16	19.8		8	27.6	

	Entire group (n = 799)		Stable (n = 103)		Decliner (n = 81)			Gainer (n = 29)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p****	**Mean**	**SD**	***p****
Pre-WTC exposure										
No	370	46.3	48	46.6	47	58.0	0.1238	8	27.6	0.0672
Yes	429	53.7	55	53.4	34	42.0		21	72.4	
Gender										
Male	653	81.7	85	82.5	61	75.3	0.2300	26	89.7	0.5654
Female	146	18.3	18	17.5	20	24.7		3	10.3	
WTC arrival < 48 h										
No	413	51.7	56	54.4	25	30.9	**0.0014**	8	27.6	**0.0108**
Yes	386	48.3	47	45.6	56	69.1		21	72.4	
Race/ethnicity										
Latino	276	34.5	35	34.0	20	24.7		6	20.7	
Non-Latino white	425	53.2	52	50.5	47	58.0	0.3920	14	48.3	0.1237
Non-Latino other	98	12.3	16	15.5	14	17.3		9	31.0	
Any BDR										
No	618	77.4	89	86.4	47	58.0	< **0.0001**	13	44.8	< **0.0001**
Yes	181	22.7	14	13.6	34	42.0		16	55.2	

WAP measured with the Simba system. The *p* values relate to the unadjusted comparisons of the decliner and gainer subgroups, with the stable subgroup

[*] *p* values for continuous measures from *t* test, *p* value for categorical measures from χ^2 or Fisher's exact test as appropriate, for comparisons between the stable vs. the decliner or the gainer subgroups. Statistically significant differences are bolded

[a] Root mean squared error, instead of SD

Table 2

Logistic regression model for the comparison of decliner (n = 81) versus stable (n = 103) subgroups

	Adjusted comparison			
	OR	**95% CI**		***p***
Wall area percent*, *5% unit*	1.47	1.12	1.95	**0.0063**
Age, *years*	1.07	1.01	1.12	**0.0134**
BMI slope, *0.2 kg/m^2/year unit*	1.48	1.18	1.87	**0.0009**
Baseline FEV_1%predicted	0.95	0.92	0.98	**0.0013**
Pre-911 exposure				
No	1	–	–	**0.0090**
Yes	0.32	0.14	0.75	
Any BDR				
No	1	–	–	**0.0185**
Yes	2.88	1.20	6.96	

WAP measured with the Simba system. The model was also adjusted for baseline smoking status, height, gender, and WTC arrival within 48 h. Statistically significant estimates are bolded