Persistent Hyperreactivity and Reactive Airway Dysfunction in Firefighters at the World Trade Center

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New York City Fire Department rescue workers experienced massive exposure to airborne particulates at the World Trade Center site. Aims of this longitudinal study were to (*1*) determine if bronchial hyperreactivity was present, persistent, and independently associated with exposure intensity, (*2*) identify objective measures shortly after the collapse that would predict persistent hyperreactivity and a diagnosis of reactive airways dysfunction 6 months post-collapse. A representative sample of 179 rescue workers stratified by exposure intensity (high, moderate, and control) without current smoking or prior respiratory disease was enrolled. Highly exposed workers arrived within 2 hours of collapse, moderately exposed workers arrived later on Days 1–2; control subjects were not exposed. Hyperreactivity at 1, 3, and 6 months post-collapse was associated with exposure intensity, independent of ex-smoking and airflow obstruction. Six months post-collapse, highly exposed workers were 6.8 times more likely than moderately exposed workers and control subjects to be hyperreactive (95% confidence interval, 1.8–25.2; p = 0.004), and hyperreactivity persisted in 55% of those hyperreactive at 1 and/or 3 months. In highly exposed subjects, hyperreactivity 1 or 3 months post-collapse was the sole predictor for reactive airways dysfunction (p = 0.021). In conclusion, development and persistence of hyperreactivity and reactive airways dysfunction were strongly and independently associated with exposure intensity. Hyperreactivity shortly post-collapse predicted reactive airways dysfunction at 6 months in highly exposed workers; this has important implications for disaster management.

Keywords: inorganic particulate matter; nonspecific bronchial hyperreactivity; reactive airways dysfunction syndrome; firefighters; World Trade Center collapse

The Fire Department of New York City's (FDNY) immediate response to the World Trade Center (WTC) attack resulted in the death of 343 firefighters and numerous injuries. Despite this staggering loss, nearly 14,000 surviving FDNY rescue workers (firefighters, emergency medical service workers and officers) continued their unprecedented rescue and recovery effort, during the course of which many were exposed to large amounts of airborne particulates and products of combustion/pyrolysis (1). Acute inflammatory reactions have been described after exposure to high concentrations of ambient particulates (2–4) and WTC dust (5).

For rescue workers and others, exposure to the WTC collapse has resulted in widespread health concerns including those related to the development of chronic inflammatory airway diseases (e.g., asthma, bronchitis, reactive airways dysfunction syndrome [RADS]), especially because nearly every FDNY rescue worker developed an acute cough and exacerbations of pre-existing asthma were observed in Manhattan residents (6). Nonspecific bronchial hyperreactivity is a requirement for the diagnosis of RADS and is a risk factor for the development of obstructive airways diseases (7–10). Yet, there is little existing literature describing the development and time course of bronchial hyperreactivity, and its relationship to exposure intensity, after natural or man-made disasters. For these reasons, we rapidly instituted a prospective comparative cohort study in FDNY rescue workers.

Our current report is a prospective, longitudinal study using a representative sample stratified on the basis of initial exposure intensity, independent of symptoms. The primary aims were to determine if nonspecific bronchial hyperreactivity was (*1*) present, persistent, and independently associated with intensity of WTC dust exposure and (*2*) associated with respiratory symptoms, medical leave time due to respiratory illness, and decline in spirometry. Secondary aims were to identify objective measures obtainable shortly after exposure (1 or 3 months post-WTC) that may be predictive of chronic bronchial hyperreactivity or RADS at 6 months post-WTC in those workers most at risk.

Only after study enrollment had been completed did we recognize the emergence of the "WTC Cough" syndrome in FDNY firefighters, using a case definition of a new/worsening persistent cough after WTC exposure, accompanied by respiratory symptoms severe enough to require at least 4 consecutive weeks of medical leave (11). The predominant pathophysiology in "WTC Cough" is airway obstruction/inflammation with a bronchodilator response in 63%, air trapping and/or bronchial wall thickening on a high-resolution computed tomographic scan in 60%, and bronchial hyperreactivity in 24% of those tested (11). At the time of enrollment, none of the subjects in this current study qualified for the diagnosis of "WTC Cough." Post-hoc analysis was performed to determine the relationship between hyperreactivity, RADS, and "WTC Cough" in study subjects.

METHODS

Exposure Groups

FDNY rescue workers were designated highly exposed if they arrived at the WTC site on the morning of Day 1 (n = 1,636; 16%); moderately exposed if they arrived on the afternoon of Day 1 or during Day 2 (n = 6,958; 69%); and less exposed if they arrived between Days 3 and 7 (n = 1,320; 13%). Nonexposed control subjects were FDNY rescue workers absent from the WTC site for the first 2 weeks or more (n = 202; 2%). FDNY officers assigned personnel to exposure designations using FDNY dispatch records, but due to the high rate of self-deploy-

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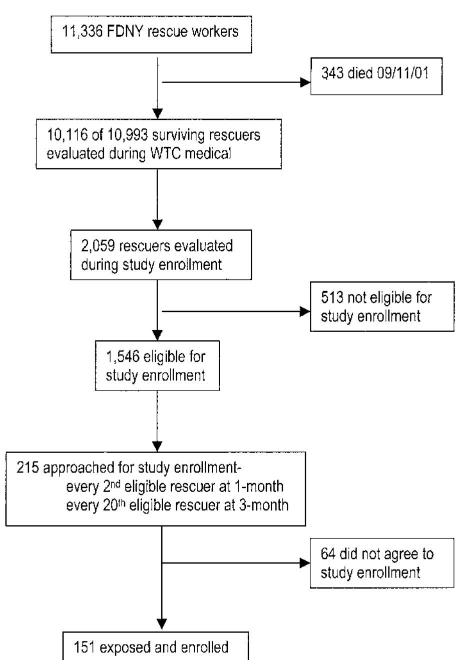
ment, final exposure designation was based on a self-administered questionnaire and confirmatory interviews. Study exclusion criteria were classification in the less exposed group, allergic history (assessed by subject interview), smoking within 4 years, FEV_1 less than 65% predicted, or use of inhaled or systemic corticosteroids within preceding month (n = 15 excluded due to this criterion). To explore potential influence on exposure, work assignments were categorized as Fire Suppression (Ladder and Engine units), Special Operations Command (Rescue, Squad, and Marine units) and others (emergency medical service and other FDNY rescue workers).

Study Design and Timeline

This prospective cohort study compared two exposed and one control cohorts representative of FDNY rescue workers who responded to the WTC disaster. Study subjects were enrolled during FDNY WTC Medical Monitoring 1 and 3 months post-WTC (Figure 1) and were offered methacholine challenge testing at 1, 3 and 6 months post-WTC. FDNY WTC Medical Monitoring was conducted 1–3 months post-WTC and was mandatory for all workers. It included an occupational health questionnaire, spirometry, chest radiograph, and other laboratory evaluations. None of the 1,546 eligible subjects were on medical leave. Challenge testing was voluntary and required informed consent as approved by the Montefiore Medical Center Institutional Review Board. At 1 month post-WTC, challenge testing was offered to every second highly or moderately exposed worker registering for WTC Medical Monitoring who met study eligibility criteria, regardless of symptoms. At 3 months, additional study subjects were enrolled, but due to the strain on resources from the larger numbers registering for WTC Medical Monitoring at that time, challenge testing was offered to every 20th highly or moderately exposed worker who met study eligibility criteria, regardless of symptoms. Of the study cohort of 151 exposed subjects, 112 returned for re-testing at 6 months (74% retention). Thirty-nine were not re-tested (31 refused, five had FEV_1 deterioration to less than 65% predicted, and three had recently received corticosteroids). Control subjects (n = 28) were recruited from FDNY firefighters who, due to prior injuries/illnesses (other than respiratory), were assigned office duties and did not work in rescue, recovery, or fire suppression activities at or near the WTC site. Of the 151 exposed rescue workers described in the current publication, 19 were diagnosed with “WTC Cough” after study enrollment. Their clinical, radiographic, and physiologic characteristics have recently been described (11).



	1-Month		3-Month		6-Month	
	Highly Exposed	*Moderately Exposed*	*Highly Exposed*	*Moderately Exposed*	*Highly Exposed*	*Moderately Exposed*
Recruited & Tested at 1-Month	77	25	56	20	53	20
Recruited & Tested at 3-Month	-	-	24	25	23	16
Total Number Tested at Each Time Point	102		125		112	

Figure 1. Source population, study sample and study time course. Derivation of the study sample from the source population, numbers of exposed workers eligible, and numbers actually enrolled for testing at each time point are shown.

Health Questionnaire and Medical Record Review

The questionnaire included items on exposure, job tasks, respiratory protection type (dust mask, N95 respirator [Kimberly-Clark, Roswell, GA], P-100 half-face respirator [3M Occupational Health and Environmental Safety Division, St. Paul, MN], and use frequency during first 2 weeks post-collapse), respiratory symptoms pre- and post-WTC, medications, and other issue. Post-WTC respiratory symptoms were assessed at the time of WTC Medical Monitoring and re-assessed at 6 months (even if ineligible or refused repeat testing) and were classified as affirmative response to at least one of the following: “daily cough, nearly constant cough, wheeze, shortness of breath, chest tightness and sleep disturbance due to cough, wheeze or shortness of breath.” We also assessed nasal and throat symptoms (“drip, congestion, and sore or hoarse throat”) and gastroesophageal reflux disease symptoms (“heartburn, regurgitation, and retrosternal chest burning”). To be considered post-WTC, confirmatory symptom responses required the descriptor of “new or definitely worsened since 9/11/01.” Medical leave durations for respiratory illness during the 6 months post-WTC were collected from the FDNY computerized medical database.

Spirometry

Spirometry (Model Portascreen; S&M Instruments, Doylestown, PA) was performed as part of FDNY WTC Medical Monitoring using American Thoracic Society guidelines (12). FVC and FEV_1 were expressed as absolute values and percent predicted (13). For all study subjects, including control subjects, spirometry at WTC Medical Monitoring was compared with FDNY spirometry from their most recent pre-WTC annual medical. For those study subjects with challenge tests at 1 month (n = 102) and at 3 months (n = 125), spirometric measurements during the challenge tests were compared with those obtained concomitantly during FDNY WTC Medical Monitoring, and no significant differences were found in absolute (in liters) or percent-predicted measures. Analyses were performed with and without adjusting FEV_1 and FVC measurements (in liters) for an expected annual decline of 25 cm^3/year. This was calculated by computing the difference in days between the most recent pre-WTC spirometry and the first post-WTC spirometry, multiplying by 25 cm^3/365 days and then subtracting this value from the difference between pre- and post-WTC measurements (14).

Methacholine Challenge Testing

Methacholine Challenge Testing required written informed consent as approved by Montefiore Medical Center’s Institutional Review Board. Testing was performed according to American Thoracic Society guidelines (15) with KoKo Spirometer (PDS Instrumentation, Louisville, CO) and methacholine (Provocholine; Methapharm, Brantford, ON, Canada) diluted in sterile 0.9% saline to concentrations of 0.025, 0.25, 2.5, 10, and 25 mg/ml. The 0.025-mg/ml methacholine solution was prepared daily. Other solutions were stored at 4°C when not used, warmed to room temperature before use, and discarded after 1 week. Aerosol generation was initiated by manual occlusion of a Y tube bypass (at nebulizer high pressure input) and coordinated with inhalation from functional residual capacity to total lung capacity over 5 seconds, followed by a 5-second breath hold. Inhalation was repeated five times for each methacholine concentration. Three minutes after aerosol inhalation, subjects performed three to five spirometry maneuvers (best quality effort selected) followed by inhalation of the next higher concentration. Administration of increasing methacholine concentrations was continued until FEV_1 declined by 20% of baseline (PC20) or the maximum concentration was administered.

Data Analysis

For univariate analyses comparing clinical characteristics of study subjects (*1*) with eligible subjects, (*2*) between differing exposure groups, (*3*) between different reactivity status at 6 months, (*4*) with and without diagnoses of RADS at 6 months, and (*5*) with and without diagnoses of "WTC Cough" at 6 months, *t* test, and analysis of variance were used for continuous variables. For variables not meeting normality assumptions, Mann–Whitney *U* or Kruskal–Wallis tests were used. Categorical variables were analyzed with χ^2 tests and Fisher's exact test if cell numbers were low. The correlation between medical leave lengths and hyperreactivity assessed as a continuous measurement at 6 months was performed with Spearman's ρ.

Hyperreactivity was assessed 1, 3, and 6 months post-WTC using categorical and continuous measures (16). Study subjects were categorized as hyperreactive if PC20 was less than or equal to 8 mg/ml (calculated by exponential interpolation) (17, 18). Assessment of hyperreactivity as a continuous measure was also performed after calculation of methacholine dose–response slopes computed by the two-point method (19). Methacholine dose–response slope was defined as the decline from the baseline FEV_1 to the FEV_1 after the last dose of methacholine administered, expressed as percent of baseline FEV_1, and divided by cumulative units inhaled. The greater the responsiveness to methacholine, the larger (more positive) the dose–response slope. At 1, 3, and 6 months, we compared proportions of hyperreactive study subjects among exposure groups (χ^2), and average rank of methacholine dose–response slopes among exposure groups (Kruskal–Wallis test). Associations between presence or absence of airway hyperreactivity and exposure group adjusted for ex-smoking status and airflow obstruction were analyzed by logistic regression. Separate logistic models were developed for examinations at 1, 3, and 6 months. Highly exposed subjects were compared with the other subjects (moderately exposed plus control subjects) for calculation of odds ratios and 95% confidence intervals. For control subjects, presence of hyperreactivity was assumed constant from 1 to 6 months post-WTC, given absence of exposure.

To assess persistence of hyperreactivity, study subjects with a 6-month exam were classified into two categories: the persistently hyperreactive with all exams hyperreactive, and the never or variably hyperreactive with none or some but not all exams hyperreactive. Proportions of highly exposed subjects in whom hyperreactivity persisted from 1 and 3 months to 6 months were compared with proportions in whom hyperreactivity did not persist (dichotomized PC20 by McNemar; dose–response slopes by Wilcoxon signed ranks test).

RADS was defined as nonspecific airway hyperreactivity (PC20 $\leqslant$ 8 mg/ml) in conjunction with respiratory symptoms at 6 months post-WTC. Predictors were characteristics that had been measured 1 or 3 months post-WTC [age, FDNY work tenure, ex-smoking status, highly vs. moderately exposed, respiratory symptoms, spirometric measurements (percent predicted FEV_1 and FVC measured pre-WTC or 1 month post-WTC, and declines in FEV_1 and FVC from pre- to 1 month post-WTC, adjusted for an expected annual decline of 25 cm^3/year) and hyperreactivity (categorized as hyperreactive at 1 or 3 months vs. never reactive at 1 and/or 3 months)]. Predictive properties of respiratory symptoms and ex-smoking status were assessed with χ^2; properties of age, work tenure, and spirometric measurements were assessed with the *t* test. McNemar's test was used to assess predictive properties of hyperreactivity at 1 or 3 months for the outcomes at 6 months of airway hyperreactivity, RADS, and "WTC Cough." Odds ratios and 95% confidence intervals were calculated for the development of RADS or "WTC Cough," given hyperreactivity 1 or 3 months post-WTC. p Values less than 0.05 were considered statistically significant, and significance tests were two-sided. Analyses were performed with SPSS statistical software.

RESULTS

Clinical Characteristics of Study Subjects Compared with Eligible Subjects

Clinical characteristics of the 179 study subjects were compared with those of the 1,395 subjects who presented for WTC Medical Monitoring and met study enrollment criteria but were not enrolled. Sex, age, ex-smoking status, and incidence of respiratory symptoms were not significantly different (Table 1). All exposed subjects reported cough within first 24 hours post-WTC. Pre-WTC, mean FVC, and FEV_1 were within normal limits, and there were no significant differences between the percentages of eligible and study subjects with spirometric measurements below 80% predicted (4.0 vs. 2.0% for FVC; 2.7 vs. 2.6% for FEV_1).

Clinical Characteristics of Study Subjects by Exposure

Comparisons between highly and moderately exposed study subjects revealed no significant differences in sex, age, ex-smoking status, and work assignment. When compared with exposed study subjects, control subjects were slightly older (p = 0.041) and were more often ex-smokers (p = 0.015). Pre-WTC mean FVC and FEV_1 were within normal limits, and there were no significant differences between exposure groups (Table 2), and there were no differences in the percentage of subjects within each exposure group (highly exposed vs. moderately exposed vs. control subjects) for spirometric measurements less than 80% predicted (3.5 vs. 0 vs. 0% for FVC; 2.3% vs. 4.4 vs. 0% for FEV_1). Both highly and moderately exposed study subjects showed significant declines in all spirometric measurements from pre-WTC to post-WTC, regardless of whether post-WTC measurements were at 1, 3, or 6 months (Table 2), but declines

TABLE 1. CLINICAL AND SPIROMETRIC CHARACTERISTICS OF TESTED SUBJECTS AND ELIGIBLE SUBJECTS

	Eligible Subjects	Tested Subjects
Total number		
Highly exposed	273	102
Moderately exposed	1,087	49
Control subjects	35	28
Sex, % male		
Highly exposed, %	98	97
Moderately exposed, %	99	100
Control subjects, %	91	96
Age, yr		
Highly exposed	43.25 ± 9.09	41.45 ± 6.71
Moderately exposed	41.24 ± 7.50	40.47 ± 7.04
Control subjects	45.17 ± 9.60	44.73 ± 9.15*
Ex-smokers		
Highly exposed, %	11	12
Moderately exposed, %	16	10
Control subjects, %	34	33†
Pre-WTC spirometry		
FVC, L; % predicted		
Highly exposed	5.07 ± 0.83; 98 ± 12	4.94 ± 0.85; 99 ± 14
Moderately exposed	5.19 ± 0.85; 101 ± 14	4.97 ± 0.75; 99 ± 13
Control subjects	4.56 ± 1.03; 95 ± 12	5.00 ± 0.76; 102 ± 13
FEV_1, L; % predicted		
Highly exposed	4.32 ± 0.69; 102 ± 13	4.22 ± 0.70; 103 ± 15
Moderately exposed	4.40 ± 0.71; 104 ± 14	4.24 ± 0.67; 102 ± 15
Control subjects	3.93 ± 0.91; 99 ± 14‡	4.35 ± 0.74; 110 ± 14
FEV_1/FVC		
Highly exposed	0.85 ± 0.05	0.86 ± 0.05
Moderately exposed	0.85 ± 0.05	0.85 ± 0.05
Control subjects	0.86 ± 0.05	0.87 ± 0.05

Definition of abbreviation: WTC = World Trade Center.

Results presented as mean ± SD.

No significant difference in demographic characteristics was noted between exposed eligible and tested subjects within exposure groups.

* p = 0.041 for tested subjects among exposure groups–high, moderate, control (analysis of variance).

† p = 0.015 for tested subjects among exposure groups–high, moderate, control (χ^2).

‡ p = 0.008 between eligible and tested subjects within control group (*t* test).

TABLE 2. SPIROMETRY IN TESTED SUBJECTS BEFORE AND AFTER ATTACK ON THE WORLD TRADE CENTER

	Pre-WTC L (*% Predicted*)	1-Month Exam L (*% Predicted*)	3-Month Exam L (*% Predicted*)	6-Month Exam L (*% Predicted*)
FVC				
Highly exposed	4.94 ± 0.85* (99 ± 14)*	4.70 ± 0.83 (94 ± 17)	4.58 ± 0.85 (93 ± 17)	4.63 ± 0.75 (90 ± 13)†
Moderately exposed	4.97 ± 0.75* (99 ± 13)*	4.59 ± 0.72 (89 ± 12)	4.65 ± 0.77 (93 ± 14)	4.67 ± 0.71 (88 ± 9)
Control subjects	5.00 ± 0.76 (102 ± 13)		4.84 ± 0.69 (101 ± 15)	
FEV_1				
Highly exposed	4.22 ± 0.70* (103 ± 15)*	3.97 ± 0.66 (96 ± 18)†	3.84 ± 0.66 (95 ± 18)†	3.88 ± 0.59 (90 ± 14)†
Moderately exposed	4.24 ± 0.67* (102 ± 15)*	3.82 ± 0.60 (91 ± 13)	3.84 ± 0.68 (93 ± 15)	3.85 ± 0.64 (89 ± 10)
Control subjects	4.35 ± 0.74* (110 ± 14)*		4.05 ± 0.62 (106 ± 15)	
FEV_1/FVC				
Highly exposed	0.86 ± 0.05*	0.79 ± 0.05	0.79 ± 0.05	0.78 ± 0.05
Moderately exposed	0.85 ± 0.05*	0.83 ± 0.06	0.82 ± 0.06	0.82 ± 0.06
Control subjects	0.87 ± 0.05*		0.84 ± 0.05	

For definition of abbreviations, *see* Table 1.
Results presented as mean ± SD.
* $p < 0.05$ between pre-WTC and post-WTC at 1-, 3- and 6-month exams within exposure group.
† $p < 0.05$ between exposure groups (high, moderate, control) at 1-, 3-, or 6-month exams (ANOVA) when absolute measurements (in liters not adjusted for annual decline) or measurements in percent predicted were compared.

were not significant when adjusted for expected annual change of 25 cm^3/year. In the first 48 hours post-WTC, respiratory protection use did not differ significantly between exposed study subjects, with only 21% of highly exposed, and 22% of moderately exposed subjects reporting frequent use of any mask type. The most commonly used type of mask was a hardware store dust mask rather than a fit-tested, National Institute for Occupational Safety and Health–certified respirator (self-contained breathing apparatus, N-95 or half-face dual cartridge P-100 respirator).

Bronchial Hyperreactivity and Exposure

Thirty-one percent (32/102) of highly exposed study subjects and 25% (37/151) of all exposed study subjects were hyperreactive (PC20 ≤ 8 mg/ml) on their first post-WTC challenge test. There was a significantly greater proportion of study subjects with hyperreactivity (PC20 ≤ 8 mg/ml methacholine) in the heavily exposed group as compared with moderately exposed or control groups at 1 month ($p = 0.004$), 3 months ($p = 0.008$), and 6 months ($p = 0.004$) (Figure 2). At each time point, there were no significant differences between moderately exposed and control groups. Similar results were obtained when hyperreactivity was analyzed as a continuous measurement, with highly exposed subjects significantly more reactive than moderately exposed or control groups ($p = 0.005$ at 3 months; $p = 0.003$ at 6 months; Figure 3). For highly exposed subjects, the median methacholine dose–response slope at 6 months had risen by 46% from the median at 1 month, indicating worsening bronchial hyperreactivity over this time period. In contrast, median dose–response slopes for moderately exposed subjects remained within 9% of the 1-month value at 3 and 6 months, indicating little change in bronchial hyperreactivity during this time period. Significant differences in bronchial hyperreactivity assessed with continuous measurements between highly and moderately exposed subjects did not exist at 1 month but emerged by 3 months (Figure 3). After adjusting for ex-smoking status and airflow obstruction, highly exposed subjects were 7.3 times (95% confidence interval, 1.5–34.1, $p = 0.012$) more likely to be hyperreactive than moderately exposed plus control subjects at 1 month, 6.3 times (95% confidence interval, 1.7–23.5, $p = 0.007$) more likely at 3 months and 6.8 times (95% confidence interval, 1.8–25.2; $p = 0.004$) more likely at 6 months. Variables describing respirator use did not significantly improve model fit.

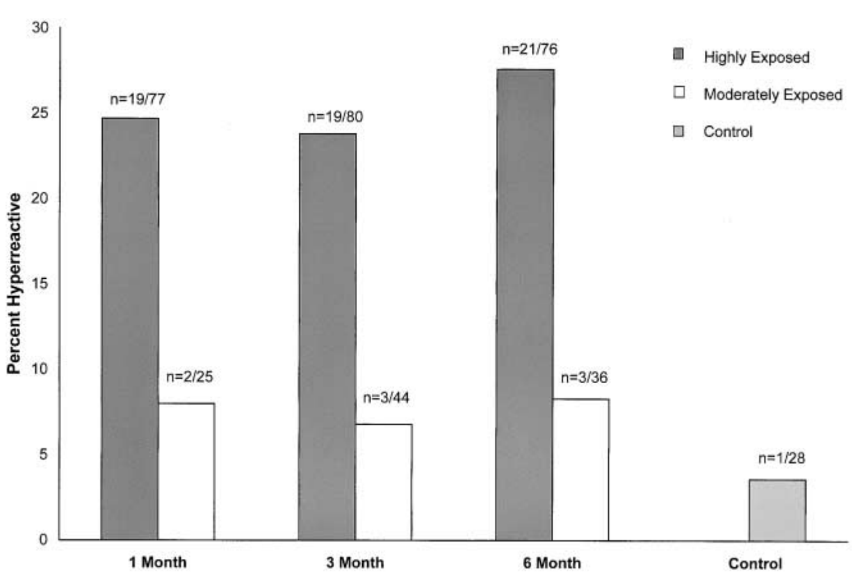


Figure 2. Airway hyperreactivity post-World Trade Center (WTC). Percentages of hyperreactive subjects at each time point and within each exposure group are indicated. Hyperreactivity was defined as methacholine PC20 less than or equal to 8 mg/ml. The proportion of hyperreactive subjects in the highly exposed group was significantly larger than in moderately exposed and control groups, at 1 month ($p = 0.004$), 3 months ($p = 0.002$), and 6 months ($p = 0.009$). Control subjects were tested at 3 months.

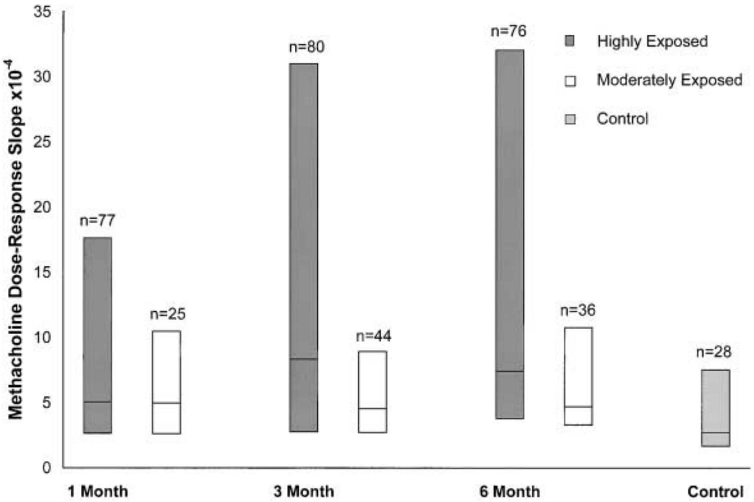


Figure 3. Airway hyperreactivity post-WTC as continuous measurements. Methacholine dose–response slope ($\times 10^{-4}$) was defined as the decline from the baseline FEV_1 to the FEV_1 after the last dose of methacholine administered, expressed as percent of baseline FEV_1, and divided by cumulative methacholine dose units inhaled. The greater the responsiveness to methacholine, the larger (more positive) is the dose–response slope. The mean rank of methacholine dose–response slopes in the highly exposed group was significantly larger than in moderately exposed and control groups at 3 months ($p = 0.005$, Mann–Whitney *U*) and 6 months ($p = 0.003$, Mann–Whitney *U*). Median and 25th–75th percentiles are indicated at each time point for each exposure group.

Hyperreactivity Persistence

Fifty-five percent (17/31) of exposed study subjects who were tested at least twice and were hyperreactive at 1 or 3 months remained hyperreactive at 6 months. One hundred percent (6/6) who were hyperreactive at both 1 and 3 months remained hyperreactive at 6 months. In contrast, only 15% (8/54) who were never hyperreactive or variably hyperreactive at 1 and 3 months became hyperreactive at 6 months. Thus, hyperreactivity at 6 months was found significantly more often in exposed subjects with hyperreactivity at both 1 and 3 months as compared with exposed study subjects who were never or variably hyperreactive at 1 and 3 months ($p = 0.008$). Similar results were obtained when hyperreactivity at 6 months was analyzed as a continuous measurement ($p = 0.002$).

Clinical Characteristics of Hyperreactive, Exposed Study Subjects at 6 Months

In those who were hyperreactive at 6 months**,** respiratory symptoms (Table 3) were reported more often ($p = 0.049$), medical leave due to respiratory illness was significantly longer ($p = 0.022$; mean number of medical leave days for respiratory illness 45 days in hyperreactive vs. 12 days in non-reactive subjects), and FEV_1 less than 80% predicted occurred significantly more frequently (18 vs. 3%; $p = 0.032$) as compared with non-reactive subjects. Similar results were obtained when hyperreactivity was analyzed as a continuous measurement ($p = 0.003$ for symptoms; $p = 0.028$ for medical leave, Spearman's $\rho = 0.21$). Only one of the 24 exposed subjects who were hyperreactive at 6 months was an ex-smoker. At 6 months post-WTC, the diagnosis of RADS (i.e., hyperreactivity and respiratory symptoms) could be applied to 16% (20/123) of all exposed study subjects: 20% (17/83) of highly exposed subjects and 8% (3/40) of moderately exposed subjects.

Predictors for 6-Month Outcomes

In highly exposed subjects, clinical and physiologic measurements at 1 or 3 months were examined for their value in predicting the development of either bronchial hyperreactivity or RADS at 6 months. Age at time of WTC collapse, FDNY work tenure, smoking status, respiratory symptoms, pre-WTC spirometry, post-WTC spirometry at 1-month, and post-minus pre-exposure spirometric changes did not predict the development of hyperreactivity or RADS at 6 months. Hyperreactivity at 1 or 3 months was predictive of RADS at 6 months ($p = 0.021$; Figure 4). Among those who were highly exposed and hyperreactive at 1 or 3 months, 52% (14/27) qualified for the diagnosis of

TABLE 3. NEW OR WORSENING RESPIRATORY SYMPTOMS IN EXPOSED SUBJECTS

	At Enrollment (*n* = *151*)		At 6 Months (*n* = *151*†)	
	Hyperreactive* (%)	Nonreactive (%)	Hyperreactive (%)	Nonreactive (%)
Daily cough	84	69‡	90	56
Dyspnea	47	33	74	35
Chest tightness	48	33	63	28
Wheeze	38	16	65	14
Any of above interfering with sleep	52§	35‡	29	13
Any respiratory symptom	88	68	93	66
Nasal or throat symptoms	88	75‡	71	58
Gastroesophageal reflux	41	28	45	29

* Hyperreactive at 1 and/or 3 months.
† For symptom reassessment at 6 months, subjects refusing follow up ($n = 31$) were considered non-reactive and subjects too ill ($n = 8$) for testing ($FEV_1 < 65\%$ predicted or steroid treatment) were considered hyperreactive.
‡ $p < 0.05$ between 3 and 6 months for subjects who were non-reactive at enrollment (McNemar).
§ $p < 0.05$ between 3 and 6 months for subjects who were hyperreactive at enrollment (McNemar).

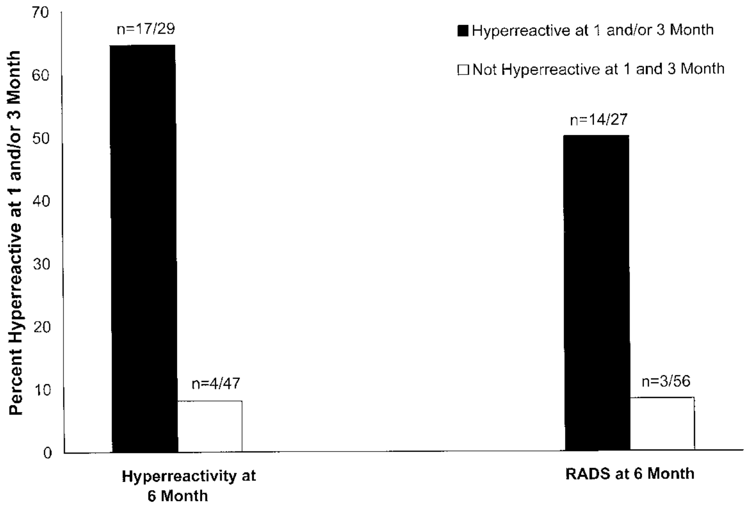


Figure 4. Predictors of hyperreactivity and reactive airways dysfunction syndrome (RADS) among highly exposed subjects at 6 months. Highly exposed subjects who were hyperreactive at 1 or at 3 months were more often hyperreactive at 6 months than those who were not hyperreactive at 1 and 3 months, but this association did not reach statistical significance ($p = 0.077$). Highly exposed subjects who were hyperreactive at 1 or at 3 months qualified for a diagnosis of RADS (defined as both symptomatic and hyperreactive) at 6 months significantly more often ($p = 0.021$) than highly exposed subjects who were not hyperreactive at 1 and 3 months. Seven subjects who did not qualify for a diagnosis of RADS because of absence of clinical symptoms at 6 months did not agree to re-assessment of their hyperreactivity status at that time.

RADS, and subjects who were hyperreactive at 1 or 3 months were 19 times more likely (95% confidence interval = 4.8–76.1) to develop RADS at 6 months compared with subjects who were not reactive at 1 and 3 months.

Clinical Characteristics of Subjects Who Developed "WTC Cough" After Study Enrollment

Nineteen of 151 (13%) exposed subjects subsequently developed "WTC Cough" after study enrollment: 16/102 (13%) in the highly exposed group, and 3/49 (6%) in the moderately exposed group. In comparing exposed subjects who developed "WTC Cough" with those who did not, there were no significant differences in age, work tenure, ex-smoking status, or the decline in FVC or FEV_1 (absolute or adjusted). In those with "WTC Cough," hyperreactivity was evident in 7/12 (58%) at 1 month, 9/15 (60%) at 3 months, and 9/18 (50%) at 6 months. Thus, only half the patients with "WTC Cough" qualified for the diagnosis of RADS (symptoms and hyperreactivity) at 6 months. Subjects who were hyperreactive at 1 or 3 months were 7.3 times more likely (95% confidence interval = 2.6–20.5) to develop "WTC Cough" as compared with subjects who were not hyperreactive at 1 and 3 months.

DISCUSSION

In this cohort of FDNY rescue workers exposed to airborne particulates during the immediate aftermath of the WTC collapse, we describe the development and time course of bronchial hyperreactivity and its relationship to exposure intensity. Exposure intensity to WTC dust and products of combustion/pyrolysis was strongly and independently associated with bronchial hyperreactivity 1, 3, and 6 months post-WTC. At 6 months, hyperreactivity persisted in 55% of those who were hyperreactive at 1 and/or 3 months. Hyperreactivity was more than a physiologic exposure marker; its presence was strongly associated with persistent respiratory symptoms and respiratory-related medical leave over the next 6 months. Moreover, hyperreactivity 1 or 3 months post-WTC was the only significant predictor for RADS at 6 months in highly exposed subjects. The identification of objective measures associated with long-term sequelae after a massive accidental exposure has important public health implications for disaster management.

Environmental data acquired after the WTC collapse have found concentrations of airborne and respirable particulates ranging up to 2.3 and 0.3 mg/m^3, respectively (1). Analysis of bulk samples of WTC dust collected 5 and 6 days post-collapse revealed a complex mixture of particulate matter and combustion/pyrolysis products, composed mostly of building debris fibers (e.g., mineral wool, fiberglass, asbestos, wood, paper, cotton) contaminated with polycyclic hydrocarbons (1, 20). More than 90% of WTC dust particles were larger than 10 μm in diameter and caustic, with alkaline pH greater than 10 noted for particles greater than 2.5 μm (20–22). Though particles greater than 2.5 μm in diameter are believed to deposit predominantly in the upper airways, analyses of induced sputa showed that more than 20% of particles were greater than 2.0 μm in 35/39 (90%) exposed FDNY firefighters (23). In contrast, similar particle size distributions were found in only 1/12 (8%) control subjects, Tel Aviv firefighters (23). Particles were also recovered by bronchoalveolar lavage in one highly exposed FDNY firefighter with eosinophilic pneumonitis (5). The increased bronchial hyperreactivity described in this study and the worsening asthma described by others in exposed Manhattan residents (6) demonstrate that clinically significant respiratory consequences can occur.

Trying to quantify the exposure intensity of rescue workers during the first week, we found neither respirator use nor work assignment to be useful. Firefighters reported that except for their self-contained breathing apparatus (lasting only 8–15 minutes), respirators were generally not available during the first days post-collapse and, when available, were rarely worn. Furthermore, the intense rescue/recovery efforts required all FDNY workers to operate closely within the rubble pile while performing similar tasks (evacuation, fire suppression, rescue/recovery). Rescue workers unanimously agreed that there were dramatic visual differences in the density of airborne particles when comparing "during the collapse" and "the first 2 days after the collapse" and thereafter. Based on these firsthand reports, we used arrival time to categorize exposure intensity, and this index proved useful in characterizing bronchial hyperreactivity and its persistence in this stratified sample. Due to the urgency of the rescue operations in the first month, detailed documentation of total work time in the collapse zone is not available. Our interviews indicate that all study subjects appear to have had similar work time and job tasks at the site, during at least the first month, so that arrival time served as the best estimate of exposure intensity.

In miners (24) and construction workers (25), hyperreactivity has only been documented after lengthy low-level exposures to airborne particulates. One study assessed hyperreactivity in miners after an acute exposure, but the major irritant was to a chemical rather than particulates (26). Prior studies assessed hyperreactivity only in symptomatic subjects, did not evaluate large numbers of exposed workers, and used a far less specific PC20 cutoff, often 32 mg/ml (24–29). After smoke inhalation, bronchial hyperreactivity may occur within hours (27–29) and one study showed persistence in 11/13 at 3 months post-exposure (29). Bronchial hyperreactivity was not observed in 23 smoke inhalation patients requiring intubation, but treatment before assessment was not described (30).

This is the only study evaluating bronchial hyperreactivity soon after acute, massive exposure to WTC dust and fires. By performing serial methacholine challenge tests, we were able to define the natural history of bronchial hyperreactivity after this exposure. Persistent hyperreactivity for at least 6 months has been described in occupational asthma resulting from sensitization (31–33) and in irritant-induced asthma, such as accidental exposure to chlorine (34), but until now has not been evaluated after acute exposure to inorganic particulates. At 6 months, we found persistent bronchial hyperreactivity in 100% (6/6) of exposed subjects who were hyperreactive at 1 and 3 months and in 55% (17/31) of exposed subjects who were tested at least twice and were hyperreactive at 1 or 3 months. It was reasonable to combine 1- and 3-month time points because dust clouds and fires persisted until early December 2001. Six months after the WTC collapse, highly exposed rescue workers were still 6.8 times more likely to have bronchial hyperreactivity as compared with moderately exposed workers and unexposed control subjects, even after adjustment for airflow obstruction and ex-smoking. Assessment of hyperreactivity with continuous measurements also revealed persistence in highly exposed subjects (Figure 3). Significant differences between highly and moderately exposed subjects required up to 3 months after the exposure to emerge fully. Time delay in the emergence of bronchial hyperreactivity has also been shown in children, suggesting that in some subjects, inflammation may have to persist before hyperreactivity develops (35).

Both study subjects and eligible subjects had similar clinical characteristics (Table 1) and spirometry (Table 2). To minimize false positives in our cohort without respiratory symptoms or disease pre-WTC, we chose a strict cutoff criterion for nonspecific bronchial hyperreactivity (PC20 $\leqslant$ 8 mg/ml methacholine). Using less stringent criteria (PC20 $\leqslant$ 16 mg/ml methacholine or PC10 $\leqslant$ 8 mg/ml histamine), population and occupational studies (without acute exposures) have generally found nonspecific hyperreactivity prevalence rates of less than 10% (36, 37), not dissimilar to our control subjects or to those with moderate exposure. Control subjects were tested only once at 3 months, not unreasonable given the low incidence and lack of variability in hyperreactivity for our moderately exposed subjects (Figure 3).

Nearly all FDNY rescue workers reported onset of an intense cough within 24 hours of working at the WTC site, and this was their most prominent respiratory symptom. At 6 months, 93% of our exposed, hyperreactive subjects continued to report respiratory symptoms (Table 3), new or significantly worse than pre-WTC. Prior studies have reported respiratory symptoms in 42% of hyperreactive individuals in the general population (36), 12% of hyperreactive workers after chronic exposure to synthetic fibers (38), and 57% of cases after acute chemical inhalation exposures (39). We also found an increased incidence of upper airway (sinus and gastroesophageal reflux disease) symptoms in hyperreactive as compared with non-reactive subjects (Table 3). Although the incidence of gastroesophageal reflux disease was not as high as we reported for "WTC Cough" (11), patient acuity was different and symptoms were assessed by a self-administered questionnaire in our current study, whereas a clinician interview was the mainstay in the "WTC Cough" study. It remains unclear whether sinusitis and gastroesophageal reflux disease are causative factors or whether they facilitate the hyperreactive process that was initiated by inhalation injury. The clinical significance of bronchial hyperreactivity in our study cohort was corroborated by significantly longer medical leave duration due to new respiratory illness in hyperreactive as compared with non-reactive subjects. Medical leave status was an independent variable because clinicians assigning medical leave had no knowledge of challenge test results.

RADS is defined in persons without prior respiratory symptoms/disease who within 24 hours of exposure to high concentrations of airborne irritants have symptoms of airway inflammation (cough, wheeze, and/or dyspnea) that persist and are associated with bronchial hyperreactivity at least 3 months post-exposure (40, 41). Airflow limitation may or may not be present on spirometry, but bronchial hyperreactivity is required (40). To eliminate false positives, we required symptoms and hyperreactivity at 6 months post-exposure, and in contrast to other studies that relied on post-exposure interviews, absence of prior respiratory symptoms/disease was confirmed by review of detailed pre-WTC medical records, including candidate and post-hire annual medicals (chest X-ray, spirometry) and FDNY injury/illness evaluations. Six months post-WTC, 16% (20/123) of all exposed study subjects—20% (17/83) of highly exposed subjects and 8% (3/40) of moderately exposed subjects—qualified for the diagnosis of RADS. Although there are several case series of RADS after exposures to chemical irritants (42–44), we found none with a control group. One study evaluated the association between RADS incidence and exposure intensity, with reported incidence rates of 21% (3/14) for highly exposed, 3% (1/30) for moderately exposed, and 0% (0/7) for less exposed workers, 8 months post-exposure to a glacial acetic acid spill (43). Although respiratory symptoms and/or decrements in pulmonary function have been noted in those exposed to the gas leak at Bhopal (45, 46), oil fires during the Gulf war (47), or volcanic ash at Mt. St. Helens (48), the incidence of bronchial hyperreactivity and/or RADS has not been reported.

Among the aims of this study was to determine if objective measures (spirometry or bronchial hyperreactivity) at time points earlier than 6 months were predictive of the development of RADS. We could find no prior reports that identified factors predictive for the development of RADS, though such indicators would clearly be useful in disaster management. In this cohort with normal spirometry (>96% with FVC and $FEV_1 \geqslant 80\%$ predicted), we found no significant associations between spirometric measurements (absolutes or declines) and the occurrence of RADS at 6 months. In contrast, bronchial hyperreactivity at 1 or 3 months (when it might still represent an acute, temporary phenomenon) emerged as the sole significant predictor of both its persistence and the development of RADS in highly exposed subjects at 6 months (Figure 4). That all hyperreactive subjects did not develop RADS demonstrates that other risk and prognostic factors are yet to be determined in this complex exposure–host response interaction.

After study enrollment was completed, we recognized and described the clinical, radiographic, and physiologic features of "WTC Cough" in a case series of 332 FDNY firefighters who required at least 4 consecutive weeks of medical leave due to respiratory illness after working at the WTC site (11). For all FDNY rescue workers, the incidence of "WTC Cough" in the first 6 months post-WTC (9/11/01to 3/11/02) was 8% in highly exposed subjects and 3% in moderately exposed subjects (11). Our current report is a longitudinal study using a representative sample stratified by initial exposure intensity, independent of symptoms. On enrollment, all subjects were on active fire/rescue duty and thus, by definition did not have "WTC Cough." Nineteen subjects subsequently developed "WTC Cough" after enrollment in this study for an incidence rate of 16% in highly exposed subjects and 6% in moderately exposed subjects—higher than we previously reported, but the current sample size was small. As participation in challenge testing at all time points was voluntary (39/151 dropouts), self-selection was a possible confounder. Subjects with minimal or no symptoms may have been under-represented due to lesser concerns about health consequences and thus, less willingness to allocate the time needed for participation in this longitudinal study. Subjects with severe symptoms may have been either under-represented (due to concern that abnormal findings may prompt medical restrictions thereby preventing full participation in the rescue effort) or over-represented (due to concern about symptoms, illness, or exposure).

We believe that the development of "WTC Cough" in most exposed subjects in this cohort did not reflect self-selection but instead was a consequence of the increased incidence of bronchial hyperreactivity. In the current cohort, bronchial hyperreactivity was found in 25% (38/151) at any time point (1, 3 or 6 months) and in 21% (24/112) at 6 months. Given that the predominant pathophysiology responsible for "WTC Cough" is airways inflammation/obstruction (bronchodilator response in 63% and hyperreactivity in 24% of those tested) (11), it is not surprising that some subjects in our current cohort developed "WTC Cough" after study enrollment. In fact, post-hoc analysis showed hyperreactivity to be a significant predictor for the development of "WTC Cough." Had we excluded subjects with "WTC Cough" post-hoc, our results would have been biased toward the less ill and would not have accurately reflected the natural history of this exposure. Exclusion of eight subjects from testing at 6 months by the protocol (low baseline FEV_1 or steroid treatment) had already biased our findings toward underestimating exposure effects. Whether "WTC Cough" patients in this study resulted from self-selection or the natural development of disease, our major findings were not solely due to subjects with "WTC Cough"—at 6 months nearly two-thirds of subjects with either bronchial hyperreactivity or RADS in this study did not have "WTC Cough."

In conclusion, rescue and recovery efforts after the WTC collapse resulted in exposure of many individuals to respirable particulates and the products of combustion/pyrolysis. We observed a significant independent association between WTC exposure intensity and nonspecific bronchial hyperreactivity 1 and 3 months post-exposure that persisted to 6 months. At 1 month post-exposure, rapid assessment of symptoms and/or spirometry were useful in characterizing the degree of acute impairment, but only hyperreactivity at 1 or 3 months post-WTC was predictive of the development of RADS in highly exposed subjects at 6 months. The persistence of hyperreactivity, as well as the development of RADS and "WTC Cough" demonstrates the need for long-term medical monitoring and treatment for those affected by this disaster. In addition, it highlights the need to provide adequate respiratory protection, as early as possible, even in the initial phase of our response to future disasters (natural and man-made). The success of such plans will depend on solving immediate supply and compliance problems that occur under difficult and extreme conditions.

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