Improvement in Severe Lower Respiratory Symptoms and Small Airway Function in World Trade Center Dust Exposed Community Members

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Objective *Longitudinal assessment of lower respiratory symptoms (LRS) in community members with World Trade Center (WTC) exposures.*
Methods *Adult members of a treatment program with complete standardized visits were evaluated (n = 798). Association of demographic characteristics, mental health symptoms and lung function with trajectory of LRS between initial and monitoring visit was evaluated.*
Results *Severe LRS were present in 70% at initial and 63% at monitoring visit. Initial severe LRS were associated with WTC dust cloud exposure and mental health symptoms. Spirometry measures were not associated with LRS severity or trajectory; improvement in LRS was associated with improved lung function measured with forced oscillometry techniques.*
Conclusion *Many community patients in a WTC treatment program had severe LRS associated with exposures and mental health symptoms. Improvement in LRS was associated with improvement in measures of small airway function.* Am. J. Ind. Med. 59:777–787, 2016. *© 2016 Wiley Periodicals, Inc.*

***KEY WORDS:* World Trade Center; oscillometry; lower respiratory symptoms; mental health; lung function**

INTRODUCTION

The destruction of the World Trade Center towers resulted in the release of over a million tons of debris and caustic dust with complex chemical components and the persistent release of fumes [Lioy et al., 2002; Reibman et al., 2016]. The disaster resulted in potential for both acute and chronic exposures to the local community [local residents, local workers, clean-up workers, students, and those passing by] as well as to the rescue workers and responders [Lioy and Georgopoulos 2006; Maslow et al., 2012; Reibman et al., 2016]. We and others have reported new-onset persistent lower respiratory symptoms (LRS) in community members exposed to the dust, gas and fumes released by the destruction of the WTC towers [Reibman et al., 2005, 2009; Lin et al., 2010]. The WTC Environmental Health Center (WTC EHC) is a treatment program serving symptomatic community members [Reibman et al., 2009]. Patients undergo an initial exam and are subsequently recalled for a routine monitoring examination.

Many of the patients in the WTC EHC enrolled with LRS of cough, shortness of breath, wheeze, and chest tightness [Reibman et al., 2009]. Despite presence of these

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LRS, spirometry has generally demonstrated normal airflow and lung volume, whereas the predominant abnormality was small airway dysfunction as assessed using oscillometry [Oppenheimer et al., 2007; Friedman et al., 2011]. In addition, we previously reported longitudinal changes in spirometry in this cohort with variability in improvement over time depending on spirometry pattern; whereas spirometry improved in many, it failed to return to the normal range in the low forced vital capacity (FVC) or low FVC/obstructed groups [Liu et al., 2012]. Persistence of abnormal FVC is compatible with persistent small airway dysfunction [Berger et al., 2013]. We now describe the longitudinal course of LRS in the patients in the WTC EHC who returned for monitoring, with a focus on those with the most severe symptoms on initial evaluation. To understand the mechanism for persistent LRS, we describe the relationship of these symptoms to exposures, comorbid conditions, as well as lung function, including measures of small airway function using impulse oscillometry (IOS) as a forced oscillation technique (FOT). We hypothesized that persistent severe LRS would be associated with persistent abnormalities in small airway function, as characterized by abnormal IOS.

METHODS

Patient Selection

Individuals were self-referred to the WTC EHC with medical and/or mental health symptoms related to September 11, 2001 exposures as previously described [Reibman et al., 2009]. The Institutional Review Board of New York University School of Medicine approved the research database (NCT00404898). Only data from patients who signed informed consent were used for analysis.

Patients were included for analysis if they completed an initial visit between August 17, 2005 and January 31, 2014, were more than 18 years of age, had no respiratory symptoms before September 11, 2001, and had completed a standardized monitoring visit by January 31, 2015. In addition, the patients had to have complete spirometry and oscillometry data at initial and monitoring visits.

Procedures

Clinical protocol

Enrollment in the WTC EHC was based on an initial evaluation to document exposures to WTC dust, gas and fumes as an area worker, resident, or clean-up worker in southern Manhattan on 9/11 or in the months after 9/11 and the presence of any physical symptom that occurred or was exacerbated after 9/11, as previously described [Reibman et al., 2009]. At an initial visit, patients underwent a multidimensional interviewer-administered questionnaire to obtain demographic and exposure information, as well as medical symptoms including severity and temporal relationship to 9/11, functional status, and severity of dyspnea (Modified Medical Research Council (MMRC) dyspnea scale). Standardized medical evaluations included pulmonary function studies (spirometry and IOS) and chest radiograph. When necessary, abnormal studies were evaluated further with more complex medical evaluations, including chest imaging and cardiac evaluations. Standardized mental health screening was also performed, including assessment for PTSD using the PTSD Checklist (PCL-17); a score >44 was considered positive for symptoms consistent with PTSD [Weathers et al., 1993]. Symptoms of depression and anxiety were assessed with the Hopkins Symptom Checklist (HSCL-25) for depression and anxiety [Derogatis et al., 1974], which assesses the presence and severity of symptoms with 15 depression items (HSCL-D) and 10 anxiety items (HSCL-A) rated on a scale from 1 to 4. A score ≥ 1.75 was used as a cutoff. The same procedures were followed during a standardized monitoring visit. The WTC EHC treatment protocol includes treatment of asthma-like symptoms based on guidelines for asthma management [National Asthma and Prevention, 2007, Boulet, 2015].

Lung function

All individuals were referred for screening lung function studies that included spirometry and IOS at initial and monitoring visits. Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society standards [Miller et al., 2005] on a Viasys Vmax spirometer (Yorba Linda, CA). Spirometry data were downloaded electronically along with an automated quality assurance code. All studies were performed in the Bellevue Hospital Center Pulmonary Function Laboratory. Percentage of predicted pre-bronchodilator forced vital capacity (% FVC) and forced expiratory volume in 1 s (% FEV_1) were derived from National Health and Nutrition Examination Survey III [Hankinson et al., 1999]. Patients were categorized as having a normal, low FVC, obstructed, or low FVC/obstructed spirometry pattern at enrollment using definitions based on the lower limits of normal as previously described [Pellegrino et al., 2005; Herbert et al., 2006].

Impulse oscillometry was performed using a Jaeger Impulse Oscillation System in accordance with published recommendations [Oostveen et al., 2003]. Data included resistance measured as oscillation frequencies of 5 (R_5) and 20 Hz (R_{20}), frequency dependence of resistance calculated as the difference between resistance at 5 and 20 Hz (R_{5-20}), and the reactance area (AX) defined as the area under the reactance curve from 5 Hz to the resonant frequency. A minimum of three trials was performed. Only data from trials with constant tidal volume were analyzed. Coherence more than 0.70 [Komarow et al., 2011] and reproducibility between trials (variability <10%) were required [Oppenheimer et al., 2007; Friedman et al., 2011]. Upper limits of normal for each IOS parameter were defined as 3.96 cm H_2O/L/s for R_5, 0.76 cm H_2O/L/s for $R_{5–20}$, and 3.6 cm H_2O/L/s for AX [Oppenheimer et al., 2007; Friedman et al., 2011]. These values for upper limits of normal agree with recent publication of normative data for oscillometry [Oostveen et al., 2013].

Definitions

Individuals were characterized as having WTC dust cloud exposure if they reported having been in an initial WTC dust cloud produced by the collapsing towers on 9/11. WTC exposure category was defined as resident, local worker, rescue/recovery worker, or clean-up worker [Reibman et al., 2009]. Patients who reported more than a 5-pack-year history of tobacco use were defined as smokers. LRS were defined by at least one symptom of cough, wheeze, chest tightness, or dyspnea, with onset after September 11, 2001, and occurring with a frequency of ≥2 times per week in the month preceding evaluation. Severe LRS were defined as LRS occurring daily or 4 or more nights/week in the month preceding evaluation or an MMRC dyspnea score of ≥2, in accordance with published asthma guidelines [National Asthma and Prevention, 2007, Boulet, 2015]. Mild LRS were defined as LRS occurring <7 days/week and <4 nights/week in the month preceding evaluation and a dyspnea score <2. Patients with no LRS were defined as those who denied any of the LRS. Because we were interested in symptoms associated with the event, patients with LRS or asthma with onset pre-9/11 were excluded from this analysis.

Symptom trajectory was defined for the patients with severe LRS at the initial visit (the Severe LRS Group) as three trajectories based on clinical data obtained at monitoring. Resolved LRS was defined as severe LRS at initial and no LRS at monitoring visit, improved LRS was defined as severe LRS at initial and mild LRS at monitoring visit, and persistent LRS was defined as severe LRS at both initial and monitoring visits.

Statistical methods

Continuous variables were summarized using mean and SD and compared across groups using the nonparametric Kruskal–Wallis test or the linear trend test. Categorical variables were summarized by counts and proportions and compared using chi-squared test. Paired data were compared using Wilcoxon signed rank test. Statistical analyses were conducted using SAS (version 9.2).

RESULTS

Baseline Characteristics and LRS Severity at Initial Visit

Of 2,499 patients over age 18 without pre-9/11 LRS with complete spirometry and forced oscillometry testing performed at an initial visit, 1,017 (41%) underwent a monitoring visit by January 31, 2015. Of these, 219 were excluded because either spirometry or FOT data at the monitoring visit were incomplete, resulting in our final population of the study cohort of 798 (Fig. 1).

The study cohort was diverse (Table I): 407 (51%) were women, and 309 (39%) were Hispanic. Mean age was 50. More than half (55%) reported being caught in the WTC dust cloud. The largest group with potential WTC exposure was the local worker group (n = 441; 55%). Individuals with a history of more than 5-pack-year smoking history comprised only 20% of the group. Mental health symptoms of anxiety, depression, and PSTD were common. The vast majority of patients (68%) had normal spirometry at the initial visit; low FVC was the most common abnormality, occurring in 15% of the cohort. To assess whether this group was similar to our population as a whole, we compared basic characteristics of the monitored patients (n = 798) to those who did not return for monitoring (n = 1700). Monitored patients versus non-monitored patients were statistically significantly more likely to be female (51% vs. 47%), Hispanic (39% vs. 32%), older (mean age 50 vs. 49), and local workers (55% vs. 52%) . In addition, they were more likely to have been caught in the dust cloud (55% vs. 49%) and to have anxiety (46% vs. 38%) or depression (57% vs. 52%). Similarly, statistically significant differences in spirometry pattern, spirometry values and IOS parameters were small in magnitude; for example, mean FEV_1/FVC was 76% ± 9% in the monitored group and 77% ± 8% in the unmonitored group ($P < 0.0007$). Thus, despite the statistical significance, due in part to the large numbers of individuals, the differences in proportions and lung function were minimal (data not shown).

Characteristics, exposures, and comorbid conditions for the study cohort are shown (Table I). Among the study cohort, 559 (70%) had severe LRS at initial visit, 137 (17%) had mild LRS, and 102 (13%) had no LRS. LRS severity was not associated with sex, income, insurance status, or smoking. There was also no significant difference in spirometry pattern across the three severity groups, with the vast majority of even the severe LRS group having a normal spirometry pattern. In contrast, patients who were older or had elevated BMI were more likely to have severe LRS at initial visit. Patients with severe LRS were more likely to report having been caught in the dust cloud or having been exposed as local workers. The Severe LRS Group was also more likely to suffer from depression, anxiety, or PTSD.

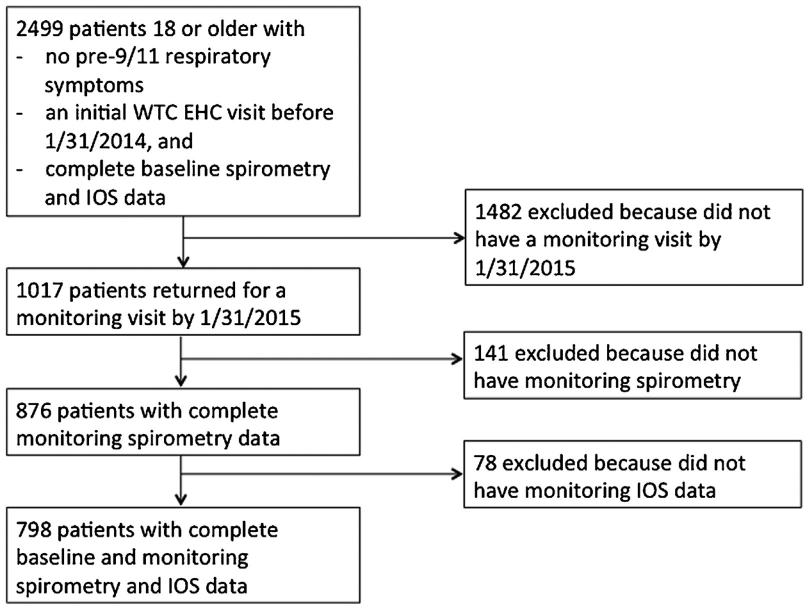

FIGURE 1. Population inclusion flowchart.

Figure 2 shows the distribution of LRS severity (none, mild, severe) at initial and at monitoring visits. Despite a small increase in the proportion of patients with mild or no LRS at the monitoring visit, more than half of the patients (63%) had severe LRS at monitoring.

Baseline Characteristics and Symptom Trajectory in the Severe LRS Group

To understand the group of patients with the most severe symptoms at initial visit, we focused subsequent analyses on this cohort (Severe LRS Group, n = 559). First, we examined self reported severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) and frequency (days/week) of each individual symptom. Both severity and frequency of individual symptoms improved significantly ($P < 0.0001$) between initial and monitoring visits (Figs. 3 and 4). Functional status as measured by dyspnea score also improved significantly between initial and monitoring visits (MMRC 1.8 vs. 1.1, $P < 0.0001$).

Among patients with severe LRS at initial visit (n = 559), symptom trajectories were as follows: resolved in 47 (8%), improved in 105 (19%), and persistently severe in 407 (73%). Table II provides patient characteristics by these symptom trajectories for the Severe LRS Group. Neither demographic characteristics nor WTC dust exposures differed between these symptom trajectory groups. The presence of positive scores for anxiety or PTSD, but not depression, was associated with persistent severe LRS. Medication use at monitoring was highest in those with persistent severe LRS.

We examined whether spirometry measures were associated with symptom trajectory, that is, whether symptoms were resolved, improved, or persistent, in the Severe LRS Group (Table III). We found that neither initial spirometry pattern nor mean spirometry values (including mean mid-expiratory flows, MMEF) at initial and monitoring visits distinguished between symptom trajectories. In addition, change in spirometry between initial and monitoring visits failed to distinguish between patients whose symptoms resolved, improved or persisted.

We considered whether IOS measures predicted symptom trajectory in the subjects with severe LRS at initial visit (Table IV). Mean IOS values were elevated in the Severe LRS Group, regardless of trajectory. However, there was no association of IOS measures at initial visit with subsequent symptom trajectory. In contrast, at monitoring there was a significant trend between R_{5-20} and AX and symptom trajectory, with higher values of R_{5-20} and AX in those with persistent severe symptoms compared with the resolved and improved LRS groups (P for trend = 0.003 and 0.008, respectively). In addition, a relationship was noted between symptom trajectory and longitudinal change in IOS parameters that reached statistical significance for R_{5-20} ($P = 0.02$) and was borderline for AX ($P = 0.08$).

In an analysis stratified by smoking status, the differential effect in IOS parameters across symptom trajectory groups remained regardless of smoking status (data not shown). In contrast, in an analysis stratified by BMI (obese vs. non-obese), the trend of worsening IOS parameters with worsening LRS trajectory was seen in the

TABLE I. Characteristics of the Population, Total (n = 798) and Stratified by LRS Severity at Initial Visit

	Total (n = 798)	No LRS (n = 102)	Mild LRS (n = 137)	Severe LRS (n = 559)	*P*-value
Sex, N (%)					
Female	407 (51)	46 (45)	64 (47)	297 (53)	0.18
Male	391 (49)	56 (56)	73 (53)	262 (47)	
Age, year					
Mean (SD)	50 (11)	48 (12)	47 (12)	52 (10)	<0.0001
Race/ethnicity, N (%)					
Hispanic	309 (39)	39 (38)	70 (51)	200 (36)	0.02
Non-Hispanic Black	175 (22)	16 (16)	23 (17)	136 (24)	
Non-Hispanic White	232 (29)	36 (35)	33 (24)	163 (29)	
Asian or other	82 (10)	11 (11)	11 (8)	60 (11)	
Income/year, N (%)*					
<$15 K	347 (43)	41(41)	61 (45)	245 (44)	0.80
>$15 K	440 (55)	59 (59)	75 (55)	306 (56)	
Insurance, N (%)*					
Uninsured	256 (32)	29 (29)	55 (40)	172 (31)	0.06
Insured	536 (67)	71 (71)	82 (60)	383 (69)	
Smoking, N (%)*					
Never or ≤5 pack-years	635 (80)	84 (82)	109 (81)	442 (80)	0.83
>5 pack-years	156 (20)	18 (18)	26 (19)	112 (20)	
Caught in WTC dust cloud, N (%)*					
No	357 (45)	55 (54)	72 (53)	230 (41)	0.008
Yes	437 (55)	47 (46)	64 (47)	326 (59)	
Exposure category, N (%)*					
Clean-up worker	143 (18)	10 (10)	38 (28)	95 (17)	0.0002
Local worker	441 (55)	51 (50)	64 (47)	326 (59)	
Rescue/recovery/other	70 (9)	14 (14)	16 (12)	40 (7)	
Resident	142 (18)	27 (26)	19 (14)	96 (17)	
Body mass index, N (%)					
Normal	212 (27)	42 (41)	35 (26)	135 (24)	0.009
Overweight	303 (38)	33 (32)	55 (40)	215 (38)	
Obese	283 (35)	27 (26)	47 (34)	209 (37)	
Spirometry pattern, N (%) V1					
Normal	543 (68)	77 (75)	99 (72)	367 (66)	0.25
Low FVC	119 (15)	14 (14)	20 (15)	85 (15)	
Obstructed	102 (13)	9 (9)	15 (11)	78 (14)	
Low VC/obstructed	34 (4)	2 (2)	3 (2)	29 (5)	
Mental health symptoms, N (%)*					
Anxiety	356 (45)	38 (38)	38 (29)	280 (51)	<0.0001
Depression	447 (56)	46 (46)	59 (45)	342 (63)	<0.0001
PTSD	327 (41)	35(35)	43(33)	249(46)	0.008

*Missing values n = 11 for income, n = 6 for insurance, n = 7 for smoking, n = 4 for dust cloud, n = 2 for exposure category, and n = 19 for mental health symptoms.

non-obese group but not in the obese group (Supplementary Table SI). When stratified by dust cloud exposure, the differential effect in IOS parameters across symptom trajectory groups was seen in those with dust cloud exposure but not in those who were not exposed to the dust cloud (Supplementary Table SII).

DISCUSSION

We report longitudinal assessment of symptoms and lung function in a group of community members with diverse WTC dust exposures monitored in a treatment program. Baseline severity of LRS was associated with WTC

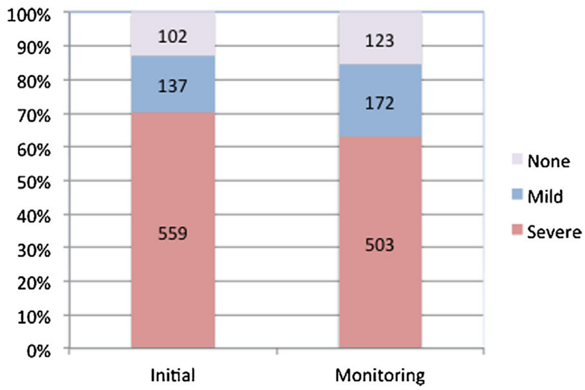

FIGURE 2. Distribution of LRS severity at initial and monitoring visits (n = 798).

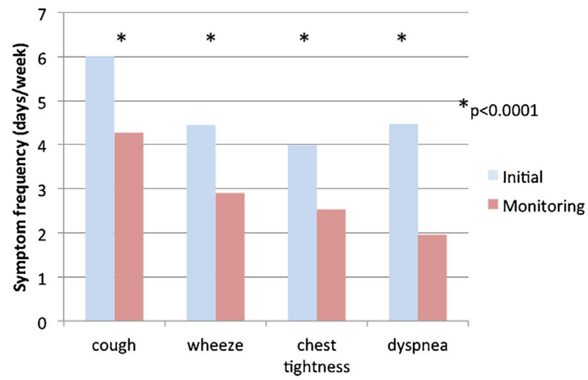

FIGURE 4. Symptom frequency, by individual symptom, for the Severe LRS Group at initial and monitoring visits (n = 559).

exposures, BMI, and mental health symptoms. We found minimal improvement in the proportion of patients with severe or mild LRS between initial and monitoring visits with a majority of patients continuing to meet asthma guideline-based criteria for severe symptoms. Improvement in symptoms in the Severe LRS Group was associated with improvement in measures of lung function that reflect small airway involvement.

In our population of nearly 800 symptomatic community members, severe LRS at initial visit was associated with dust cloud exposure, exposure as a local worker, elevated BMI, and presence of mental health symptoms. In contrast, spirometry was not associated with baseline LRS severity.

Longitudinal analysis was focused on patients with the most severe symptoms at initial visit in order to understand the course of symptoms and correlates of symptom trajectories in our most severely affected patients. Although dyspnea scores and self-reported severity and frequency of individual symptoms improved between initial and monitoring visits, most (73%) had persistent severe LRS at monitoring. Only some showed improvement (19%) or resolution (8%) of LRS. Baseline characteristics were examined to determine whether they predicted these

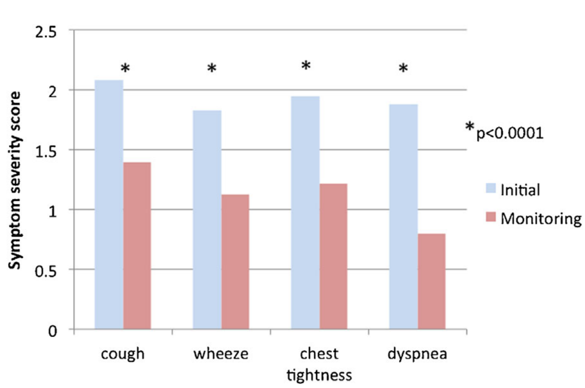

FIGURE 3. Severity score, by individual symptom, for the Severe LRS Group at initial and monitoring visits (n = 559).

symptom trajectories. Symptom trajectory did not correlate with any clinical characteristic at baseline except for mental health symptoms. Both symptom scores consistent with PTSD or anxiety were associated with persistent severe LRS.

Our finding of an association between lower respiratory symptoms and mental health symptoms is consistent with prior studies showing co-existence of medical and mental health symptoms in a variety of symptomatic WTC dust exposed populations, including firefighters, rescue and recovery workers, and community members [Jordan et al., 2015; Kotov et al., 2015; Yip et al., 2016a,b]. A dose-response relationship between the number of mental health conditions and poorer asthma control in WTC Registry enrollees with post-9/11 asthma has also been described [Jordan et al., 2015]. However, the relationship between mental health symptoms and lower respiratory symptoms is poorly understood; it has been difficult to discern the relative contribution from lung/airway disease versus manifestations of mental health comorbidity with heightened awareness of symptoms. In accordance with these studies, we show that both the presence of baseline LRS and the trajectory of LRS are associated with positive screening tests for mental health symptoms. However, our analysis suggests additional contributions to baseline and persistent LRS with physiologic measures.

Indeed, our study adds to our understanding of these relationships by analyzing baseline symptom severity and its subsequent improvement with measures of lung function. In accord with prior observations, spirometric measures were normal in the majority of subjects and remained unchanged independent of changes in LRS. This finding was true for basic spirometry measures of FEV_1 and FVC as well as baseline or monitoring MMEF across symptom trajectory groups.

Thus, the presence of abnormal small airway function in the majority of subjects at baseline provided a potential correlate for symptom trajectory. Although baseline IOS values did not correlate with symptom trajectory,

TABLE II. Characteristics, by Symptom Trajectory for the Severe LRS Group (n = 559)

	Resolved (47)	Improved (105)	Persistent (407)	*P*-value
Sex, N (%)				
Female	22 (47)	57 (54)	218 (54)	0.66
Male	25 (53)	48 (46)	189 (46)	
Age, year				
Mean (SD)	52 (9)	51 (11)	52 (10)	0.87
Race/ethnicity, N (%)				
Hispanic	16 (34)	42 (40)	142 (35)	0.42
Non-Hispanic Black	10 (21)	21 (20)	105 (26)	
Non-Hispanic White	12 (26)	33 (31)	118 (29)	
Asian or other	9 (19)	9 (9)	42 (10)	
Income/year, N (%)*				
<$15 K	22 (47)	55 (52)	168 (42)	0.16
>$15 K	25 (53)	50 (48)	231 (58)	
Insurance, N (%)*				
Uninsured	18 (40)	38 (36)	116 (29)	0.13
Insured	27 (60)	67 (64)	289 (71)	
Smoking, N (%)*				
Never or </ = 5 pack-years	37 (79)	78 (74)	327 (81)	0.27
>5 pack-years	10 (21)	27 (26)	75 (19)	
Caught in WTC dust cloud, N (%)*				
No	20 (43)	44 (42)	166 (41)	0.97
Yes	27 (57)	61 (58)	238 (59)	
Exposure category, N (%)*				
Clean-up worker	8 (17)	24 (23)	63 (16)	0.15
Local worker	25 (53)	60 (58)	241 (59)	
Rescue/recovery/other	3 (6)	2 (2)	35 (8)	
Resident	11 (23)	18 (17)	67 (17)	
Body mass index, N (%)				
Normal	13 (28)	24 (23)	98 (24)	0.27
Overweight	19 (40)	49 (47)	147 (36)	
Obese	15 (32)	32 (30)	162 (40)	
Mental health symptoms, N (%)*				
Anxiety	13 (28)	53 (52)	214 (53)	0.005
Depression	23 (50)	61 (60)	258 (65)	0.12
PTSD	11 (24)	43 (42)	195 (49)	0.004
Medication use at monitoring, N (%)				
Any inhaled medications	21 (45)	81 (77)	323 (79)	<0.0001
Bronchodilators	16 (34)	74 (70)	302 (74)	<0.0001
ICS or ICS/LABA	18 (38)	57 (55)	277 (68)	<0.0001

*Missing values n = 8 for income, n = 4 for insurance, n = 1 for smoking, n = 3 for dust cloud, n = 2 for exposure category, and n = 12 for mental health symptoms.

symptomatic improvement was associated with improvement in R_{5-20} and AX. R_{5-20} and AX reflect non-uniformity in the distribution of airflow in the peripheral lung and, therefore, the data are consistent with improved small airway function in the subjects with improved LRS. These findings were not detected with MMEF, which reflects function of both large and small airways. Thus, our findings are consistent with prior studies indicating that measurements obtained using IOS provide additive information to that provided by spirometry by specifically measuring distal airway function [Oppenheimer et al., 2007; Friedman et al., 2011, Berger et al, 2013].

It has been shown in a variety of WTC-exposed populations that the vast majority of patients with lower

TABLE III. Spirometry, by Symptom Trajectory, for the Severe LRS Group (n = 559)

	Resolved (47)	Improved (105)	Persistent (407)	*P*-value (K–W)	*P*-value (trend)
Spirometry pattern, N (%) V1					
Normal	32 (68)	70 (67)	265 (65)	0.93	
Low FVC	6 (13)	14 (13)	65 (16)		
Obstructed	7 (15)	17 (16)	54 (13)		
Low VC/obstructed	2 (4)	4 (4)	23 (6)		
Spirometry at V1, mean (SD)					
FVC, % predicted	95 (16)	95 (16)	92 (17)	0.24	0.23
FEV_1, % predicted	90 (17)	90 (17)	88 (19)	0.40	0.31
FEV_1/FVC, %	76 (8)	75 (10)	76 (9)	0.67	0.78
MMEF, % predicted	87 (33)	80 (31)	81 (33)	0.49	0.47
Spirometry at M1, mean (SD)					
FVC, % predicted	94 (16)	97 (15)	92 (18)	0.15	0.18
FEV_1, % predicted	91 (16)	92 (18)	88 (19)	0.12	0.06
FEV_1/FVC, %	76 (7)	75 (9)	75 (9)	0.51	0.23
MMEF, % predicted	87 (31)	83 (34)	79 (33)	0.20	0.06
Spirometry delta (M1-V1) mean (SD)					
FVC, % predicted	1.0 (7.8)	1.6 (11.6)	1.0 (10.9)	0.47	0.80
FEV_1, % predicted	1.7 (8.0)	2.4 (10.2)	0.26 (11.3)	0.11	0.11
FEV_1/FVC, %	−0.17 (4.1)	−0.12 (4.5)	−0.99 (4.8)	0.12	0.08
MMEF, % predicted	0.52 (19)	3.2 (18)	−2.3 (20)	0.05	0.05

V1 = initial visit, M1 = monitoring visit.

respiratory symptoms do have normal spirometry. However, regardless of which prediction models are used, there is a very wide range of values that are considered normal for any individual. For example, in firefighters, spirometry values after 9/11 remained in the normal range for most; it was only the presence of pre-9/11 spirometry data that allowed for the detection of a significant loss of lung function after 9/11 [Aldrich et al., 2010]. Similarly, we have shown longitudinal improvement in spirometry in our community population, despite initial values in the normal range [Liu et al., 2012].

Our current findings are consistent with prior studies of spirometry and IOS suggesting small airway abnormalities in WTC-exposed community members. While most WTC EHC patients have normal spirometry, the most common spirometric abnormality is a low FVC [Reibman et al., 2009]. Detailed physiologic studies suggest that this

TABLE IV. Impulse Oscillometry, by Symptom Trajectory, for the Severe LRS Group (n = 559)

	Resolved (47)	Improved (105)	Persistent (407)	*P*-value (K–W)	*P*-value (trend)
Oscillometry at V1, median (IQR)					
R_5, cm H_2O/l/s	4.88 (2.77)	4.77 (2.55)	5.01 (2.51)	0.51	0.32
R_{5-20}, cm H_2O/l/s	0.91 (0.87)	0.88 (1.22)	1.04 (1.28)	0.58	0.30
AX, cm H_2O/l	5.73 (9.47)	5.79 (9.56)	7.61 (11.28)	0.32	0.19
Oscillometry at M1, median (IQR)					
R_5, cm H_2O/l/s	4.64 (2.98)	4.87 (2.66)	5.08 (2.64)	0.08	0.07
R_{5-20}, cm H_2O/l/s	0.76 (0.93)	0.92 (0.83)	1.21 (1.19)	0.002	0.003
AX, cm H_2O/l	4.83 (7.27)	6.26 (9.90)	8.58 (13.72)	0.003	0.008
Oscillometry delta M1-V1, median (IQR)					
R_5, cm H_2O/l/s	−0.22 (1.27)	−0.13 (1.57)	0.03(1.71)	0.35	0.25
R_{5-20}, cm H_2O/l/s	−0.060 (0.47)	0.02 (0.65)	0.12 (0.83)	0.009	0.02
AX, cm H_2O/l	−0.32 (4.57)	0.01 (5.59)	0.96 (6.88)	0.007	0.08

V1 = initial visit, M1 = monitoring visit.

restrictive pattern is due to airway dysfunction with distal airway closure [Berger et al., 2013]. In prior longitudinal analyses in the WTC EHC population, spirometry improved over time in the population as a whole, including in those with normal baseline spirometry, with the greatest improvement noted in subjects with low VC at baseline [Liu et al., 2012] but without a return of VC values to normal, suggesting partially reversible airway abnormality. Ongoing inflammation has been demonstrated many years after 9/11 with an association between C-reactive protein levels with WTC dust exposure, persistent LRS, and abnormalities in spirometry and IOS parameters. [Kazeros et al., 2015]. Notably, correlation was demonstrated between C-reactive protein and IOS measures of small airway function. Furthermore, pathologic studies in small numbers of WTC-exposed individuals similarly locate the site of pathologic change within the distal lung. [Caplan-Shaw et al., 2011]. Similar distal airway abnormalities were seen in a rescue and recovery group [Wu et al., 2010].

Our study has several limitations. Our population is a self-selected group presenting to a program for treatment of symptoms and not a representative sample of all exposed community members; however, our aim was to understand the course and correlates of LRS in this symptomatic group. In addition, our study population was limited to those who returned for a standardized monitoring visit (40%). We anticipated statistical significance between the monitored and unmonitored groups on many parameters because of our large sample size. Indeed, monitored patients were statistically significantly different from unmonitored patients in terms of basic demographics, exposures, and mental health symptoms and lung function. However, although statistically significant, the differences in proportions or values were minimal. Based on these findings, we do not believe that there is a major bias in our monitoring group and that in general, the results reported are informative to improve our understanding of our entire cohort.

Many patients underwent their initial evaluation in the WTC EHC several years after the disaster. It would have been optimal to have enrolled patients within the first few years after the events of 9/11. Unfortunately, there was no funded program for treatment of community members with physical symptoms after 9/11 exposures until 2005 when the first Red Cross-funded program was established at Bellevue Hospital Center. Federal funding to support the activities of the program was not available until 2008 and the Zadroga Act was not implemented until 2011 [Reibman et al., 2016]. The continued enrollment into the program speaks to the continued need for care for these patients and the difficulties with educating a community about the program, particularly a disparate community. Many patients who have recently enrolled had sought medical care with other physicians over the years, many had not been aware of the program, and some had early onset of symptoms but no resources to seek care outside a funded program. Furthermore, the Zadroga Act sets up clear inclusion criteria, including specific criteria regarding exposure details and timing of onset of symptoms. Those who do not meet these criteria (based on biologic plausibility) would not be accepted into the program and would therefore not be included in this study.

Additionally, we found that severe LRS persist despite a high level of respiratory medication use. Indeed the persistence and severity of symptoms was not due to a lack of treatment. In fact, patients with persistently severe LRS reported significantly higher medication use across all medication types, including oral and inhaled corticosteroids and short- and long-acting bronchodilators. While medicines are provided free of charge in the WTC EHC, we were unable to assess adherence directly. Our analysis of symptom trajectory was based on a within-subject comparison, obviating the need for multivariate analysis. Of course, it is possible that there are unaccounted factors within individuals that changed over time; however, our analysis of smoking status and BMI showed no significant changes within subjects over time (data not shown).

Our stratified analyses of smoking and BMI provide additional insight into LRS trajectories. In an analysis stratified by smoking status, the differential effect in IOS parameters across symptom trajectory groups remained regardless of smoking status. In contrast, in an analysis stratified by BMI (obese vs. non-obese), the trend of worsening IOS parameters with worsening LRS trajectory was seen in the non-obese group but not in the obese group, consistent with our understanding of the effect of obesity on IOS measures—which would be unlikely to change without a change in BMI—as well as the high variance of IOS measures in the obese group. When stratified by dust cloud exposure, the differential effect in IOS parameters across symptom trajectory groups was seen in those with dust cloud exposure group but not in those who were not exposed to the dust cloud, suggesting that heavy dust exposure did, in fact, affect the distal airways in a dose-dependent manner.

We now show a high prevalence of persistent severe LRS in a cohort undergoing treatment for 9/11-related medical symptoms. Presence of severe LRS at baseline was associated with WTC exposures and mental health symptoms as well as abnormalities in lung function. In contrast, persistence of symptoms was not associated with WTC exposures, but remained associated with elevated scores for PTSD and anxiety. However, improvements in symptoms over time correlated with improvements in distal airway function. Despite this improvement, measurements did not return to normal. Our findings indicate complex causes of persistent LRS. However, the presence of partial reversibility of distal airway dysfunction after WTC exposures either as a result of treatment or other factors suggests a physiologic and treatable component of these symptoms. Our study suggests the need for ongoing clinical monitoring and continued research to elucidate the underlying pathophysiologic mechanisms for respiratory symptoms and distal airway dysfunction, to identify patients who benefit most from our current therapies, and to explore new approaches to treatment.

AUTHORS' CONTRIBUTIONS

Caralee Caplan-Shaw participated in conception and design of the work, creation of a data dictionary and definitions, acquisition, analysis and interpretation of the work with the help of the statistical team, and drafting of the paper. Angeliki Kazeros and Deepak Pradhan participated in conception and design of the work and interpretation of the work with the help of the statistical team. Maria-Elena Fernandez-Beros participated in the creation of the database and data collection. Kenneth Berger and Roberta Goldring participated in conception and design of the work, analysis and interpretation of the work, particularly in relation to the lung function data, and critical revisions for important intellectual content. Michael Marmor, Sibo Zhao, Mengling Liu, and Yongzhao Shao participated in conception and design of the work and performed the statistical analysis of the data. Nomi Levy-Carrick, Rebecca Rosen, and Lucia Ferri participated in conception and design of the work, analysis and interpretation of the work, particularly in relation to the mental health data. Joan Reibman participated in the conception and the design of the work, creation of the research database, organization of data collection, interpretation of the data, and drafting and revising the work. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

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ETHICS APPROVAL AND INFORMED CONSENT

The Institutional Review Board of New York University School of Medicine approved the research database (NCT00404898). All patients provided written informed consent.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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SUPPORTING INFORMATION

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