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OCCUPATIONAL ALLERGIES (JA POOLE, SECTION EDITOR)

Airway Disease in Rescue/Recovery Workers: Recent Findings from the World Trade Center Collapse

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Abstract
Purpose of Review Our goal is to summarize the airway disease literature since September 11, 2001 (9/11), focusing on studies published since 2011 in World Trade Center-exposed rescue/recovery workers.
Recent Findings Since 2011, studies have confirmed relationships between initial World Trade Center exposure intensity, severity of symptoms, airway disease diagnoses, and biomarkers of disease progression.
Summary Studies continue to document ongoing morbidity in rescue/recovery workers over 10 years after 9/11. Future research should further identify correlates of symptom persistence and new airway disease diagnoses. The unique characteristics of the airway diseases in this population warrant ongoing monitoring and treatment.

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Introduction

After the September 11, 2001 (9/11) terrorist attacks on the World Trade Center (WTC), thousands of first responders including Fire Department of the City of New York (FDNY) firefighters and emergency medical service workers (EMS), police, and other workers (construction and sanitation), as well as community residents were exposed to smoke, dust, and gaseous substances. Exposure from pulverized building materials and from aerosolized particles was further aggravated by fires that continued through December 2001. Lioy and colleagues characterized the WTC dust as containing metals, inorganic species, asbestos, pesticides, polycyclic aromatic hydrocarbons (PAHs), and other hydrocarbons [1]. Gypsum and calcite were found in WTC particulate matter analyses and are known to irritate the mucous membranes of the nose, throat, and airways [2]. In addition, much of the WTC particulate matter was found to be highly alkaline (pH 9–11) and to be greater than 10 μm [1], a size that typically undergoes nasopharyngeal filtration and deposition [3]. However, given the overwhelming extent of dust exposure and increased respiratory demand during work, both upper and lower airways were likely exposed. Evidence of this was supplied by Fireman et al. in their study which demonstrated that FDNY firefighters with significant WTC dust cloud exposure who underwent sputum induction after 9/11 had an increase in larger size particles found in sputum samples when compared to controls (Israeli firefighters) [4]. The official recovery and clean-up efforts continued until May 30, 2002, although the disaster site was active for months longer, potentially

exposing an estimated 60,000–70,000 workers to airway irritants through re-aerosolized dust [5].

After 9/11, several responder monitoring programs were developed to monitor the health, especially the respiratory status of rescue/recovery workers (Table 1). The FDNY WTC Health Program (FDNY WTC-HP) was the first, as it was an extension of an existing occupational health service, in place for years prior to the disaster. This program is an integrated monitoring and treatment program that was created especially for the WTC-exposed FDNY workforce. It provides annual monitoring/wellness exams for active and retired WTC-exposed personnel, and treatment services, as needed. The General Responder WTC Health Program (General Responder Health Consortium) at Mount Sinai Medical Center and other New York City area clinics evaluate non-FDNY responders including construction, law enforcement, and volunteers [6]. The WTC Health Registry at the New York City Department of Health and Mental Health follows WTC-exposed individuals through repeated surveys, but does not provide health services [7]. The Bellevue WTC Environmental Health Center (WTC EHC) evaluates neighborhood residents, local workers, and clean-up workers/volunteers [8]. This review focuses mostly on studies reporting on rescue/recovery workers.

Respiratory Disease and Outcomes in Rescue/Recovery Workers During the First Decade Post-9/11

In the first 10 years post-9/11, several studies were published using data obtained from the above monitoring programs which helped identify and characterize respiratory diseases that developed after 9/11. For example, 90% of FDNY rescue/recovery workers were found to have acute respiratory symptoms within 48 hours of 9/11, including wheezing, chest tightness, nasal congestion, and acute cough. The incidence of new respiratory symptoms did not begin to decline until February 2002 [9, 10]. Data published from the FDNY WTC-HP cohort were uniquely valuable in that virtually all FDNY rescue/recovery workers who were present on 9/11 or soon thereafter had been evaluated prior to 9/11 as part of their routine monitoring; they had pre-exposure lung function measurements (spirometry) and had met rigorous physical health standards to join the FDNY. Thus, respiratory dysfunction including cough, asthma, obstructive disease, and bronchial hyperreactivity can be directly attributed to WTC exposures on or after 9/11. Arrival time for work at the WTC site and duration (in months) of work at the WTC site are often used as surrogates for exposure intensity in the FDNY and other cohorts since no measurements of air quality or airborne particles were completed in the first 48 hours after 9/11. In the FDNY cohort, those who first arrived early the morning of 9/11 were the most highly exposed to the dust cloud created during and after the collapses of the WTC towers. Next, those who arrived in the afternoon of 9/11 are considered the next most highly exposed, followed by those who arrived on September 12, 2001, and then by those who arrived on days 3–14 with lower exposures to dust. Workers who arrived after day 14 are considered to have minimal dust exposure [11]. Several studies found an association between bronchial hyperreactivity, FEV_1 (forced expiratory volume in 1 second) reduction, airway obstruction, persistent respiratory symptoms, reactive airways dysfunction syndrome (RADS), and early arrival time and prolonged duration of work at the WTC site [10–15]. Similar findings were reported among police, ironworkers, and sanitation workers who responded to WTC site in the early days after 9/11 [16–18]. Furthermore, Aldrich and colleagues, using data from the FDNY WTC-HP, demonstrated a statistically significant FEV_1 decline in the first year for those who worked at the disaster site on the morning of 9/11 or within the first 14 days, without significant recovery over the subsequent 6 years [19]. Finally, studies have also highlighted the association between mental and physical health disorders and respiratory illness, showing an association between asthma symptoms and probable post-traumatic stress disorder (PTSD) and gastroesophageal reflux symptoms (GERS) [11, 20].

Previous review articles have concentrated on the first decade post-9/11 [21]. The goal of the current review is to summarize the recent literature published since 2011 on airway disease in WTC-exposed rescue/recovery workers. Occupational airway disease includes several subtypes of disease such as work-exacerbated asthma (those with previous asthma), occupational asthma, irritant-induced asthma, RADS, and occupational COPD [22–26]. In this WTC-exposed population, however, identifying a specific airway disease diagnosis, such as asthma, has been a challenge due to both disease misclassification and disease overlap. There is significant overlap between chronic bronchitis, bronchiolitis, COPD, emphysema, and asthma. In addition, most studies rely on a diagnosis of asthma that is based on self-report of a physician diagnosis by a responder, without confirmation. Another limitation in WTC studies is that some defined high and low exposure to irritants at the WTC site differently. For the purpose of this review, WTC-associated airway disease will be identified as follows: occupational asthma, RADS, lower respiratory symptoms, WTC cough, occupational obstructive airways disease, and bronchial hyperreactivity.

Respiratory Disease and Outcomes in Rescue/Recovery Workers Published After 2011

Lung Function Changes Over Time and Its Relationship to Symptoms, Recovery, and Bronchial Hyperreactivity

Several studies have examined the changes in lung function over time. In 2016, Aldrich and colleagues reported that after

Table 1 Respiratory publications among rescue/recovery workers by World Trade Center (WTC)cohort

Cohort	WTC Rescue/ Recovery Workers Population Size	2001-2010 Publications[a]	2011-2016 Publications[a]
Fire Department of the City of New York, World Trade Center Health Program	N=16,190	Aldrich et al. *N Engl J Med*, 2010; Banauch et al. *MMWR Morb Mortal Wkly Rep*, 2002; Banauch et al. *Am J Respir Crit Care Med*, 2003; Banauch et al. *Chest*, 2010; Banauch et al. *Crit Care Med*, 2005; Banauch et al. *Curr Opin Pulm Med*, 2005; Banauch et al. *Am J Respir Crit Care Med*, 2006; Banauch, et al. *Disaster Med Public Health Prep*, 2008; Feldman et al. *Chest*, 2004; Fireman et al. *Environ Health Perspect*, 2004; Prezant et al. *MMWR Morb Mortal Wkly Rep*, 2002; Prezant et al. *Mt Sinai J Med*, 2008; Rom et al. *Proc Am Thorac Soc*, 2010; Rom et al. *Am J Respir Crit Care Med*, 2002; Webber et al. *Environ Health Perspect*, 2009; Weiden et al. *Chest*, 2010	Aldrich et al. *Chest*, 2016; Aldrich et al. *Chest*, 2016; Cho et al. *Respiratory medicine*, 2014; Cho et al. *J Mol Biomark Diagn* 2014; Cho et al. *J Clin Immunol*, 2013; Glaser et al. *Am J Epidemiol*, 2014; Hall et al. *PLoS currents*, 2015; Kwon et al. *PloS one*, 2013; Naveed et al. *Am J Respir Crit Care Med* 2012; Niles et al. *Am J Ind Med*, 2013; Niles et al. *Chest*, 2011; Nolan et al. *Respiratory research*, 2014; Nolan et al. *Chest*, 2012; Schenck et al. *BMJ open*, 2014; Soo et al. *Chest*, 2012; Tsukiji et al. *Biomarkers* 2014; Weakley et al. *Prev Med*, 2011; Weakley et al. *Prev Med*, 2013; Webber, et al. *Am J Ind Med*, 2011; Weiden et al. *Semin Respir Crit Care Med*, 2015; Weiden et al. *Eur Respir J*, 2013; Yip et al. *Occup Environ Med*, 2016
General Responder Cohort, World Trade Center Health Program	N=27,449	de la Hoz *Curr Allergy Asthma Rep*, 2010; de la Hoz et al. *J Occup Environ Med*, 2008; de la Hoz et al. *Int Arch Occup Environ Health*, 2008; de la Hoz et al. *J Occup Environ Med*, 2009; Enright et al. *Mt Sinai J Med*, 2008; Enright et al. *Respir Care*, 2010; Herbert et al. *Environ Health Perspect*, 2006; Landrigan et al. *Environ Health Perspect*, 2004; Mendelson et al. *J Occup Environ Med*, 2007; Moline et al. *Cancer investigation*, 2006; Skloot et al. *Chest*, 2004; Skloot et al. *Chest*, 2009; Tao et al. *J Occup Environ Med*, 2007; Wu et al. *Environ Health Perspect*, 2010	Altman et al. *Int Arch Occup Environ Health*, 2011; de la Hoz *Curr Opin Allergy Clin Immunol*, 2011; Jiang et al. *Am J Ind Med*, 2016; Jurek and Maldonado *Annals of epidemiology*, 2016; Kim et al. *Am J Ind Med*, 2012; Lucchini et al. *G Ital Med Lav Ergon*, 2012; Luft et al. *Psychol Med*, 2012; Mindlis et al. *J Asthma*, 2016; Udasin et al. *J Occup Environ Med*, 2011; Wisnivesky, et al. *Lancet*, 2011; Xu et al. *Ann Allergy Asthma Immunol*, 2016
World Trade Center Health Registry	N=30,665	Brackbill et al. *JAMA*, 2009; Farfel et al. *J Urban Health*, 2008; Wheeler et al. *Environ Health Perspect*, 2007	Antao et al. *Am J Ind Med*, 2011; Brackbill et al. *Am J Epidemiol*, 2014; Con et al. *Am J Ind Med*, 2016; Friedman et al. *Occup Environ Med*, 2016; Friedman et al. *Am J Ind Med*, 2013; Friedman et al. *Am J Respir Crit Care Med*, 2011; Jordan et al. *J Asthma*, 2015; Li et al. *Am J Ind Med*, 2016; Li et al. *Am J Gastroenterol*, 2011; Maslow et al. *Am J Public Health*, 2012; Nair et al. *Am J Public Health*, 2012; Perlman et al. *Lancet*, 2011
Bellevue WTC Environmental Health Center	N=766	Lin et al. *Am J Epidemiol*, 2005; Lin et al. *J Asthma*, 2007; Lin et al. *Int J Occup Environ Health*, 2010; Oppenheimer et al. *Chest*, 2007; Reibman et al. *Environ Health Perspect*, 2005	Berger et al. *Am J Ind Med*, 2016; Berger et al. *ERJ open research*, 2015; Caplan-Shaw et al. *Am J Ind Med*, 2016; Kazeros et al. *J Asthma*, 2013; Kazeros et al. *J Occup Environ Med*, 2015; Liu et al. *J Occup Environ Med*, 2012; Trasande et al. *Sci Total Environ*, 2013

[a] Publications are restricted to those that included rescue/recovery workers

the initial decline in FEV_1% predicted seen immediately after 9/11, FEV_1% predicted remained relatively stable through September 2014. They also noted through 2014 that there was a significantly greater decline in FEV_1 in more highly WTC-exposed firefighters versus lesser exposed [27••]. In a study published in 2015, Berger et al. examined both spirometry and oscillometry in community members who had WTC dust exposure [28]. They compared spirometry, oscillometry, and symptoms in both symptomatic individuals in the WTC EHC cohort and asymptomatic participants in the WTC Health Registry. Unlike the WTC-exposed firefighter cohort, most participants, both asymptomatic and symptomatic, had normal spirometry. However, abnormal oscillometry measurements increased with both severity and frequency of wheeze in the symptomatic cohort, even in those with normal spirometry [28]. In 2016, Berger et al., using methacholine challenge

testing (MCT) and oscillometry, found that WTC-exposed participants who became symptomatic after MCT had abnormalities in oscillometry. The authors suggest that reactivity in small airways may explain the presence and severity of lower respiratory symptoms [29].

Lung function has also been shown to correlate with symptom recovery and airway disease diagnoses. Soo and colleagues evaluated the relationship between FEV_1% predicted and the probability of recovery from lower respiratory symptoms (cough, wheeze, or dyspnea) in WTC-exposed firefighters in the FDNY WTC-HP cohort [30]. Lower respiratory symptoms were evaluated using self-administered questionnaires over 9 years after 9/11. Overall, among firefighters who were initially symptomatic, only 37% reported recovery from symptoms. Firefighters with the lowest FEV_1% predicted at baseline had the lowest probability of symptom recovery (25%) compared with those with the highest FEV_1% predicted at baseline, who had a higher probability of recovery (45%). Similarly, Webber and colleagues found that FDNY rescue/recovery workers with the lowest FEV_1% quintile included those with physician-diagnosed asthma (41.1%) and COPD/emphysema (50.6%), suggesting that disease correlated with FEV_1 reduction and resulted after WTC exposure [31]. Niles and colleagues also reported that firefighters who both self-reported symptoms and had abnormal lung function in 2005 were more likely to acquire airway disease diagnoses of asthma, COPD/emphysema, and/or bronchitis later [32].

In addition, several studies have evaluated other factors affecting the likelihood of symptom recovery such as arrival time to work at the WTC and medication use. Soo et al. found a relationship between symptom recovery and arrival time to the WTC site: rescue/recovery workers who arrived on the morning of 9/11 were less likely to recover than those who arrived on days 3–14 after 9/11 [30]. They also found that participants who reported using respiratory medications such as bronchodilators, inhaled steroids, montelukast, or nebulized medications were less likely to report symptom recovery when compared to those who did not use medications (HR 0.52), as medication use is a likely indicator of disease severity.

Similar to likelihood of symptom recovery, exposure intensity has also been associated with the diagnosis of airways disease. Hall et al. evaluated the association between new physician-diagnosed obstructive airway disease (OAD), defined as asthma, chronic bronchitis, or COPD/emphysema, and WTC exposure in FDNY firefighters [33]. They found the most intensely exposed firefighters had the highest incidence of new OAD diagnoses compared with those with less exposure. The association was highest in the first 15 months after 9/11. The risk was somewhat attenuated during the period between 16 and 84 months, and by 85–120 months after 9/11 the difference was no longer statistically significant. When asthma and non-asthma OAD were evaluated separately, similar results were seen. Webber et al. found a relationship between the prevalence of FDNY physician-diagnosed post-9/11 asthma and WTC exposure in FDNY firefighters and EMS workers. There was an increased prevalence of post-9/11 asthma among those who arrived on the morning of 9/11 (11.4%) compared with those who arrived 3–14 days after 9/11 (5.3%) [31]. Unlike other studies, in both the Webber et al. and Hall et al. studies, asthma was clearly defined and was determined from a physician diagnosis in the FDNY medical records rather than identified only by self-reports [31, 33]. They required that FDNY physician diagnoses be documented on at least two separate visits since 9/11, including at least one during the study period.

Several studies have evaluated incidence rates for asthma in rescue/recovery workers. Niles et al. reported that between 2005 and 2010, significantly more WTC-exposed firefighters were diagnosed with asthma, increasing in prevalence from 8.3 to 18% in that sample. The prevalence of other airway diseases (bronchitis and COPD/emphysema) also increased from 18.5 to 33.6% [32]. Weakley and colleagues evaluated the prevalence of self-reported asthma between 2005 and 2010 in WTC-exposed firefighters [34]. They reported that the prevalence of current asthma in those ages 45–65 increased over time from 8.9 to 14.9% in 2009, which was three times higher than reported nationally in a similar group in the general population. In 2016, Yip and colleagues reported the prevalence of physician-diagnosed asthma between 2001 and 2015 among WTC-exposed FDNY firefighters as 21% and as 10.3% in FDNY WTC-exposed EMS workers [35]. Some of the post-9/11 increase in prevalence in the FDNY cohort can be explained by increased awareness by physicians and firefighters after additional resources were allocated to treating FDNY rescue/recovery workers. Kim et al. also reported an increased prevalence of lifetime asthma (self-reported) in non-FDNY WTC rescue/recovery workers from the General Responder Program [36]. Lifetime prevalence of asthma increased from 2.9% prior to 9/11 to 19.4% in 2007, compared to the general population which was stable at 10%. There was also an increase in "12-month asthma" (defined as ≥1 attacks in the prior 12 months) between 2000 and 2007 in rescue/recovery workers in the same cohort (0.2% prior to 9/11 to 7.8% in 2007) compared to approximately 4% in the general population. Wisnivesky and colleagues evaluated the cumulative incidence of asthma in the WTC rescue/recovery workers from the same cohort as Kim et al., the General Responder cohort [36, 37•]. They reported a cumulative incidence of self-reported asthma that was notably increased from 10.5% prior to 9/11 to 27.6% in September 2010. The first year after 9/11, the annual incidence of asthma was the highest (3.4%); annual incidence stabilized at approximately 2% (range from 1.8 to 2.5%) each year until the end of follow-up in 2010 [37•]. Unlike the FDNY cohort, the WTC rescue/recovery workers in the General Responder cohort included police officers, construction workers, and municipal workers who were not required to meet rigorous pre-employment standards required

by the FDNY, partially explaining their higher pre-9/11 rates of asthma.

Aldrich and colleagues evaluated changes in bronchial hyperreactivity (BHR) and its association with FEV_1% predicted, respiratory medication use, and resolution of symptoms over time [38••]. In 2013–2014, they evaluated BHR using methacholine challenge testing (MCT) in WTC-exposed firefighters who had undergone baseline MCT within 2 years after 9/11. Although the overall degree of BHR remained stable, they reported a baseline prevalence (obtained from 2001–2003) of 16%, which increased to 25% at follow-up (obtained from 2013 to 2014). Of those with BHR at baseline, 57.1% had BHR at follow-up and 42.9% with BHR at baseline no longer had BHR at follow-up. In addition, 19% of firefighters developed new BHR at follow-up. There was a greater decline in FEV_1 in those with BHR at follow-up than in those without BHR at follow-up. Interestingly, the use of corticosteroid therapy had no effect on BHR, although those who received corticosteroid therapy had a slower FEV_1 decline rate. This study helped characterize WTC-associated airway disease as one that shares some features of occupational asthma (BHR and response to corticosteroids), but differs in its persistence, even after removal from the exposure source.

Overall, findings from the WTC literature support a continued association between lung function decline, symptom recovery, and airway disease diagnoses with the level of WTC exposure. Specifically, higher intensity WTC exposure is associated with the following: worse lung function (decreased FEV_1% predicted), less reversibility of lower respiratory symptoms, BHR, and a greater likelihood of an OAD diagnosis. Lung function and symptom recovery were further confounded by the use of respiratory medications and BHR.

Respiratory Symptoms/Disease and Physical Health Comorbidities

In the years after 9/11, several physical comorbidities such as gastroesophageal reflux symptoms or disease (GERS/GERD) were found to coexist with respiratory symptoms and disease. Li and colleagues evaluated the association between GERS and asthma among rescue/recovery workers in the WTC Health Registry cohort 5–6 years and again 10–11 years after 9/11 [39, 40]. Participants were identified as having GERS if they had a history of heartburn, reflux symptoms, or indigestion. They found an increase in the cumulative incidence of persistent GERS in rescue/recovery workers with asthma (self-reported) when compared to those without asthma. The cumulative incidence of GERS differed from 25% in those with high WTC exposure without asthma to 33% in those with high WTC exposure with asthma. In addition, the cumulative incidence of GERS in those with asthma was greater in responders who were highly exposed (33%) compared to those with asthma who had low levels of exposure (8%) [39]. Consistent with their earlier study, in 2016 Li et al. published findings that rescue/recovery workers with GERS at baseline had an increased risk of developing persistent GERS in 2011–2012 if they also reported early post-9/11 asthma (RR 1.2). They also demonstrated an increased risk of late-onset GERS (reported in 2011–2012, but not reported in prior interviews) in those with early post 9/11 asthma (RR 1.2) [40].

Similarly, Wisnivesky et al. noted that 8.6% of rescue/recovery workers in the General Responder cohort reported comorbid diagnoses of asthma, GERD, and sinusitis. Participants with asthma were also noted to have sinusitis without GERD (4.7%) or GERD without sinusitis (4.1%) [37•]. Weakley and colleagues reported significant comorbidity between lower respiratory symptoms (dyspnea or wheeze) and GERS (25.4%) and LRS and upper respiratory symptoms (nasal/sinus drip/congestion or sore/hoarse throat, 29.6%) in the 5–9 years after 9/11 in WTC-exposed firefighters [34].

Jordan and colleagues described the relationship between asthma control and comorbid conditions such as GERS and obstructive sleep apnea (OSA) from a 2011–2012 survey conducted with the WTC Health Registry cohort [41]. In patients with GERS, there was a significantly higher prevalence of poorly or very poorly controlled asthma (49.3 and 60.5%, respectively) compared with those with controlled asthma (29.5%). They also found a significantly higher prevalence of physician-diagnosed OSA in those with poorly and very poorly controlled asthma (34.2 and 40.6%, respectively) versus those with controlled asthma and OSA (17.6%). These findings were based on their entire study population, which included rescue/recovery workers, other workers/volunteers, commuters, and community members/local residents.

This literature review demonstrates a significant relationship between respiratory diseases, more specifically asthma, and comorbid GERD, upper respiratory disease, and/or OSA. Coexistence is more likely in the setting of early WTC arrival time and persistent or increasingly severe symptoms, suggesting that control of at least one disease process likely contributes to control of the other(s). It also stresses the importance of screening for common comorbid conditions when one is diagnosed.

Respiratory Symptoms/Disease and Mental Health Comorbidities

Several studies after 9/11 have identified an association between respiratory disease and mental health symptoms. In most studies, mental health symptoms were identified using standardized and validated patient screening questionnaires and were not diagnosed directly by clinicians. Wisnivesky and colleagues studied a cohort of WTC rescue/recovery workers between July 16, 2002 and September 11, 2010, identifying those with self-reported diagnoses of asthma and mental health disorders [37•]. Asthma was defined in those who

self-reported a physician diagnosis and also by including those under a physician's care, those taking asthma medications, or those who reported having had an acute asthma attack within 1 month prior to the index follow-up visit. Of rescue workers with asthma, 48.3% also screened positive for one or more mental health disorder such as probable PTSD, depression, or panic disorder.

In a study published in 2011, Niles and colleagues evaluated the association between WTC cough syndrome symptoms (at least one symptom of upper respiratory, of lower respiratory, and of GERD), FEV_1% predicted, and PTSD symptoms in WTC-exposed firefighters within the first year after 9/11 and then again 3–4 years later [42]. They found a significant association between WTC cough syndrome and probable PTSD at baseline (OR 1.21) and after 3–4 years of follow-up (OR 1.21). Additionally, there was a relationship between the number of WTC cough syndrome symptoms at baseline and the number of PTSD symptoms at both baseline and at follow-up (OR 1.46 and OR 1.49, respectively). No association was found between FEV_1% predicted and PTSD symptoms.

More recently, Mindlis and colleagues evaluated the relationship between asthma and PTSD among 181 rescue/recovery workers in the General Responder cohort diagnosed with asthma [43]. The participants were all diagnosed with asthma either after 9/11 or had previous asthma that worsened after 9/11. Previous asthma diagnoses were verified by the medical record and PTSD was diagnosed by a physician during the study. They reported that among rescue/recovery workers with asthma, 28% also had PTSD. The study also monitored inpatient and outpatient healthcare utilization due to asthma. They found that patients with PTSD compared to those with sub-threshold PTSD scores or no PTSD had statistically significant worse asthma control. In addition, those with PTSD required significantly more inpatient care due to asthma exacerbations compared to those without PTSD (33 and 10%, respectively). Finally, those with PTSD also had significantly lower asthma quality of life scores compared to those without PTSD. Friedman and colleagues (2016) demonstrated a relationship between persistence of lower respiratory symptoms (LRS) and mental health in 9/11 rescue/recovery workers in the WTC Health Registry cohort [44]. LRS were defined as self-reported cough, wheeze, dyspnea, or inhaler use within 30 days of the interview date and as being persistent if present 10 years after 9/11. Of rescue/recovery workers, 18.7% were identified as having persistent LRS; those with persistent LRS were 50% more likely to report poor mental health when compared with those with no LRS.

Overall, the literature demonstrates a significant association between WTC-related respiratory disorders and mental health symptoms, as well as a correlation between mental health symptoms and severity of respiratory illness and disease-related quality of life. These studies suggest that improvement of one comorbid condition could help improve symptoms of overlapping WTC-related conditions.

Lung Function and Smoking and Smoking Cessation

Only a few studies have evaluated the effects of smoking and smoking cessation on lung function in WTC-exposed rescue/recovery workers. Soo and colleagues demonstrated that rescue/recovery workers who were current smokers were less likely to have symptom recovery (HR 0.79) than never-smokers [30]. In 2016, Aldrich and colleagues reported that among WTC-exposed firefighters, current smokers were more likely to have impaired lung function (FEV_1 less than lower limits of normal) when compared with never-smokers. Of current smokers, 32.2% had a decline in FEV_1 (when controlled for age and the expected decline after 9/11) compared with 17% of never-smokers. They also found that former smokers who quit between September 11, 2001 and March 10, 2008 were more likely to have impaired FEV_1% predicted than never-smokers, but less so than current smokers [27••]. These results suggest the continued benefit of smoking cessation, despite intense WTC exposure. Hall and colleagues, however, found no association between smoking status and OAD diagnoses among WTC-exposed firefighters in the 10 years after 9/11 [33]. Further studies are necessary to define the role of tobacco abuse in WTC-related OAD.

Biomarkers and WTC Respiratory Dysfunction

Recent publications now focus on metabolic, vascular, and inflammatory biomarkers in relation to respiratory disease in WTC rescue/recovery workers. Weiden and colleagues have evaluated the relationship between serum biomarkers obtained from the FDNY cohort within 6 months after 9/11 and the development of WTC-lung injury (WTC-LI) as defined by an FEV_1 less than the lower limit of normal [45•]. FEV_1 measurements were obtained annually and lung function recovery was identified if there was FEV_1 recovery within 7 years after the initial decline noted in the first year after 9/11. Weiden et al. demonstrated that increased levels of matrix metalloproteinases (MMP) such as MMP-1 reduced the odds of recovering lung function within 7 years after 9/11. Conversely, MMP-2 and tissue inhibitors of matrix metalloproteinases (TIMP-1) expression was increased in the small subset of firefighters who did regain lung function within 7 years after 9/11, suggesting these are protective against lung injury. They also reported that an increase of lipid metabolites (lysophosphatidic acid and apolipoprotein A1), elevated C-reactive protein, and apolipoprotein A2 were associated with increased odds of developing WTC-LI [45•]. Consistent with earlier findings from Banauch et al. [46], Weiden and colleagues also found a greater decline in FEV_1 with increasing alpha-1 antitrypsin (AAT) deficiency [45•].

Using the same cohort, Naveed and colleagues reported a relationship between abnormal triglycerides and HDL and elevated heart rate and leptin levels to the risk of developing abnormal lung function after 9/11 [47]. In 2012, Nolan et al. reported that elevated serum macrophage-derived chemokine (MDC) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were also associated with an increased risk of developing an FEV_1 less than the lower limit of normal within 7 years after 9/11 [48].

Finally, Kazeros et al. measured the peripheral eosinophil count of individuals in the WTC Environmental Health Center (EHC) cohort, which included local workers, residents, and clean-up workers [49]. They compared the presence of elevated eosinophil count, asthma-like symptoms (wheeze, chest tightness, cough), and spirometry data. They found significantly more individuals with wheeze had elevated peripheral eosinophils than those without wheeze (21 and 13%, respectively). Although few had obstructive airflow pattern on spirometry, those with elevated eosinophil count were more likely to have airflow obstruction (16% with obstruction and 7% without obstruction).

Future studies involving biomarker abnormalities may help to better define those at risk for lung injury, its persistence, and its recovery.

Treatment and Healthcare Utilization

Several studies have evaluated treatment and healthcare utilization in rescue/recovery workers with WTC-related respiratory disease. In an analysis of WTC-exposed FDNY firefighters by Niles et al., there was a notable increase in work-related disability retirements after 9/11. Specifically, most disability retirements were due to airway disease [42]. The number of retirements for airways disease peaked in the second year after 9/11 and remained elevated when compared with the number of pre-9/11 retirements. In addition, over 70% of respiratory-related disability retirements occurred in firefighters who arrived to work at the WTC on the day of 9/11 (morning or afternoon), suggesting that intense exposure and severe respiratory symptoms may have substantially contributed to respiratory disability.

In 2013, Niles and colleagues identified factors that increased the likelihood that FDNY firefighters would be evaluated by a physician for respiratory conditions and treatment between September 2009 and September 2010 [32]. FDNY firefighters who arrived within 3 days after 9/11 and those who were over 45 years of age on 9/11 were statistically more likely to seek evaluation from a FDNY physician for respiratory symptoms in the final year of the study. In addition, those who reported having one to four respiratory symptoms or sought any physician evaluation for respiratory symptoms within 4 years after 9/11 were also most likely to undergo continued or repeated physician evaluation for respiratory issues in the final year of the study. Finally, many factors (age 45 or older on 9/11, asthma or other OAD diagnosis within 4 years of 9/11, one to four respiratory symptoms within 4 years of 9/11, and abnormal FEV_1% predicted by year 4 after 9/11) were significantly associated with filling over $1000 worth of respiratory prescription medications between 2009 and 2010.

Clearly, the need for continued treatment and healthcare services for WTC rescue/recovery workers remains substantial. Understanding the trajectory of these diseases and planning for the long-term health needs of responders remain critical areas of ongoing investigation.

Conclusion

The above reviewed studies highlight several key factors in our understanding of WTC-related airway disease. First, the phenotype of WTC-related airway disease remains difficult to accurately describe. Traditionally, irritant-induced, occupational asthma is a disease that improves with removal from the exposure source. However, several studies have shown that some WTC rescue/recovery workers experienced progressive lung dysfunction and some even had a latency period between the exposure and symptom presentation or a respiratory diagnosis. If symptoms occurred shortly after initial WTC exposure and there is persistence of BHR then RADS would be the diagnosis. For those with a delay in symptoms and abnormal lung function, occupational COPD would be a more likely diagnosis. The WTC-related cough, however, is typically dry and not entirely consistent with the definition of chronic bronchitis. Diffusion abnormalities are rare and CT scan findings of emphysema are uncommon. WTC-related airway disease is likely an entity that overlaps with RADS, occupational asthma, and COPD. Second, even more than 10 years after 9/11, there remains a strong association between WTC exposure intensity, persistence of respiratory symptoms, lung function abnormalities, and a diagnosis of respiratory disease. As highlighted, bronchial hyperreactivity, physical and mental health comorbidities, and smoking status all affect the extent and persistence of respiratory symptoms and lung function. In the future, biomarker studies may help characterize WTC-related airway disease in terms of its inflammatory characteristics, and help identify those most sensitive to injury and those most likely to recover. Perhaps the most important issue to highlight is the critical need for continued monitoring and treatment of rescue/recovery workers several decades after a disaster since it is clear that the extensive health effects of 9/11 exposure could not have been predicted. The health outcomes of these workers is yet to be fully understood, but with continued resources and investigation, there is hope that we will gain a better understanding of the full scope of WTC airway diseases.

Compliance with Ethical Standards

Conflict of Interest Drs. Cleven, Webber, Zeig-Owens, Hena, and Prezant declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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