FDNY WTC DATA CENTER BIBLIOGRAPHY

Peer Reviewed Publications

2002

Banauch, G., McLaughlin, M., Hirschhorn, R., Corrigan, M., Kelly, K. and Prezant, D. (2002). "Injuries and illnesses among New York City Fire Department rescue workers after responding to the World Trade Center attacks." MMWR Morb Mortal Wkly Rep. C. Centers for Disease and Prevention. **51 Spec No:** 1-5.

Within minutes of the terrorist attacks on September 11, 2001, the Fire Department of New York City (FDNY) operated a continuous rescue/recovery effort at the World Trade Center (WTC) site. Medical officers of FDNY Bureau of Health Services (FDNY-BHS) responded to provide emergency medical services (see box). The collapse of the WTC towers and several adjacent structures resulted in a vast, physically dangerous disaster zone. The height of the WTC towers produced extraordinary forces during their collapse, pulverizing considerable portions of the buildings' structural components and exposing first responders and civilians to substantial amounts of airborne particulate matter. Fires burned continuously under the debris until mid-December 2001. Because of ongoing fire activity and the large numbers of civilians and rescue workers who were killed during the attacks, approximately 11,000 FDNY firefighters and many emergency medical service (EMS) personnel worked on or directly adjacent to the rubble and incurred substantial exposures (Figure). This report describes morbidity and mortality in FDNY rescue workers during the 11-month period after the WTC attacks and documents a substantial increase in respiratory and stress-related illness compared with the time period before the WTC attacks. These findings demonstrate the need to provide acute and long-term medical monitoring, treatment, and counseling to FDNY rescue workers exposed to this disaster and to solve supply, compliance, and supervision problems so that respiratory protection can be rapidly provided at future disasters.

Prezant, D., Kelly, K., Jackson, B., Peterson, D., Feldman, D., Baron, S., Mueller, C., Bernard, B., Lushniak, B., Smith, L., BerryAnn, R. and Hoffman, B. (2002). "Use of respiratory protection among responders at the World Trade Center site--New York City, September 2001." MMWR Morb Mortal Wkly Rep. C. Centers for Disease and Prevention. **51 Spec No:** 6-8.

The terrorist attacks on the World Trade Center (WTC) on September 11,2001, created an occupational health and safety challenge for New York City (NYC) firefighters and rescue workers responding to the disaster. Immediate respiratory hazards included explosions, fire, falling debris, and dust clouds containing particulate matter comprised of pulverized building materials. Ongoing risks included lingering particulate matter in the air and intermittent combustion products from initial and persistent fires beneath the rubble pile. Because the nature and extent of exposures in disaster situations are complex and difficult to characterize, the use of adequate personal protective equipment (PPE), including respiratory protection, is essential in protecting the health of firefighters and other rescue workers. During the weeks after September 11, the NYC Fire Department's Bureau of Health Services (FDNY-BHS) and CDC's National Institute for Occupational Safety and Health (NIOSH) organized a collaborative study to evaluate occupational hazards and exposures for these workers, including their use of respiratory protection. This report summarizes the results of that study, which indicate that the majority of firefighters did not use adequate respiratory protection during the first week of the rescue/recovery operation.

Rom, W. N., Weiden, M., Garcia, R., Yie, T. A., Vathesatogkit, P., Tse, D. B., McGuinness, G., Roggli, V. and Prezant, D. (2002). "Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust." Am J Respir Crit Care Med **166**(6): 797-800.

We report a sentinel case of acute eosinophilic pneumonia in a firefighter exposed to high concentrations of World Trade Center dust during the rescue effort from September 11 to 24. The firefighter presented with a Pa(O2) of 53 mm Hg and responded to oxygen and corticosteroids. Computed tomography scan showed patchy ground glass density, thickened bronchial walls, and bilateral pleural effusions. Bronchoalveolar lavage recovered 70% eosinophils, with only 1% eosinophils in peripheral blood. Eosinophils were not degranulated and increased levels of interleukin-5 were measured in bronchoalveolar lavage and serum. Mineralogic analysis counted 305 commercial asbestos fibers/10(6) macrophages including those with high aspect ratios, and significant quantities of fly ash and degraded fibrous glass. Acute eosinophilic pneumonia is a rare consequence of acute high dust exposure. World Trade Center dust consists of large

particle-size silicates, but fly ash and asbestos fibers may be found in bronchoalveolar lavage cells.

Szeinuk, J., Herbert, R., Clark, N., Milek, D., Levin, S., Prezant, D. and Gillio, R. (2002). "Clinician's guide to irritative and respiratory problems in relation to environmental exposures from the World Trade Center disaster." 2005, from http://www.wtcexams.org/pdfs/clinicians_guide_to_irritative_and_respiratory_problems_v3.pdf.

2003

Banauch, G. I., Alleyne, D., Sanchez, R., Olender, K., Cohen, H. W., Weiden, M., Kelly, K. J. and Prezant, D. J. (2003). "Persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center." Am J Respir Crit Care Med **168**(1): 54-62.

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.

Edelman, P., Osterloh, J., Pirkle, J., Caudill, S. P., Grainger, J., Jones, R., Blount, B., Calafat, A., Turner, W., Feldman, D., Baron, S., Bernard, B., Lushniak, B. D., Kelly, K. and Prezant, D. (2003). "Biomonitoring of chemical exposure among New York City firefighters responding to the World Trade Center fire and collapse." Environ Health Perspect 111(16): 1906-1911.

The collapse of the World Trade Center (WTC) on 11 September 2001 exposed New York City firefighters to smoke and dust of unprecedented magnitude and duration. The chemicals and the concentrations produced from any fire are difficult to predict, but estimates of internal dose exposures can be assessed by the biological monitoring of blood and urine. We analyzed blood and urine specimens obtained from 321 firefighters responding to the WTC fires and collapse for 110 potentially fire-related chemicals. Controls consisted of 47 firefighters not present at the WTC. Sampling occurred 3 weeks after 11 September, while fires were still burning. When reference or background ranges were available, most chemical concentrations were found to be generally low and not outside these ranges. Compared with controls, the exposed firefighters showed significant differences in adjusted geometric means for six of the chemicals and significantly greater detection rates for an additional three. Arrival time was a significant predictor variable for four chemicals. Special Operations Command firefighters (n = 95), compared with other responding WTC firefighters (n = 226), had differences in concentrations or detection rate for 14 of the chemicals. Values for the Special Operations Command firefighters were also significantly different from the control group values for these same chemicals and for two additional chemicals. Generally, the chemical concentrations in the other firefighter group were not different from those of controls. Biomonitoring was used to characterize firefighter exposure at the WTC disaster. Although some of the chemicals analyzed showed statistically significant differences, these differences were generally small.

2004

Feldman, D. M., Baron, S. L., Bernard, B. P., Lushniak, B. D., Banauch, G., Arcentales, N., Kelly, K. J. and Prezant, D. J. (2004). "Symptoms, respirator use, and pulmonary function changes among New York City firefighters responding to the World Trade Center disaster." Chest **125**(4): 1256-1264.

CONTEXT: New York City firefighters responding to the World Trade Center (WTC) disaster on September 11, 2001, were exposed to numerous hazards. A medical screening program was conducted 3 weeks after the disaster on a sample of firefighters. OBJECTIVES: To determine whether arrival time at the WTC and other exposure variables (including respirator use) were associated with symptoms and changes in pulmonary function (after exposure - before exposure). DESIGN: A cross-sectional comparison of firefighters representing the following groups: (1) firefighters who arrived before/during the WTC collapse, (2) firefighters who arrived 1 to 2 days after the collapse, (3) firefighters who arrived 3 to 7 days after the collapse, and (4) unexposed firefighters. SETTING: Fire Department of New York City (FDNY) Bureau of Health Services on October 1 to 5, 2001. POPULATION: A stratified random sample of 362 of 398 recruited working firefighters (91%). Of these, 149 firefighters (41%) were present at the WTC collapse, 142 firefighters (39%) arrived after the collapse but within 48 h, 28 firefighters (8%) arrived 3 to 7 days after the collapse, and 43 firefighters (12%) were unexposed. MAIN OUTCOME MEASURES: New/worsening symptoms involving the eyes, skin, respiratory system, and nose and throat (NT), and changes in spirometry from before to after exposure. RESULTS: During the first 2 weeks at the WTC site, 19% of study firefighters reported not using a respirator; 50% reported using a respirator but only rarely. Prevalence ratios (PRs) for skin, eye, respiratory, and NT symptoms showed a dose-response pattern between exposure groups based on time of arrival at the WTC site, with PRs between 2.6 and 11.4 with 95% confidence intervals (CIs) excluding 1.0 for all but skin symptoms. For those spending > 7 days at the site, the PR for respiratory symptoms was 1.32 (95% CI, 1.13 to 1.55), compared with those who were exposed for < 7 days. Mean spirometry results before and after exposure were within normal limits. The change in spirometry findings (after exposure - before exposure) showed near-equal reductions for FVC and FEV(1). These reductions were greater than the annual reductions measured in a referent population of incumbent FDNY firefighters prior to September 11 (p <or= 0.05). There was a 60% increased risk of a decline of >or= 450 mL in FEV(1) in those arriving during the first 48 h compared to the referent (p <or= 0.05). CONCLUSIONS: The symptoms and pulmonary function changes following exposure at the WTC demonstrate the need for improvements in respirators and their use, as well as long-term medical monitoring of rescue workers.

Truncale, T., Brooks, S., Prezant, D. J., Banauch, G. I. and Nemery, B. (2004). "World Trade Center dust and airway reactivity." Am J Respir Crit Care Med 169(7): 883-884; author reply 884-885.

Comment on persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center.

Fireman, E. M., Lerman, Y., Ganor, E., Greif, J., Fireman-Shoresh, S., Lioy, P. J., Banauch, G. I., Weiden, M., Kelly, K. J. and Prezant, D. J. (2004). "Induced sputum assessment in New York City firefighters exposed to World Trade Center dust." Environ Health Perspect 112(15): 1564-1569.

New York City Firefighters (FDNY-FFs) were exposed to particulate matter and combustion/pyrolysis products during and after the World Trade Center (WTC) collapse. Ten months after the collapse, induced sputum (IS) samples were obtained from 39 highly exposed FDNY-FFs (caught in the dust cloud during the collapse on 11 September 2001) and compared to controls to determine whether a unique pattern of inflammation and particulate matter deposition, compatible with WTC dust, was present. Control subjects were 12 Tel-Aviv, Israel, firefighters (TA-FFs) and 8 Israeli healthcare workers who were not exposed to WTC dust. All controls volunteered for this study, had never smoked, and did not have respiratory illness. IS was processed by conventional methods. Retrieved cells were differentially counted, and metalloproteinase-9 (MMP-9), particle size distribution (PSD), and mineral composition were measured. Differential cell counts of FDNY-FF IS differed from those of health care worker controls ($p < 0.05$) but not from those of TA-FFs. Percentages of neutrophils and eosinophils increased with greater intensity of WTC exposure (< 10 workdays or greater than or equal to 10 workdays; neutrophils $p = 0.046$; eosinophils $p = 0.038$). MMP-9 levels positively correlated to neutrophil counts ($p = 0.002$; $r = 0.449$). Particles were larger and more irregularly shaped in FDNY-FFs (1-50 microm; zinc, mercury, gold, tin, silver) than in TA-FFs (1-10 microm; silica, clays). PSD was similar to that of WTC dust samples. In conclusion, IS from highly exposed FDNY-FFs demonstrated inflammation, PSD, and particle composition that was different from nonexposed controls and consistent with WTC dust exposure.

2005

Banauch, G. I., Dhala, A., Alleyne, D., Alva, R., Santhyadka, G., Krasko, A., Weiden, M., Kelly, K. J. and Prezant,

D. J. (2005). "Bronchial hyperreactivity and other inhalation lung injuries in rescue/recovery workers after the World Trade Center collapse." Crit Care Med **33**(1 Suppl): S102-106.

BACKGROUND: The collapse of the World Trade Center (WTC) on September 11, 2001 created a large-scale disaster site in a dense urban environment. In the days and months thereafter, thousands of rescue/recovery workers, volunteers, and residents were exposed to a complex mixture of airborne pollutants. METHODS: We review current knowledge of aerodigestive inhalation lung injuries resulting from this complex exposure and present new data on the persistence of nonspecific bronchial hyperreactivity (methacholine PC20 < or =8 mg/mL) in a representative sample of 179 Fire Department of the City of New York (FDNY) rescue workers stratified by exposure intensity (according to arrival time) who underwent challenge testing at 1, 3, 6, and 12 months post-collapse. RESULTS: Aerodigestive tract inflammatory injuries, such as declines in pulmonary function, reactive airways dysfunction syndrome (RADS), asthma, reactive upper airways dysfunction syndrome (RUDS), gastroesophageal reflux disease (GERD), and rare cases of inflammatory pulmonary parenchymal diseases, have been documented in WTC rescue/recovery workers and volunteers. In FDNY rescue workers, we found persistent hyperreactivity associated with exposure intensity, independent of airflow obstruction. One year post-collapse, 23% of highly exposed subjects were hyperreactive as compared with only 11% of moderately exposed and 4% of controls. At 1 yr, 16% met the criteria for RADS. CONCLUSIONS: While it is too early to ascertain all of the long-term effects of WTC exposures, continued medical monitoring and treatment is needed to help those exposed and to improve our prevention, diagnosis, and treatment protocols for future disasters.

Banauch, G. I., Dhala, A. and Prezant, D. J. (2005). "Pulmonary disease in rescue workers at the World Trade Center site." Curr Opin Pulm Med **11**(2): 160-168.

PURPOSE OF REVIEW: The catastrophic collapse of the World Trade Center (WTC) towers on September 11, 2001 created a large-scale disaster site in a densely populated urban environment. Over the ensuing months, tens of thousands of rescue, recovery and cleanup workers, volunteers, and residents of the adjacent community were exposed to a complex mixture of airborne pollutants. This review focuses on currently described respiratory syndromes, symptoms, and physiologic derangements in WTC rescue, recovery, and cleanup workers, discusses potential long-term effects on respiratory health, and draws parallels to community findings. RECENT FINDINGS: Detailed qualitative and quantitative analyses of airborne pollutants with their changing composition during initial rescue/recovery and subsequent cleanup have been published. Major concerns include persistent aerodigestive tract inflammatory syndromes, such as reactive airways dysfunction syndrome (RADS), reactive upper airways dysfunction syndrome (RUDS), gastroesophageal reflux disease (GERD), and inflammatory pulmonary parenchymal syndromes, as well as respiratory tract and nonrespiratory malignancies. Aerodigestive tract inflammatory syndromes have now been documented in WTC exposed occupational groups, and syndrome incidence has been linked to WTC airborne pollutant exposure intensity. Community based investigations have yielded similar findings. SUMMARY: While it is too early to ascertain long-term effects of WTC dust exposure, current studies already demonstrate a definite link between exposure to WTC-derived airborne pollutants and respiratory disease, both in the occupational and the community setting. A better understanding of causes and effects of this exposure will help in developing appropriate preventative tools for rescue workers in future disasters.

2006

Bars, M. P., Banauch, G. I., Appel, D., Andreachi, M., Mouren, P., Kelly, K. J. and Prezant, D. J. (2006). ""Tobacco Free With FDNY": the New York City Fire Department World Trade Center Tobacco Cessation Study." Chest **129**(4): 979-987.

CONTEXT: After the World Trade Center (WTC) collapse, 15% (1,767) of rescue workers from the Fire Department of the City of New York (FDNY) considered themselves to be current cigarette smokers. Post-WTC collapse, 98% reported acute respiratory symptoms, and 81% reported health concerns. Nonetheless, 29% of current smokers increased tobacco use, and 23% of ex-smokers resumed cigarette smoking. OBJECTIVE: To determine the effect of a comprehensive tobacco-cessation program using combination tobacco-dependency treatment medications adjusted to the individual's daily tobacco use. DESIGN: FDNY cigarette smokers enrolled in "Tobacco Free With FDNY," a no-cost quit-smoking program providing counseling, support, and medications. At the end of the 3-month treatment phase and at the 6-month and 12-month follow-up visits, abstinence rates were confirmed by expired carbon monoxide levels or by the

verification of a household member. SETTING: FDNY Bureau of Health Services between August 1, 2002 and October 30, 2002. PARTICIPANTS: A total of 220 current cigarette smokers from the FDNY. RESULTS: At study enrollment, the mean (+/- SD) tobacco use was 20 +/- 7 cigarettes per day, and the mean tobacco dependency, as assessed by a modified Fagerstrom test score, was 6.7 +/- 2.5 (maximum score, 10). Based on tobacco use, 20% of enrollees used three types of nicotine medications, 64% used two types, 14% used one type, and 3% used no medications. Additionally, 14% of enrollees used bupropion sustained release. The confirmed continuous abstinence rates were 47%, 36%, and 37%, respectively, after 3 months of treatment and at the 6-month and 12-month follow-up. Abstinence rates did not correlate with the history of tobacco use but correlated inversely with tobacco dependency. Adverse events and maximal nicotine medication use were unrelated, and no one experienced a serious adverse event. CONCLUSION: Tobacco dependency treatment using combination nicotine medications is effective and safe. Future studies should consider the following: (1) both history of tobacco use and withdrawal symptoms to determine the number and dose of nicotine medications; and (2) continuing combination treatment for > 3 months.

Banauch, G. I., Hall, C., Weiden, M., Cohen, H. W., Aldrich, T. K., Christodoulou, V., Arcentales, N., Kelly, K. J. and Prezant, D. J. (2006). "Pulmonary function after exposure to the World Trade Center collapse in the New York City Fire Department." Am J Respir Crit Care Med **174**(3): 312-319.

RATIONALE: On September 11, 2001, the World Trade Center collapse created an enormous urban disaster site with high levels of airborne pollutants. First responders, rescue and recovery workers, and residents have since reported respiratory symptoms and developed pulmonary function abnormalities. OBJECTIVES: To quantify respiratory health effects of World Trade Center exposure in the New York City Fire Department. MEASUREMENTS: Longitudinal study of pulmonary function in 12,079 New York City Fire Department rescue workers employed on or before 09/11/2001. Between 01/01/1997 and 09/11/2002, 31,994 spirometries were obtained and the FEV(1) and FVC were analyzed for differences according to estimated World Trade Center exposure intensity. Adjusted average FEV(1) during the first year after 09/11/2001 was compared with the 5 yr before 09/11/2001. Median time between 09/11/2001 and a worker's first spirometry afterwards was 3 mo; 90% were assessed within 5 mo. MAIN RESULTS: World Trade Center-exposed workers experienced a substantial reduction in adjusted average FEV(1) during the year after 09/11/2001 (372 ml; 95% confidence interval, 364-381 ml; $p < 0.001$) This exposure-related FEV(1) decrement equaled 12 yr of aging-related FEV(1) decline. Moreover, exposure intensity assessed by initial arrival time at the World Trade Center site correlated linearly with FEV(1) reduction in an exposure intensity-response gradient ($p = 0.048$). Respiratory symptoms also predicted a further FEV(1) decrease ($p < 0.001$). Similar findings were observed for adjusted average FVC. CONCLUSIONS: World Trade Center exposure produced a substantial reduction in pulmonary function in New York City Fire Department rescue workers during the first year after 09/11/2001.

Lioy, P. J., Pellizzari, E. and Prezant, D. (2006). "The World Trade Center aftermath and its effects on health: understanding and learning through human-exposure science." Environ Sci Technol **40**(22): 6876-6885.

2007

Izbicki, G., Chavko, R., Banauch, G. I., Weiden, M. D., Berger, K. I., Aldrich, T. K., Hall, C., Kelly, K. J. and Prezant, D. J. (2007). "World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers." Chest **131**(5): 1414-1423.

BACKGROUND: Previous reports suggest that sarcoidosis occurs with abnormally high frequency in firefighters. We sought to determine whether exposure to World Trade Center (WTC) "dust" during the collapse and rescue/recovery effort increased the incidence of sarcoidosis or "sarcoid-like" granulomatous pulmonary disease (SLGPD). METHODS: During the 5 years after the WTC disaster, enrollees in the Fire Department of New York (FDNY) WTC monitoring and treatment programs who had chest radiograph findings suggestive of sarcoidosis underwent evaluation, including the following: chest CT imaging, pulmonary function, provocative challenge, and biopsy. Annual incidence rates were compared to the 15 years before the WTC disaster. RESULTS: After WTC dust exposure, pathologic evidence consistent with new-onset sarcoidosis was found in 26 patients: all 26 patients had intrathoracic adenopathy, and 6 patients (23%) had extrathoracic disease. Thirteen patients were identified during the first year after WTC dust exposure (incidence rate, 86/100,000), and 13 patients were identified during the next 4 years (average annual incidence rate, 22/100,000; as compared to 15/100,000 during the 15 years before the WTC

disaster). Eighteen of 26 patients (69%) had findings consistent with asthma. Eight of 21 patients (38%) agreeing to challenge testing had airway hyperreactivity (AHR), findings not seen in FDNY sarcoidosis patients before the WTC disaster. CONCLUSION: After the WTC disaster, the incidence of sarcoidosis or SLGPD was increased among FDNY rescue workers. This new information about the early onset of WTC-SLGPD and its association with asthma/AHR has important public health consequences for disease prevention, early detection, and treatment following environmental/occupational exposures.

Alvarez, J., Rosen, C., Davis, K., Smith, G. and Corrigan, M. (2007). ""Stay connected": psychological services for retired firefighters after 11 September 2001." Prehosp Disaster Med **22**(1): 49-54.

INTRODUCTION: A large number of firefighters retired after 11 September 2001. These retirees were confronted with multiple challenges, including grief, trauma-related physical injuries and psychological distress, difficulties related to the transition of their roles, and deterioration of social support. OBJECTIVE: The Fire Department of New York (FDNY) Counseling Service Unit's "Stay Connected" Program designed and implemented after 11 September 2001 is described in this report. This unique program was designed to use a combination of peer outreach and professional counseling to address the mental health needs of retiring firefighters and their families. METHODS: Descriptive information about the intervention program was gathered through semi-structured interviews with Counseling Service Unit staff. Client satisfaction surveys were collected during three six-week periods. RESULTS: Quantitative data indicate that clients rated their overall satisfaction with the clerical and counseling staff a perfect 4 out of 4. The report of their overall satisfaction with the services also was nearly at ceiling (3.99 out 4). The perceived helpfulness of the services in resolving the problems experienced by the clients increased significantly over time. Qualitative data indicate that peer involvement and intensive community outreach, i.e., social events, wellness activities, and classes, were integral to the success of the intervention. CONCLUSIONS: This project provided valuable lessons about how to develop and implement a "culturally competent" intervention program for public safety workers retiring after a disaster. Creative, proactive, non-traditional outreach efforts and leveraging peers for credibility and support were particularly important.

2008

Friedman, S., Cone, J., Eros-Sarnyai, M., Prezant, D., Hoz, R. d. l., Clark, N., Milek, D., SLevin and Gillio, R. (2008). "Clinical guidelines for adults exposed to the World Trade Center disaster." City Health Information **27**(6): 41-54.

Prezant, D. J. (2008). "World Trade Center Cough Syndrome and its treatment." Lung **186 Suppl 1**: S94-102.

To date, the main respiratory health consequence from the collapse of the World Trade Center (WTC) on September 11, 2001 has been the "WTC Cough Syndrome" (chronic rhinosinusitis, asthma, and/or bronchitis, often complicated by gastroesophageal reflux dysfunction). Syndrome incidence and severity have been linked to WTC dust exposure intensity. While it is too early to ascertain long-term effects of WTC dust exposure, effective treatment guidelines have been designed through a collaborative effort by the three established centers of excellence for WTC medical monitoring and treatment and the WTC Registry. These treatment recommendations are described here.

Banauch, G. I., Izbicki, G., Christodoulou, V., Weiden, M. D., Webber, M. P., Cohen, H., Gustave, J., Chavko, R., Aldrich, T. K., Kelly, K. J. and Prezant, D. J. (2008). "Trial of prophylactic inhaled steroids to prevent or reduce pulmonary function decline, pulmonary symptoms, and airway hyperreactivity in firefighters at the world trade center site." Disaster Med Public Health Prep **2**(1): 33-39.

BACKGROUND: Inhaled corticosteroids (ICS) are the most effective anti-inflammatory treatment for asthmatics. This trial evaluated the effects of prophylactic ICS in firefighters exposed to the World Trade Center disaster. METHODS: Inhaled budesonide via a dry powder inhaler (Pulmicort Turbuhaler, AstraZeneca, Wilmington, DE) was offered on-site to New York City firefighters between September 18 and 25, 2001. One to 2 years later, firefighters (n = 64) who completed 4 weeks of daily ICS treatment were evaluated and compared with an age- and exposure-matched comparison group (n = 72) who did not use ICS. RESULTS: When spirometry results at the final visit were compared with those from the weeks following the 9/11 disaster, the treatment group had a greater increase in forced vital capacity (P = .009) and possibly a slower decline in forced expiratory volume at 1 second (P = .11), as well as a greater improvement in perceived well-being as assessed by the St George's Respiratory Questionnaire (P < .01).

There was no difference in airway hyperreactivity and no evidence of adverse effects from ICS. CONCLUSIONS: Because the potential for hazardous exposures is great at many disasters, disease prevention programs based on environmental controls and respiratory protection are warranted immediately. Our results suggest that, pending further study with a larger sample, prophylactic ICS should be considered, along with respiratory protection, to minimize possible lung insult.

Prezant, D. J., Levin, S., Kelly, K. J. and Aldrich, T. K. (2008). "Upper and lower respiratory diseases after occupational and environmental disasters." Mt Sinai J Med **75**(2): 89-100.

Respiratory consequences from occupational and environmental disasters are the result of inhalation exposures to chemicals, particulate matter (dusts and fibers) and/or the incomplete products of combustion that are often liberated during disasters such as fires, building collapses, explosions and volcanoes. Unfortunately, experience has shown that environmental controls and effective respiratory protection are often unavailable during the first days to week after a large-scale disaster. The English literature was reviewed using the key words-disaster and any of the following: respiratory disease, pulmonary, asthma, bronchitis, sinusitis, pulmonary fibrosis, or sarcoidosis. Respiratory health consequences after aerosolized exposures to high-concentrations of particulates and chemicals can be grouped into 4 major categories: 1) upper respiratory disease (chronic rhinosinusitis and reactive upper airways dysfunction syndrome), 2) lower respiratory diseases (reactive [lower] airways dysfunction syndrome, irritant-induced asthma, and chronic obstructive airways diseases), 3) parenchymal or interstitial lung diseases (sarcoidosis, pulmonary fibrosis, and bronchiolitis obliterans, and 4) cancers of the lung and pleura. This review describes several respiratory consequences of occupational and environmental disasters and uses the World Trade Center disaster to illustrate in detail the consequences of chronic upper and lower respiratory inflammation.

2009

Corrigan, M., McWilliams, R., Kelly, K. J., Niles, J., Cammarata, C., Jones, K., Wartenberg, D., Hallman, W. K., Kipen, H. M., Glass, L., Schorr, J. K., Feirstein, I. and Prezant, D. J. (2009). "A computerized, self-administered questionnaire to evaluate posttraumatic stress among firefighters after the World Trade Center collapse." Am J Public Health **99 Suppl 3**: S702-709.

OBJECTIVES: We sought to determine the frequency of psychological symptoms and elevated posttraumatic stress disorder (PTSD) risk among New York City firefighters after the World Trade Center (WTC) attack and whether these measures were associated with Counseling Services Unit (CSU) use or mental health-related medical leave over the first 2.5 years after the attack.
METHODS: Shortly after the WTC attack, a computerized, binary-response screening questionnaire was administered. Exposure assessment included WTC arrival time and "loss of a co-worker while working at the collapse." We determined elevated PTSD risk using thresholds derived from Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, and a sensitivity-specificity analysis.
RESULTS: Of 8487 participants, 76% reported at least 1 symptom, 1016 (12%) met criteria for elevated PTSD risk, and 2389 (28%) self-referred to the CSU, a 5-fold increase from before the attack. Higher scores were associated with CSU use, functional job impairment, and mental health-related medical leave. Exposure-response gradients were significant for all outcomes.
CONCLUSIONS: This screening tool effectively identified elevated PTSD risk, higher CSU use, and functional impairment among firefighters and therefore may be useful in allocating scarce postdisaster mental health resources.

Webber, M. P., Gustave, J., Lee, R., Niles, J. K., Kelly, K., Cohen, H. W. and Prezant, D. J. (2009). "Trends in respiratory symptoms of firefighters exposed to the world trade center disaster: 2001-2005." Environ Health Perspect **117**(6): 975-980.

BACKGROUND: Respiratory symptoms, either newly reported after the World Trade Center (WTC) disaster on 11 September 2001 (9/11) or increased in severity, have been well documented in WTC-exposed workers and New York City residents. However, considerable uncertainty exists over the persistence of symptoms. OBJECTIVES: In this study, our goals were to describe trends in post-9/11 respiratory and gastro-esophageal reflux disease (GERD) symptoms in WTC-exposed firefighters and to examine symptom progression in the cohort that completed both year 1 and year 4 questionnaires.
METHODS: We analyzed questionnaire responses from 10,378 firefighters in yearly intervals, from 2 October 2001 to 11 September 2005, defining exposure based on arrival time at the WTC site. For the

cohort of 3,722 firefighters who completed the two questionnaires, we also calculated exposure duration summing months of work at the site. RESULTS: In cross-sectional analyses, the prevalence of dyspnea, wheeze, rhinosinusitis, and GERD remained relatively stable, whereas cough and sore throat declined, especially between 1 and 2 years post-9/11. We found a dose-response relationship between arrival time and symptoms in all years ($p < 0.01$). Logistic models of symptoms at year 4 in the cohort demonstrated independent effects of earlier arrival and longer work duration: each additional month of work increased the odds of symptoms 8-11%. CONCLUSIONS: Protracted work exposures increased the odds of respiratory and GERD symptoms 4 years later. In most large disasters, exposures may be unavoidable during the rescue phase, but our data strongly suggest the need to minimize additional exposures during recovery and cleanup phases.

2010

Chiu, S., Webber, M. P., Zeig-Owens, R., Gustave, J., Lee, R., Kelly, K. J., Rizzotto, L. and Prezant, D. J. (2010). "Validation of the Center for Epidemiologic Studies Depression Scale in screening for major depressive disorder among retired firefighters exposed to the World Trade Center disaster." J Affect Disord **121**(3): 212-219.

BACKGROUND: We evaluated the performance of a modified Center of Epidemiologic Studies Depression Scale (CES-D-m), which captured symptoms in the past month, in comparison to the Diagnostic Interview Schedule (DIS) in identification of major depressive disorder (MDD) in World Trade Center (WTC)-exposed retired Fire Department, City of New York (FDNY) firefighters. METHODS: From 12/2005 to 7/2007, FDNY enrolled retired firefighters in its Medical Monitoring and Treatment Program. All participants completed the CES-D-m and the DIS on the same day. Sensitivity, specificity, receiver operating characteristic (ROC) curves, and Youden's index were used to assess properties of the CES-D-m. Multivariate logistic regression analyses were also used. RESULTS: 7% of 1915 retired male firefighters were diagnosed with MDD using the DIS. Using the most common CES-D cutoff score of 16, the prevalence of elevated risk was 36%, which declined to 23% using a cutoff score of 22, as determined by Youden's index. At 22, CES-D-m sensitivity was 0.84, specificity was 0.82, and the area under the ROC curve was 0.89 relative to DIS MDD diagnosis. LIMITATIONS: Participants were more likely than non-participants to live in the New York City area. CONCLUSIONS: This is the first study of WTC rescue/recovery workers to assess the performance of a one-month version of the CES-D. The CES-D-m performed well in identifying those at elevated risk. Since diagnostic follow-up is time consuming and costly, it is important to correctly distinguish those at elevated risk using a screening tool that has been validated in the population under study.

Weiden, M. D., Ferrier, N., Nolan, A., Rom, W. N., Comfort, A., Gustave, J., Zeig-Owens, R., Zheng, S., Goldring, R. M., Berger, K. I., Cosenza, K., Lee, R., Webber, M. P., Kelly, K. J., Aldrich, T. K. and Prezant, D. J. (2010). "Obstructive airways disease with air trapping among firefighters exposed to World Trade Center dust." Chest **137**(3): 566-574.

BACKGROUND: The World Trade Center (WTC) collapse produced a massive exposure to respirable particulates in New York City Fire Department (FDNY) rescue workers. This group had spirometry examinations pre-September 11, 2001, and post-September 11, 2001, demonstrating declines in lung function with parallel declines in FEV(1) and FVC. To date, the underlying pathophysiologic cause for this has been open to question. METHODS: Of 13,234 participants in the FDNY-WTC Monitoring Program, 1,720 (13%) were referred for pulmonary subspecialty evaluation at a single institution. Evaluation included 919 full pulmonary function tests, 1,219 methacholine challenge tests, and 982 high-resolution chest CT scans. RESULTS: At pulmonary evaluation (median 34 months post-September 11, 2001), median values were FEV(1) 93% predicted (interquartile range [IQR], 83%-101%), FVC 98% predicted (IQR, 89%-106%), and FEV(1)/FVC 0.78 (IQR, 0.72-0.82). The residual volume (RV) was 123% predicted (IQR, 106%-147%) with nearly all participants having normal total lung capacity, functional residual capacity, and diffusing capacity of carbon monoxide. Also, 1,051/1,720 (59%) had obstructive airways disease based on at least one of the following: FEV(1)/FVC, bronchodilator responsiveness, hyperreactivity, or elevated RV. After adjusting for age, gender, race, height and weight, and tobacco use, the decline in FEV(1) post-September 11, 2001, was significantly correlated with increased RV percent predicted ($P < .0001$), increased bronchodilator responsiveness ($P < .0001$), and increased hyperreactivity ($P = .0056$). CT scans demonstrated bronchial wall thickening that was significantly associated with the decline in FEV(1) post-September 11, 2001 ($P = .024$), increases in hyperreactivity ($P < .0001$), and

increases in RV (P < .0001). Few had evidence for interstitial disease. CONCLUSIONS: Airways obstruction was the predominant physiologic finding underlying the reduction in lung function post-September 11, 2001, in FDNY WTC rescue workers presenting for pulmonary evaluation.

Aldrich, T. K., Gustave, J., Hall, C. B., Cohen, H. W., Webber, M. P., Zeig-Owens, R., Cosenza, K., Christodoulou, V., Glass, L., Al-Othman, F., Weiden, M. D., Kelly, K. J. and Prezant, D. J. (2010). "Lung function in rescue workers at the World Trade Center after 7 years." N Engl J Med **362**(14): 1263-1272.

BACKGROUND: The terrorist attacks on the World Trade Center on September 11, 2001, exposed thousands of Fire Department of New York City (FDNY) rescue workers to dust, leading to substantial declines in lung function in the first year. We sought to determine the longer-term effects of exposure. METHODS: Using linear mixed models, we analyzed the forced expiratory volume in 1 second (FEV(1)) of both active and retired FDNY rescue workers on the basis of spirometry routinely performed at intervals of 12 to 18 months from March 12, 2000, to September 11, 2008. RESULTS: Of the 13,954 FDNY workers who were present at the World Trade Center between September 11, 2001, and September 24, 2001, a total of 12,781 (91.6%) participated in this study, contributing 61,746 quality-screened spirometric measurements. The median follow-up was 6.1 years for firefighters and 6.4 years for emergency-medical-services (EMS) workers. In the first year, the mean FEV(1) decreased significantly for all workers, more for firefighters who had never smoked (a reduction of 439 ml; 95% confidence interval [CI], 408 to 471) than for EMS workers who had never smoked (a reduction of 267 ml; 95% CI, 263 to 271) (P<0.001 for both comparisons). There was little or no recovery in FEV(1) during the subsequent 6 years, with a mean annualized reduction in FEV(1) of 25 ml per year for firefighters and 40 ml per year for EMS workers. The proportion of workers who had never smoked and who had an FEV(1) below the lower limit of the normal range increased during the first year, from 3% to 18% for firefighters and from 12% to 22% for EMS workers, stabilizing at about 13% for firefighters and 22% for EMS workers during the subsequent 6 years. CONCLUSIONS: Exposure to World Trade Center dust led to large declines in FEV(1) for FDNY rescue workers during the first year. Overall, these declines were persistent, without recovery over the next 6 years, leaving a substantial proportion of workers with abnormal lung function.

Rom, W. N., Reibman, J., Rogers, L., Weiden, M. D., Oppenheimer, B., Berger, K., Goldring, R., Harrison, D. and Prezant, D. (2010). "Emerging exposures and respiratory health: World Trade Center dust." Proc Am Thorac Soc **7**(2): 142-145.

The attack on the World Trade Center (WTC) on 9/11/2001 produced a massive dust cloud with acute exposure, and the rubble pile burning over 3 months exposed more than 300,000 residents, rescue workers, and clean-up workers. Firefighters in the New York City Fire Department had significant respiratory symptoms characterized by cough, dyspnea, gastroesophageal reflux, and nasal stuffiness with a significant 1-year decline in FVC and FEV(1). Bronchial hyperreactivity measured by methacholine challenge correlated with bronchial wall thickening on CT scans. Compared with the NHANES III data for FVC and FEV(1), 32% of 2,000 WTC dust-exposed residents and clean-up workers were below the lower 5th percentile. The most common abnormality was a low FVC pattern, a finding similar to that also described for individuals in rescue and recovery activities. Among those complaining of respiratory symptoms and normal spirometry, almost half had abnormalities detected with impedance oscillometry consistent with distal airways' disease. Follow-up with the WTC Health Registry and the WTC Environmental Health Center will help discern whether treatment with anti-inflammatory medications or bronchodilators in those with respiratory symptoms may prevent the development of chronic obstructive pulmonary disease.

Berninger, A., Webber, M. P., Cohen, H. W., Gustave, J., Lee, R., Niles, J. K., Chiu, S., Zeig-Owens, R., Soo, J., Kelly, K. and Prezant, D. J. (2010). "Trends of elevated PTSD risk in firefighters exposed to the World Trade Center disaster: 2001-2005." Public Health Rep **125**(4): 556-566.

OBJECTIVES: We identified trends in the prevalence of elevated posttraumatic stress disorder (PTSD) risk as determined by the Fire Department of the City of New York (FDNY)-modified PTSD Checklist in World Trade Center (WTC)-exposed firefighters. We also examined trends in relation to WTC exposure, social support, change in recreational activities, and functional health. METHODS: We analyzed 16,826 questionnaires from 10,074 firefighters in yearly intervals, from September 12, 2001, to September 11, 2005. RESULTS: The prevalence of elevated PTSD risk increased over time, from 9.8% in year 1 to 10.6% in year 4 (p < 0.0001). Earliest arrival at the WTC site (odds ratio [OR] = 6.0; 95% confidence interval [CI] 4.4, 8.3), prolonged work at the site (OR = 2.0; 95% CI 1.8, 2.3), providing supervision without previous

supervisory experience (OR = 4.1; 95% CI 2.8, 6.1), and retirement due to a WTC-related disability (OR=1.3; 95% CI 1.1, 1.5) were associated with ever having elevated PTSD risk. Difficulty functioning at home was strongly associated with elevated PTSD risk (ORs ranged from 17.0 [95% CI 14.5, 20.0] in year 1 to 26.7 [95% CI 20.3, 35.2] in year 3), as was difficulty functioning at work (ORs ranged from 12.1 [95% CI 10.2, 14.2] in year 1 to 23.0 [95% CI 14.6, 36.3] in year 2). CONCLUSIONS: Elevated PTSD risk was associated with exposure to the WTC site as well as functional impairment, and remained largely unabated during the first four years of the study. Screening for elevated PTSD risk may be useful in identifying those who could benefit from interventions during long-term follow-up, as well as in the immediate aftermath of disasters.

Banauch, G. I., Brantly, M., Izbicki, G., Hall, C., Shanske, A., Chavko, R., Santhyadka, G., Christodoulou, V., Weiden, M. D. and Prezant, D. J. (2010). "Accelerated spirometric decline in New York City firefighters with alpha(1)-antitrypsin deficiency." Chest **138**(5): 1116-1124.

BACKGROUND: On September 11, 2001, the World Trade Center (WTC) collapse caused massive air pollution, producing variable amounts of lung function reduction in the New York City Fire Department (FDNY) rescue workforce. alpha(1)-Antitrypsin (AAT) deficiency is a risk factor for obstructive airway disease. METHODS: This prospective, longitudinal cohort study of the first 4 years post-September 11, 2001, investigated the influence of AAT deficiency on adjusted longitudinal spirometric change (FEV(1)) in 90 FDNY rescue workers with WTC exposure. Workers with protease inhibitor (Pi) Z heterozygosity were considered moderately AAT deficient. PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity was considered mild deficiency, and PiM homozygosity was considered normal. Alternately, workers had low AAT levels if serum AAT was </= 20 mumol/L. RESULTS: In addition to normal aging-related decline (37 mL/y), significant FEV(1) decline accelerations developed with increasing AAT deficiency severity (110 mL/y for moderate and 32 mL/y for mild) or with low AAT serum levels (49 mL/y). Spirometric rates pre-September 11, 2001, did not show accelerations with AAT deficiency. Among workers with low AAT levels, cough persisted in a significant number of participants at 4 years post-September 11, 2001. CONCLUSIONS: FDNY rescue workers with AAT deficiency had significant spirometric decline accelerations and persistent airway symptoms during the first 4 years after WTC exposure, representing a novel gene-by-environment interaction. Clinically meaningful decline acceleration occurred even with the mild serum AAT level reductions associated with PiS heterozygosity (without concomitant PiZ heterozygosity).

Berninger, A., Webber, M. P., Weakley, J., Gustave, J., Zeig-Owens, R., Lee, R., Al-Othman, F., Cohen, H. W., Kelly, K. and Prezant, D. J. (2010). "Quality of life in relation to upper and lower respiratory conditions among retired 9/11-exposed firefighters with pulmonary disability." Qual Life Res **19**(10): 1467-1476.

PURPOSE: To examine health-related quality of life (HRQoL) and World Trade Center (WTC) cough syndrome conditions in male firefighters who retired due to a 9/11-related pulmonary disability. METHODS: From 3/1/2008 to 1/31/2009, we contacted 275 disability-retired firefighters and compared their HRQoL and current aerodigestive conditions to those from WTC-exposed non-disabled retired and active firefighters. Relationships between HRQoL and explanatory variable(s) were examined using multivariable linear regression models. RESULTS: Mean physical component summary (PCS) scores were lowest in disabled retirees compared with non-disabled retirees and actives: 36.4 (9.6), 49.4 (8.7), and 53.1 (5.1), respectively ($P < 0.0001$). Mean mental component summary (MCS) scores were closer: 44.5 (11.9), 48.1 (8.5), and 48.7 (7.4), respectively ($P < 0.0001$). In multivariable models, after adjustment for many factors, PCS scores were not associated with early WTC arrival, but were inversely associated with disability retirement and all WTC cough syndrome conditions. MCS scores were inversely associated with early WTC arrival and most WTC cough syndrome conditions, but were not associated with disability retirement. CONCLUSION: WTC cough syndrome conditions predict lower HRQoL scores even 8 years after exposure, independent of retirement status. These data suggest that monitoring physical conditions of individuals with occupational exposures might help identify those at risk for impaired HRQoL.

Berninger, A., Webber, M. P., Niles, J. K., Gustave, J., Lee, R., Cohen, H. W., Kelly, K., Corrigan, M. and Prezant, D. J. (2010). "Longitudinal study of probable post-traumatic stress disorder in firefighters exposed to the World Trade Center disaster." Am J Ind Med **53**(12): 1177-1185.

BACKGROUND: Symptoms of post-traumatic stress disorder (PTSD) have been reported even years after

the terrorist attacks of September 11, 2001 (9/11). METHODS: We used screening tools to assess the prevalence of probable PTSD in 9/11-exposed firefighters at two time points, within 6 months of 9/11 (baseline) and 3-4 years post-disaster (follow-up). RESULTS: Five thousand six hundred fifty-six individuals completed assessments at both times. 15.5% reported probable PTSD post-9/11, 8.6% at baseline and 11.1% at follow-up, on average 2.9 (SD 0.5) years later. Analyses revealed that nearly half of all probable PTSD occurred as delayed onset (absent baseline, present follow-up). Compared with the resilient group (no probable PTSD at either time), probable PTSD at baseline, and delayed onset at follow-up were each associated with concomitant functional impairment (OR 19.5 and 18.9), respectively. CONCLUSION: Similar percentages of firefighters met criteria for baseline and delayed onset probable PTSD at follow-up, years later. Both were associated with substantial functional impairment. Early risk identification could provide opportunities for mental health interventions before symptoms compromise work and social relationships.

2011

Webber, M. P., Lee, R., Soo, J., Gustave, J., Hall, C. B., Kelly, K. and Prezant, D. (2011). "Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers." Sleep Breath **15**(3): 283-294.

PURPOSE: World Trade Center (WTC)-exposed rescue/recovery workers continue to have high rates of gastroesophageal reflux disease (GERD), chronic rhinosinusitis, and posttraumatic stress disorder (PTSD) symptoms. This study examines the relationship between these WTC-related conditions and being at high risk for obstructive sleep apnea (OSA). MATERIALS AND METHODS: The Fire Department of the City of New York (FDNY) performs periodic health evaluations on FDNY members every 12 to 18 months. Evaluations consist of physician examinations and self-administered health questionnaires, which, since 2005, have incorporated questions about sleep problems that were adapted from the Berlin Questionnaire. The study population consisted of 11,701 male firefighters and emergency medical service personnel. Incidence analyses were limited to a cohort (n = 4,576) who did not meet the criterion for being at high risk for OSA at baseline (between September 12, 2005 and September 8, 2006) and had at least one follow-up assessment, on average, 1.4 (+/-0.5) years later. RESULTS: The baseline prevalence of high risk for OSA was 36.5%. By follow-up, 16.9% of those not at high risk initially became at high risk for OSA. In multivariable logistic regression models predicting incident high risk for OSA, independent predictors included: earlier time of arrival at the WTC site, GERD, chronic rhinosinusitis, PTSD symptoms, self-assessed fair/poor health, low body mass index (BMI < 18.5 kg/m(2)), and, as expected, BMI > 30 kg/m(2) and weight gain of >/=10 lb (4.5 kg). CONCLUSIONS: We found significant associations between being at high risk for OSA and common WTC-related conditions, although the responsible causative mechanisms remain unknown. Since the etiology of OSA is likely multifactorial, improvement may require successful treatment of both OSA and its comorbid conditions.

Chiu, S., Webber, M. P., Zeig-Owens, R., Gustave, J., Lee, R., Kelly, K. J., Rizzotto, L., McWilliams, R., Schorr, J. K., North, C. S. and Prezant, D. J. (2011). "Performance characteristics of the PTSD Checklist in retired firefighters exposed to the World Trade Center disaster." Ann Clin Psychiatry **23**(2): 95-104.

BACKGROUND: Since the World Trade Center (WTC) attacks on September 11, 2001, the Fire Department, City of New York Monitoring Program has provided physical and mental health screening services to rescue/recovery workers. This study evaluated performance of the self-report PTSD Checklist (PCL) as a screening tool for risk of posttraumatic stress disorder (PTSD) in firefighters who worked at Ground Zero, compared with the interviewer-administered Diagnostic Interview Schedule (DIS). METHODS: From December 2005 to July 2007, all retired firefighter enrollees completed the PCL and DIS on the same day. Sensitivity, specificity, receiver operating characteristic (ROC) curves, and Youden index (J) were used to assess properties of the PCL and to identify an optimum cutoff score. RESULTS: Six percent of 1,915 retired male firefighters were diagnosed with PTSD using the DIS to assess DSM-IV criteria. Depending on the PCL cutoff, the prevalence of elevated risk relative to DSM-IV criteria varied from 16% to 22%. Youden index identified an optimal cutoff score of 39, in contrast with the frequently recommended cutoff of 44. At 39, PCL sensitivity was 0.85, specificity was 0.82, and the area under the ROC curve was 0.91 relative to DIS PTSD diagnosis. CONCLUSIONS: This is the first study to validate the PCL in retired firefighters and determine the optimal cutoff score to maximize opportunities for PTSD diagnosis and treatment.

Chiu, S., Niles, J. K., Webber, M. P., Zeig-Owens, R., Gustave, J., Lee, R., Rizzotto, L., Kelly, K. J., Cohen, H. W. and Prezant, D. J. (2011). "Evaluating risk factors and possible mediation effects in posttraumatic depression and posttraumatic stress disorder comorbidity." Public Health Rep **126**(2): 201-209.

OBJECTIVES: On September 11, 2001 (9/11), attacks on the World Trade Center (WTC) killed 341 Fire Department of the City of New York (FDNY) firefighters and injured hundreds more. Previous WTC-related studies reported high rates of comorbid depression and posttraumatic stress disorder (PTSD), identifying disability retirement, alcohol use, and early arrival at the WTC site as correlates. However, those studies did not evaluate risk factors that could have mediated the observed comorbidity. We identified unique risk factors for each condition in an effort to better understand comorbidity. METHODS: We screened retired WTC-exposed firefighters using self-administered questionnaires including the Center for Epidemiologic Studies Depression Scale, the Post Traumatic Stress Disorder Checklist, and the Alcohol Use Disorders Identification Test. We performed regression analyses to compare independent predictors of elevated depression and PTSD risk, and also tested a mediation hypothesis. RESULTS: From December 2005 to July 2007, 23% and 22% of 1,915 retirees screened positive for elevated depression and PTSD risk, respectively, with comorbidity > 70%. Controlling for comorbidity, we identified unique risk factors for (1) depression: problem alcohol use and (2) PTSD: early arrival at the WTC site. CONCLUSIONS: Our data support the premise that PTSD and depression are different responses to trauma with unique risk factors. The data also suggest a hypothesis that PTSD mediates the relationship between early WTC arrival and depression, while depression mediates the relationship between alcohol use and PTSD, a more complex relationship than shown in previous studies. Clinicians should consider these factors when evaluating patients for depression and PTSD.

Niles, J. K., Webber, M. P., Gustave, J., Cohen, H. W., Zeig-Owens, R., Kelly, K. J., Glass, L. and Prezant, D. J. (2011). "Comorbid trends in World Trade Center cough syndrome and probable posttraumatic stress disorder in firefighters." Chest **140**(5): 1146-1154.

BACKGROUND: We describe the relationship between World Trade Center (WTC) cough syndrome symptoms, pulmonary function, and symptoms consistent with probable posttraumatic stress disorder (PTSD) in WTC-exposed firefighters in the first year post-September 11, 2001 (baseline), and 3 to 4 years later (follow-up). METHODS: Five thousand three hundred sixty-three firefighters completed pulmonary function tests (PFTs) and questionnaires at both times. Relationships among WTC cough syndrome, probable PTSD, and PFTs were analyzed using simple and multivariable models. We also examined the effects of cofactors, including WTC exposure. RESULTS: WTC cough syndrome was found in 1,561 firefighters (29.1%) at baseline and 1,186 (22.1%) at follow-up, including 559 with delayed onset (present only at follow-up). Probable PTSD was found in 458 firefighters (8.5%) at baseline and 548 (10.2%) at follow-up, including 343 with delayed onset. Baseline PTSD symptom counts and probable PTSD were associated with WTC cough syndrome at baseline, at follow-up, and in those with delayed-onset WTC cough syndrome. Similarly, WTC cough syndrome symptom counts and WTC cough syndrome at baseline were associated with probable PTSD at baseline, at follow-up, and in those with delayed-onset probable PTSD. WTC arrival time and work duration were cofactors of both outcomes. A small but consistent association existed between pulmonary function and WTC cough syndrome, but none with PTSD. CONCLUSIONS: The study showed a moderate association between WTC cough syndrome and probable PTSD. The presence of one contributed to the likelihood of the other, even after adjustment for shared cofactors such as WTC exposure.

Niles, J. K., Webber, M. P., Gustave, J., Zeig-Owens, R., Lee, R., Glass, L., Weiden, M. D., Kelly, K. J. and Prezant, D. J. (2011). "The impact of the World Trade Center attack on FDNY firefighter retirement, disabilities, and pension benefits." Am J Ind Med **54**(9): 672-680.

BACKGROUND: Our goal was to examine the effect of the World Trade Center (WTC) attack and subsequent New York City Fire Department (FDNY) rescue/recovery activities on firefighter retirements. We also analyzed the financial impact associated with the increased number and proportion of service-connected "accidental" disability retirements on the FDNY pension system. METHODS: A total of 7,763 firefighters retired between 9/11/1994 and 9/10/2008. We compared the total number of retirements and the number and proportion of accidental disability retirements 7 years before and 7 years after the WTC attack. We categorized WTC-related accidental disability retirements by medical cause and worked with the New

York City Office of the Actuary to approximate the financial impact by cause. RESULTS: In the 7 years before 9/11 there were 3,261 retirements, 48% (1,571) of which were accidental disability retirements. In the 7 years after 9/11, there were 4,502 retirements, 66% (2,970) were accidental disability retirements, of which 47% (1,402) were associated with WTC-related injuries or illnesses. After 9/11, the increase in accidental disability retirements was, for the most part, due to respiratory-related illnesses. Additional increases were attributed to psychological-related illnesses and musculoskeletal injuries incurred at the WTC site. Pension benefits associated with WTC-related accidental disability retirements have produced an increased financial burden of over $826 million on the FDNY pension system. CONCLUSIONS: The WTC attacks affected the health of the FDNY workforce resulting in more post-9/11 retirements than expected, and a larger proportion of these retirees with accidental disability pensions.

Soo, J., Webber, M. P., Gustave, J., Lee, R., Hall, C. B., Cohen, H. W., Kelly, K. J. and Prezant, D. J. (2011). "Trends in probable PTSD in firefighters exposed to the World Trade Center disaster, 2001-2010." Disaster Med Public Health Prep **5 Suppl 2**: S197-203.

OBJECTIVE: We present the longest follow-up, to date, of probable posttraumatic stress disorder (PTSD) after the 2001 terrorist attacks on the World Trade Center (WTC) in New York City firefighters who participated in the rescue/recovery effort. METHODS: We examined data from 11,006 WTC-exposed firefighters who completed 40,672 questionnaires and reported estimates of probable PTSD by year from serial cross-sectional analyses. In longitudinal analyses, we used separate Cox models with data beginning from October 2, 2001, to identify variables associated with recovery from or delayed onset of probable PTSD. RESULTS: The prevalence of probable PTSD was 7.4% by September 11, 2010, and continued to be associated with early arrival at the WTC towers during every year of analysis. An increasing number of aerodigestive symptoms (hazard ratio [HR] 0.89 per symptom, 95% confidence interval [CI] 0.86-.93) and reporting a decrease in exercise, whether the result of health (HR 0.56 vs no change in exercise, 95% CI 0.41-.78) or other reasons (HR 0.76 vs no change in exercise, 95% CI 0.63-.92), were associated with a lower likelihood of recovery from probable PTSD. Arriving early at the WTC (HR 1.38 vs later WTC arrival, 95% CI 1.12-1.70), an increasing number of aerodigestive symptoms (HR 1.45 per symptom, 95% CI 1.40-1.51), and reporting an increase in alcohol intake since September 11, 2001 (HR 3.43 vs no increase in alcohol intake, 95% CI 2.67-4.43) were associated with delayed onset of probable PTSD. CONCLUSIONS: Probable PTSD continues to be associated with early WTC arrival even 9 years after the terrorist attacks. Concurrent conditions and behaviors, such as respiratory symptoms, exercise, and alcohol use also play important roles in contributing to PTSD symptoms.

Zeig-Owens, R., Webber, M. P., Hall, C. B., Schwartz, T., Jaber, N., Weakley, J., Rohan, T. E., Cohen, H. W., Derman, O., Aldrich, T. K., Kelly, K. and Prezant, D. J. (2011). "Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study." Lancet **378**(9794): 898-905.

BACKGROUND: The attacks on the World Trade Center (WTC) on Sept 11, 2001 (9/11) created the potential for occupational exposure to known and suspected carcinogens. We examined cancer incidence and its potential association with exposure in the first 7 years after 9/11 in firefighters with health information before 9/11 and minimal loss to follow-up. METHODS: We assessed 9853 men who were employed as firefighters on Jan 1, 1996. On and after 9/11, person-time for 8927 firefighters was classified as WTC-exposed; all person-time before 9/11, and person-time after 9/11 for 926 non-WTC-exposed firefighters, was classified as non-WTC exposed. Cancer cases were confirmed by matches with state tumour registries or through appropriate documentation. We estimated the ratio of incidence rates in WTC-exposed firefighters to non-exposed firefighters, adjusted for age, race and ethnic origin, and secular trends, with the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) reference population. CIs were estimated with overdispersed Poisson models. Additional analyses included corrections for potential surveillance bias and modified cohort inclusion criteria. FINDINGS: Compared with the general male population in the USA with a similar demographic mix, the standardised incidence ratios (SIRs) of the cancer incidence in WTC-exposed firefighters was 1.10 (95% CI 0.98-1.25). When compared with non-exposed firefighters, the SIR of cancer incidence in WTC-exposed firefighters was 1.19 (95% CI 0.96-1.47) corrected for possible surveillance bias and 1.32 (1.07-1.62) without correction for surveillance bias. Secondary analyses showed similar effect sizes. INTERPRETATION: We reported a modest excess of cancer cases in the WTC-exposed cohort. We remain cautious in our interpretation of this finding because the time since 9/11 is short for cancer outcomes, and the reported excess of cancers is not limited to specific organ types. As in any observational study, we cannot rule out the possibility that effects

in the exposed group might be due to unidentified confounders. Continued follow-up will be important and should include cancer screening and prevention strategies. FUNDING: National Institute for Occupational Safety and Health.

Webber, M. P., Glaser, M. S., Weakley, J., Soo, J., Ye, F., Zeig-Owens, R., Weiden, M. D., Nolan, A., Aldrich, T. K., Kelly, K. and Prezant, D. (2011). "Physician-diagnosed respiratory conditions and mental health symptoms 7-9 years following the World Trade Center disaster." Am J Ind Med **54**(9): 661-671.

BACKGROUND: This study examines the prevalence of physician-diagnosed respiratory conditions and mental health symptoms in firefighters and emergency medical service workers up to 9 years after rescue/recovery efforts at the World Trade Center (WTC). METHODS: We analyzed Fire Department of New York (FDNY) physician and self-reported diagnoses by WTC exposure and quintiles of pulmonary function (FEV1% predicted). We used screening instruments to assess probable post-traumatic stress disorder (PTSD) and probable depression. RESULTS: FDNY physicians most commonly diagnosed asthma (8.8%) and sinusitis (9.7%). The highest prevalence of physician-diagnosed obstructive airway disease (OAD) was in the lowest FEV1% predicted quintile. Participants who arrived earliest on 9/11 were more likely to have physician-diagnosed asthma (OR = 1.4). Seven percent had probable PTSD. 19.4% had probable depression. CONCLUSIONS: Self-reported and physician-diagnosed respiratory conditions remain common, especially among those who arrived earliest at the WTC site. OAD was associated with the lowest pulmonary function. Since respiratory and mental health conditions remain prevalent, ongoing monitoring and treatment is important.

Weakley, J., Webber, M. P., Gustave, J., Kelly, K., Cohen, H. W., Hall, C. B. and Prezant, D. J. (2011). "Trends in respiratory diagnoses and symptoms of firefighters exposed to the World Trade Center disaster: 2005-2010." Prev Med **53**(6): 364-369.

OBJECTIVES: To compare the prevalence of self-reported respiratory diagnoses in World Trade Center-exposed Fire Department of New York City firefighters to the prevalence in demographically similar National Health Interview Survey participants by year; and, 2) to describe the prevalence of World Trade Center-related symptoms up to 9 years post-9/11. METHODS: We analyzed 45,988 questionnaires completed by 10,999 firefighters from 10/2/2001 to 9/11/2010. For comparison of diagnosis rates, we calculated 95% confidence intervals around yearly firefighter prevalence estimates and generated odds ratios and confidence intervals to compare the odds of diagnoses in firefighters to the National Health Interview Survey prevalence, by smoking status. RESULTS: Overall, World Trade Center-exposed firefighters had higher respiratory diagnosis rates than the National Health Interview Survey; Fire Department of New York City rates also varied less by smoking status. In 2009, bronchitis rates in firefighters aged 45-65 were 13.3 in smokers versus 13.1 in never-smokers while in the National Health Interview Survey, bronchitis rates were doubled for smokers: 4.3 vs. 2.1. In serial cross-sectional analyses, the prevalence of most symptoms stabilized by 2005, at ~10% for cough to ~48% for sinus. CONCLUSIONS: We found generally higher rates of respiratory diagnoses in World Trade Center-exposed firefighters compared to US males, regardless of smoking status. This underscores the impact of World Trade Center exposure and the need for continued monitoring and treatment of this population.

2012

Naveed, B., Weiden, M.D., Kwon, S., Gracely, E.J., Comfort, A.L., Ferrier, N., Kasturiarachchi, K.J., Cohen, H.W., Aldrich, T.K., Rom, W.N., Kelly, K., Prezant, D.J., Nolan, A. (2012) “Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study.” Am J Respir Crit Care Med. 185(4): 392-399.

RATIONALE:Cross-sectional studies demonstrate an association between metabolic syndrome and impaired lung function.

OBJECTIVES:To define if metabolic syndrome biomarkers are risk factors for loss of lung function after irritant exposure.

METHODS: A nested case-control study of Fire Department of New York personnel with normal pre-September 11th FEV(1) and who presented for subspecialty pulmonary evaluation before March 10, 2008. We correlated metabolic syndrome biomarkers obtained within 6 months of World Trade Center dust exposure with subsequent FEV(1). FEV(1) at subspecialty pulmonary evaluation within 6.5 years defined disease status; cases had FEV(1) less than lower limit of normal, whereas control subjects had FEV(1)

greater than or equal to lower limit of normal.
MEASUREMENTS AND MAIN RESULTS: Clinical data and serum sampled at the first monitoring examination within 6 months of September 11, 2001, assessed body mass index, heart rate, serum glucose, triglycerides and high-density lipoprotein (HDL), leptin, pancreatic polypeptide, and amylin. Cases and control subjects had significant differences in HDL less than 40 mg/dl with triglycerides greater than or equal to 150 mg/dl, heart rate greater than or equal to 66 bpm, and leptin greater than or equal to 10,300 pg/ml. Each increased the odds of abnormal FEV(1) at pulmonary evaluation by more than twofold, whereas amylin greater than or equal to 116 pg/ml decreased the odds by 84%, in a multibiomarker model adjusting for age, race, body mass index, and World Trade Center arrival time. This model had a sensitivity of 41%, a specificity of 86%, and a receiver operating characteristic area under the curve of 0.77.
CONCLUSIONS: Abnormal triglycerides and HDL and elevated heart rate and leptin are independent risk factors of greater susceptibility to lung function impairment after September 11, 2001, whereas elevated amylin is protective. Metabolic biomarkers are predictors of lung disease, and may be useful for assessing risk of impaired lung function in response to particulate inhalation.

Nolan, A., Naveed, B., Comfort, A. L., Ferrier, N., Hall, C. B., Kwon, S., Kasturiarachchi, K. J., Cohen, H. W., Zeig-Owens, R., Glaser, M. S., Webber, M. P., Aldrich, T. K., Rom, W. N., Kelly, K., Prezant, D. J. and Weiden, M. D. (2012). "Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust." Chest **142**(2): 412-418.

BACKGROUND: The World Trade Center (WTC) collapse on September 11, 2001, produced airflow obstruction in a majority of firefighters receiving subspecialty pulmonary evaluation (SPE) within 6.5 years post-September 11, 2001. METHODS: In a cohort of 801 never smokers with normal pre-September 11, 2001, FEV1, we correlated inflammatory biomarkers and CBC counts at monitoring entry within 6 months of September 11, 2001, with a median FEV(1) at SPE (34 months; interquartile range, 25-57). Cases of airflow obstruction had FEV(1) less than the lower limit of normal (LLN) (100 of 801; 70 of 100 had serum), whereas control subjects had FEV(1) greater than or equal to LLN (153 of 801; 124 of 153 had serum). RESULTS: From monitoring entry to SPE years later, FEV(1) declined 12% in cases and increased 3% in control subjects. Case subjects had elevated serum macrophage derived chemokine (MDC), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor, and interferon inducible protein-10 levels. Elevated GM-CSF and MDC increased the risk for subsequent FEV(1) less than LLN by 2.5-fold (95% CI, 1.2-5.3) and 3.0-fold (95% CI, 1.4-6.1) in a logistic model adjusted for exposure, BMI, age on September 11, 2001, and polymorphonuclear neutrophils. The model had sensitivity of 38% (95% CI, 27-51) and specificity of 88% (95% CI, 80-93). CONCLUSIONS: Inflammatory biomarkers can be risk factors for airflow obstruction following dust and smoke exposure. Elevated serum GM-CSF and MDC levels soon after WTC exposure were associated with increased risk of airflow obstruction in subsequent years. Biomarkers of inflammation may help identify pathways producing obstruction after irritant exposure.

Naveed, B., Weiden, M. D., Kwon, S., Gracely, E. J., Comfort, A. L., Ferrier, N., Kasturiarachchi, K. J., Cohen, H. W., Aldrich, T. K., Rom, W. N., Kelly, K., Prezant, D. J. and Nolan, A. (2012). "Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study." Am J Respir Crit Care Med **185**(4): 392-399.

RATIONALE: Cross-sectional studies demonstrate an association between metabolic syndrome and impaired lung function. OBJECTIVES: To define if metabolic syndrome biomarkers are risk factors for loss of lung function after irritant exposure. METHODS: A nested case-control study of Fire Department of New York personnel with normal pre-September 11th FEV(1) and who presented for subspecialty pulmonary evaluation before March 10, 2008. We correlated metabolic syndrome biomarkers obtained within 6 months of World Trade Center dust exposure with subsequent FEV(1). FEV(1) at subspecialty pulmonary evaluation within 6.5 years defined disease status; cases had FEV(1) less than lower limit of normal, whereas control subjects had FEV(1) greater than or equal to lower limit of normal.
MEASUREMENTS AND MAIN RESULTS: Clinical data and serum sampled at the first monitoring examination within 6 months of September 11, 2001, assessed body mass index, heart rate, serum glucose, triglycerides and high-density lipoprotein (HDL), leptin, pancreatic polypeptide, and amylin. Cases and control subjects had significant differences in HDL less than 40 mg/dl with triglycerides greater than or equal to 150 mg/dl, heart rate greater than or equal to 66 bpm, and leptin greater than or equal to 10,300 pg/ml. Each increased the odds of abnormal FEV(1) at pulmonary evaluation by more than twofold, whereas amylin greater than or equal to 116 pg/ml decreased the odds by 84%, in a multibiomarker model

adjusting for age, race, body mass index, and World Trade Center arrival time. This model had a sensitivity of 41%, a specificity of 86%, and a receiver operating characteristic area under the curve of 0.77. CONCLUSIONS: Abnormal triglycerides and HDL and elevated heart rate and leptin are independent risk factors of greater susceptibility to lung function impairment after September 11, 2001, whereas elevated amylin is protective. Metabolic biomarkers are predictors of lung disease, and may be useful for assessing risk of impaired lung function in response to particulate inhalation.

Soo, J., Webber, M. P., Hall, C. B., Cohen, H. W., Schwartz, T. M., Kelly, K. J. and Prezant, D. J. (2012). "Pulmonary function predicting confirmed recovery from lower-respiratory symptoms in World Trade Center-exposed firefighters, 2001 to 2010." Chest **142**(5): 1244-1250.

BACKGROUND: We examined the relationship between pulmonary function (FEV 1) and confirmed recovery from three lower-respiratory symptoms (LRSs) (cough, dyspnea, and wheeze) up to 9 years after symptom onset. METHODS: The study included white and black male World Trade Center (WTC)-exposed firefighters who reported at least one LRS on a medical monitoring examination during the fi rst year after September 11, 2001. Confirmed recovery was defined as reporting no LRSs on two consecutive and all subsequent examinations. FEV 1 was assessed at the fi rst post-September 11, 2001, examination and at each examination where symptom information was ascertained. We used stratified Cox regression models to analyze FEV 1 , WTC exposure, and other variables in relation to confirmed symptom recovery. RESULTS: A total of 4,368 fi refighters met inclusion criteria and were symptomatic at year 1, of whom1,592 (36.4%) experienced confirmed recovery. In univariable models, fi rst post-September 11,2001, concurrent, and difference between fi rst post-September 11, 2001, and concurrent FEV 1 values were all significantly associated with confirmed recovery. In adjusted analyses, both fi rst post-September 11, 2001, FEV 1 (hazard ratio [HR], 1.07 per 355-mL difference; 95% CI, 1.04-1.10) and FEV 1 % predicted (HR, 1.08 per 10% predicted difference; 95% CI, 1.04-1.12) predicted confirmed recovery. WTC exposure had an inverse association with confirmed recovery in the model with FEV 1 , with the earliest arrival group less likely to recover than the latest arrival group (HR, 0.73;95% CI, 0.58-0.92). CONCLUSIONS: Higher FEV 1 and improvement in FEV 1 after September 11, 2001, predicted confirmed LRS recovery, supporting a physiologic basis for recovery and highlighting consideration of spirometry as part of any postexposure respiratory health assessment.

Weiden, M. D., Naveed, B., Kwon, S., Segal, L. N., Cho, S. J., Tsukiji, J., Kulkarni, R., Comfort, A. L., Kasturiarachchi, K. J., Prophete, C., Cohen, M. D., Chen, L. C., Rom, W. N., Prezant, D. J. and Nolan, A. (2012). "Comparison of WTC dust size on macrophage inflammatory cytokine release in vivo and in vitro." PLoS One 7(7): e40016.

BACKGROUND: The WTC collapse exposed over 300,000 people to high concentrations of WTC-PM; particulates up to approximately 50 mm were recovered from rescue workers' lungs. Elevated MDC and GM-CSF independently predicted subsequent lung injury in WTC-PM-exposed workers. Our hypotheses are that components of WTC dust strongly induce GM-CSF and MDC in AM; and that these two risk factors are in separate inflammatory pathways. METHODOLOGY/PRINCIPAL FINDINGS: Normal adherent AM from 15 subjects without WTC-exposure were incubated in media alone, LPS 40 ng/mL, or suspensions of WTC-PM(10-53) or WTC-PM(2.5) at concentrations of 10, 50 or 100 microg/mL for 24 hours; supernatants assayed for 39 chemokines/cytokines. In addition, sera from WTC-exposed subjects who developed lung injury were assayed for the same cytokines. In the in vitro studies, cytokines formed two clusters with GM-CSF and MDC as a result of PM(10-53) and PM(2.5). GM-CSF clustered with IL-6 and IL-12(p70) at baseline, after exposure to WTC-PM(10-53) and in sera of WTC dust-exposed subjects (n = 70) with WTC lung injury. Similarly, MDC clustered with GRO and MCP-1. WTC-PM(10-53) consistently induced more cytokine release than WTC-PM(2.5) at 100 microg/mL. Individual baseline expression correlated with WTC-PM-induced GM-CSF and MDC. CONCLUSIONS: WTC-PM(10-53) induced a stronger inflammatory response by human AM than WTC-PM(2.5). This large particle exposure may have contributed to the high incidence of lung injury in those exposed to particles at the WTC site. GM-CSF and MDC consistently cluster separately, suggesting a role for differential cytokine release in WTC-PM injury. Subject-specific response to WTC-PM may underlie individual susceptibility to lung injury after irritant dust exposure.

2013

Kwon, S., Weiden, M.D., Echevarria, G.C., Comfort, A.L., Naveed, B., Prezant, D.J., Rom, W.N., Nolan, A. (2013) "Early elevation of serum mmp-3 and MMP-12 predicts protection from World Trade Center-lung injury in New York City Firefighters: a nested case-control study." PLoS One. 8(10): doi: 10.1371.

OBJECTIVE: After 9/11/2001, some Fire Department of New York (FDNY) workers had excessive lung function decline. We hypothesized that early serum matrix metalloproteinases (MMP) expression predicts World Trade Center-Lung Injury (WTC-LI) years later.
METHODS: This is a nested case-control analysis of never-smoking male firefighters with normal pre-exposure Forced Expiratory Volume in one second (FEV1) who had serum drawn up to 155 days post 9/11/2001. Serum MMP-1, 2,3,7,8, 9, 12 and 13 were measured. Cases of WTC-LI (N = 70) were defined as having an FEV1 one standard deviation below the mean (FEV1 ≤ 77%) at subspecialty pulmonary evaluation (SPE) which was performed 32 months (IQR 21-53) post-9/11. Controls (N = 123) were randomly selected. We modeled MMP's ability as a predictor of cases status with logistic regression adjusted for time to blood draw, exposure intensity, weight gain and pre-9/11 FEV1.
RESULTS: Each log-increase in MMP-3 and MMP-12 showed reduced odds of developing WTC-LI by 73% and 54% respectively. MMP-3 and MMP-12 consistently clustered together in cases, controls, and the cohort. Increasing time to blood draw significantly and independently increased the risk of WTC-LI.
CONCLUSIONS: Elevated serum levels of MMP-3 and MMP-12 reduce the risk of developing WTC-LI. At any level of MMP-3 or 12, increased time to blood draw is associated with a diminished protective effect.

Cho, S. J., Nolan, A., Echevarria, G. C., Kwon, S., Naveed, B., Schenck, E., Tsukiji, J., Prezant, D. J., Rom, W. N. and Weiden, M. D. (2013). "Chitotriosidase is a biomarker for the resistance to World Trade Center lung injury in New York City firefighters." J Clin Immunol. 33(6): 1134-1142.

PURPOSE: World Trade Center (WTC) exposure caused airflow obstruction years after exposure. Chitinases and IgE are innate and humoral mediators of obstructive airway disease. We investigated if serum expression of chitinases and IgE early after WTC exposure predicts subsequent obstruction.
METHODS: With a nested case-control design, 251 FDNY personnel had chitotriosidase, YKL-40 and IgE measured in serum drawn within months of 9/11/2001. The main outcome was subsequent Forced Expiratory Volume after 1 second/Forced Vital Capacity (FEV1/FVC) less than the lower limit of normal (LLN). Cases (N = 125) had abnormal FEV1/FVC whereas controls had normal FEV1/FVC (N = 126). In a secondary analysis, resistant cases (N = 66) had FEV1 (>/=107%) one standard deviation above the mean. Logistic regression adjusted for age, BMI, exposure intensity and post-exposure FEV1/FVC modeled the association between early biomarkers and later lung function.
RESULTS: Cases and Controls initially lost lung function. Controls recovered to pre-9/11 FEV1 and FVC while cases continue to decline. Cases expressed lower serum chitotriosidase and higher IgE levels. Increase in IgE increased the odds of airflow obstruction and decreased the odds of above average FEV1. Alternately, increasing chitotriosidase decreased the odds of abnormal FEV1/FVC and increased the odds of FEV1 >/= 107%. Serum YKL-40 was not associated with FEV1/FVC or FEV1 in this cohort.
CONCLUSIONS: Increased serum chitotriosidase reduces the odds of developing obstruction after WTC-particulate matter exposure and is associated with recovery of lung function. Alternately, elevated IgE is a risk factor for airflow obstruction and progressive lung function decline.

Niles, J. K., Webber, M. P., Cohen, H. W., Hall, C. B., Zeig-Owens, R., Ye, F., Glaser, M. S., Weakley, J., Weiden, M. D., Aldrich, T. K., Nolan, A., Glass, L., Kelly, K. J. and Prezant, D. J. (2013). "The respiratory pyramid: From symptoms to disease in World Trade Center exposed firefighters." Am J Ind Med. 56(8): 870-880.

BACKGROUND: This study utilizes a four-level pyramid framework to understand the relationship between symptom reports and/or abnormal pulmonary function and diagnoses of airway diseases (AD), including asthma, recurrent bronchitis and COPD/emphysema in WTC-exposed firefighters. We compare the distribution of pyramid levels at two time-points: by 9/11/2005 and by 9/11/2010.
METHODS: We studied 6,931 WTC-exposed FDNY firefighters who completed a monitoring exam during the early period and at least two additional follow-up exams 9/11/2005-9/11/2010.
RESULTS: By 9/11/2005 the pyramid structure was as follows: 4,039 (58.3%) in Level 1, no respiratory evaluation or treatment; 1,608 (23.2%) in Level 2, evaluation or treatment without AD diagnosis; 1,005 (14.5%) in Level 3, a single AD diagnosis (asthma, emphysema/COPD, or recurrent bronchitis); 279 (4.0%) in Level 4, asthma and another AD. By 9/11/2010, the pyramid distribution changed considerably,

with Level 1 decreasing to 2,612 (37.7% of the cohort), and Levels 3 (N = 1,530) and 4 (N = 796) increasing to 22.1% and 11.5% of the cohort, respectively. Symptoms, spirometry measurements and healthcare utilization were associated with higher pyramid levels.
CONCLUSIONS: Respiratory diagnoses, even four years after a major inhalation event, are not the only drivers of future healthcare utilization. Symptoms and abnormal FEV-1 values must also be considered if clinicians and healthcare administrators are to accurately anticipate future treatment needs, years after initial exposure.

Weakley, J., Webber, M. P., Ye, F., Zeig-Owens, R., Cohen, H. W., Hall, C. B., Kelly, K. and Prezant, D. J. (2013). "Agreement between obstructive airways disease diagnoses from self-report questionnaires and medical records." Prev Med. 57(1): 38-42.

OBJECTIVE: To evaluate agreement between self-reported obstructive airways disease (OAD) diagnoses of asthma, bronchitis, and chronic obstructive pulmonary disease (COPD)/emphysema obtained from the New York City Fire Department (FDNY) monitoring questionnaires with physician diagnoses from FDNY medical records. METHOD: We measured sensitivity, specificity, and agreement between self-report and physician OAD diagnoses in FDNY members enrolled in the World Trade Center (WTC) monitoring program who completed a questionnaire between 8/2005-1/2012. Using logistic models, we identified characteristics of those who self-report a physician diagnosis that is also reported by FDNY physicians. RESULTS: 20.3% of the study population (N=14,615) self-reported OAD, while 15.1% received FDNY physician OAD diagnoses. Self-reported asthma had the highest sensitivity (68.7%) and overall agreement (91.9%) between sources. Non-asthma OAD had the lowest sensitivity (32.1%). Multivariate analyses showed that among those with an OAD diagnosis from FDNY medical records, inhaler use (OR=4.90, 95% CI=3.84-6.26) and respiratory symptoms (OR=1.55 [95% CI=1.25-1.92]-1.77 [95% CI=1.37-2.27]) were associated with self-reported OAD diagnoses. CONCLUSION: Among participants in the WTC monitoring program, sensitivity for self-reported OAD diagnoses ranges from good to poor and improves by considering inhaler use. These findings highlight the need for improved patient communication and education, especially for bronchitis or COPD/emphysema.

Weiden, M. D., Naveed, B., Kwon, S., Cho, S. J., Comfort, A. L., Prezant, D. J., Rom, W. N. and Nolan, A. (2013). "Cardiovascular biomarkers predict susceptibility to lung injury in World Trade Center dust-exposed firefighters." Eur Respir J. 41(5): 1023-1030.

Pulmonary vascular loss is an early feature of chronic obstructive pulmonary disease. Biomarkers of inflammation and of metabolic syndrome predict loss of lung function in World Trade Center (WTC) lung injury (LI). We investigated if other cardiovascular disease (CVD) biomarkers also predicted WTC-LI. This nested case-cohort study used 801 never-smoker, WTC-exposed firefighters with normal pre-9/11 lung function presenting for subspecialty pulmonary evaluation (SPE) before March 2008. A representative subcohort of 124 out of 801 subjects with serum drawn within 6 months of 9/11 defined CVD biomarker distribution. Post-9/11 forced expiratory volume in 1 s (FEV1) at defined cases were as follows: susceptible WTC-LI cases with FEV1 </=77% predicted (66 out of 801) and resistant WTC-LI cases with FEV1 >/=107% predicted (68 out of 801). All models were adjusted for WTC exposure intensity, body mass index at SPE, age on 9/11 and pre-9/11 FEV1. Susceptible WTC-LI cases had higher levels of apolipoprotein-AII, C-reactive protein and macrophage inflammatory protein-4 with significant relative risks (RRs) of 3.85, 3.93 and 0.26, respectively, with an area under the curve (AUC) of 0.858. Resistant WTC-LI cases had significantly higher soluble vascular cell adhesion molecule and lower myeloperoxidase, with RRs of 2.24 and 2.89, respectively (AUC 0.830). Biomarkers of CVD in serum 6 months post-9/11 predicted either susceptibility or resistance to WTC-LI. These biomarkers may define pathways either producing or protecting subjects from pulmonary vascular disease and associated loss of lung function after an irritant exposure.

2014

Niles, J.K., Webber, M.P., Liu, X., Zeig-Owens, R., Hall, C.B., Cohen H.W., Glaser, M.S., Weakley, J., Schwartz, T.M., Weiden, M.D., Nolan, A., Aldrich, T.K., Glass, L., Kelly, K.J., Prezant, D.J. (2014) “The upper respiratory pyramid: early factors and later treatment utilization in World Trade Center exposed firefighers.” Am J Ind Med. 57(8): 857-865.

BACKGROUND: We investigated early post 9/11 factors that could predict rhinosinusitis healthcare utilization costs up to 11 years later in 8,079 World Trade Center-exposed rescue/recovery workers.
METHODS: We used bivariate and multivariate analytic techniques to investigate utilization outcomes; we also used a pyramid framework to describe rhinosinusitis healthcare groups at early (by 9/11/2005) and late (by 9/11/2012) time points.
RESULTS: Multivariate models showed that pre-9/11/2005 chronic rhinosinusitis diagnoses and nasal symptoms predicted final year healthcare utilization outcomes more than a decade after WTC exposure. The relative proportion of workers on each pyramid level changed significantly during the study period.
CONCLUSIONS: Diagnoses of chronic rhinosinusitis within 4 years of a major inhalation event only partially explain future healthcare utilization. Exposure intensity, early symptoms and other factors must also be considered when anticipating future healthcare needs.

Tsukiji, J., Cho, S.J., Echevarria, G.C., Kwon, S., Joseph, P., Schenck, E.J., Naveed, B., Prezant, D.J., Rom, W.N., Schmidt, A.M., Weiden, M.D., Nolan, A. (2014) "Lysophosphatidic acid and apolipoprotein A1 predicts increased risk of developing World Trade Center-lung injury: a nested case-control study." Biomarkers. 19(2): 159-165.

RATIONALE: Metabolic syndrome, inflammatory and vascular injury markers measured in serum after World Trade Center (WTC) exposures predict abnormal FEV1. We hypothesized that elevated LPA levels predict FEV_1 < LLN.
METHODS: Nested case-control study of WTC-exposed firefighters. Cases had FEV_1 < LLN. Controls derived from the baseline cohort. Demographics, pulmonary function, serum lipids, LPA and ApoA1 were measured.
RESULTS: LPA and ApoA1 levels were higher in cases than controls and predictive of case status. LPA increased the odds by 13% while ApoA1 increased the odds by 29% of an FEV_1 < LLN in a multivariable model.
CONCLUSIONS: Elevated LPA and ApoA1 are predictive of a significantly increased risk of developing an FEV_1 < LLN.

Glaser, M.S., Shah, N., Webber, M.P., Zeig-Owens, R., Jaber, N., Appel, D.W., Hall, C.B., Weakley, J., Cohen, H.W., Shulman, L., Kelly, K., Prezant, D. (2014) "Obstructive sleep apnea and World Trade Center exposure." J Occup Environ Med. 56(10S): S30-S34.

OBJECTIVES: To describe the proportion of at-risk World Trade Center (WTC)-exposed rescue/recovery workers with polysomnogram-confirmed obstructive sleep apnea (OSA) and examine the relationship between WTC exposure, physician-diagnosed gastroesophageal reflux disease (GERD), and rhinosinusitis and OSA.
METHODS: A total of 636 male participants completed polysomnography from September 24, 2010, to September 23, 2012. Obstructive sleep apnea was classified as mild, moderate, or severe. Associations were tested using nominal polytomous logistic regression.
RESULTS: Eighty-one percent of workers were diagnosed with OSA. Using logistic regression models, severe OSA was associated with WTC exposure on September 11, 2001 (odds ratio, 1.91; 95% confidence interval, 1.15 to 3.17), GERD (odds ratio, 2.75; 95% confidence interval, 1.33 to 5.70), and comorbid GERD/rhinosinusitis (odds ratio, 2.31; 95% confidence interval, 1.22 to 4.40).
CONCLUSIONS: We found significant associations between severe OSA and WTC exposure, and with diseases prevalent in this population. Accordingly, we recommend clinical evaluation, including polysomnography, for patients with high WTC exposure, other OSA risk factors, and a physician diagnosis of GERD or comorbid GERD and rhinosinusitis.

Cho SJ; Echevarria GC; Lee YI; Kwon S; Park KY; Tsukiji J; Rom WN; Prezant DJ; Nolan A; Weiden MD. (2014) "YKL-40 is a Protective Biomarker for Fatty Liver in World Trade Center Particulate Matter-Exposed Firefighters." Journal of molecular biomarkers & diagnosis. 5.

BACKGROUND: Serum biomarkers of metabolic syndrome predict abnormal lung function in World Trade Center particulate matter (WTC-PM)-exposed Fire Department of New York (FDNY) rescue workers. In animal models, exposure to ambient PM induces non-alcoholic fatty liver disease (NAFLD), a well-known comorbidity of metabolic syndrome. YKL-40 is an inflammatory biomarker for both liver and lung disease. We tested if YKL-40 is a biomarker for NAFLD in this dust-exposed cohort.
METHODS: Using a nested case-control design, we studied 131 FDNY personnel who had Computer Tomography performed within 5 years post 9/11. NAFLD was defined by a liver/spleen attenuation ratio of

≤1. Serum biomarkers, lipid panel and liver function were measured in serum that had been drawn within 6 months of September 11, 2001. YKL-40 and chitotriosidase were assayed by ELISA. We tested biomarker and NAFLD association using logistic regression adjusted for age, BMI, and post-911 lung function. RESULTS: NAFLD was present in 29/131 (22%) of the cohort. In a multivariable model increasing YKL-40 was protective while increasing triglyceride and alkaline phosphatase were risk factors for NAFLD. CONCLUSIONS: Increased YKL-40 is a protective biomarker in non-alcoholic fatty liver disease. Further studies may reveal a link between PM-induced lung and liver diseases.

Nolan A; Kwon S; Cho SJ; Naveed B; Comfort AL; Prezant DJ; Rom WN; Weiden MD. (2014) "MMP-2 and TIMP-1 Predict Healing of WTC-Lung Injury in New York City Firefighters." Respiratory research. 15(1):5-5.

RATIONALE: After 9/11/2001, most FDNY workers had persistent lung function decline but some exposed workers recovered. We hypothesized that the protease/anti-protease balance in serum soon after exposure predicts subsequent recovery.
METHODS: We performed a nested case-control study measuring biomarkers in serum drawn before 3/2002 and subsequent forced expiratory volume at one second (FEV1) on repeat spirometry before 3/2008. Serum was assayed for matrix metalloproteinases (MMP-1,2,3,7,8,9,12 and 13) and tissue inhibitors of metalloproteinases (TIMP-1,2,3,4). The representative sub-cohort defined analyte distribution and a concentration above 75th percentile defined elevated biomarker expression. An FEV1 one standard deviation above the mean defined resistance to airway injury. Logistic regression was adjusted for pre-9/11 FEV1, BMI, age and exposure intensity modeled the association between elevated biomarker expression and above average FEV1.
RESULTS: FEV1 in cases and controls declined 10% of after 9/11/2001. Cases subsequently returned to 99% of their pre-exposure FEV1 while decline persisted in controls. Elevated TIMP-1 and MMP-2 increased the odds of resistance by 5.4 and 4.2 fold while elevated MMP-1 decreased it by 0.27 fold.
CONCLUSION: Resistant cases displayed healing, returning to 99% of pre-exposure values. High TIMP-1 and MMP-2 predict healing. MMP/TIMP balance reflects independent pathways to airway injury and repair after WTC exposure.

Weakley, J., Webber, M.P., Ye, F., Zeig-Owens, R., Cohen, H.W., Hall, C.B., Kelly, K., Prezant, D.J. (2014) "Agreement between upper respiratory diagnoses from self-report questionnaires and medical records in an occupational health setting." Am J Ind Med. 57(10): 1181-1187.

BACKGROUND: The Fire Department of the City of New York World Trade Center Health Program (FDNY-WTCHP) monitors and treats WTC-related illnesses through regular physical exams, self-administered health questionnaires and treatment visits, as indicated.
METHODS: We measured positive and negative predictive values (PPV, NPV) of self-reported diagnoses of GERD and rhinosinusitis from the health questionnaires in relation to FDNY physician diagnoses from the medical record.
RESULTS: Self-reported GERD had PPV and NPV of 54.0% and 95.7%, respectively; for rhinosinusitis, the PPV and NPV were 48.2% and 91.9%. These characteristics improved considerably (PPV 78.0% GERD and PPV 76.5% rhinosinusitis) in a subpopulation receiving medications from the FDNY-WTCHP.
CONCLUSION: The PPV of self-reported diagnoses demonstrates only modest value in predicting physician diagnoses, although high NPVs suggest benefit in ruling out disease. In subgroups selected for their higher disease prevalence, self-reported diagnoses may be considerably more useful.

Cho, S.J., Echevarria, G.C., Kwon, S., Naveed, B., Schenck, E.J., Tsukiji, J., Rom, W.N., Prezant, D.J., Nolan, A., Weiden, M.D. (2014). "One airway: Biomarkers of protection from upper and lowser airway injury after World Trade Center exposure." Respir Med. 108(1): 162-170.

BACKGROUND: Firefighters exposed to World Trade Center (WTC) dust have developed chronic rhinosinusitis (CRS) and abnormal forced expiratory volume in 1 s (FEV1). Overlapping but distinct immune responses may be responsible for the clinical manifestations of upper and lower airway injury. We investigated whether a panel of inflammatory cytokines, either associated or not associated with WTC-LI, can predict future chronic rhinosinusitis disease and its severity.
METHODS: Serum obtained within six months of 9/11/2001 from 179 WTC exposed firefighters presenting for subspecialty evaluation prior to 3/2008 was assayed for 39 cytokines. The main outcomes were medically managed CRS (N = 62) and more severe CRS cases requiring sinus surgery (N = 14). We tested biomarker-CRS severity association using ordinal logistic regression analysis.

RESULTS: Increasing serum IL-6, IL-8, GRO and neutrophil concentration reduced the risk of CRS progression. Conversely, increasing TNF-α increased the risk of progression. In a multivariable model adjusted for exposure intensity, increasing IL-6, TNF-α and neutrophil concentration remained significant predictors of progression. Elevated IL-6 levels and neutrophil counts also reduced the risk of abnormal FEV1 but in contrast to CRS, increased TNF-α did not increase the risk of abnormal FEV1.
CONCLUSIONS: Our study demonstrates both independent and overlapping biomarker associations with upper and lower respiratory injury, and suggests that the innate immune response may play a protective role against CRS and abnormal lung function in those with WTC exposure.

Schenck, E.J., Echevarria, G.C., Girvin, F.G., Kwon, S., Comfort, A.L., Rom, W.N., Prezant, .J., Weiden, M.D., Nolan, A. "Enlarged pulmonary artery is predicted by vascular injury biomarkers and is associated with WTC-Lung injury in exposed firefighters: a case-control study. BMJ Open. e005575.

OBJECTIVES: We hypothesise that there is an association between an elevated pulmonary artery/aorta (PA/A) and World Trade Center-Lung Injury (WTC-LI). We assessed if serum vascular disease biomarkers were predictive of an elevated PA/A.
DESIGN: Retrospective case-cohort analysis of thoracic CT scans of WTC-exposed firefighters who were symptomatic between 9/12/2001 and 3/10/2008. Quantification of vascular-associated biomarkers from serum collected within 200 days of exposure.
SETTING: Urban tertiary care centre and occupational healthcare centre.
PARTICIPANTS: Male never-smoking firefighters with accurate pre-9/11 forced expiratory volume in 1 s (FEV1)≥75%, serum sampled ≤200 days of exposure was the baseline cohort (n=801). A subcohort (n=97) with available CT scans and serum biomarkers was identified. WTC-LI was defined as FEV1≤77% at the subspecialty pulmonary evaluation (n=34) and compared with controls (n=63) to determine the associated PA/A ratio. The subcohort was restratified based on PA/A≥0.92 (n=38) and PA/A<0.92(n=59) to determine serum vascular biomarkers that were predictive of this vasculopathy.
OUTCOME MEASURES: The primary outcome of this study was to identify a PA/A ratio in a cohort of individuals exposed to WTC dust that was associated with WTC-LI. The secondary outcome was to identify serum biomarkers predictive of the PA/A ratio using logistic regression.
RESULTS: PA/A≥0.92 was associated with WTC-LI, OR of 4.02 (95% CI 1.21 to 13.41; p=0.023) when adjusted for exposure, body mass index and age at CT. Elevated macrophage derived chemokine and soluble endothelial selectin were predictive of PA/A≥0.92, (OR, 95% CI 2.08, 1.05 to 4.11, p=0.036; 1.33, 1.06 to 1.68, p=0.016, respectively), while the increased total plasminogen activator inhibitor 1 was predictive of not having PA/A≥0.92 (OR 0.88, 0.79 to 0.98; p=0.024). CONCLUSIONS: Elevated PA/A was associated with WTC-LI. Development of an elevated PA/A was predicted by biomarkers of vascular disease found in serum drawn within 6 months of WTC exposure. Increased PA/A is a potentially useful non-invasive biomarker of WTC-LI and warrants further study.

Glaser, M.S., Webber, M.P., Zeig-Owens, R., Weakley, J., Liu, X., Ye, F., Cohen, H.W., Aldrich, T.K., Kelly, K.J., Nolan, A., Weiden, M.D., Prezant, D.J., Hall, C.B. (2014). "Estimating the time interval between exposure to the World Trade Center disaster and incident diagnoses of obstructive airway disease." Am J Epidemiol 180(3): 272-279.

Respiratory disorders are associated with occupational and environmental exposures. The latency period between exposure and disease onset remains uncertain. The World Trade Center (WTC) disaster presents a unique opportunity to describe the latency period for obstructive airway disease (OAD) diagnoses. This prospective cohort study of New York City firefighters compared the timing and incidence of physician-diagnosed OAD relative to WTC exposure. Exposure was categorized by WTC arrival time as high (on the morning of September 11, 2001), moderate (after noon on September 11, 2001, or on September 12, 2001), or low (during September 13-24, 2001). We modeled relative rates and 95% confidence intervals of OAD incidence by exposure over the first 5 years after September 11, 2001, estimating the times of change in the relative rate with change point models. We observed a change point at 15 months after September 11, 2001. Before 15 months, the relative rate for the high- versus low-exposure group was 3.96 (95% confidence interval: 2.51, 6.26) and thereafter, it was 1.76 (95% confidence interval: 1.26, 2.46). Incident OAD was associated with WTC exposure for at least 5 years after September 11, 2001. There were higher rates of new-onset OAD among the high-exposure group during the first 15 months and, to a lesser extent, throughout follow-up. This difference in relative rate by exposure occurred despite full and free access to health care for all WTC-exposed firefighters, demonstrating the persistence of WTC-associated OAD risk.

2015

Weiden, M.D., Kwon, S., Caraher, E., Berger, K.I., Reibman, J., Rom, W.N., Prezant, D.J., Nolan, A. (2015) "Biomarkers of World Trade Center particulate matter exposure: physiology of distal airway and blood biomarkers that predict FEV_1 decline." Semin Respir Crit Care Med. 36(3): 323-333.

> Biomarkers can be important predictors of disease severity and progression. The intense exposure to particulates and other toxins from the destruction of the World Trade Center (WTC) overwhelmed the lung's normal protective barriers. The Fire Department of New York (FDNY) cohort not only had baseline pre-exposure lung function measures but also had serum samples banked soon after their WTC exposure. This well-phenotyped group of highly exposed first responders is an ideal cohort for biomarker discovery and eventual validation. Disease progression was heterogeneous in this group in that some individuals subsequently developed abnormal lung function while others recovered. Airflow obstruction predominated in WTC-exposed patients who were symptomatic. Multiple independent disease pathways may cause this abnormal FEV1 after irritant exposure. WTC exposure activates one or more of these pathways causing abnormal FEV1 in an individual. Our hypothesis was that serum biomarkers expressed within 6 months after WTC exposure reflect active disease pathways and predict subsequent development or protection from abnormal FEV1 below the lower limit of normal known as WTC-Lung Injury (WTC-LI). We utilized a nested case-cohort control design of previously healthy never smokers who sought subspecialty pulmonary evaluation to explore predictive biomarkers of WTC-LI. We have identified biomarkers of inflammation, metabolic derangement, protease/antiprotease balance, and vascular injury expressed in serum within 6 months of WTC exposure that were predictive of their FEV1 up to 7 years after their WTC exposure. Predicting future risk of airway injury after particulate exposures can focus monitoring and early treatment on a subset of patients in greatest need of these services.

Loupasakis, K., Berman, J., Jaber, N., Zeig-Owens, R., Webber, M.P., Glaser, M.S., Moir, W., Qayyum, B., Weiden, M.D., Nolan, A., Aldrich, T.K., Kelly, K.J., Prezant, D.J. (2015)"Refractory sarcoid arthritis in world trade center-exposed New York city firefighters: a case series." J Clin Rheumatol. 21(1):19-23.

> OBJECTIVE: The objective of this study was to describe cases of sarcoid arthritis in firefighters from the Fire Department of the City of New York (FDNY) who worked at the World Trade Center (WTC) site.
> METHODS: All WTC-exposed FDNY firefighters with sarcoidosis and related chronic inflammatory arthritis (n = 11) are followed jointly by the FDNY-WTC Health Program and the Rheumatology Division at the Hospital for Special Surgery. Diagnoses of sarcoidosis were based on clinical, radiographic, and pathological criteria. Patient characteristics, WTC exposure information, smoking status, date of diagnosis, and pulmonary findings were obtained from FDNY-WTC database. Joint manifestations (symptoms and duration, distribution of joints involved), radiographic findings, and treatment responses were obtained from chart review.
> RESULTS: Nine of 60 FDNY firefighters who developed sarcoidosis since 9/11/2001 presented with polyarticular arthritis. Two others diagnosed pre-9/11/2001 developed sarcoid arthritis after WTC exposure. All 11 were never cigarette smokers, and all performed rescue/recovery at the WTC site within 3 days of the attacks. All had biopsy-proven pulmonary sarcoidosis, and all required additional disease-modifying antirheumatic drugs for adequate control (stepwise progression from hydroxychloroquine to methotrexate to anti-tumor necrosis factor α agents) of their joint manifestations.
> CONCLUSIONS: Chronic inflammatory polyarthritis appears to be an important manifestation of sarcoidosis in FDNY firefighters with sarcoidosis and WTC exposure. Their arthritis is chronic and, unlike arthritis in non-WTC-exposed sarcoid patients, inadequately responsive to conventional oral disease-modifying antirheumatic drugs, often requiring anti-tumor necrosis factor α agents. Further studies are needed to determine the generalizability of these findings to other groups with varying levels of WTC exposure or with other occupational/environmental exposures.

Hall, C.B., Liu, X., Zeig-Owens, R., Webber, M.P., Aldrich, T.K., Weakley, J., Cohen, H.W., Glaser, M.S., Olivieri, B.L., Weiden, M.D., Nolan, A., Kelly, K.J., Prezant, D.J. (2015) "The duration of an exposure response gradient between incident obstructive airways disease and work at the World Trade Center site: 2001-2011." PLoS Curr. Volume 7(Disasters).

> BACKGROUND: Adverse respiratory effects of World Trade Center (WTC) exposure have been widely

documented, but the length of time that exposure remains associated with disease is uncertain. We estimate the incidence of new cases of physician-diagnosed obstructive airway disease (OAD) as a function of time since 9/11/2001 in WTC-exposed firefighters.
METHODS: Exposure was categorized by first WTC arrival time: high (9/11/2001 AM); moderate (9/11/2001 PM or 9/12/2001); or low (9/13-24/2001). We modeled relative rates (RR) and 95% confidence intervals (CI) of OAD incidence by exposure over the first 10 years post-9/11/2001, estimating the time(s) of change in the RR with change point models. We further examined the relationship between self-reported lower respiratory symptoms and physician diagnoses.
RESULTS: Change points were observed at 15 and 84 months post-9/11/2001, with relative incidence rates for the high versus low exposure group of 4.02 (95% CI 2.62-6.16) prior to 15 months, 1.90 (95% CI 1.49-2.44) from months 16 to 84, and 1.20 (95% CI 0.92-1.56) thereafter. Incidence in all exposure groups increased after the WTC health program began to offer free coverage of OAD medications in month 63. Self-reported lower respiratory symptoms in the first 15 months had 80.6% sensitivity, but only 35.9% specificity, for eventual OAD diagnoses.
CONCLUSIONS: New OAD diagnoses are associated with WTC exposure for at least seven years. Some portion of the extended duration of that association may be due to delayed diagnoses. Nevertheless, our results support recognizing OAD among rescue workers as WTC-related even when diagnosed years after exposure.

Webber, M.P., Moir, W, Zeig-Owens, R., Glaser, M.S., Jaber, N., Hall, C., Berman, J., Qayyum, B., Loupasakis, K., Kelly, K.., Prezant, D.J. (2015) "Nested case-control study of selected systemic autoimmuine diseases in World Trade Center rescue/recovery workers." Arthritis Rheumatol. 67(5): 1369-1376.

OBJECTIVE: To test the a priori hypothesis that acute and chronic work exposures to the World Trade Center (WTC) site on or after September 11, 2001 were associated with risk of new-onset systemic autoimmune diseases.
METHODS: A nested case-control study was performed in WTC rescue/recovery workers who had received a rheumatologist-confirmed systemic autoimmune disease diagnosis between September 12, 2001 and September 11, 2013 (n = 59), each of whom was individually matched to 4 randomly selected controls (n = 236) on the basis of year of hire (±1 year), sex, race, and work assignment (firefighter or emergency medical service). Acute exposure was defined according to the earliest time of arrival (morning of 9/11 versus later) at the WTC site, and chronic exposure was defined as duration (number of months) of WTC site-related work. Rheumatologists were blinded with regard to each subject's exposure status. The conditional odds ratios (CORs) with 95% confidence intervals (95% CIs) for incident autoimmune disease were derived from exact conditional logistic regression models.
RESULTS: Rheumatoid arthritis was the most common autoimmune diagnosis (37% of subjects), followed by spondyloarthritis (22%), inflammatory myositis (14%), systemic lupus erythematosus (12%), systemic sclerosis (5%), Sjögren's syndrome (5%), antiphospholipid syndrome (3%), and granulomatosis with polyangiitis (Wegener's) (2%). The COR for incident autoimmune disease increased by 13% (COR 1.13, 95% CI 1.02-1.26) for each additional month worked at the WTC site. These odds were independent of the association between high acute exposure (working during the morning of 9/11) and disease outcome, which conveyed an elevated, but not statistically significant, risk (COR 1.85, 95% CI 0.86-3.89).
CONCLUSION: Prolonged work at the WTC site, independent of acute exposure, was an important predictor of post-9/11 systemic autoimmune diseases. The WTC Health Program should expand surveillance efforts for those with extended exposures, as early detection can facilitate early treatment, which has been shown to minimize organ damage and improve quality of life.

Yip, J., Zeig-Owens, R., Webber, M.P., Kablanian, A., Hall, C.B., Vossbrinck, M., Liu, X., Weakley, J., Schwartz, T., Kelly, K.J., Prezant, D.J. (2015) "World Trade Center-related physical and mental health burden among New York City Fire Department emergency medical service workers." Occup Environ Med. *doi:10.1136*

OBJECTIVES: To describe the health burden among Fire Department of the City of New York (FDNY) emergency medical service (EMS) workers and examine its association with work at the World Trade Center (WTC) disaster site.
METHODS: In this observational cohort study, we used FDNY physician diagnoses to estimate the cumulative incidence of physical health conditions including rhinosinusitis, gastroesophageal reflux disease (GERD), obstructive airways disease (OAD) and cancer among EMS workers and demographically similar

firefighters who were active on 11 September 2001 (9/11). Validated screening instruments were used to estimate the prevalence of probable post-traumatic stress disorder (PTSD), probable depression and probable harmful alcohol use. We also analysed the association between health conditions and WTC-exposure.
RESULTS: Among 2281 EMS workers, the 12-year post-9/11 cumulative incidence (11 September 2001 to 31 December 2013) of rhinosinusitis was 10.6%; GERD 12.1%; OAD 11.8%; cancer 3.1%. The prevalence of probable PTSD up to 12 years after exposure was 7%; probable depression 16.7%; and probable harmful alcohol use 3%. Compared with unexposed, EMS workers who arrived earliest at the site had higher adjusted relative risks (aRR) for most conditions, including rhinosinusitis (aRR=3.7; 95% CI 2.2 to 6.0); GERD (aRR=3.8; 95% CI 2.4 to 6.1); OAD (aRR=2.4: 95% CI 1.7 to 3.6); probable PTSD (aRR=7.0; 95% CI 3.6 to 13.5); and, probable depression (aRR=2.3; 95% CI 1.6 to 3.1).
CONCLUSIONS: In this 12-year study, we documented a high burden of health conditions associated with WTC-exposure among FDNY EMS workers. These findings underscore the importance of continued monitoring and treatment of this workforce.

2016

Kwon S, Putman B, Weakley J, Hall CB, Zeig-Owens R, Schwartz T, Olivieri B, Singh A, Huie M, Morrison D, Webber MP, Cohen HW, Kelly KJ, Aldrich TK, Nolan A, Prezant DJ, Shohet MR, Weiden MD. (2016) "Blood Eosinophils and World Tade Center Exposure Predict Surgery in Chronic Rhinosinusitis: A 13.5-Year Longitudinal Study." Ann Am Thorac Soc. *doi: 10.1513*

OBJECTIVES:To identify predictors of surgical intervention for chronic rhinosinusitis in firefighters exposed to airborne irritants at the WTC collapse site.
METHODS:We assessed in 8,227 firefighters with WTC-exposure between 9/11/2001 (9/11) and 9/25/2001, including WTC-site arrival time, months of rescue/recovery work, and eosinophil concentration measured between 9/11 and 3/10/2003. We assessed the association of serum cytokines and immunoglobulins with eosinophil concentration and surgery for rhinosinusitis in 112 surgical cases and 376 controls with serum available from the first 6 months after exposure to the WTC collapse site.
MEASUREMENTS AND MAIN RESULTS: Between 9/11 and 3/10/2015, the surgery rate was 0.47 cases per 100 person years. In the first 18 months post 9/11, surgical patients had higher mean blood eosinophil levels than study cohort patients(219±155 vs. 191±134; P <0.0001). Increased surgery risk was associated with increasing blood eosinophil counts (HR 1.12 per 100 cells/uL; 95% CI 1.07 to1.17; P <0.001); arriving at the WTC site 9/11 or 9/12/2001 (HR 1.43; 95% CI 1.04 to 1.99; P=0.03); and working ≥6 months at the WTC-site (HR 1.48; 95% CI 1.14 to 1.93; P<0.01). Median blood eosinophil levels for surgery patients were above levels for the cohort in all 18-month intervals 3/11/2000 through 3/10/2015 using 51,163 measurements representing 97,733 person-years of observation. Increasing age, increasing IL-17A and low IgA in serum from 2001-2002 predicted blood eosinophil concentration in surgical patients but not in controls (R2=0.26, p<0.0001 vs. R2=0.008, p=0.56).
CONCLUSIONS: Increasing blood eosinophil concentration predicts surgical intervention for chronic rhinosinusitis, particularly in those with intense acute and prolonged exposure to airborne irritants. WTC-exposed FDNY firefighters who underwent irritant-associated sinus surgery are immunologically different from the cohort. Surgical patients have a higher blood eosinophil levels that is associated with mediators of mucosal immunity.

Girvin F., Zeig-Owens R., Gupta D., Schwartz T., Liu Y., Weiden M.D., Prezant D.J., Naidich D.P. (2016) "Radiologic Features of World Trade Center-related Sarcoidosis in Exposed NYC Fire Department Rescue Workers." J Thoracic Imaging. *doi: 10.1097*

PURPOSE: An increased incidence of sarcoidosis has been demonstrated in firefighters, supporting the concern that occupational/environmental exposure may pose an etiologic risk factor. This incidence increased further after September 11, 2001 following exposure to World Trade Center (WTC) dust and gases. We review computed tomography (CT) features in this population, comparing the range of findings and physiological correlates with those typically reported in unexposed individuals with pulmonary sarcoidosis.
MATERIALS AND METHODS: With CT imaging we retrospectively identified 46 patients with WTC-

related sarcoidosis, between March 18, 2002 and April 5, 2014. Scans were independently reviewed by 2 dedicated thoracic radiologists and assessed for disease patterns and correlation with pulmonary functions. RESULTS: The majority (37/46; 80%) had symmetric mediastinal and hilar lymphadenopathy. Similarly, most (38/46; 83%) had perilymphatic nodules. Foci of ill-defined ground glass attenuation were present in 6 (13%). Coalescent nodularity was present in 15 (33%). Only 3 (7%) had parenchymal reticulation. A mixed pattern of lung findings was present in 21 (46%). When all forms of parenchymal disease were scored by zonal distribution, 21 (46%) had parenchymal disease predominantly involving mid and upper lungs; 11/46 (24%) had a random distribution without zonal predominance; 6/46 (13%) demonstrated atypical lower zone predominance. Whereas 15/46 (33%) had obstructive airways disease on pulmonary function tests, there were no CT findings that were predictive of obstructive airways disease. CONCLUSIONS: The majority of cases of WTC-related sarcoidosis demonstrated typical radiographic appearances of sarcoidosis, with symmetric hilar and mediastinal lymphadenopathy and mid to upper lung perilymphatic nodules; these findings were consistent with other previously reported cases of sarcoid-like granulomatous disease in association with various alternate underlying etiologies. There was no correlation between disease patterns or extent on CT and pulmonary function testing, likely at least in part due to the overall mild extent of disease in this population.

Yip J, Zeig-Owens R, Webber MP, Kablanian A, Hall CB, Vossbrinck M, Liu X, Weakley J, Schwartz T, Kelly KJ, Prezant DJ. (2016) "Health conditions as mediators of the association between World Trade Center exposure and health-related quality of life in firefighters and EMS workers." J OccupEnviron Med. *doi: 10.1136*

OBJECTIVE: Studies have reported reduced health-related quality of life (HrQoL) in rescue/recovery workers for years post-disaster. Few have examined specific post-disaster physical and mental health conditions as mediators of the association between exposure to disaster and HrQoL.
METHODS: We used the Short Form-12 to measure HrQoL in 7,190 male World Trade Center (WTC)-exposed first responders. Potential mediators included physician diagnoses obtained from medical records and mental health conditions obtained from questionnaires.
RESULTS: Among moderately and highly WTC-exposed workers, health conditions fully mediated the observed relationship between WTC-exposure and physical health functioning of HrQoL, and substantially mediated the association between WTC-exposure and mental health functioning.
CONCLUSIONS: Because WTC-related health conditions explain the relationship between WTC-exposure and HrQoL, medical monitoring with treatment of affected populations is necessary to mitigate the adverse effects of WTC-exposure on HrQoL.

Aldrich, T.K., Vossbrinck, M., Zeig-Owens, R., Hall, C.B., Schwartz, T., Moir, W., Webber, M.P., Cohen, H., Nolan A., Weiden, M.D., Christodoulou, V., Kelly, K.J., Prezant, D.J. (2016) "Lung function trajectories in WTC-exposed NYC firefighters over 13 years: the roles of smoking and smoking cessation. CHEST. *doi: 10.1016*

BACKGROUND: World Trade Center (WTC)-exposed Fire Department of the City of New York firefighters lost, on average, 10% of lung function after September 11, 2011, and >10% developed new obstructive airways disease. There was little recovery (on average) over the first 6 years. Follow-up into the next decade allowed us to determine the longer-term exposure effects and the roles of cigarette smoking and cessation on lung function trajectories.
METHODS: We examined serial measurements of FEV1 from March 11, 2000, to September 10, 2014, among 10,641 WTC-exposed Fire Department of the City of New York firefighters with known smoking and body weight histories.
RESULTS: The median number of FEV1 measurements during follow-up was 9; 15% of firefighters arrived at the WTC during the morning of September 11, 2001; and 65% never smoked. Firefighters arriving the morning of September 11, 2001 averaged lower lung function than did lesser exposed firefighters; this difference remained significant during most of follow-up ($P < .05$). Never smokers had significantly better lung function than current smokers; former smokers fell in between, depending upon their cessation date. Those arriving the morning of September 11, 2001 were more likely to have an FEV1 < lower limits of normal compared with those arriving between September 13, 2001, and September 24, 2001 (OR = 1.70, $P < .01$). Current smokers were more likely to have an FEV1 < lower limits of normal compared with never smokers (OR = 2.06, $P < .01$), former smokers who quit before September 11, 2001 (OR = 1.96, $P < .01$), or those who quit between September 11, 2001 and March 10, 2008 (OR = 1.49, $P < .01$).

CONCLUSIONS: Thirteen years after September 11, 2001, most firefighters continued to show a lack of lung function recovery, with the trajectory of decline differing by WTC exposure and smoking status. Unlike the immutable effect of WTC exposure, we demonstrated the benefit on lung function of smoking cessation in this unique occupational/environmental cohort

Zeig-Owens, R., Kablanian, A., Webber, M.P., Liu Y., Mayerson E., Schwartz, T., Jaber, N., Kelly, K.J., Prezant, D.J. (2016) "Agreement between self-reported cancer diagnoses and confirmed cancer diagnoses in New York City firefighters and EMS workers." Public Health Reports. 131(1):153-9.

OBJECTIVES: Because of the delay in availability of cancer diagnoses from state cancer registries, self-reported diagnoses may be valuable in assessing the current cancer burden in many populations. We evaluated agreement between self-reported cancer diagnoses and state cancer registry-confirmed diagnoses among 21,437 firefighters and emergency medical service workers from the Fire Department of the City of New York. We also investigated the association between World Trade Center (WTC) exposure and other characteristics in relation to accurate reporting of cancer diagnoses.
METHODS: Participants self-reported cancer status in questionnaires from October 2, 2001, to December 31, 2011. We obtained data on confirmed cancer diagnoses from nine state cancer registries, which we used as our gold standard. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), comparing self-reported cancer diagnoses with confirmed cancer diagnoses. We used multivariable logistic regression models to assess the association between WTC exposure and correct self-report of cancer status, false-positive cancer reports, and false-negative cancer reports.
RESULTS: Sensitivity and specificity for all cancers combined were 90.3% and 98.7%, respectively. Specificities and NPVs remained high in different cancer types, while sensitivities and PPVs varied considerably. WTC exposure was not associated with accurate reporting.
CONCLUSION: We found high specificities, NPVs, and general concordance between self-reported cancer diagnoses and registry-confirmed diagnoses. Given the low population prevalence of cancer, self-reported cancer diagnoses may be useful for determining non-cancer cases. Because of the low sensitivities and PPVs for some individual cancers, however, case confirmation with state cancer registries or medical records remains critically important.

Webber, M.P., Moir, W., Zeig-Owens, R., Glaser, M.S., Jaber, N., Hall, C., Berman, J., Qayyum, B., Loupsasakis, K., Kelly, K.J., Prezant, D.J. (2016) "Incidence of Systemic Autoimmune Diseases in World Trade Center-Exposed Firefighters and Emergency Medical Workers." Mayo Clin Proc. 91(1):23-32.

OBJECTIVE: To estimate the incidence of selected systemic autoimmune diseases (SAIDs) in approximately 14,000 male rescue/recovery workers enrolled in the Fire Department of the City of New York (FDNY) World Trade Center (WTC) Health Program and to compare FDNY incidence to rates from demographically similar men in the Rochester Epidemiology Project (REP), a population-based database in Olmsted County, Minnesota.
PATIENTS AND METHODS: We calculated incidence for specific SAIDs (rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, and others) and combined SAIDs diagnosed from September 12, 2001, through September 11, 2014, and generated expected sex- and age-specific rates based on REP rates. Rates were stratified by level of WTC exposure (higher vs lower). Standardized incidence ratios (SIRs), which are the ratios of the observed number of cases in the FDNY group to the expected number of cases based on REP rates, and 95% CIs were calculated.
RESULTS: We identified 97 SAID cases. Overall, FDNY rates were not significantly different from expected rates (SIR, 0.97; 95% CI, 0.77-1.21). However, the lower WTC exposure group had 9.9 fewer cases than expected, whereas the higher WTC exposure group had 7.7 excess cases.
CONCLUSION: Most studies indicate that the healthy worker effect reduces the association between exposure and outcome by about 20%, which we observed in the lower WTC exposure group. Overall rates masked differences in incidence by level of WTC exposure, especially because the higher WTC exposure group was relatively small. Continued surveillance for early detection of SAIDs in high WTC exposure populations is required to identify and treat exposure-related adverse effects.

Boffetta, P., Zeig-Owens, R., Wallenstein, S., Li, J., Brackbill, R., Cone, J., Farfel, M., Holden W., Lucchini R., Webber M.P., Prezant, D.J., Stellman, S. (2016) "Cancer in World Trade Center responders: Findings from multiple cohorts and options for future study. Am J Ind Med. 59(2):96-105.

BACKGROUND: Three longitudinal studies of cancer incidence in varied populations of World Trade Center responders have been conducted.
METHODS: We compared the design and results of the three studies.
RESULTS: Separate analyses of these cohorts revealed excess cancer incidence in responders for all cancers combined and for cancers of the thyroid and prostate. Methodological dissimilarities included recruitment strategies, source of cohort members, demographic characteristics, overlap between cohorts, assessment of WTC and other occupational exposures and confounders, methods and duration of follow-up, approaches for statistical analysis, and latency analyses.
CONCLUSIONS: The presence of three cohorts strengthens the effort of identifying and quantifying the cancer risk; the heterogeneity in design might increase sensitivity to the identification of cancers potentially associated with exposure. The presence and magnitude of an increased cancer risk remains to be fully elucidated. Continued long-term follow up with minimal longitudinal dropout is crucial to achieve this goal.

Weakley, J., Hall, C.B., Webber, M.P., Liu, X., Zeig_Owens, R., Cohen, H., Aldrich, T.K., Prezant, D.J. (2016) "The effect of World Trade Center exposure on the latency of chronic rhinosinusitis diagnoses in NYC Firefighters: 2001-2011." Occup Environ Med. 73(4):280-3.

OBJECTIVE: To assess how the effect of World Trade Center (WTC) exposure on physician-diagnosed chronic rhinosinusitis (CRS) in firefighters changed during the decade following the attack on 9/11 (11 September 2001 to 10 September 2011).
METHODS: We examined temporal effects on the relation between WTC exposure and the incidence of physician diagnosed CRS in firefighters changed during the decade following the attack on 9/11 (11 September 2001 to 10 September 2011). Exposure was grouped by time of arrival at the WTC site as follows: (high) morning 11 September 2001 (n=1623); (moderate) afternoon 11 September 2001 or 12 September 2001 (n=7025); or (low) 13-24 September 2001 (n=1200). Piecewise exponential survival models were used to estimate incidences by exposure group, with change points in the relative incidences estimated by maximum likelihood.
RESULTS: Incidences dramatically increased after 2007 due to a programmatic change that provided free medical treatment, but increases were similar in all exposure groups. For this reason, we observed no change point during the study period, meaning the relative incidence by exposure group (high vs moderate vs low) of CRS disease did not significantly change over the study period. The relative rate of developing CRS was 1.99 (95% CI=1.64 to 2.41) for high versus low exposure, and 1.52 (95% CI=1.28 to 1.80) for moderate versus low exposure during the 10-year follow-up period.
CONCLUSIONS:The risk of CRS in FDNY firefighters appears increased with WTC-exposure, and has not diminished by time since exposure.

Aldrich, T.K., Weakley, J., Dhar, S., Hall, C.B., Crosse, T., Banauch, G.I., Weiden, M.D., Izbicki, G., Cohen, H.W., Gupta, A., King, C., Christodoulou, V., Webber, M.P., Zeig-Owens, R., Moir, W., Nolan, A., Kelly, K..J., Prezant, D.J. (2016) "Bronchial reactivity and the course of lung function 13 years after World Trade Center exposure." Chest. *Doi: 10.1016*

BACKGROUND: World Trade Center (WTC)-exposed rescue/recovery workers endured massive respiratory insult from inhalation of particulate matter and gases, resulting in respiratory symptoms, loss of lung function, and, for many, bronchial hyperreactivity (BHR). The persistence of respiratory symptoms and lung function abnormalities has been well-documented, while persistence of BHR has not been investigated.
METHODS:173 WTC-exposed firefighters with bronchial reactivity measured within 2 years after 9/11/2001 (9/11), (baseline methacholine challenge test [MCT]), were re-evaluated in 2013-2014 (follow-up-MCT). FEV1 measurements were obtained from the late pre-9/11, early post-9/11 and late post-9/11 periods. Respiratory symptoms and corticosteroid treatment were recorded.
RESULTS: Bronchial reactivity remained stable (within 1 doubling dilution) for most (n=101, 58%). 16 of 28 (57%) with BHR (PC20<8mg/ml) at baseline had BHR at follow up, and an additional 27 of the 145 (19%) without BHR at baseline had BHR at follow-up. In multivariable models, we found that BHR baseline was strongly associated with BHR follow-up (OR=6.46) and that BHR at follow-up was associated with an estimated 15.4 ml/year greater FEV1 decline than experienced by those without BHR at follow-up. Annual FEV1 decline was moderated by corticosteroid use.

CONCLUSIONS: Persistent BHR and its deleterious influence on lung function suggest a role for airway inflammation in perpetuation of WTC-associated airway disease. In future massive occupational exposure to inorganic dust/gases, we recommend early and serial pulmonary function testing, including measurements of bronchial reactivity, when possible, and inhaled corticosteroid therapy for those with symptoms or pulmonary function tests consistent with airway disease.

Yip, J., Webber, M.P., Zeig-Owens, R., Vossbrinck, M., Singh, A., Kelly, K., Prezant, D.J. "FDNY and 9/11: Clinical services and health outcomes in World Trade Center-exposed firefighters and EMS workers from 2001-2016." Am J Ind Med.

BACKGROUND: After the World Trade Center (WTC) attacks on September 11, 2001, the Fire Department of the City of New York (FDNY) instituted a WTC medical monitoring and treatment program and established a data center to document health outcomes in the WTC-exposed workforce of ~16,000 firefighters and EMS workers.
METHODS: FDNY schedules routine monitoring exams every 12-18 months and physical and mental health treatment appointments, as required.
RESULTS: FDNY research studies have consistently found that early arrival to work and/or prolonged work at the WTC-site increased the risks for adverse physical and mental health outcomes. To date, a substantial proportion has been diagnosed with obstructive airways disease, chronic rhinosinusitis, and gastroesophageal reflux disease; a quarter has two or more of these conditions.
CONCLUSIONS: While much has been learned, the entire spectrum and trajectory of WTC-related disorders and their mechanisms of onset and persistence remain to be fully described.

Moir, W., Zeig-Owens, R., Daniels, R.D., Hall, C.B., Webber, M.P., Jaber, N., Yiin, J.H., Schwartz, T., Liu, X., Vossbrinck, M., Kelly, K., Prezant, D. "Post-9/11 cancer incidence in World Trade Center-exposed New York City firefighters as compared to a pooled cohort of firefighters from San Francisco, Chicago and Philadelphia (9/11/2001-2009)." Am J Ind Med.

BACKGROUND: We previously reported a modest excess of cancer cases in World Trade Center (WTC) exposed firefighters as compared with the general population. This study aimed to separate the potential carcinogenic effects of firefighting and WTC-exposure by using a cohort of non-WTC-exposed firefighters as the referent group.
Methods: Relative rates (RRs) for all cancers combined and individual cancer subtypes from 9/11/2001-12/31/2009 were modelled using Poisson regression comparing 11,457 WTC-exposed firefighters to 8,220 non-WTC-exposed firefighters from San Francisco, Chicago, and Philadelphia.
Results: Compared with non-WTC-exposed firefighters, there was no difference in the RR of all cancers combined for WTC-exposed firefighters (RR=0.96, 95% CI: 0.83-1.12). Thyroid cancer was significantly elevated (RR=3.82, 95% CI: 1.07-20.81) over the entire study; this was attenuated (RR=3.43, 95% CI: 0.94-18.94) and non-significant in a secondary analysis controlling for possible surveillance bias. Prostate cancer was elevated during the latter half (1/1/2005-12/31/2009; RR=1.38, 95% CI: 1.01-1.88).
Conclusions: Further follow-up is needed with this referent population to assess the relationship between WTC-exposure and cancers with longer latency periods.

Zeig-Owens, R., Nolan, A., Putman, B., Singh, A., Prezant, D.J., Weiden, M.D. "Biomarkers of Patient Intrinsic Risk for Upper and Lower Airway Injury after Exposure to the World Trade Center Atrocity." Am J Ind Med.

Background: High rates of upper and lower airways disease have occurred in Fire Department of the City of New York (FDNY) workers exposed to the World Trade Center (WTC) disaster site. Most experienced acute declines in pulmonary function, and some continued to experience decline over 14 years of follow-up. Similarly, some with rhinosinusitis had symptoms requiring sinus surgery. Aim: To increase generalizability of biomarker investigation, we describe biomarkers of risk for upper and lower airway injury that do not require stored serum. Methods: We review WTC biomarker literature. Results: Cytokines expressed in stored serum from the first 6 months post-9/11 can identify individuals at higher risk for future abnormal pulmonary function. Conclusion: This research will help identify individuals at high risk of lung and sinus disease that develop after these, or future, irritant exposures for intensive monitoring and treatment. It may also identify targets for effective therapeutic interventions.

2017

Caraher, E. J., et al. (2017). "Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: A case-cohort study and murine model of acute particulate exposure." PLoS One **12**(9): e0184331.

World Trade Center-particulate matter(WTC-PM) exposure and metabolic-risk are associated with WTC-Lung Injury(WTC-LI). The receptor for advanced glycation end-products (RAGE) is most highly expressed in the lung, mediates metabolic risk, and single-nucleotide polymorphisms at the AGER-locus predict forced expiratory volume(FEV). Our objectives were to test the hypotheses that RAGE is a biomarker of WTC-LI in the FDNY-cohort and that loss of RAGE in a murine model would protect against acute PM-induced lung disease. We know from previous work that early intense exposure at the time of the WTC collapse was most predictive of WTC-LI therefore we utilized a murine model of intense acute PM-exposure to determine if loss of RAGE is protective and to identify signaling/cytokine intermediates. This study builds on a continuing effort to identify serum biomarkers that predict the development of WTC-LI. A case-cohort design was used to analyze a focused cohort of male never-smokers with normal pre-9/11 lung function. Odds of developing WTC-LI increased by 1.2, 1.8 and 1.0 in firefighters with soluble RAGE (sRAGE)>/=97pg/mL, CRP>/=2.4mg/L, and MMP-9</=397ng/mL, respectively, assessed in a multivariate logistic regression model (ROCAUC of 0.72). Wild type(WT) and RAGE-deficient(Ager-/-) mice were exposed to PM or PBS-control by oropharyngeal aspiration. Lung function, airway hyperreactivity, bronchoalveolar lavage, histology, transcription factors and plasma/BAL cytokines were quantified. WT-PM mice had decreased FEV and compliance, and increased airway resistance and methacholine reactivity after 24-hours. Decreased IFN-gamma and increased LPA were observed in WT-PM mice; similar findings have been reported for firefighters who eventually develop WTC-LI. In the murine model, lack of RAGE was protective from loss of lung function and airway hyperreactivity and was associated with modulation of MAP kinases. We conclude that in a multivariate adjusted model increased sRAGE is associated with WTC-LI. In our murine model, absence of RAGE mitigated acute deleterious effects of PM and may be a biologically plausible mediator of PM-related lung disease.

Cleven, K. L., et al. (2017). "Airway Disease in Rescue/Recovery Workers: Recent Findings from the World Trade Center Collapse." Curr Allergy Asthma Rep **17**(1): 5.

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. 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.

Liu, X., et al. (2017). "The Effect of World Trade Center Exposure on the Timing of Diagnoses of Obstructive Airway Disease, Chronic Rhinosinusitis, and Gastroesophageal Reflux Disease." Front Public Health **5**: 2.

OBJECTIVES: In a cohort of rescue/recovery workers exposed to the dust that resulted from the collapse of the World Trade Center (WTC), we assessed how a diagnosis of obstructive airways disease (OAD) affected the likelihood of a subsequent diagnosis of chronic rhinosinusitis (CRS) or gastroesophageal reflux disease (GERD). We also assessed whether OAD acted as a mediator of the association between exposure to the WTC rescue/recovery effort and CRS and GERD diagnoses. METHODS: In this prospective cohort study, we analyzed Fire Department of the City of New York physician diagnoses of OAD, CRS, and GERD that were first documented between September 11, 2001, and September 10, 2011, among 8,968 WTC-exposed firefighters. We used piecewise exponential survival models to evaluate whether OAD was a risk factor for either CRS or GERD and to assess OAD as a possible mediator. RESULTS: An OAD diagnosis significantly increased the risks for subsequent CRS [relative rate (RR), 4.24; 95% CI, 3.78-4.76] and GERD (RR, 3.21; 95% CI, 2.93-3.52) diagnoses. Further, 21% of the WTC exposure effect (high vs. low intensity) on GERD and 13% of the effect (high vs. low intensity) on CRS were mediated by a prior OAD diagnosis.

CONCLUSION: Individuals with an OAD diagnosis had elevated risks for subsequent diagnoses of CRS or GERD. Part of the effect of WTC exposure on CRS and GERD diagnoses is mediated by prior diagnoses of OAD; this mediation effect of OAD may reflect biological pathways or healthcare utilization practices.

Vossbrinck, M., et al. (2017). "Post-9/11/2001 lung function trajectories by sex and race in World Trade Center-exposed New York City emergency medical service workers." Occup Environ Med **74**(3): 200-203.

OBJECTIVE: To determine whether lung function trajectories after 9/11/2001 (9/11) differed by sex or race/ethnicity in World Trade Center-exposed Fire Department of the City of New York emergency medical service (EMS) workers. METHOD: Serial cross-sectional study of pulmonary function tests (PFTs) taken between 9/11 and 9/10/2015. We used data from routine PFTs (forced expiratory volume in 1 s (FEV(1)) and FEV(1)% predicted), conducted at 12-18 month intervals. FEV(1) and FEV(1)% predicted were assessed over time, stratified by sex, and race/ethnicity. We also assessed FEV(1) and FEV(1)% predicted in current, former and never-smokers. RESULTS: Among 1817 EMS workers, 334 (18.4%) were women, 979 (53.9%) self-identified as white and 939 (51.6%) were never-smokers. The median follow-up was 13.1 years (IQR 10.5-13.6), and the median number of PFTs per person was 11 (IQR 7-13). After large declines associated with 9/11, there was no discernible recovery in lung function. In analyses limited to never-smokers, the trajectory of decline in adjusted FEV(1) and FEV(1)% predicted was relatively parallel for men and women in the 3 racial/ethnic groups. Similarly, small differences in FEV(1) annual decline between groups were not clinically meaningful. Analyses including ever-smokers were essentially the same. CONCLUSIONS: 14 years after 9/11, most EMS workers continued to demonstrate a lack of lung function recovery. The trajectories of lung function decline, however, were parallel by sex and by race/ethnicity. These findings support the use of routine, serial measures of lung function over time in first responders and demonstrate no sex or racial sensitivity to exposure-related lung function decline.

Webber, M. P., et al. (2017). "Post-9/11 sarcoidosis in WTC-exposed firefighters and emergency medical service workers." Respir Med **132**: 232-237.

INTRODUCTION: The World Trade Center (WTC) disaster released a huge quantity and variety of toxicants into the environment. To-date, studies from each of the three major cohorts of WTC-exposed workers have suggested "greater than expected" numbers of post-9/11 cases in some workers. We undertook this study to estimate the incidence of post-9/11 sarcoidosis in approximately 13,000 male firefighters and EMS workers enrolled in The Fire Department of the City of New York (FDNY) WTC Health Program; to compare FDNY incidence to rates from unexposed, demographically similar men in the Rochester Epidemiology Project (REP); and, to examine rates by level of WTC exposure. METHODS: We calculated incidence of sarcoidosis diagnosed from 9/12/2001 to 9/11/2015, and generated expected sex- and age-specific rates based on REP rates. Standardized incidence ratios (SIR) based on REP rates, and 95% confidence intervals (95% CI) were estimated. Two sensitivity analyses limited cases to those with intra-thoracic symptoms or biopsy confirmation. RESULTS: We identified 68 post-9/11 cases in the FDNY cohort. Overall, FDNY rates were significantly higher than expected rates (SIR = 2.8; 95% CI = 2.2, 3.6). Including only symptomatic cases, the SIR decreased (SIR = 2.2; 95% CI = 1.5, 3.0), but remained significantly elevated. SIRs ranged from 2.7 (95% CI = 2.0, 3.5) in the lower WTC exposure group to 4.2 (95% CI = 1.9, 8.0) in the most highly exposed. CONCLUSIONS: We found excess incident post-9/11 sarcoidosis in WTC-exposed workers. Continued surveillance, particularly of those most highly exposed, is necessary to identify those with sarcoidosis and to follow them for possible adverse effects including functional impairments and organ damage.

2018

Crowley, G., et al. (2018). "Metabolomics of World Trade Center-Lung Injury: a machine learning approach." BMJ Open Respir Res **5**(1): e000274.

INTRODUCTION: Biomarkers of metabolic syndrome expressed soon after World Trade Center (WTC) exposure predict development of WTC Lung Injury (WTC-LI). The metabolome remains an untapped resource with potential to comprehensively characterise many aspects of WTC-LI. This case-control study identified a clinically relevant, robust subset of metabolic contributors of WTC-LI through comprehensive high-dimensional metabolic profiling and integration of machine learning techniques. METHODS: Never-smoking, male, WTC-exposed firefighters with normal pre-9/11 lung function were segregated by post-9/11

lung function. Cases of WTC-LI (forced expiratory volume in 1s <lower limit of normal, n=15) and controls (n=15) were identified from previous cohorts. The metabolome of serum drawn within 6 months of 9/11 was quantified. Machine learning was used for dimension reduction to identify metabolites associated with WTC-LI. RESULTS: 580 metabolites qualified for random forests (RF) analysis to identify a refined metabolite profile that yielded maximal class separation. RF of the refined profile correctly classified subjects with a 93.3% estimated success rate. 5 clusters of metabolites emerged within the refined profile. Prominent subpathways include known mediators of lung disease such as sphingolipids (elevated in cases of WTC-LI), and branched-chain amino acids (reduced in cases of WTC-LI). Principal component analysis of the refined profile explained 68.3% of variance in five components, demonstrating class separation. CONCLUSION: Analysis of the metabolome of WTC-exposed 9/11 rescue workers has identified biologically plausible pathways associated with loss of lung function. Since metabolites are proximal markers of disease processes, metabolites could capture the complexity of past exposures and better inform treatment. These pathways warrant further mechanistic research.

Haider, S. H., et al. (2018). "Predictive Biomarkers of Gastroesophageal Reflux Disease and Barrett's Esophagus in World Trade Center Exposed Firefighters: a 15 Year Longitudinal Study." Sci Rep **8**(1): 3106.

Gastroesophageal reflux disease (GERD) and Barrett's Esophagus (BE), which are prevalent in the World Trade Center (WTC) exposed and general populations, negatively impact quality of life and cost of healthcare. GERD, a risk factor of BE, is linked to obstructive airways disease (OAD). We aim to identify serum biomarkers of GERD/BE, and assess the respiratory and clinical phenotype of a longitudinal cohort of never-smoking, male, WTC-exposed rescue workers presenting with pulmonary symptoms. Biomarkers collected soon after WTC-exposure were evaluated in optimized predictive models of GERD/BE. In the WTC-exposed cohort, the prevalence of BE is at least 6 times higher than in the general population. GERD/BE cases had similar lung function, D (LCO) , bronchodilator response and long-acting beta-agonist use compared to controls. In confounder-adjusted regression models, TNF-alpha >/= 6 pg/mL predicted both GERD and BE. GERD was also predicted by C-peptide >/= 360 pg/mL, while BE was predicted by fractalkine >/= 250 pg/mL and IP-10 >/= 290 pg/mL. Finally, participants with GERD had significantly increased use of short-acting beta-agonist compared to controls. Overall, biomarkers sampled prior to GERD/BE presentation showed strong predictive abilities of disease development. This study frames future investigations to further our understanding of aerodigestive pathology due to particulate matter exposure.

Hena, K. M., et al. (2018). "Clinical Course of Sarcoidosis in World Trade Center-Exposed Firefighters." Chest **153**(1): 114-123.

BACKGROUND: Sarcoidosis is believed to represent a genetically primed, abnormal immune response to an antigen exposure or inflammatory trigger, with both genetic and environmental factors playing a role in disease onset and phenotypic expression. In a population of firefighters with post-World Trade Center (WTC) 9/11/2001 (9/11) sarcoidosis, we have a unique opportunity to describe the clinical course of incident sarcoidosis during the 15 years postexposure and, on average, 8 years following diagnosis. METHODS: Among the WTC-exposed cohort, 74 firefighters with post-9/11 sarcoidosis were identified through medical records review. A total of 59 were enrolled in follow-up studies. For each participant, the World Association of Sarcoidosis and Other Granulomatous Diseases organ assessment tool was used to categorize the sarcoidosis involvement of each organ system at time of diagnosis and at follow-up. RESULTS: The incidence of sarcoidosis post-9/11 was 25 per 100,000. Radiographic resolution of intrathoracic involvement occurred in 24 (45%) subjects. Lung function for nearly all subjects was within normal limits. Extrathoracic involvement increased, most prominently joints (15%) and cardiac (16%) involvement. There was no evidence of calcium dysmetabolism. Few subjects had ocular (5%) or skin (2%) involvement, and none had beryllium sensitization. Most (76%) subjects did not receive any treatment. CONCLUSIONS: Extrathoracic disease was more prevalent in WTC-related sarcoidosis than reported for patients with sarcoidosis without WTC exposure or for other exposure-related granulomatous diseases (beryllium disease and hypersensitivity pneumonitis). Cardiac involvement would have been missed if evaluation stopped after ECG, 48-h recordings, and echocardiogram. Our results also support the need for advanced cardiac screening in asymptomatic patients with strenuous, stressful, public safety occupations, given the potential fatality of a missed diagnosis.

Landgren, O., et al. (2018). "Multiple Myeloma and Its Precursor Disease Among Firefighters Exposed to the World Trade Center Disaster." JAMA Oncol **4**(6): 821-827.

IMPORTANCE: The World Trade Center (WTC) attacks on September 11, 2001, created an unprecedented environmental exposure to known and suspected carcinogens suggested to increase the risk of multiple myeloma. Multiple myeloma is consistently preceded by the precursor states of monoclonal gammopathy of undetermined significance (MGUS) and light-chain MGUS, detectable in peripheral blood. OBJECTIVE: To characterize WTC-exposed firefighters with a diagnosis of multiple myeloma and to conduct a screening study for MGUS and light-chain MGUS. DESIGN, SETTING, AND PARTICIPANTS: Case series of multiple myeloma in firefighters diagnosed between September 11, 2001, and July 1, 2017, together with a seroprevalence study of MGUS in serum samples collected from Fire Department of the City of New York (FDNY) firefighters between December 2013 and October 2015. Participants included all WTC-exposed FDNY white, male firefighters with a confirmed physician diagnosis of multiple myeloma (n = 16) and WTC-exposed FDNY white male firefighters older than 50 years with available serum samples (n = 781). EXPOSURES: WTC exposure defined as rescue and/or recovery work at the WTC site between September 11, 2001, and July 25, 2002. MAIN OUTCOMES AND MEASURES: Multiple myeloma case information, and age-adjusted and age-specific prevalence rates for overall MGUS (ie, MGUS and light-chain MGUS), MGUS, and light-chain MGUS. RESULTS: Sixteen WTC-exposed white male firefighters received a diagnosis of multiple myeloma after September 11, 2001; median age at diagnosis was 57 years (interquartile range, 50-68 years). Serum/urine monoclonal protein isotype/free light-chain data were available for 14 cases; 7 (50%) had light-chain multiple myeloma. In a subset of 7 patients, myeloma cells were assessed for CD20 expression; 5 (71%) were CD20 positive. In the screening study, we assayed peripheral blood from 781 WTC-exposed firefighters. The age-standardized prevalence rate of MGUS and light-chain MGUS combined was 7.63 per 100 persons (95% CI, 5.45-9.81), 1.8-fold higher than rates from the Olmsted County, Minnesota, white male reference population (relative rate, 1.76; 95% CI, 1.34-2.29). The age-standardized prevalence rate of light-chain MGUS was more than 3-fold higher than in the same reference population (relative rate, 3.13; 95% CI, 1.99-4.93). CONCLUSIONS AND RELEVANCE: Environmental exposure to the WTC disaster site is associated with myeloma precursor disease (MGUS and light-chain MGUS) and may be a risk factor for the development of multiple myeloma at an earlier age, particularly the light-chain subtype.

Putman, B., et al. (2018). "Risk factors for post-9/11 chronic rhinosinusitis in Fire Department of the City of New York workers." Occup Environ Med **75**(12): 884-889.

OBJECTIVES: Chronic rhinosinusitis (CRS) has high socioeconomic burden but underexplored risk factors. The collapse of the World Trade Center (WTC) towers on 11 September 2001 (9/11) caused dust and smoke exposure, leading to paranasal sinus inflammation and CRS. We aim to determine which job tasks are risk factors for CRS in WTC-exposed Fire Department of the City of New York (FDNY) firefighters and emergency medical services (EMS) workers. METHODS: This cohort study included a 16-year follow-up of 11 926 WTC-exposed FDNY rescue/recovery workers with data on demographics, WTC exposure, job tasks and first post-9/11 complete blood counts. Using multivariable Cox regression, we assessed the associations of WTC exposure, work assignment (firefighter/EMS), digging and rescue tasks at the WTC site and blood eosinophil counts with subsequent CRS, adjusting for potential confounders. RESULTS: The rate of CRS was higher in firefighters than EMS (1.80/100 person-years vs 0.70/100 person-years; $p<0.001$). The combination of digging and rescue work was a risk factor for CRS (HR 1.54, 95% CI 1.23 to 1.94, $p<0.001$) independent of work assignment and WTC exposure. CONCLUSIONS: Compared with EMS, firefighters were more likely to engage in a combination of digging and rescue work, which was a risk factor for CRS. Chronic irritant exposures associated with digging and rescue work may account for higher post-9/11 CRS rates among firefighters.

Singh, A., et al. (2018). "Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure: A Longitudinal Study." Chest **154**(6): 1301-1310.

BACKGROUND: Previously healthy firefighters with World Trade Center (WTC) dust exposure developed airway disease. Risk factors for irritant-associated asthma/COPD overlap are poorly defined. METHODS: This study included 2,137 WTC-exposed firefighters who underwent a clinically indicated bronchodilator pulmonary function test (BD-PFT) between 9/11/2001 and 9/10/2017. A post-BD FEV(1) increase of > 12% and 200 mL from baseline defined asthma, and a post-BD FEV(1)/FVC ratio < 0.7 identified COPD cases. Participants who met both criteria had asthma/COPD overlap. Eosinophil levels were measured on screening

blood tests performed shortly after 9/11/2001 and prior to BD-PFT; a subgroup of participants also had serum IgE and 21 cytokines measured (n = 215). Marginal Cox regression models for multiple events assessed the associations of eosinophil levels or serum biomarkers with subsequent diagnosis, with age, race, smoking, WTC exposure, first post-9/11 FEV(1)/FVC ratio, and BMI included as covariates. RESULTS: BD-PFT diagnosed asthma/COPD overlap in 99 subjects (4.6%), isolated-asthma in 202 (9.5%), and isolated-COPD in 215 (10.1%). Eosinophil concentration >/= 300 cells/muL was associated with increased risk of asthma/COPD overlap (hazard ratio [HR], 1.85; 95% CI, 1.16-2.95) but not with isolated-asthma or isolated-COPD. Serum IL-4 also predicted asthma/COPD overlap (HR, 1.51 per doubling of cytokine concentration; 95% CI, 1.17-1.95). Greater IL-21 concentration was associated with both isolated-asthma and isolated-COPD (HRs of 1.73 [95% CI, 1.27-2.35] and 2.06 [95% CI, 1.31-3.23], respectively). CONCLUSIONS: In WTC-exposed firefighters, elevated blood eosinophil and IL-4 levels are associated with subsequent asthma/COPD overlap. Disease-specific T-helper cell type 2 biomarkers present years before diagnosis suggest patient-intrinsic predisposition to irritant-associated asthma/COPD overlap.

Singh, A., et al. (2018). "Estimation of Future Cancer Burden Among Rescue and Recovery Workers Exposed to the World Trade Center Disaster." JAMA Oncol **4**(6): 828-831.

IMPORTANCE: Elevated rates of cancer have been reported in individuals exposed to the World Trade Center (WTC) disaster, including Fire Department of the City of New York (FDNY) rescue and recovery workers. OBJECTIVE: To project the future burden of cancer in WTC-exposed FDNY rescue and recovery workers by estimating the 20-year cancer incidence. DESIGN, SETTING, AND PARTICIPANTS: A total of 14 474 WTC-exposed FDNY employees who were cancer-free on January 1, 2012; subgroup analyses were conducted of the cohort's white male population (n = 12 374). In this closed-cohort study, we projected cancer incidence for the January 1, 2012, to December 31, 2031, period. Simulations were run using demographic-specific New York City (NYC) cancer and national mortality rates for each individual, summed for the whole cohort, and performed 1000 times to produce mean estimates. Additional analyses in the subgroup of white men compared case counts produced by using 2007-2011 FDNY WTC Health Program (FDNY-WTCHP) cancer rates vs NYC rates. Average and 20-year aggregate costs of first-year cancer care were estimated using claims data. EXPOSURES: World Trade Center disaster exposure defined as rescue and recovery work at the WTC site at any time from September 11, 2001, to July 25, 2002. MAIN OUTCOMES AND MEASURES: (1) Projected number of incident cancers in the full cohort, based on NYC cancer rates; (2) cancer incidence estimates in the subgroup projected using FDNY-WTCHP vs NYC rates; and (3) estimated first-year treatment costs of incident cancers. RESULTS: On January 1, 2012, the cohort was 96.8% male, 87.1% white, and had a mean (SD) age of 50.2 (9.2) years. The projected number of incident cancer cases was 2960 (95% CI, 2883-3037). In our subgroup analyses using FDNY-WTCHP vs NYC cancer rates, the projected number of new cases in white men was elevated (2714 [95% CI, 2638-2786] vs 2596 [95% CI, 2524-2668]). Accordingly, we expect more prostate (1437 [95% CI, 1383-1495] vs 863 [95% CI, 816-910]), thyroid (73 [95% CI, 60-86] vs 57 [95% CI, 44-69]), and melanoma cases (201 [95% CI, 179-223] vs 131 [95% CI, 112-150), but fewer lung (237 [95% CI, 212-262] vs 373 [95% CI, 343-405]), colorectal (172 [95% CI, 152-191] vs 267 [95% CI, 241-292]), and kidney cancers (66 [95% CI, 54-80] vs 132 [95% CI, 114-152]) (P < .001 for all comparisons). The estimated 20-year cost of first-year treatment was $235 835 412 (95% CI, $187 582 227-$284 088 597). CONCLUSIONS AND RELEVANCE: We project that the FDNY-WTCHP cohort will experience a greater cancer burden than would be expected from a demographically similar population. This underscores the importance of cancer prevention efforts and routine screening in WTC-exposed rescue and recovery workers.

Webber, M. P., et al. (2018). "Incidence and prevalence of antibody to hepatitis C virus in FDNY first responders before and after work at the World Trade Center disaster site." Am J Ind Med.

BACKGROUND: The goals of this study were to assess the impact of work at the World Trade Center (WTC) site in relation to new, post-9/11/2001 (9/11) antibody to hepatitis C Virus (anti-HCV); and, evaluate secular trends in WTC-exposed male Fire Department of New York City (FDNY) Firefighters and Emergency Medical Services (EMS) responders. METHODS: FDNY monitors responder health through physical exams and routine blood work. We used descriptive statistics to compare trans-9/11 and post-9/11 incidence and to assess trends in prevalence from 2000 to 2012. RESULTS: Trans-9/11 incidence of new anti-HCV was 0.42 per 100 persons compared with post-9/11 incidence of 0.34 (P = 0.68). Overall seroprevalence was 1.3%; rates declined from 1.79 per 100 to 0.49 per 100 over time (P < 0.0001). CONCLUSIONS: Work at the WTC

was not associated with new infection. Biennial seroprevalence in responders declined over time, supporting the FDNY decision to discontinue routine annual testing in this cohort.

Zeig-Owens, R., et al. (2018). "Blood Leukocyte Concentrations, FEV(1) Decline, and Airflow Limitation. A 15-Year Longitudinal Study of World Trade Center-exposed Firefighters." Ann Am Thorac Soc **15**(2): 173-183.

RATIONALE: Rescue/recovery work at the World Trade Center disaster site (WTC) caused a proximate decline in lung function in Fire Department of the City of New York firefighters. A subset of this cohort experienced an accelerated rate of lung function decline over 15 years of post-September 11, 2001 (9/11) follow-up. OBJECTIVES: To determine if early postexposure blood leukocyte concentrations are biomarkers for subsequent FEV(1) decline and incident airflow limitation. METHODS: Individual rates of forced expiratory volume in 1 second (FEV(1)) change were calculated for 9,434 firefighters using 88,709 spirometric measurements taken between September 11, 2001, and September 10, 2016. We categorized FEV(1) change rates into three trajectories: accelerated FEV(1) decline (FEV(1) loss >64 ml/yr), expected FEV(1) decline (FEV(1) loss between 0 and 64 ml/yr), and improved FEV(1) (positive rate of change >0 ml/yr). Occurrence of FEV(1)/FVC less than 0.70 after 9/11 defined incident airflow limitation. Using regression models, we assessed associations of post-9/11 blood eosinophil and neutrophil concentrations with subsequent FEV(1) decline and airflow limitation, adjusted for age, race, smoking, height, WTC exposure level, weight change, and baseline lung function. RESULTS: Accelerated FEV(1) decline occurred in 12.7% of participants (1,199 of 9,434), whereas post-9/11 FEV(1) improvement occurred in 8.3% (780 of 9,434). Higher blood eosinophil and neutrophil concentrations were each associated with accelerated FEV(1) decline after adjustment for covariates (odds ratio [OR], 1.10 per 100 eosinophils/mul; 95% confidence interval [CI], 1.05-1.15; and OR, 1.10 per 1,000 neutrophils/mul; 95% CI, 1.05-1.15, respectively). Multivariable-adjusted linear regression models showed that a higher blood neutrophil concentration was associated with a faster rate of FEV(1) decline (1.14 ml/yr decline per 1,000 neutrophils/mul; 95% CI, 0.69-1.60 ml/yr; $P < 0.001$). Higher blood eosinophil concentrations were associated with a faster rate of FEV(1) decline in ever-smokers (1.46 ml/yr decline per 100 eosinophils/mul; 95% CI, 0.65-2.26 ml/yr; $P < 0.001$) but not in never-smokers (P for interaction = 0.004). Higher eosinophil concentrations were also associated with incident airflow limitation (adjusted hazard ratio, 1.10 per 100 eosinophils/mul; 95% CI, 1.04-1.15). Compared with the expected FEV(1) decline group, individuals experiencing accelerated FEV(1) decline were more likely to have incident airflow limitation (adjusted OR, 4.12; 95% CI, 3.30-5.14). CONCLUSIONS: Higher post-9/11 blood neutrophil and eosinophil concentrations were associated with subsequent accelerated FEV(1) decline in WTC-exposed firefighters. Both higher blood eosinophil concentrations and accelerated FEV(1) decline were associated with incident airflow limitation in WTC-exposed firefighters.

2019

Cleven, K. L., et al. (2019). "Genetic Variants Associated with FDNY WTC-Related Sarcoidosis." Int J Environ Res Public Health **16**(10).

Sarcoidosis is a systemic granulomatous disease of unknown etiology. It may develop in response to an exposure or inflammatory trigger in the background of a genetically primed abnormal immune response. Thus, genetic studies are potentially important to our understanding of the pathogenesis of sarcoidosis. We developed a case-control study which explored the genetic variations between firefighters in the Fire Department of the City of New York (FDNY) with World Trade Center (WTC)-related sarcoidosis and those with WTC exposure, but without sarcoidosis. The loci of fifty-one candidate genes related to granuloma formation, inflammation, immune response, and/or sarcoidosis were sequenced at high density in enhancer/promoter, exonic, and 5' untranslated regions. Seventeen allele variants of human leukocyte antigen (HLA) and non-HLA genes were found to be associated with sarcoidosis, and all were within chromosomes 1 and 6. Our results also suggest an association between extrathoracic involvement and allele variants of HLA and non-HLA genes found not only on chromosomes 1 and 6, but also on chromosomes 16 and 17. We found similarities between genetic variants with WTC-related sarcoidosis and those reported previously in sporadic sarcoidosis cases within the general population. In addition, we identified several allele variants never previously reported in association with sarcoidosis. If confirmed in larger studies with known environmental exposures, these novel findings may provide insight into the gene-environment interactions key to the development of sarcoidosis.

Cohen, H. W., et al. (2019). "Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster." JAMA Netw Open **2**(9): e199775.

IMPORTANCE: Published studies examining the association between World Trade Center (WTC) exposure on and after September 11, 2001, and longer-term cardiovascular disease (CVD) outcomes have reported mixed findings. OBJECTIVE: To assess whether WTC exposure was associated with elevated CVD risk in Fire Department of the City of New York (FDNY) firefighters. DESIGN, SETTINGS, AND PARTICIPANTS: In this cohort study, the association between WTC exposure and the risk of CVD was assessed between September 11, 2001, and December 31, 2017, in FDNY male firefighters. Multivariable Cox regression analyses were used to estimate CVD risk in association with 2 measures of WTC exposure: arrival time to the WTC site and duration of work at the WTC site. Data analyses were conducted from May 1, 2018, to March 8, 2019. MAIN OUTCOMES AND MEASURES: The primary CVD outcome included myocardial infarction, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. The secondary outcome (all CVD) included all primary outcome events or any of the following: transient ischemic attack; stable angina, defined as either use of angina medication or cardiac catheterization without intervention; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery). RESULTS: There were 489 primary outcome events among 9796 male firefighters (mean [SD] age on September 11, 2001, was 40.3 [7.4] years and 7210 individuals [73.6%] were never smokers). Age-adjusted incident rates of CVD were higher for firefighters with greater WTC exposure. The multivariable adjusted hazard ratio (HR) for the primary CVD outcome was 1.44 (95% CI, 1.09-1.90) for the earliest arrival group compared with those who arrived later. Similarly, those who worked at the WTC site for 6 or more months vs those who worked less time at the site were more likely to have a CVD event (HR, 1.30; 95% CI, 1.05-1.60). Well-established CVD risk factors, including hypertension (HR, 1.41; 95% CI, 1.10-1.80), hypercholesterolemia (HR, 1.56; 95% CI, 1.28-1.91), diabetes (HR, 1.99; 95% CI, 1.33-2.98), and smoking (current: HR, 2.13; 95% CI, 1.68-2.70; former: HR, 1.55; 95% CI, 1.23-1.95), were significantly associated with CVD in the multivariable models. Analyses with the all-CVD outcome were similar. CONCLUSIONS AND RELEVANCE: The findings of the study suggest a significant association between greater WTC exposure and long-term CVD risk. The findings appear to reinforce the importance of long-term monitoring of the health of survivors of disasters.

Colbeth, H. L., et al. (2019). "Persistent self-reported ear and hearing problems among World Trade Center-exposed firefighters and emergency medical service workers, 2001-2017-A longitudinal cohort analysis." Am J Ind Med **62**(1): 43-49.

BACKGROUND: The goal of this study was to estimate the impact of exposure to the World Trade Center (WTC) site on annual and persistent rates of otalgia and hearing impairment among Fire Department of the City of New York (FDNY) Firefighters and Emergency Medical Service Workers (EMS). METHODS: Responders completed routine physical health questionnaires at monitoring visits. We used logistic and marginal logistic regression models to explore the association between otalgia and hearing impairment and WTC arrival time. RESULTS: The highest-exposed group had greater odds of persistent ear symptoms (OR 1.33, 95%CI 1.11-1.59) compared with the least-exposed; the odds of persistent hearing problems between the groups were not significantly different. We found consistent WTC-exposure gradients when the average population odds of these outcomes were assessed each year. CONCLUSIONS: Our findings demonstrate that the odds of long-term ear symptoms were significantly associated with the intensity of WTC exposure.

Colbeth, H. L., et al. (2019). "Post-9/11 Peripheral Neuropathy Symptoms among World Trade Center-Exposed Firefighters and Emergency Medical Service Workers." Int J Environ Res Public Health **16**(10).

Peripheral neuropathy can result from numerous conditions including metabolic disorders, inflammatory disease, or exposure to environmental or biological toxins. We analyzed questionnaire data from 9239 Fire Department of the City of New York (FDNY) World Trade Center (WTC)-exposed firefighters and emergency medical service workers (EMS) to evaluate the association between work at the WTC site and subsequent peripheral neuropathy symptoms using the validated Diabetic Neuropathy Symptom (DNS) score. We grouped the population into an "Indicated" group with conditions known to be associated with paresthesia (N = 2059) and a "Non-Indicated" group without conditions known to be associated (N = 7180). The level of WTC exposure was categorized by time of arrival to the WTC. Overall, 25% of workers aged 40 and older reported peripheral neuropathy symptoms: 30.6% in the Indicated and 23.8% in the Non-Indicated groups, respectively. Multivariable logistic models performed on the Non-Indicated group, and on the Non-Indicated

in comparison with non-WTC exposed National Health and Nutrition Examination Survey (NHANES), found that the highest level of WTC-exposure was significantly associated with DNS positive outcomes, after controlling for potential confounders. In conclusion, this study suggests that symptoms of peripheral neuropathy and paresthesias are common and are associated with WTC-exposure intensity.

Crowley, G., et al. (2019). "Assessing the Protective Metabolome Using Machine Learning in World Trade Center Particulate Exposed Firefighters at Risk for Lung Injury." Sci Rep **9**(1): 11939.

The metabolome of World Trade Center (WTC) particulate matter (PM) exposure has yet to be fully defined and may yield information that will further define bioactive pathways relevant to lung injury. A subset of Fire Department of New York firefighters demonstrated resistance to subsequent loss of lung function. We intend to characterize the metabolome of never smoking WTC-exposed firefighters, stratified by resistance to WTC-Lung Injury (WTC-LI) to determine metabolite pathways significant in subjects resistant to the loss of lung function. The global serum metabolome was determined in those resistant to WTC-LI and controls (n = 15 in each). Metabolites most important to class separation (top 5% by Random Forest (RF) of 594 qualified metabolites) included elevated amino acid and long-chain fatty acid metabolites, and reduced hexose monophosphate shunt metabolites in the resistant cohort. RF using the refined metabolic profile was able to classify cases and controls with an estimated success rate of 93.3%, and performed similarly upon cross-validation. Agglomerative hierarchical clustering identified potential influential pathways of resistance to the development of WTC-LI. These pathways represent potential therapeutic targets and warrant further research.

Flamme, G. A., et al. (2019). "Hearing Loss Among World Trade Center Firefighters and Emergency Medical Service Workers." J Occup Environ Med **61**(12): 996-1003.

OBJECTIVE: To determine if World Trade Center (WTC) exposure is associated with hearing loss. METHODS: Logistic regression to evaluate the immediate impact of WTC exposure and parametric survival analysis to assess longitudinal outcomes. RESULTS: Those arriving on the morning of September 11, 2001 had elevated odds of low-frequency (odds ratio [OR]: 1.24; 95% confidence interval [CI]: 1.04 to 1.47) and high-frequency (OR: 1.16; 95% CI: 1.02 to 1.31) hearing loss at their first post-September 11, 2001 examination. Longitudinally, participants arriving before September 13, 2001 and spending more than or equal to 6 months at the WTC-site had greater risk of hearing loss in the low frequencies (risk ratio [RR]: 1.31; 95% CI: 1.05 to 1.60) and high frequencies (RR: 1.37; 95% CI: 1.22 to 1.54). By 2016, 3194 (37%) had abnormal hearing sensitivity in either ear and 1751 (20%) in both ears. CONCLUSIONS: More heavily WTC-exposed workers were at increased risk of hearing loss, and group differences persisted for at least 15 years. Those with abnormal hearing sensitivity may benefit from interventions such as hearing aids and other rehabilitation.

Kwon, S., et al. (2019). "Validation of Predictive Metabolic Syndrome Biomarkers of World Trade Center Lung Injury: A 16-Year Longitudinal Study." Chest **156**(3): 486-496.

BACKGROUND: Metabolic syndrome (MetSyn) predicted future development of World Trade Center lung injury (WTC-LI) in a subgroup of firefighters who never smoked and were male. An intracohort validation of MetSyn as a predictor of WTC-LI is examined in the cohort exposed to the World Trade Center (WTC) that has been followed longitudinally for 16 years. METHODS: Results of pulmonary function tests (n = 98,221) in workers exposed to the WTC (n = 9,566) were evaluated. A baseline cohort of firefighters who had normal FEV(1) before 9/11 and who had had serum drawn before site closure on July 24, 2002 (n = 7,487) was investigated. Case subjects with WTC-LI (n = 1,208) were identified if they had at least two measured instances of FEV(1) less than the lower limit of normal (LLN). Cox proportional hazards modeled early MetSyn biomarker ability to predict development of FEV(1) less than the LLN. RESULTS: Case subjects were more likely to smoke, be highly exposed, and have MetSyn. There was a significant exposure dose response; the individuals most highly exposed had a 30.1% increased risk of developing WTC-LI, having MetSyn increased risk of developing WTC-LI by 55.7%, and smoking increased risk by 15.2%. There was significant interaction between smoking and exposure. CONCLUSIONS: We validated the usefulness of MetSyn to predict future WTC-LI in a larger population of individuals who were exposed. MetSyn defined by dyslipidemia, insulin resistance, and cardiovascular disease suggests that systemic inflammation can contribute to future lung function loss.

Kwon, S., et al. (2019). "Metabolic Syndrome Biomarkers of World Trade Center Airway Hyperreactivity: A 16-Year Prospective Cohort Study." Int J Environ Res Public Health **16**(9).

> Airway hyperreactivity (AHR) related to environmental exposure is a significant public health risk worldwide. Similarly, metabolic syndrome (MetSyn), a risk factor for obstructive airway disease (OAD) and systemic inflammation, is a significant contributor to global adverse health. This prospective cohort study followed N = 7486 World Trade Center (WTC)-exposed male firefighters from 11 September 2001 (9/11) until 1 August 2017 and investigated N = 539 with newly developed AHR for clinical biomarkers of MetSyn and compared them to the non-AHR group. Male firefighters with normal lung function and no AHR pre-9/11 who had blood drawn from 9 September 2001-24 July 2002 were assessed. World Trade Center-Airway Hyperreactivity (WTC-AHR) was defined as either a positive bronchodilator response (BDR) or methacholine challenge test (MCT). The electronic medical record (EMR) was queried for their MetSyn characteristics (lipid profile, body mass index (BMI), glucose), and routine clinical biomarkers (such as complete blood counts). We modeled the association of MetSyn characteristics at the first post-9/11 exam with AHR. Those with AHR were significantly more likely to be older, have higher BMIs, have high intensity exposure, and have MetSyn. Smoking history was not associated with WTC-AHR. Those present on the morning of 9/11 had 224% increased risk of developing AHR, and those who arrived in the afternoon of 9/11 had a 75.9% increased risk. Having >/=3 MetSyn parameters increased the risk of WTC-AHR by 65.4%. Co-existing MetSyn and high WTC exposure are predictive of future AHR and suggest that systemic inflammation may be a contributor.

Liu, C., et al. (2019). "Abnormalities on Chest Computed Tomography and Lung Function Following an Intense Dust Exposure: A 17-Year Longitudinal Study." Int J Environ Res Public Health **16**(9).

> Fire Department of the City of New York (FDNY) firefighters experienced intense dust exposure working at the World Trade Center (WTC) site on and after 11/9/2001 (9/11). We hypothesized that high-intensity WTC exposure caused abnormalities found on chest computed tomography (CT). Between 11/9/2001-10/9/2018, 4277 firefighters underwent a clinically-indicated chest CT. Spirometric measurements and symptoms were recorded during routine medical examinations. High-intensity exposure, defined as initial arrival at the WTC on the morning of 9/11, increased the risk of bronchial wall thickening, emphysema, and air trapping. Early post-9/11 symptoms of wheeze and shortness of breath were associated with bronchial wall thickening, emphysema, and air trapping. The risk of accelerated forced expiratory volume at one second (FEV(1)) decline (>64 mL/year decline) increased with bronchial wall thickening and emphysema, but decreased with air trapping. The risk of airflow obstruction also increased with bronchial wall thickening and emphysema but decreased with air trapping. In a previously healthy occupational cohort, high-intensity WTC exposure increased the risk for CT abnormalities. Bronchial wall thickening and emphysema were associated with respiratory symptoms, accelerated FEV(1) decline, and airflow obstruction. Air trapping was associated with respiratory symptoms, although lung function was preserved. Physiologic differences between CT abnormalities suggest that distinct types of airway injury may result from a common exposure.

Putman, B., et al. (2019). "Low serum IgA and airway injury in World Trade Center-exposed firefighters: a 17-year longitudinal study." Thorax **74**(12): 1182-1184.

> Serum IgA </=70 mg/dL (low IgA) is associated with exacerbations of chronic obstructive pulmonary disease. The association of low IgA with longitudinal lung function is poorly defined. This study included 917 World Trade Center (WTC)-exposed firefighters with longitudinal spirometry measured between September 2001 and September 2018 and IgA measured between October 2001 and March 2002. Low IgA, compared with IgA >70 mg/dL, was associated with lower forced expiratory volume in 1 s (FEV(1)) % predicted in the year following 11 September 2001 (94.1% vs 98.6%, p<0.001), increased risk of FEV(1)/FVC <0.70 (HR 3.8, 95% CI 1.6 to 8.8) and increased antibiotic treatment (22.5/100 vs 11.6/100 person-years, p=0.002). Following WTC exposure, early IgA </=70 mg/dL was associated with worse lung function and increased antibiotic treatment.

2020

Colbeth, H. L., et al. (2020). "Evaluation of Medical Surveillance and Incidence of Post-September 11, 2001, Thyroid Cancer in World Trade Center-Exposed Firefighters and Emergency Medical Service Workers." JAMA Intern Med **180**(6): 888-895.

IMPORTANCE: Elevated incidence rates of thyroid cancer among World Trade Center (WTC)-exposed individuals may be associated with the identification of asymptomatic cancers during medical surveillance. OBJECTIVE: To examine the association between WTC exposure and thyroid cancer among Fire Department of the City of New York (hereafter, Fire Department) rescue/recovery workers as well as the association with medical surveillance. DESIGN, SETTING, AND PARTICIPANTS: This closed-cohort study classified the method of detection (asymptomatic and symptomatic) of thyroid cancers in 14 987 men monitored through the Fire Department-WTC Health Program diagnosed from September 12, 2001, to December 31, 2018. Age-, sex-, and histologic-specific Fire Department incidence rates were calculated and compared with demographically similar men in Olmsted County, Minnesota, from the Rochester Epidemiology Project using age-standardized rates, relative rates (RRs), and 95% CIs. The secondary analysis was restricted to papillary carcinomas. EXPOSURES: World Trade Center exposure was defined as rescue/recovery work at the WTC site from September 11, 2001, to July 25, 2002. MAIN OUTCOMES AND MEASURES: The outcomes evaluated comprised (1) number of incident thyroid cancers and their detection method categorizations in the Fire Department and Rochester Epidemiology Project cohorts; (2) Fire Department, Rochester Epidemiology Project, and Surveillance, Epidemiology, and End Results-21 age-standardized incidence rates of thyroid cancer; and (3) RRs comparing Fire Department and Rochester Epidemiology Project overall and by detection method categorization. RESULTS: Seventy-two post-9/11 Fire Department cases of thyroid cancer were identified. Among the 65 cases (90.3%) with a categorized detection method, 53 cases (81.5%) were asymptomatic and 12 cases (18.5%) were symptomatic. Median (interquartile range) age at diagnosis was 50.2 (44.0-58.6) vs 46.6 (43.9-52.9) years for asymptomatic vs symptomatic cases. Associated primarily with asymptomatic cancers, the overall age-standardized incidence of Fire Department thyroid cancers (24.7; 95% CI, 17.4-52.3) was significantly higher than the Rochester Epidemiology Project (10.4; 95% CI, 8.5-12.7) and Surveillance, Epidemiology, and End Results-21 (9.1; 95% CI, 9.0-9.1) per 100 000 person-years. Furthermore, the RR of thyroid cancer among symptomatic men in Fire Department cases was not significantly different from that of men in the Rochester Epidemiology Project (0.8; 95% CI, 0.4-1.5); however, the rate of asymptomatic cancers was more than 3-fold that of the Rochester Epidemiology Project rate (RR, 3.1; 95% CI, 2.1-4.7). CONCLUSIONS AND RELEVANCE: Excess asymptomatic thyroid cancer in Fire Department WTC-exposed rescue/recovery workers is apparently attributable to the identification of occult lesions during medical surveillance. Among WTC-exposed cohorts and the general population, these findings appear to have important implications for how thyroid cancer incidence rates are interpreted and how diagnoses should be managed.

Colbeth, H. L., et al. (2020). "Mortality among Fire Department of the City of New York Rescue and Recovery Workers Exposed to the World Trade Center Disaster, 2001-2017." Int J Environ Res Public Health **17**(17).

The World Trade Center (WTC) attacks on 9/11/2001 have consistently been associated with elevated rates of physical and mental health morbidities, while evidence about mortality has been limited. We examined mortality between 9/12/2001 and 12/31/2017 among 15,431 WTC-exposed Fire Department of the City of New York (FDNY) firefighters and emergency medical service providers (EMS), specifically assessing associations between intensity of WTC-exposure and mortality risk. Standardized mortality ratios (SMR) and 95% confidence intervals (CI) compared FDNY cohort mortality with the US general population using life table analysis. Deaths were identified via linkage to the National Death Index. Cox proportional hazards regression models were used to identify associations between intensity of WTC-exposure and mortality, accounting for age, sex, race/ethnicity, smoking history, and other relevant confounders. We identified 546 deaths and a lower than expected all-cause mortality rate (SMR = 0.34; 95% CI, 0.31-0.37). No cause-specific SMRs were meaningfully elevated. Mortality hazard ratios showed no association or linear trend with level of WTC-exposure. Our results provide evidence of the healthy worker effect, despite exposure to the World Trade Center. More follow-up time may be needed to assess the full impact of WTC-exposure on mortality in this occupational population.

Haider, S. H., et al. (2020). "Multiomics of World Trade Center Particulate Matter-induced Persistent Airway Hyperreactivity. Role of Receptor for Advanced Glycation End Products." Am J Respir Cell Mol Biol **63**(2): 219-233.

Pulmonary disease after World Trade Center particulate matter (WTC-PM) exposure is associated with dyslipidemia and the receptor for advanced glycation end products (RAGE); however, the mechanisms are not well understood. We used a murine model and a multiomics assessment to understand the role of RAGE in the pulmonary long-term effects of a single high-intensity exposure to WTC-PM. After 1 month, WTC-PM-exposed wild-type (WT) mice had airway hyperreactivity, whereas RAGE-deficient (Ager(-/-)) mice were protected. PM-exposed WT mice also had histologic evidence of airspace disease, whereas Ager(-/-) mice remained unchanged. Inflammatory mediators such as G-CSF (granulocyte colony-stimulating factor), IP-10 (IFN-gamma-induced protein 10), and KC (keratinocyte chemoattractant) were differentially expressed after WTC-PM exposure. WTC-PM induced alpha-SMA, DIAPH1 (protein diaphanous homolog 1), RAGE, and significant lung collagen deposition in WT compared with Ager(-/-) mice. Compared with WT mice with PM exposure, relative expression of phosphorylated to total CREB (cAMP response element-binding protein) and JNK (c-Jun N-terminal kinase) was significantly increased in the lung of PM-exposed Ager(-/-) mice, whereas Akt (protein kinase B) was decreased. Random forests of the refined lung metabolomic profile classified subjects with 92% accuracy; principal component analysis captured 86.7% of the variance in three components and demonstrated prominent subpathway involvement, including known mediators of lung disease such as vitamin B(6) metabolites, sphingolipids, fatty acids, and phosphatidylcholines. Treatment with a partial RAGE antagonist, pioglitazone, yielded similar fold-change expression of metabolites (N(6)-carboxymethyllysine, 1-methylnicotinamide, N(1)+N(8)-acetylspermidine, and succinylcarnitine [C4-DC]) between WT and Ager(-/-) mice exposed to WTC-PM. RAGE can mediate WTC-PM-induced airway hyperreactivity and warrants further investigation.

Kwon, S., et al. (2020). "Food Intake REstriction for Health OUtcome Support and Education (FIREHOUSE) Protocol: A Randomized Clinical Trial." Int J Environ Res Public Health **17**(18).

Fire Department of New York (FDNY) rescue and recovery workers exposed to World Trade Center (WTC) particulates suffered loss of forced expiratory volume in 1 s (FEV(1)). Metabolic Syndrome increased the risk of developing WTC-lung injury (WTC-LI)(.) We aim to attenuate the deleterious effects of WTC exposure through a dietary intervention targeting these clinically relevant disease modifiers. We hypothesize that a calorie-restricted Mediterranean dietary intervention will improve metabolic risk, subclinical indicators of cardiopulmonary disease, quality of life, and lung function in firefighters with WTC-LI. To assess our hypothesis, we developed the Food Intake REstriction for Health OUtcome Support and Education (FIREHOUSE), a randomized controlled clinical trial (RCT). Male firefighters with WTC-LI and a BMI > 27 kg/m(2) will be included. We will randomize subjects (1:1) to either: (1) Low Calorie Mediterranean (LoCalMed)-an integrative multifactorial, technology-supported approach focused on behavioral modification, nutritional education that will include a self-monitored diet with feedback, physical activity recommendations, and social cognitive theory-based group counseling sessions; or (2) Usual Care. Outcomes include reduction in body mass index (BMI) (primary), improvement in FEV(1), fractional exhaled nitric oxide, pulse wave velocity, lipid profiles, targeted metabolic/clinical biomarkers, and quality of life measures (secondary). By implementing a technology-supported LoCalMed diet our FIREHOUSE RCT may help further the treatment of WTC associated pulmonary disease.

Lam, R., et al. (2020). "Synergistic Effect of WTC-Particulate Matter and Lysophosphatidic Acid Exposure and the Role of RAGE: In-Vitro and Translational Assessment." Int J Environ Res Public Health **17**(12).

World Trade Center particulate matter (WTC-PM)-exposed firefighters with metabolic syndrome (MetSyn) have a higher risk of WTC lung injury (WTC-LI). Since macrophages are crucial innate pulmonary mediators, we investigated WTC-PM/lysophosphatidic acid (LPA) co-exposure in macrophages. LPA, a low-density lipoprotein metabolite, is a ligand of the advanced glycation end-products receptor (AGER or RAGE). LPA and RAGE are biomarkers of WTC-LI. Human and murine macrophages were exposed to WTC-PM, and/or LPA, and compared to controls. Supernatants were assessed for cytokines/chemokines; cell lysate immunoblots were assessed for signaling intermediates after 24 h. To explore the translatability of our in-vitro findings, we assessed serum cytokines/chemokines and metabolites of symptomatic, never-smoking WTC-exposed firefighters. Agglomerative hierarchical clustering identified phenotypes of WTC-PM-induced inflammation. WTC-PM induced GM-CSF, IL-8, IL-10, and MCP-1 in THP-1-derived macrophages and induced IL-1alpha, IL-10, TNF-alpha, and NF-kappaB in RAW264.7 murine macrophage-like cells. Co-exposure induced synergistic elaboration of IL-10 and MCP-1 in THP-1-derived macrophages. Similarly, co-exposure synergistically induced IL-10 in murine macrophages. Synergistic effects were seen in the context of a downregulation of NF-kappaB, p-Akt, -STAT3, and -STAT5b. RAGE expression after co-exposure

increased in murine macrophages compared to controls. In our integrated analysis, the human cytokine/chemokine biomarker profile of WTC-LI was associated with discriminatory metabolites (fatty acids, sphingolipids, and amino acids). LPA synergistically elaborated WTC-PM's inflammatory effects in vitro and was partly RAGE-mediated. Further research will focus on the intersection of MetSyn/PM exposure.

Putman, B., et al. (2020). "Factors Predicting Treatment of World Trade Center-Related Lung Injury: A Longitudinal Cohort Study." Int J Environ Res Public Health **17**(23).

The factors that predict treatment of lung injury in occupational cohorts are poorly defined. We aimed to identify patient characteristics associated with initiation of treatment with inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) >2 years among World Trade Center (WTC)-exposed firefighters. The study population included 8530 WTC-exposed firefighters. Multivariable logistic regression assessed the association of patient characteristics with ICS/LABA treatment for >2 years over two-year intervals from 11 September 2001-10 September 2017. Cox proportional hazards models measured the association of high probability of ICS/LABA initiation with actual ICS/LABA initiation in subsequent intervals. Between 11 September 2001-1 July 2018, 1629/8530 (19.1%) firefighters initiated ICS/LABA treatment for >2 years. Forced Expiratory Volume in 1 s (FEV(1)), wheeze, and dyspnea were consistently and independently associated with ICS/LABA treatment. High-intensity WTC exposure was associated with ICS/LABA between 11 September 2001-10 September 2003. The 10th percentile of risk for ICS/LABA between 11 September 2005-10 Septmeber 2007 was associated with a 3.32-fold increased hazard of actual ICS/LABA initiation in the subsequent 4 years. In firefighters with WTC exposure, FEV(1), wheeze, and dyspnea were independently associated with prolonged ICS/LABA treatment. A high risk for treatment was identifiable from routine monitoring exam results years before treatment initiation.

Putman, B., et al. (2020). "Dyspnea and Inhaled Corticosteroid and Long-acting beta-Agonist Therapy in an Occupational Cohort: A Longitudinal Study." Ann Am Thorac Soc **17**(6): 770-773.

Singh, A., et al. (2020). "World Trade Center exposure, post-traumatic stress disorder, and subjective cognitive concerns in a cohort of rescue/recovery workers." Acta Psychiatr Scand **141**(3): 275-284.

OBJECTIVE: To determine whether World Trade Center (WTC)-exposure intensity and post-traumatic stress disorder (PTSD) are associated with subjective cognitive change in rescue/recovery workers. METHOD: The population included 7875 rescue/recovery workers who completed a subjective cognition measure, the Cognitive Function Instrument (CFI), between 3/1/2018 and 2/28/2019 during routine monitoring, indicating whether they had experienced cognitive and functional difficulties in the past year. Higher scores indicated greater self-perceived cognitive change. Probable PTSD, depression, and alcohol abuse were evaluated by validated mental health screeners. Logistic regression assessed the associations of WTC exposure and current PTSD with top-quartile (>/=2) CFI score, and of early post-9/11 PTSD with top-quartile CFI in a subpopulation (N = 6440). Models included demographics, smoking, depression, and alcohol abuse as covariates. RESULTS: Mean age at CFI completion was 56.7 +/- 7.7 (range: 36-81). Participants with high-intensity WTC exposure had an increased likelihood of top-quartile CFI score (odds ratio[OR] vs. low exposure: 1.32, 95%CI: 1.07-1.64), controlling for covariates. Current and early PTSD were both associated with top-quartile CFI (OR: 3.25, 95%CI: 2.53-4.19 and OR: 1.56, 95%CI: 1.26-1.93) respectively. CONCLUSIONS: High-intensity WTC exposure was associated with self-reported cognitive change 17 years later in rescue/recovery workers, as was PTSD. Highly WTC-exposed subgroups may benefit from additional cognitive evaluation and monitoring of cognition over time.

Singh, A., et al. (2020). "PTSD and Depressive Symptoms as Potential Mediators of the Association between World Trade Center Exposure and Subjective Cognitive Concerns in Rescue/Recovery Workers." Int J Environ Res Public Health **17**(16).

We observed that World Trade Center (WTC) exposure, post-traumatic stress disorder (PTSD) symptoms and depressive symptoms were associated with subjective cognitive concerns in Fire Department of the City of New York (FDNY) rescue/recovery workers. This follow-up study examined whether PTSD symptoms and/or depressive symptoms mediate the observed association between WTC exposure and subjective cognitive concerns. We included WTC-exposed FDNY workers who completed the Cognitive Function Instrument (CFI), measuring self-perceived cognitive decline (N = 9516). PTSD symptoms and depressive symptoms

were assessed using the PCL-S and CES-D, respectively. Multivariable linear regression estimated the association between WTC exposure and CFI score, adjusting for confounders. Mediation analyses followed the methods of Vanderweele (2014). Participants' average age at CFI assessment was 56.6 +/- 7.6 years. Higher-intensity WTC exposure was associated with worse CFI score, an effect that was entirely mediated by PTSD symptoms (%mediated: 110.9%; 95%CI: 83.1-138.9). When substituting depressive symptoms for PTSD symptoms, the WTC exposure-CFI association was largely mediated (%mediated: 82.1%; 95%CI: 60.6-103.7). Our findings that PTSD symptoms and depressive symptoms mediate the association between WTC exposure and subjective cognitive concerns indicate that in the absence of these symptoms, WTC exposure in rescue/recovery workers would not be associated with subjective cognition. Interventions targeting PTSD and depression may have additional value in mitigating cognitive decline in WTC-exposed populations.

2021

Brackbill, R. M., et al. (2021). "Combining Three Cohorts of World Trade Center Rescue/Recovery Workers for Assessing Cancer Incidence and Mortality." Int J Environ Res Public Health **18**(4).

Three cohorts including the Fire Department of the City of New York (FDNY), the World Trade Center Health Registry (WTCHR), and the General Responder Cohort (GRC), each funded by the World Trade Center Health Program have reported associations between WTC-exposures and cancer. Results have generally been consistent with effect estimates for excess incidence for all cancers ranging from 6 to 14% above background rates. Pooling would increase sample size and de-duplicate cases between the cohorts. However, pooling required time consuming steps: obtaining Institutional Review Board (IRB) approvals and legal agreements from entities involved; establishing an honest broker for managing the data; de-duplicating the pooled cohort files; applying to State Cancer Registries (SCRs) for matched cancer cases; and finalizing analysis data files. Obtaining SCR data use agreements ranged from 6.5 to 114.5 weeks with six states requiring >20 weeks. Records from FDNY (n = 16,221), WTCHR (n = 29,372), and GRC (n = 33,427) were combined de-duplicated resulting in 69,102 unique individuals. Overall, 7894 cancer tumors were matched to the pooled cohort, increasing the number cancers by as much as 58% compared to previous analyses. Pooling resulted in a coherent resource for future research for studies on rare cancers and mortality, with more representative of occupations and WTC- exposure.

Cleven, K. L., et al. (2021). "Twenty-Year Reflection on the Impact of World Trade Center Exposure on Pulmonary Outcomes in Fire Department of the City of New York (FDNY) Rescue and Recovery Workers." Lung **199**(6): 569-578.

After the terrorist attacks on September 11, 2001 (9/11), many rescue/recovery workers developed respiratory symptoms and pulmonary diseases due to their extensive World Trade Center (WTC) dust cloud exposure. Nearly all Fire Department of the City of New York (FDNY) workers were present within 48 h of 9/11 and for the next several months. Since the FDNY had a well-established occupational health service for its firefighters and Emergency Medical Services workers prior to 9/11, the FDNY was able to immediately start a rigorous monitoring and treatment program for its WTC-exposed workers. As a result, respiratory symptoms and diseases were identified soon after 9/11. This focused review summarizes the WTC-related respiratory diseases that developed in the FDNY cohort after 9/11, including WTC cough syndrome, obstructive airways disease, accelerated lung function decline, airway hyperreactivity, sarcoidosis, and obstructive sleep apnea. Additionally, an extensive array of biomarkers has been identified as associated with WTC-related respiratory disease. Future research efforts will not only focus on further phenotyping/treating WTC-related respiratory disease but also on additional diseases associated with WTC exposure, especially those that take decades to develop, such as cardiovascular disease, cancer, and interstitial lung disease.

Cleven, K. L., et al. (2021). "Performance of Risk Factor-Based Guidelines and Model-Based Chest CT Lung Cancer Screening in World Trade Center-Exposed Fire Department Rescue/Recovery Workers." Chest **159**(5): 2060-2071.

BACKGROUND: Lung cancer is a leading cause of cancer incidence and death in the United States. Risk factor-based guidelines and risk model-based strategies are used to identify patients who could benefit from low-dose chest CT (LDCT) screening. Few studies compare guidelines or models within the same cohort. We evaluate lung cancer screening performance of two risk factor-based guidelines (US Preventive Services Task

Force 2014 recommendations [USPSTF-2014] and National Comprehensive Cancer Network Group 2 [NCCN-2]) and two risk model-based strategies, Prostate Lung Colorectal and Ovarian Cancer Screening (PLCOm2012) and the Bach model) in the same occupational cohort. RESEARCH QUESTION: Which risk factor-based guideline or model-based strategy is most accurate in detecting lung cancers in a highly exposed occupational cohort? STUDY DESIGN AND METHODS: Fire Department of City of New York (FDNY) rescue/recovery workers exposed to the September 11, 2001 attacks underwent LDCT lung cancer screening based on smoking history and age. The USPSTF-2014, NCCN-2, PLCOm2012 model, and Bach model were retrospectively applied to determine how many lung cancers were diagnosed using each approach. RESULTS: Among the study population (N = 3,953), 930 underwent a baseline scan that met at least one risk factor or model-based LDCT screening strategy; 73% received annual follow-up scans. Among the 3,953, 63 lung cancers were diagnosed, of which 50 were detected by at least one LDCT screening strategy. The NCCN-2 guideline was the most sensitive (79.4%; 50/63). When compared with NCCN-2, stricter age and smoking criteria reduced sensitivity of the other guidelines/models (USPSTF-2014 [44%], PLCOm2012 [51%], and Bach[46%]). The 13 missed lung cancers were mainly attributable to smoking less and quitting longer than guideline/model eligibility criteria. False-positive rates were similar across all four guidelines/models. INTERPRETATION: In this cohort, our findings support expanding eligibility for LDCT lung cancer screening by lowering smoking history from >/=30 to >/=20 pack-years and age from 55 years to 50 years old. Additional studies are needed to determine its generalizability to other occupational/environmental exposed cohorts.

Crowley, G., et al. (2021). "PEDF, a pleiotropic WTC-LI biomarker: Machine learning biomarker identification and validation." PLoS Comput Biol **17**(7): e1009144.

Biomarkers predict World Trade Center-Lung Injury (WTC-LI); however, there remains unaddressed multicollinearity in our serum cytokines, chemokines, and high-throughput platform datasets used to phenotype WTC-disease. To address this concern, we used automated, machine-learning, high-dimensional data pruning, and validated identified biomarkers. The parent cohort consisted of male, never-smoking firefighters with WTC-LI (FEV1, %Pred< lower limit of normal (LLN); n = 100) and controls (n = 127) and had their biomarkers assessed. Cases and controls (n = 15/group) underwent untargeted metabolomics, then feature selection performed on metabolites, cytokines, chemokines, and clinical data. Cytokines, chemokines, and clinical biomarkers were validated in the non-overlapping parent-cohort via binary logistic regression with 5-fold cross validation. Random forests of metabolites (n = 580), clinical biomarkers (n = 5), and previously assayed cytokines, chemokines (n = 106) identified that the top 5% of biomarkers important to class separation included pigment epithelium-derived factor (PEDF), macrophage derived chemokine (MDC), systolic blood pressure, macrophage inflammatory protein-4 (MIP-4), growth-regulated oncogene protein (GRO), monocyte chemoattractant protein-1 (MCP-1), apolipoprotein-AII (Apo-AII), cell membrane metabolites (sphingolipids, phospholipids), and branched-chain amino acids. Validated models via confounder-adjusted (age on 9/11, BMI, exposure, and pre-9/11 FEV1, %Pred) binary logistic regression had AUCROC [0.90(0.84-0.96)]. Decreased PEDF and MIP-4, and increased Apo-AII were associated with increased odds of WTC-LI. Increased GRO, MCP-1, and simultaneously decreased MDC were associated with decreased odds of WTC-LI. In conclusion, automated data pruning identified novel WTC-LI biomarkers; performance was validated in an independent cohort. One biomarker-PEDF, an antiangiogenic agent-is a novel, predictive biomarker of particulate-matter-related lung disease. Other biomarkers-GRO, MCP-1, MDC, MIP-4-reveal immune cell involvement in WTC-LI pathogenesis. Findings of our automated biomarker identification warrant further investigation into these potential pharmacotherapy targets.

Flamme, G. A., et al. (2020). "Population-based age adjustment tables for use in occupational hearing conservation programs." Int J Audiol **59**(sup1): S20-S30.

Objective: In occupational hearing conservation programmes, age adjustments may be used to subtract expected age effects. Adjustments used in the U.S. came from a small dataset and overlooked important demographic factors, ages, and stimulus frequencies. The present study derived a set of population-based age adjustment tables and validated them using a database of exposed workers.Design: Cross-sectional population-based study and retrospective longitudinal cohort study for validation.Study sample: Data from the U.S. National Health and Nutrition Examination Survey (unweighted n = 9937) were used to produce these tables. Male firefighters and emergency medical service workers (76,195 audiograms) were used for validation.Results: Cross-sectional trends implied less change with age than assumed in current U.S. regulations. Different trends were observed among people identifying with non-Hispanic Black race/ethnicity.

Four age adjustment tables (age range: 18-85) were developed (women or men; non-Hispanic Black or other race/ethnicity). Validation outcomes showed that the population-based tables matched median longitudinal changes in hearing sensitivity well.Conclusions: These population-based tables provide a suitable replacement for those implemented in current U.S. regulations. These tables address a broader range of worker ages, account for differences in hearing sensitivity across race/ethnicity categories, and have been validated for men using longitudinal data.

Goldfarb, D. G., et al. (2021). "Impact of healthcare services on thyroid cancer incidence among World Trade Center-exposed rescue and recovery workers." Am J Ind Med **64**(10): 861-872.

BACKGROUND: A recent study of World Trade Center (WTC)-exposed firefighters and emergency medical service workers demonstrated that elevated thyroid cancer incidence may be attributable to frequent medical testing, resulting in the identification of asymptomatic tumors. We expand on that study by comparing the incidence of thyroid cancer among three groups: WTC-exposed rescue/recovery workers enrolled in a New York State (NYS) WTC-medical monitoring and treatment program (MMTP); WTC-exposed rescue/recovery workers not enrolled in an MMTP (non-MMTP); and the NYS population. METHODS: Person-time began on 9/12/2001 or at enrollment in a WTC cohort and ended at death or on 12/31/2015. Cancer data were obtained through linkages with 13 state cancer registries. We used Poisson regression to estimate rate ratios (RRs) and 95% confidence intervals (CIs) for MMTP and non-MMTP participants. NYS rates were used as the reference. To estimate potential changes over time in WTC-associated risk, change points in RRs were estimated using profile likelihood. RESULTS: The thyroid cancer incidence rate among MMTP participants was more than twice that of NYS population rates (RR = 2.31; 95% CI = 2.00-2.68). Non-MMTP participants had a risk similar to NYS (RR = 0.96; 95% CI = 0.72-1.28). We observed no change points in the follow-up period. CONCLUSION: Our findings support the hypothesis that no-cost screening (a benefit provided by WTC-MMTPs) is associated with elevated identification of thyroid cancer. Given the high survival rate for thyroid cancer, it is important to weigh the costs and benefits of treatment, as many of these cancers were asymptomatic and may have been detected incidentally.

Goldfarb, D. G., et al. (2021). "Lung function decline before and after treatment of World Trade Center associated obstructive airways disease with inhaled corticosteroids and long-acting beta agonists." Am J Ind Med **64**(10): 853-860.

BACKGROUND: Greater than average loss of one-second forced expiratory volume (FEV(1)) is a risk factor for asthma, chronic obstructive pulmonary disease (COPD), and asthma/COPD overlap syndrome in World Trade Center (WTC)-exposed firefighters. Inhaled corticosteroids and long-acting beta agonists (ICS/LABA) are used to treat obstructive airways disease but their impact on FEV(1) -trajectory in this population is unknown. METHODS: The study population included WTC-exposed male firefighters who were treated with ICS/LABA for 2 years or longer (with initiation before 2015), had at least two FEV(1) measurements before ICS/LABA initiation and two FEV(1) measurements posttreatment between September 11, 2001 and September 10, 2019. Linear mixed-effects models were used to estimate FEV(1) -slope pre- and post-treatment. RESULTS: During follow-up, 1023 WTC-exposed firefighters were treated with ICS/LABA for 2 years or longer. When comparing intervals 6 years before and 6 years after treatment, participants had an 18.7 ml/year (95% confidence interval [CI]: 11.3-26.1) improvement in FEV(1) -slope after adjustment for baseline FEV(1) , race, height, WTC exposure, weight change, blood eosinophil concentration, and smoking status. After stratification by median date of ICS/LABA initiation (January 14, 2010), earlier ICS/LABA-initiators had a 32.5 ml/year (95% CI: 19.5-45.5) improvement in slope but later ICS/LABA-initiators had a nonsignificant FEV(1) -slope improvement (7.9 ml/year, 95% CI: -0.5 to 17.2). CONCLUSIONS: WTC-exposed firefighters treated with ICS/LABA had improved FEV(1) slope after initiation, particularly among those who started earlier. Treatment was, however, not associated with FEV(1) -slope improvement if started after the median initiation date (1/14/2010), likely because onset of disease began before treatment initiation. Research on alternative treatments is needed for patients with greater than average FEV(1) -decline who have not responded to ICS/LABA.

Goldfarb, D. G., et al. (2021). "Cancer survival among World Trade Center rescue and recovery workers: A collaborative cohort study." Am J Ind Med **64**(10): 815-826.

BACKGROUND: World Trade Center (WTC)-exposed responders may be eligible to receive no-cost medical monitoring and treatment for certified conditions, including cancer. The survival of responders with cancer has not previously been investigated. METHODS: This study compared the estimated relative survival of WTC-exposed responders who developed cancer while enrolled in two WTC medical monitoring and treatment programs in New York City (WTC-MMTP responders) and WTC-exposed responders not enrolled (WTC-non-MMTP responders) to non-responders from New York State (NYS-non-responders), all restricted to the 11-southernmost NYS counties, where most responders resided. Parametric survival models estimated cancer-specific and all-cause mortality. Follow-up ended at death or on December 31, 2016. RESULTS: From January 1, 2005 to December 31, 2016, there were 2,037 cancer cases and 303 deaths (248 cancer-related deaths) among WTC-MMTP responders, 564 cancer cases, and 143 deaths (106 cancer-related deaths) among WTC-non-MMTP responders, and 574,075 cancer cases and 224,040 deaths (158,645 cancer-related deaths) among the NYS-non-responder population. Comparing WTC-MMTP responders with NYS-non-responders, the cancer-specific mortality hazard ratio (HR) was 0.72 (95% confidence interval [CI] = 0.64-0.82), and all-cause mortality HR was 0.64 (95% CI = 0.58-0.72). The cancer-specific HR was 0.94 (95% CI = 0.78-1.14), and all-cause mortality HR was 0.93 (95% CI = 0.79-1.10) comparing WTC-non-MMTP responders to the NYS-non-responder population. CONCLUSIONS: WTC-MMTP responders had lower mortality compared with NYS-non-responders, after controlling for demographic factors and temporal trends. There may be survival benefits from no-out-of-pocket-cost medical care which could have important implications for healthcare policy, however, other occupational and socioeconomic factors could have contributed to some of the observed survival advantage.

Goldfarb, D. G., et al. (2021). "Temporal association of prostate cancer incidence with World Trade Center rescue/recovery work." Occup Environ Med **78**(10): 699-706.

BACKGROUND: The World Trade Center (WTC) attacks on 11 September 2001 created a hazardous environment with known and suspected carcinogens. Previous studies have identified an increased risk of prostate cancer in responder cohorts compared with the general male population. OBJECTIVES: To estimate the length of time to prostate cancer among WTC rescue/recovery workers by determining specific time periods during which the risk was significantly elevated. METHODS: Person-time accruals began 6 months after enrolment into a WTC cohort and ended at death or 12/31/2015. Cancer data were obtained through linkages with 13 state cancer registries. New York State was the comparison population. We used Poisson regression to estimate hazard ratios and 95% CIs; change points in rate ratios were estimated using profile likelihood. RESULTS: The analytic cohort included 54 394 male rescue/recovery workers. We observed 1120 incident prostate cancer cases. During 2002-2006, no association with WTC exposure was detected. Beginning in 2007, a 24% increased risk (HR: 1.24, 95% CI 1.16 to 1.32) was observed among WTC rescue/recovery workers when compared with New York State. Comparing those who arrived earliest at the disaster site on the morning of 11 September 2001 or any time on 12 September 2001 to those who first arrived later, we observed a positive, monotonic, dose-response association in the early (2002-2006) and late (2007-2015) periods. CONCLUSIONS: Risk of prostate cancer was significantly elevated beginning in 2007 in the WTC combined rescue/recovery cohort. While unique exposures at the disaster site might have contributed to the observed effect, screening practices including routine prostate specific antigen screening cannot be discounted.

Kwon, S., et al. (2021). "Dynamic Metabolic Risk Profiling of World Trade Center Lung Disease: A Longitudinal Cohort Study." Am J Respir Crit Care Med **204**(9): 1035-1047.

Rationale: Metabolic syndrome (MetSyn) increases the risk of World Trade Center (WTC) lung injury (LI). However, the temporal relationship of MetSyn, exposure intensity, and lung dysfunction is not well understood. Objective: To model the association of longitudinal MetSyn characteristics with WTC lung disease to define modifiable risk. Methods: Firefighters, for whom consent was obtained (N = 5,738), were active duty on September 11, 2001 (9/11). WTC-LI (n = 1,475; FEV(1)% predicted <lower limit of normal [LLN]) and non-WTC-LI (n = 4,263; FEV(1)% predicted ⩾LLN at all exams) was the primary outcome, and FVC% predicted <LLN and FEV(1)/FVC <0.70 were secondary outcomes. We assessed 1) the effect of concurrent MetSyn on longitudinal lung function by linear mixed models, 2) the temporal effect of MetSyn and exposure by Weibull proportional hazards, 3) the effects of MetSyn's rate of change by two-stage models, and 4) the nonlinear joint effect of longitudinal MetSyn components by a partially linear single-index model (PLSI). Measurements and Main Results: WTC-LI cases were more often ever-smokers, arrived in the morning (9/11), and had MetSyn. Body mass index ⩾30 kg/m(2) and high-density lipoprotein <40 mg/dl were

most contributory to concurrent loss of FEV(1)% predicted and FVC% predicted while conserving FEV(1)/FVC. Body mass index ⩾30 kg/m(2) and dyslipidemia significantly predicted WTC-LI, FVC% predicted <LLN in a Weibull proportional hazards model. Dynamic risk assessment of WTC-LI on the basis of MetSyn and exposure showed how reduction of MetSyn factors further reduces WTC-LI likelihood in susceptible populations. PLSI demonstrates that MetSyn has a nonlinear relationship with WTC lung disease, and increases in cumulative MetSyn risk factors exponentially increase WTC-LI risk. An interactive metabolic-risk modeling application was developed to simplify PLSI interpretation. Conclusions: MetSyn and WTC exposure contribute to the development of lung disease. Dynamic risk assessment may be used to encourage treatment of MetSyn in susceptible populations. Future studies will focus on dietary intervention as a disease modifier.

Lam, R., et al. (2021). "Dietary phenotype and advanced glycation end-products predict WTC-obstructive airways disease: a longitudinal observational study." Respir Res **22**(1): 19.

BACKGROUND: Diet is a modifier of metabolic syndrome which in turn is associated with World Trade Center obstructive airways disease (WTC-OAD). We have designed this study to (1) assess the dietary phenotype (food types, physical activity, and dietary habits) of the Fire Department of New York (FDNY) WTC-Health Program (WTC-HP) cohort and (2) quantify the association of dietary quality and its advanced glycation end product (AGE) content with the development of WTC-OAD. METHODS: WTC-OAD, defined as developing WTC-Lung Injury (WTC-LI; FEV(1) < LLN) and/or airway hyperreactivity (AHR; positive methacholine and/or positive bronchodilator response). Rapid Eating and Activity Assessment for Participants-Short Version (REAP-S) deployed on 3/1/2018 in the WTC-HP annual monitoring assessment. Clinical and REAP-S data of consented subjects was extracted (7/17/2019). Diet quality [low-(15-19), moderate-(20-29), and high-(30-39)] and AGE content per REAP-S questionnaire were assessed for association with WTC-OAD. Regression models adjusted for smoking, hyperglycemia, hypertension, age on 9/11, WTC-exposure, BMI, and job description. RESULTS: N = 9508 completed the annual questionnaire, while N = 4015 completed REAP-S and had spirometry. WTC-OAD developed in N = 921, while N = 3094 never developed WTC-OAD. Low- and moderate-dietary quality, eating more (processed meats, fried foods, sugary drinks), fewer (vegetables, whole-grains),and having a diet abundant in AGEs were significantly associated with WTC-OAD. Smoking was not a significant risk factor of WTC-OAD. CONCLUSIONS: REAP-S was successfully implemented in the FDNY WTC-HP monitoring questionnaire and produced valuable dietary phenotyping. Our observational study has identified low dietary quality and AGE abundant dietary habits as risk factors for pulmonary disease in the context of WTC-exposure. Dietary phenotyping, not only focuses our metabolomic/biomarker profiling but also further informs future dietary interventions that may positively impact particulate matter associated lung disease.

Maura, F., et al. (2021). "Initial Whole-Genome Sequencing of Plasma Cell Neoplasms in First Responders and Recovery Workers Exposed to the World Trade Center Attack of September 11, 2001." Clin Cancer Res **27**(7): 2111-2118.

PURPOSE: The World Trade Center (WTC) attack of September 11, 2001 created an unprecedented environmental exposure to known and suspected carcinogens. High incidence of multiple myeloma and precursor conditions has been reported among first responders to the WTC disaster. To expand on our prior screening studies, and to characterize the genomic impact of the exposure to known and potential carcinogens in the WTC debris, we were motivated to perform whole-genome sequencing (WGS) of WTC first responders and recovery workers who developed a plasma cell disorder after the attack. EXPERIMENTAL DESIGN: We performed WGS of nine CD138-positive bone marrow mononuclear samples from patients who were diagnosed with plasma cell disorders after the WTC disaster. RESULTS: No significant differences were observed in comparing the post-WTC driver and mutational signature landscapes with 110 previously published WGSs from 56 patients with multiple myeloma and the CoMMpass WGS cohort (n = 752). Leveraging constant activity of the single-base substitution mutational signatures 1 and 5 over time, we estimated that tumor-initiating chromosomal gains were windowed to both pre- and post-WTC exposure. CONCLUSIONS: Although limitations in sample size preclude any definitive conclusions, our findings suggest that the observed increased incidence of plasma cell neoplasms in this population is due to complex and heterogeneous effects of the WTC exposure that may have initiated or contributed to progression of malignancy.

Mueller, A. K., et al. (2021). "PTSD symptoms, depressive symptoms, and subjective cognitive concerns in WTC-exposed and non-WTC-exposed firefighters." Am J Ind Med **64**(10): 803-814.

BACKGROUND: Firefighting has been associated with posttraumatic stress disorder (PTSD) and other mental health conditions. We previously found that among Fire Department of the City of New York (FDNY) responders to the World Trade Center (WTC) disaster, higher-intensity WTC-exposure predicted PTSD symptoms, depressive symptoms, and subjective cognitive concerns. The present study aims to compare these symptoms in the FDNY WTC-exposed cohort versus a comparison cohort of non-FDNY, non-WTC-exposed firefighters. METHODS: The study population included WTC-exposed male firefighters from FDNY (N = 8466) and non-WTC-exposed male firefighters from Chicago (N = 1195), Philadelphia (N = 770), and San Francisco (N = 650) fire departments who were employed on 9/11/2001 and completed a health questionnaire between 3/1/2018 and 12/31/2020. Current PTSD symptoms, depressive symptoms, and subjective cognitive concerns were assessed via validated screening instruments. Multivariable linear regression analyses stratified by fire department estimated the impact of covariates on each outcome. RESULTS: Adjusted mean PTSD symptom scores ranged from 23.5 +/- 0.6 in Chicago firefighters to 25.8 +/- 0.2 in FDNY, and adjusted mean depressive symptom scores ranged from 7.3 +/- 0.5 in Chicago to 9.4 +/- 0.6 in Philadelphia. WTC-exposure was associated with fewer subjective cognitive concerns (beta = -0.69 +/- 0.05, $p < .001$) after controlling for covariates. Across cohorts, older age was associated with more cognitive concerns, but fewer PTSD and depressive symptoms. CONCLUSIONS: WTC-exposed firefighters had fewer cognitive concerns compared with non-WTC-exposed firefighters. We were unable to estimate associations between WTC exposure and PTSD symptoms or depressive symptoms due to variability between non-WTC-exposed cohorts. Longitudinal follow-up is needed to assess PTSD, depressive, and cognitive symptom trajectories in firefighter populations as they age.

Webber, M. P., et al. (2021). "Cancer incidence in World Trade Center-exposed and non-exposed male firefighters, as compared with the US adult male population: 2001-2016." Occup Environ Med **78**(10): 707-714.

OBJECTIVE: To compare cancer incidence in Fire Department of the City of New York (FDNY) firefighters who worked at the World Trade Center (WTC) site to incidence in a population of non-WTC-exposed firefighters, the Career Firefighter Health Study (CFHS) cohort, and to compare rates from each firefighter cohort to rates in demographically similar US males. METHODS: FDNY (N=10 786) and CFHS (N=8813) cohorts included male firefighters who were active on 11 September 2001 (9/11) and were followed until death or 31 December 2016. Cases were identified from 15 state cancer registries. Poisson regression models assessed cancers in each group (FDNY and CFHS) versus US males, and associations between group and cancer rates; these models estimated standardised incidence ratios (SIRs) and adjusted relative rates (RRs), respectively. Secondary analyses assessed surveillance bias and smoking history. RESULTS: We identified 915 cancer cases in 841 FDNY firefighters and 1002 cases in 909 CFHS firefighters. FDNY had: higher rates for all cancers (RR=1.13; 95% CI 1.02 to 1.25), prostate (RR=1.39; 95% CI 1.19 to 1.63) and thyroid cancer (RR=2.53; 95% CI 1.37 to 4.70); younger median ages at diagnosis (55.6 vs 59.4; $p<0.001$, all cancers); and more cases with localised disease when compared with CFHS. Compared with US males, both firefighter cohorts had elevated SIRs for prostate cancer and melanoma. Control for surveillance bias in FDNY reduced most differences. CONCLUSIONS: Excess cancers occurred in WTC-exposed firefighters relative to each comparison group, which may partially be explained by heightened surveillance. Two decades post-9/11, clearer understanding of WTC-related risk requires extended follow-up and modelling studies (laboratory or animal based) to identify workplace exposures in all firefighters.

Weiden, M. D., et al. (2021). "Serum Th-2 cytokines and FEV(1) decline in WTC-exposed firefighters: A 19-year longitudinal study." Am J Ind Med **64**(10): 845-852.

BACKGROUND: Accelerated-FEV(1) -decline, defined as rate of decline in FEV(1) > 64 ml/year, is a risk factor for asthma and chronic obstructive pulmonary disease in World Trade Center (WTC)-exposed firefighters. Accelerated-FEV(1) -decline in this cohort is associated with elevated blood eosinophil concentrations, a mediator of Th-2 response. We hypothesized that an association exists between Th-2 biomarkers and FEV(1) decline rate in those with accelerated-FEV(1) -decline. METHODS: Serum was drawn from Fire Department of the City of New York (FDNY) firefighters 1-6 months (early) (N = 816) and 12-13 years (late) (N = 983) after 9/11/2001. Th-2 biomarkers IL-4, IL-13, and IL-5 were assayed by multiplex Luminex. Individual FEV(1) decline rates were calculated using spirometric measurements taken: (1) between 9/11/2001 and 9/10/2020 for the early biomarker group and (2) between late measurement date

and 9/10/2020 for the late biomarker group. Associations of early and late Th-2 biomarkers with subsequent FEV(1) decline rates were analyzed using multivariable linear regression controlling for demographics, smoking status, and other potential confounders. RESULTS: In WTC-exposed firefighters with accelerated-FEV(1) -decline, IL-4, IL-13, and IL-5 measured 1-6 months post-9/11/2001 were associated with greater FEV(1) decline ml/year between 9/11/2001 and 9/10/2020 (-2.9 +/- 1.4 ml/year per IL-4 doubling; -8.4 +/- 1.2 ml/year per IL-13 doubling; -7.9 +/- 1.3 ml/year per IL-5 doubling). Among late measured Th-2 biomarkers, only IL-4 was associated with subsequent FEV(1) decline rate (-4.0 +/- 1.6 ml/year per IL-4 doubling). CONCLUSIONS: In WTC-exposed firefighters with accelerated-FEV(1) -decline, elevated serum IL-4 measured both 1-6 months and 12-13 years after 9/11 is associated with greater FEV(1) decline/year. Drugs targeting the IL-4 pathway may improve lung function in this high-risk subgroup.

Zeig-Owens, R., et al. (2021). "Assembling the Career Firefighter Health Study cohort: A methods overview." Am J Ind Med **64**(8): 680-687.

BACKGROUND: Studies of World Trade Center (WTC)-exposed rescue/recovery workers report the increased occurrence of health conditions after work at the WTC disaster site. However, the extent to which these associations are due to WTC exposure is unclear, in part due to the lack of suitable comparison groups. Accordingly, we identified a previously assembled National Institute for Occupational Safety and Health (NIOSH) cohort of career firefighters from three US cities (n = 29,992). Here, we document the challenges in establishing this non-WTC-exposed firefighter cohort for the goal of tracking and comparing cancer and chronic health conditions in WTC-exposed and non-WTC-exposed firefighters. METHODS: Follow-up process included institutional review board applications, data use agreements, state cancer registry linkages and vital status determination for the NIOSH firefighter cohort. After completion of these steps, we undertook outreach to the three original city fire departments and union officials, before contact tracing and direct recruitment of 14,566 living firefighters to complete a confidential health survey. We staggered recruitment efforts by the city, using letters, postcards, emails, videos, and telephone outreach. Participants who completed the survey received $10. RESULTS: A total of 4962 of 14,566 alive firefighters responded to the baseline survey (34.1% response rate). Respondents were older and more likely to be non-Hispanic white than nonrespondents. CONCLUSIONS: We provide an overview of the process for the first survey to collect information on physical and mental health conditions among US firefighters. The data collected will have an important impact on studies of WTC rescue/recovery work, firefighting, and related health conditions.

2022

Boffetta, P., et al. (2022). "Temporal Aspects of the Association between Exposure to the World Trade Center Disaster and Risk of Cutaneous Melanoma." JID Innov **2**(1): 100063.

Rescue/recovery workers who responded to the World Trade Center (WTC) attacks were exposed to known/suspected carcinogens. Studies have identified a trend toward an elevated risk of cutaneous melanoma in this population; however, few found significant increases. Furthermore, temporal aspects of the association have not been investigated. A total of 44,540 non-Hispanic White workers from the WTC Combined Rescue/Recovery Cohort were studied between March 12, 2002 and December 31, 2015. Cancer data were obtained through linkages with 13 state registries. Poisson regression was used to estimate hazard ratios and 95% confidence intervals using the New York State population as the reference; change points in hazard ratios were estimated using profile likelihood. We observed 247 incident cases of melanoma. No increase in incidence was detected during 2002-2004. From 2005 to 2015, the hazard ratio was 1.34 (95% confidence interval = 1.18-1.52). A dose–response relationship was observed by arrival time at the WTC site. Risk was elevated just over 3 years after the attacks. Whereas WTC-related exposures to UVR or other agents might have contributed to this result, exposures other than those at the WTC site, enhanced medical surveillance, and lack of a control group with a similar proportion of rescue/recovery workers cannot be discounted. Our results support continued study of this population for melanoma.

Cleven, K. L., et al. (2022). "Risk Factors for COVID-19 in a Retired FDNY WTC-Exposed Cohort." Int J Environ Res Public Health **19**(15).

We evaluated the incidence and risk factors for COVID-19 in a prospectively followed cohort of Fire Department of the City of New York (FDNY) World Trade Center (WTC)-exposed workers, thus reducing the

potential for selection bias, a limitation in published studies of hospitalized individuals. Participants were retired FDNY WTC-exposed rescue/recovery workers with >/=1 medical visit between 1 March 2020 and 1 August 2021. The cumulative incidence was calculated using self-reported COVID-19 diagnoses. Cox regression was performed to evaluate the association of WTC-exposure and COVID-19, adjusting for history of comorbidities, age, race, work assignment (emergency medical service providers vs. firefighter), and sex. The cumulative incidence of COVID-19 was 130 per 1000. The adjusted models showed the risk of infection was greater in those with highest WTC exposure versus less exposure (hazard ratio (HR) = 1.14 (95% CI 1.00-1.31)). Older age was associated with a lower risk of infection HR = 0.97 (95% CI 0.96-0.98). WTC-associated diseases (obstructive airways disease and interstitial lung disease) were not COVID-19 risk factors. This study is the first to show an association between WTC exposure and the risk of COVID-19. While participants are retired from FDNY work, the youngest individuals may still be in the workforce, explaining why younger age was a significant risk for COVID-19.

Clouston, S. A. P., et al. (2022). "Cognitive impairment and World Trade Centre-related exposures." Nat Rev Neurol **18**(2): 103-116.

On 11 September 2001 the World Trade Center (WTC) in New York was attacked by terrorists, causing the collapse of multiple buildings including the iconic 110-story 'Twin Towers'. Thousands of people died that day from the collapse of the buildings, fires, falling from the buildings, falling debris, or other related accidents. Survivors of the attacks, those who worked in search and rescue during and after the buildings collapsed, and those working in recovery and clean-up operations were exposed to severe psychological stressors. Concurrently, these 'WTC-affected' individuals breathed and ingested a mixture of organic and particulate neurotoxins and pro-inflammogens generated as a result of the attack and building collapse. Twenty years later, researchers have documented neurocognitive and motor dysfunctions that resemble the typical features of neurodegenerative disease in some WTC responders at midlife. Cortical atrophy, which usually manifests later in life, has also been observed in this population. Evidence indicates that neurocognitive symptoms and corresponding brain atrophy are associated with both physical exposures at the WTC and chronic post-traumatic stress disorder, including regularly re-experiencing traumatic memories of the events while awake or during sleep. Despite these findings, little is understood about the long-term effects of these physical and mental exposures on the brain health of WTC-affected individuals, and the potential for neurocognitive disorders. Here, we review the existing evidence concerning neurological outcomes in WTC-affected individuals, with the aim of contextualizing this research for policymakers, researchers and clinicians and educating WTC-affected individuals and their friends and families. We conclude by providing a rationale and recommendations for monitoring the neurological health of WTC-affected individuals.

Ferastraoaru, D., et al. (2022). "Relationship between low serum immunoglobulin E levels and malignancies in 9/11 World Trade Center responders." Ann Allergy Asthma Immunol **129**(6): 769-775.

BACKGROUND: Individuals with very low immunoglobulin E (IgE) levels have a high risk of developing malignancy. Previous studies have revealed that World Trade Center (WTC) responders exposed to carcinogens have an elevated risk of some cancers. OBJECTIVE: To evaluate the association between low-serum IgE levels and cancer development in WTC-exposed responders. METHODS: IgE levels were measured in 1851 WTC responders after September 11, 2001. This is the first pilot study in humans comparing the odds of developing cancer in this high-risk population, between the "low-IgE" (IgE in the lowest third percentile) vs "non-low-IgE" participants. RESULTS: A significantly higher proportion of hematologic malignancies was found in low-IgE (4/55, 7.3%) compared with non-low-IgE (26/1796, 1.5%, P < .01) responders. The proportion of solid tumors were similar in both groups (5.5% vs 11.4%, P > .05). After adjustment for relevant confounders (race, sex, age at blood draw, WTC arrival time, smoking status), the low-IgE participants had 7.81 times greater odds (95% confidence interval, 1.77-29.35) of developing hematologic cancer when compared with non-low-IgE participants. The hematologic cancers found in this cohort were leukemia (n = 1), multiple myeloma (n = 1), and lymphoma (n = 2). No statistical significance was found when estimating the odds ratio for solid tumors in relation to IgE levels. CONCLUSION: WTC responders with low serum IgE levels had the highest odds of developing hematologic malignancies. This hypothesis-generating study suggests that low serum IgE levels might be associated with the development of specific malignancies in at-risk individuals exposed to carcinogens. Larger, multicenter studies with adequate follow-up of individuals with different IgE levels are needed to better evaluate this relationship.

Jasra, S., et al. (2022). "High burden of clonal hematopoiesis in first responders exposed to the World Trade Center disaster." Nat Med **28**(3): 468-471.

> The terrorist attacks on the World Trade Center (WTC) created an unprecedented environmental exposure to aerosolized dust, gases and potential carcinogens. Clonal hematopoiesis (CH) is defined as the acquisition of somatic mutations in blood cells and is associated with smoking and exposure to genotoxic stimuli. Here we show that deep targeted sequencing of blood samples identified a significantly higher proportion of WTC-exposed first responders with CH (10%; 48 out of 481) when compared with non-WTC-exposed firefighters (6.7%; 17 out of 255; odds ratio, 3.14; 95% confidence interval, 1.64-6.03; P = 0.0006) after controlling for age, sex and race/ethnicity. The frequency of somatic mutations in WTC-exposed first responders showed an age-related increase and predominantly affected DNMT3A, TET2 and other CH-associated genes. Exposure of lymphoblastoid cells to WTC particulate matter led to dysregulation of DNA replication at common fragile sites in vitro. Moreover, mice treated with WTC particulate matter developed an increased burden of mutations in hematopoietic stem and progenitor cell compartments. In summary, the high burden of CH in WTC-exposed first responders provides a rationale for enhanced screening and preventative efforts in this population.

Zeig-Owens, R., et al. (2022). "Myeloma precursor disease (MGUS) among rescue and recovery workers exposed to the World Trade Center disaster." Blood Cancer J **12**(8): 120.

> An elevated risk of myeloma precursor disease, monoclonal gammopathy of undetermined significance (MGUS), was identified among Fire Department of the City of New York (FDNY) World Trade Center (WTC)-exposed firefighters. Further investigation was needed to determine if these findings were reproducible in a more heterogeneous WTC-exposed rescue/recovery workers cohort, the Stony Brook University-General Responder Cohort GRC (SBU-GRC). MGUS risk was compared between the cohorts and to published general population estimates from Olmsted County, MN, USA. In this observational seroprevalence study, odds ratios (OR) and age-standardized risk ratios (RR) of MGUS (M-spike and light-chain-MGUS combined), M-spike, and light-chain-MGUS were estimated using logistic regression. Age-standardized prevalences were calculated for white males aged 50-79; RRs were estimated by comparing risk in the WTC-exposed cohort with the Olmsted County screened cohort. SBU-GRC had elevated odds of MGUS compared with FDNY (OR = 1.38; 95%CI = 1.00-1.89). The age-standardized prevalence of MGUS was 9.0/100 persons (95%CI = 7.5-10.6), over two-fold higher than the general population (RR = 2.08; 95%CI = 1.72-2.51); the age-standardized prevalence of light-chain-MGUS was 3.5-fold higher (RR = 3.54; 95%CI = 2.52-4.97). This study adds to mounting evidence supporting an association between WTC/environmental exposures and MGUS among rescue/recovery workers. Access to MGUS screenings for the entire WTC-exposed cohort could allow for treatment interventions that improve survival.

2023

Goldfarb, D. G., et al. (2023). "Association of Lung Function Decline with All-Cause and Cancer-Cause Mortality after World Trade Center Dust Exposure." Ann Am Thorac Soc **20**(8): 1136-1143.

> Rationale: In numerous cohorts, lung function decline is associated with all-cause and cardiovascular-cause mortality, but the association between the decrease in forced expiratory volume in 1 second (FEV(1)) and cancer-cause mortality, particularly after occupational/environmental exposure(s), is unclear. Exposure to dust/smoke from the World Trade Center (WTC) disaster caused inflammation and lung injury in Fire Department of the City of New York rescue/recovery workers. In addition, prior research found that >10% of the cohort experienced greater than twice the age-related decrease in FEV(1) (⩾64 ml/yr). Objectives: To evaluate the association of longitudinal lung function with all-cause and cancer-cause mortality after exposure to the WTC disaster. Methods: We conducted a prospective cohort study using longitudinal prebronchodilator FEV(1) data for 12,264 WTC-exposed firefighters and emergency medical service providers. All-cause and cancer-cause mortality were ascertained using National Death Index data from September 12, 2001, through December 31, 2021. Joint longitudinal survival models evaluated the association of baseline FEV(1) and change in FEV(1) from baseline with all-cause and cancer-cause mortality adjusted for age, race/ethnicity, height, smoking, work assignment (firefighters vs. emergency medical service providers), and WTC exposure. Results: By December 31, 2021, 607 of the 12,264 individuals in the cohort (4.9%) had died (crude rate = 259.5 per 100,000 person-years), and 190 of 12,264 (1.5%) had died from cancer (crude rate = 81.2 per 100,000 person-years). Baseline FEV(1) was ⩾80% predicted in 10,970 of the 12,264 (89.4%); final FEV(1)

was ⩾80% in 9,996 (81.5%). Lower FEV(1) at baseline was associated with greater risk for all-cause mortality (hazard ratio [HR] per liter = 2.32; 95% confidence interval [95% CI] = 1.98-2.72) and cancer-cause mortality (HR per liter = 1.99; 95% CI = 1.49-2.66). Longitudinally, each 100-ml/yr decrease in FEV(1) was associated with an 11% increase in all-cause mortality (HR = 1.11; 95% CI = 1.06-1.15) and a 7% increase in cancer-cause mortality (HR = 1.07; 95% CI = 1.00-1.15). Compared with FEV(1) decrease <64 ml/yr, those with FEV(1) decrease ⩾64 ml/yr had higher all-cause (HR = 2.91; 95% CI = 2.37-3.56) and cancer-cause mortality (HR = 2.68; 95% CI = 1.90-3.79). Conclusions: Baseline FEV(1) and longitudinal FEV(1) decrease are associated with increased risk of all-cause and cancer-cause mortality in a previously healthy occupational cohort, the majority of whom had normal lung function, after intense exposure to dust/smoke. Further investigation is needed to define pathways by which lung function impacts mortality after an irritant exposure.

Khalifeh, M., et al. (2023). "Cancer incidence in World Trade Center rescue and recovery workers by race and ethnicity." Am J Ind Med **66**(12): 1048-1055.

INTRODUCTION: It is unclear whether differences in health outcomes by racial and ethnic groups among World Trade Center (WTC) rescue and recovery workers reflect those of the population of New York State (NYS) or show distinct patterns. We assessed cancer incidence in WTC workers by self-reported race and ethnicity, and compared it to population figures for NYS. METHODS: A total of 61,031 WTC workers enrolled between September 11, 2001 and January 10, 2012 were followed to December 31, 2015. To evaluate the association between race/ethnicity and cancer risk, Poisson regression analysis was used to estimate hazard ratios (HR) adjusted for WTC exposure, age, calendar year, sex and, for lung cancer, cigarette smoking. RESULTS: In comparison to Whites, Black workers had a higher incidence of prostate cancer (HR = 1.99, 95% CI = 1.69-2.34) and multiple myeloma (HR = 3.57, 95% CI = 1.97-6.45), and a lower incidence of thyroid (HR = 0.41, 95% CI = 0.22-0.78) and colorectal cancer (HR = 0.57; 95% CI = 0.33-0.98). Hispanic workers had a higher incidence of liver cancer (HR = 4.03, 95% CI = 2.23-7.28). Compared with NYS population, White workers had significantly higher incidence of prostate cancer (HR = 1.26, 95% CI = 1.18-1.35) and thyroid cancer (HR = 1.80, 95% CI = 1.55-2.08), while Black workers had significantly higher incidence of prostate cancer (HR = 1.22, 95% CI = 1.05-1.40). CONCLUSION: Cancer incidence in WTC workers generally reflects data from the NYS population, but some differences were identified that merit further investigation.

Li, J., et al. (2023). "A 15-year follow-up study of mortality in a pooled cohort of World Trade Center rescue and recovery workers." Environ Res **219**: 115116.

INTRODUCTION: Hazardous exposures from the World Trade Center (WTC) terrorist attacks have been linked to increased incidence of adverse health conditions, often associated with increased mortality. We assessed mortality in a pooled cohort of WTC rescue/recovery workers over 15 years of follow-up. MATERIALS AND METHODS: We analyzed mortality through 2016 in a pooled and deduplicated cohort of WTC rescue/recovery workers from three WTC-exposed cohorts (N = 60,631): the Fire Department of the City of New York (FDNY); the WTC Health Registry (WTCHR); and the General Responder Cohort (GRC). Standardized mortality ratios (SMRs) were estimated to assess mortality vs. the US and NY state populations. Multivariable Cox proportional hazards models were used to examine associations of WTC exposures (date of first arrival, working on the WTC debris pile) with mortality risk. RESULTS: There were 1912 deaths over 697,943.33 person-years of follow-up. The SMR for all-cause mortality was significantly lower-than-expected, both when using US (SMR 0.43, 95% confidence interval [CI] 0.42-0.45) and NYS (SMR 0.51, 95% CI 0.49-0.53) as reference populations. SMRs were not elevated for any of the 28 major causes of death. Arriving at the WTC site on 9/11-9/17/2001 vs. 9/18/2001-6/30/2002 was associated with 30-50% higher risk of all-cause, heart disease and smoking-related mortality in non-FDNY/non-GRC members. Conversely, arriving on 9/11/2001 vs. 9/18/2001-6/30/2002 was associated with 40% lower all-cause and smoking-related mortality risk in FDNY members. Working on vs. off the WTC pile was associated with an increased risk of all-cause mortality in non-FDNY/non-GRC members (adjusted hazard ratio [aHR] 1.25, 95% CI 1.04-1.50), and cancer-specific mortality in GRC members (aHR 1.39, 95% CI 1.05-1.84), but lower mortality risks were found in FDNY members. CONCLUSIONS: We did not observe excess mortality among WTC rescue/recovery workers compared with general populations. However, significantly increased mortality risks among some sub-groups with high WTC exposure warrant further investigation.

Mueller, A. K., et al. (2023). "Comparing self-reported obstructive airway disease in firefighters with and without World Trade Center exposure." Am J Ind Med **66**(3): 243-251.

BACKGROUND: The degree to which routine, non-World Trade Center (WTC) firefighting exposures contribute to the WTC exposure-obstructive airway disease (OAD) relationship is unknown. Our objective was to compare the frequency of self-reported OAD diagnoses in WTC-exposed firefighters from the Fire Department of the City of New York (FDNY) compared with non-WTC-exposed firefighters from other cities and the general population. METHODS: A total of 9792 WTC-exposed male FDNY firefighters and 3138 non-WTC-exposed male firefighters from Chicago, Philadelphia, and San Francisco who were actively employed on 9/11/01 and completed a health questionnaire were included. Logistic regression estimated odds ratios of self-reported asthma and COPD diagnoses in firefighters (WTC-exposed vs. non-WTC-exposed; all firefighters vs. general population), adjusting for age, race, smoking status, and last medical visit. RESULTS: WTC-exposed firefighters were, on average, younger on 9/11 (mean +/- SD = 40.2 +/- 7.4 vs. 44.1 +/- 9.1) and less likely to report ever-smoking (32.9% vs. 41.8%) than non-WTC-exposed firefighters. Odds of any OAD and asthma were 4.5 and 6.3 times greater, respectively, in WTC-exposed versus non-WTC-exposed. Odds of COPD were also greater in WTC-exposed versus non-WTC-exposed, particularly among never-smokers. Compared with the general population, WTC-exposed firefighters had greater odds of both asthma and COPD, while the nonexposed had lower odds of asthma and greater odds of COPD. CONCLUSIONS: Odds ratios for OAD diagnoses were greater in WTC-exposed firefighters versus both non-WTC-exposed and the general population after adjusting for covariates. While asthma and other OADs are known occupational hazards of firefighting, WTC exposure significantly compounded these adverse respiratory effects.

Singh, A., et al. (2023). "All-cause and cause-specific mortality in a cohort of WTC-exposed and non-WTC-exposed firefighters." Occup Environ Med **80**(6): 297-303.

OBJECTIVE: To compare mortality rates in World Trade Center (WTC)-exposed Fire Department of the City of New York (FDNY) firefighters with rates in similarly healthy, non-WTC-exposed/non-FDNY firefighters, and compare mortality in each firefighter cohort with the general population. METHODS: 10 786 male WTC-exposed FDNY firefighters and 8813 male non-WTC-exposed firefighters from other urban fire departments who were employed on 11 September 2001 were included in the analyses. Only WTC-exposed firefighters received health monitoring via the WTC Health Programme (WTCHP). Follow-up began 11 September 2001 and ended at the earlier of death date or 31 December 2016. Death data were obtained from the National Death Index and demographics from the fire departments. We estimated standardised mortality ratios (SMRs) in each firefighter cohort versus US males using demographic-specific US mortality rates. Poisson regression models estimated relative rates (RRs) of all-cause and cause-specific mortality in WTC-exposed versus non-WTC-exposed firefighters, controlling for age and race. RESULTS: Between 11 September 2001 and 31 December 2016, there were 261 deaths among WTC-exposed firefighters and 605 among non-WTC-exposed. Both cohorts had reduced all-cause mortality compared with US males (SMR (95% CI)=0.30 (0.26 to 0.34) and 0.60 (0.55 to 0.65) in WTC-exposed and non-WTC-exposed, respectively). WTC-exposed firefighters also had lower rates of all-cause mortality (RR=0.54, 95% CI=0.49 to 0.59) and cancer-specific, cardiovascular-specific and respiratory disease-specific mortality compared with non-WTC-exposed firefighters. CONCLUSION: Both firefighter cohorts had lower than expected all-cause mortality. Fifteen years post 11 September 2001, mortality was lower in WTC-exposed versus non-WTC-exposed firefighters. Lower mortality in the WTC-exposed suggests not just a healthy worker effect, but additional factors such as greater access to free health monitoring and treatment that they receive via the WTCHP.

LETTERS

Webber, M.P., Berman, J., Qayyum, B., Jaber, N., Prezant, D.J. (2015) “Reply.” Arthritis Rheumatol.

CHAPTERS AND MONOGRAPHS:

1. Weiden M, Banauch G, Kelly KJ, and Prezant DJ. Firefighters Health and Health Effects of the World Trade

Center Collapse. In: Environmental and Occupational Medicine. Pgs 477-490. 4th Edition, Edited by Rom WN and Markowitz S. Lippincott-Raven Inc. Philadelphia, 2007.

2. Kelly KJ, Niles J, McLaughlin MT, Carrol S, Corrigan M, Al-Othman F, and Prezant DJ. World Trade Center health Impacts on FDNY Rescue Workers – a six year assessment, September 2001 to 2007. Fire Department of the City of New York, October 2007. Available on-line at:
http://www.nyc.gov/html/om/pdf/2007/wtc_health_impacts_on_fdny_rescue_workers_sept_2007.pdf

3. Prezant DJ, Levin S, Kelly KJ, Aldrich TK. Pulmonary and Airway Complications Related to September 11th. In: Interstitial Pulmonary and Bronchiolar Disorders, Pgs 573-590. Edited by Lynch JP; Lung Biology in Health and Disease Vol 227 Ex Editor Lenfant C. Informa Healthcare USA Inc., New York, 2008

4. Paul Greene, Dianne Kane, Grace Christ, Sallie Lynch and Malachy Corrigan. FDNY crisis counseling: innovative responses to 9/11 firefighters, families, and communities. Published 2005.A textbook in counseling at FDNY after WTC.