

FINAL PROGRESS REPORT

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Project Title: Chronic Obstructive Pulmonary Disease in WTC Workers - Diagnoses and Transitions

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Table of Contents

Title Page	1
Abstract	3
Section 1:	4
Section 2:	6

List of Terms and Abbreviations

COPD	Chronic obstructive pulmonary disease
FVC	Forced vital capacity
QCT	Quantitative computed tomography
WTCCTIA	WTC Pulmonary Evaluation Unit Chest CT Imaging Archive

Project Title: Pulmonary Diseases in WTC Workers: Symptoms, Function, and Chest CT Correlates

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Abstract

Background: The overall goal of this project is to characterize the WTC-related lower airway disorders, to investigate newly developed obesity-related imaging markers that may be associated with unfavorable disease expression and functional outcomes and assess their interaction with WTC occupational exposure level. To that end, we will utilize the WTC Pulmonary Evaluation Unit Chest CT Imaging Archive (WTCCTIA), a large database with more than 3000 chest CT images on 1700 WTC workers, all members of the Mount Sinai WTC General Responders' Cohort (MS WTC GRC), that became operational in February 2016 and we established with our previous project. On that subcohort, we have also linked extensive datasets with disease symptoms, both pre-WTC and WTC-related occupational exposures, detailed pulmonary function and longitudinal spirometry measurements and weight trends, visual imaging classification and grading, and quantitative computer assisted method (QCAM) measurements of airway, and pulmonary parenchymal abnormalities. With our research project renewal, we continued to enrich most sources of data with periodic updates, in order to characterize the WTC-related lower airway diseases and their most important adverse prognostic risk factors and evaluate their longitudinal trajectories.

Methods: We proposed the following three specific aims (SA):

Specific Aim 1: to use cluster analysis to find and delineate the clinical phenotypes of chronic lower airway disease in a subset of WTCCTIA population without *a priori* criteria. We used demographic characteristics, obesity status, smoking history, pre-WTC and WTC occupational exposure, chest CT imaging and lung function data.

Specific Aim 2: to assess the relationship between quantitative chest CT indicators of visceral and parietal adipose tissue accumulation and two well-defined adverse lower respiratory effects, namely physician-diagnosis of incident asthma and accelerated longitudinal FEV₁ decline, as well as the clusters identified in SA1.

Specific Aim 3: To test whether visceral/parietal adiposity interacts with WTC exposure level on increasing the risks of two well-defined adverse lower respiratory effects, namely physician-diagnosis of incident asthma and accelerated longitudinal FEV₁ decline, as well as the clusters identified in SA1.

Section 1 of the Final Progress Report (2-page limit)

Significant or Key Findings. Cluster analyses initially identified a low FVC and a COPD/emphysema cluster. Further analyses, including sociodemographic variables, smoking status and intensity, baseline weight and weight gain, WTC exposure, dyspnea, spirometric pattern, bronchodilator response, and QCT metrics (WAP, Pi10, LAV% and HAV%) suggested 4 clusters. The first cluster includes mostly COPD patients with evidence of obstruction and higher LAV% and WAP. The second cluster includes the low FVC subjects, with early arrival at the WTC disaster, substantial dyspnea, as well as QCT metric of WAP. The third cluster seems to group the Latino females, who tend to be nonsmokers, and have low LAV%. The fourth cluster seems to group the predominantly male Caucasian weight gainers, with mostly normal spirometries. We are adding more variables to the model, particularly to derive more information on that fourth cluster. We presented an abstract and are preparing a manuscript for submission.

Our studies with QCT indicators of visceral (pericardial, visceral) adiposity have not suggested a stronger association with adverse respiratory outcomes when compared to body mass index, so we continue to use the latter in our studies, as our group was one of the first to find a positive association between a QCT marker of airway wall thickening and BMI. We have not detected thus far any interaction between adiposity and WTC exposure level.

Translation of Findings. The Centers for Disease Control identifies the prevention and control of chronic diseases as its most pressing motivation to bridge research and practice. This project was motivated by the concern about chronic respiratory disease in a cohort on longitudinal surveillance, that was exposed occupationally to a poorly characterized mixture of inhaled toxicants. Our work has shown that other competing risk factors for adverse respiratory outcomes, besides WTC exposures, likely include tobacco smoking, pre-WTC occupational exposures, the high prevalence of overweight and obesity in these cohorts, and factors such as poor socioeconomic status, and psychiatric comorbidity. All of those aspects are amenable to interventions which could potentially mitigate the development of chronic respiratory diseases, and in fact the WTC Health Program includes services that could address them (except for overweight/obesity).

Our studies are framed within the discovery phase of the knowledge to action plan of the CDC. In our studies, we estimated for the first time the cumulative prevalence of spirometrically defined low forced vital capacity (low FVC) and chronic obstructive pulmonary disease (COPD) in the WTC GRC and documented a linearly decreasing cross-sectional prevalence of current tobacco smoking and the high and increasing prevalence of overweight/obesity. We also documented the association of WTC occupational exposure intensity (as suggested by arrival at the disaster site within the first 48 hours of the terrorist attack) for COPD, asthma-COPD overlap, and low FVC, three very important types of chronic respiratory illness in this population, as is the case in the general population of this country. As part as the translation of our

approach and experience to practice, we incorporated our methodologies (longitudinal spirometry, quantitative CT imaging) into a book chapter on occupational COPD. Our plan is to refine and further develop those recommendations within the next few years.

Research Outcomes/Impact. The findings from this study can inform the implementation of effective longitudinal surveillance of occupational cohorts. The experience of the WTC rescue and recovery workers may demonstrate the adverse impact of a hazardous respiratory exposure, but also the adverse impact of overweight/obesity on respiratory health, considering that active tobacco smoking prevalence demonstrated a steady reduction as a result of multiple interventions that preceded the WTC Health Program. As a result, it suggested the need to incorporate into occupational surveillance preventive services and programs to improve the adoption of healthy habits.

This project contributed the first comprehensive analysis of the longitudinal spirometry findings in the largest occupational cohort within the WTC Health Program, the General Responders' Cohort. It provided the first estimation of the prevalence of COPD in the WTC occupational cohorts after close to 20 years of longitudinal follow up, using fairly universally accepted spirometric definitions (those of the Global Initiative for Chronic Obstructive Lung Disease, GOLD). This project was also the first to apply and publish stringent spirometry quality assurance criteria to select suitable data for analyses and deployed quantitative chest CT techniques to the assessment of the lung diseases observed in these workers. We examined the different patterns of spirometric impairment, and the risk factors for transitions between them.

Background for the Project

Several overlapping mostly chronic diseases have consistently been described in the former workers and volunteers who participated in the rescue, search, recovery, and service restoration at the WTC disaster site in 2001 and 2002 [de la Hoz, Shohet, Chasan, et al. 2008; Mendelson et al. 2007; de la Hoz, Christie, et al. 2008; de la Hoz, Aurora, et al. 2010; Napier et al. 2017; de la Hoz et al. 2010; de la Hoz, Shohet, Bienenfeld, et al. 2008; de la Hoz, Shohet, et al. 2008; Wisnivesky et al. 2008; de la Hoz et al. 2020]. This proposal will focus on WTC-related lower airway diseases, which the principal investigator of this proposal classified on the basis of clinical data [de la Hoz, Shohet, Chasan, et al. 2008; de la Hoz 2010] to form the basis of the effective treatment guidelines in use at the Mount Sinai WTC Health Effects Treatment Program (presently WTC Health Program Clinical Center of Excellence), the largest program of its kind. With more than 40,000 workers and volunteers exposed [Woskie et al. 2011] to a complex but poorly characterized mix of dust, smoke, volatile organic compounds, and, possibly, carcinogens [Lioy et al. 2002; Geyh et al. 2005], the early manifestations of disease [CDCP 2002 ; Levin et al. 2002; Prezant et al. 2002] have evolved into one of the largest occupational disease episodes in the history of the United States. One of the main challenges facing pulmonologists and researchers, is that the WTC-related lower airway diseases are both heterogeneous and very often escape established nosological classifications [de la Hoz 2010], and a considerable number of publications use only symptoms [Prezant et al. 2002; Luft et al. 2012] to define them. Although these disorders seem all plausible results of irritant-induced airway mucosal inflammation, they may have also represented a short- and medium-term effect, and there is a need for further characterization to inform the process of surveillance for their evolution, 15 years after the initial injury [Szeinuk et al. 2008; Guidotti et al. 2011].

Chest CT scanning continues to evolve as one of the most powerful clinical and research tools in respiratory medicine, and technical advances allowing increased resolution, along with decreased radiation dose, have further enhanced its potential as a screening tool for the early detection of several lung diseases, particularly cancer [International Early Lung Cancer Action Project et al. 2006], but also emphysema [Zulueta et al. 2012], and interstitial lung diseases [Doyle et al. 2012].

In our previous project, we obtained systematic readings of ~3000 CT scans performed on 1710 WTC workers, documenting the findings in two standardized visual CT evaluation data forms, the recently proposed International Classification of High-Resolution Computed Tomography for Occupational and Environmental Respiratory Diseases (ICOERD) [Kusaka et al. 2005] as well as the Mount Sinai Lung and Cardiac Screening Program (MS LCSP). Those validated forms systematically assess the presence, and semiquantitatively score the extent of emphysema, evidence of small airways and interstitial lung disease changes, and coronary artery calcifications. In addition, we quantitatively extracted information on those features using quantitative computer-assisted methods (QCAMs) [Coxson 2012; San José Estépar et al. 2008].

Use of these comprehensive approaches maximizes the ability to extract and

quantify the extent of CT abnormalities and complement clinical and functional assessments in the characterization of the lower airway diseases that may have resulted from the WTC occupational exposures. Moreover, we expect to be able to characterize some of their most important prognostic factors, with an emphasis on obesity. This analysis is unique in the WTC population, will complement other studies being conducted in this population and, most importantly, will be applicable to the diagnosis and surveillance of this and other populations at risk for occupational respiratory disease, and have broader implications to the understanding of obstructive airway diseases in the general population.

Specific Aims, Methodology, and Results

The project began in September 2012 and was renewed in September 2017. The specific aims of the 2017 renewal were as follows:

Specific Aim 1: we proposed to use cluster analysis to find and delineate the clinical phenotypes of chronic lower airway disease in a subset of WTC Chest CT Imaging Archive population without *a priori* criteria. We used demographic characteristics, obesity status, smoking history, pre-WTC and WTC occupational exposure, chest CT imaging and lung function data.

Cluster analyses initially identify a low FVC and a COPD/emphysema cluster, whose QCT metrics we characterized in our study [Weber et al. 2020]. Further analyses, including sociodemographic variables, smoking status and intensity, baseline weight and weight gain, WTC exposure, dyspnea, spirometric pattern, bronchodilator response, and QCT metrics (WAP, Pi10, LAV% and HAV%) suggested 4 clusters [de la Hoz et al. 2021]. The first cluster includes mostly COPD patients with evidence of obstruction and higher LAV% and WAP. The second cluster includes the low FVC subjects, with early arrival at the WTC disaster, substantial dyspnea, as well as QCT metric of WAP. The third cluster seems to group the Latino females, who tend to be nonsmokers, and have low LAV%. The fourth cluster seems to group the predominantly male Caucasian weight gainers, with mostly normal spirometries. We are adding more variables to the model, particularly to derive more information on that fourth cluster.

In conjunction with our cluster analysis findings, In our study of WTCCTIA workers with consistent low FVC impairment, compared to subjects with consistently normal spirometry, and subjects with “stable” COPD (i.e., who had met at least twice the COPD defining spirometric definition [Vogelmeier et al. 2017] of post-bronchodilator FEV_1/FVC ratio < 0.7), we demonstrated an association of proximal airway inflammation (as suggested by wall area percent, WAP) with a persistent low FVC pattern, even after adjustment for important and relevant covariates, such as BMI [de la Hoz et al. 2019] and smoking. WAP did not seem different between the low FVC and the COPD subgroups and was higher in both than in the normal spirometry subgroup. As expected, COPD participants in that study were more likely to have higher QCT measurements of distal airway inflammation, and emphysema than those of both normal and low FVC spirometry participants [Weber et al. 2020].

Specific Aim 2: To assess the relationship between quantitative chest CT indicators of visceral and parietal adipose tissue accumulation and two well-defined adverse lower respiratory effects, namely physician-diagnosis of incident asthma and

accelerated longitudinal FEV₁ decline, as well as the clusters identified in Specific Aim 1.

Specific Aim 3: To test whether visceral/parietal adiposity interacts with WTC exposure level on increasing the risks of two well-defined adverse lower respiratory effects, namely physician-diagnosis of incident asthma and accelerated longitudinal FEV₁ decline, as well as the clusters identified in Specific Aim 1.

Our studies with QCT indicators of visceral (pericardial, visceral) adiposity [de la Hoz et al. 2019] have not suggested a stronger association with adverse respiratory outcomes when compared to body mass index, so we continue to use the latter in our studies, as our group was one of the first to find a positive association between a QCT marker of airway wall thickening and BMI [de la Hoz et al. 2019]. We have not detected thus far any interaction between adiposity and WTC exposure level.

Progress Report Publication List

We have published the following manuscripts, and are preparing manuscripts based on already presented abstracts presented at the international meetings of the American Thoracic Society and the European Respiratory Society, as contemplated in the dissemination plan:

Published articles:

- Napier CO, Mbadugha OL, Bienenfeld LA, Doucette JT, Lucchini R, Luna-Sánchez S, de la Hoz RE: [2017] Obesity and weight gain among former World Trade Center workers and volunteers. *Arch Environ Occup Health* 72:106-110.
- de la Hoz RE, Liu X, Doucette JT, Reeves AP, Bienenfeld LA, Wisnivesky JP, Celedón JC, Lynch DA, San José Estépar R: [2018] Increased airway wall thickness is associated with adverse longitudinal first-second forced expiratory volume trajectories of former World Trade Center workers. *Lung* 196:481-489.
- de la Hoz RE, Weber J, Xu D, Doucette JT, Liu X, Carson DA, Celedón JC: [2019] Chest CT scan findings in World Trade Center workers. *Arch Environ Occup Health* 74:263-270.
- de la Hoz RE, Jeon Y, Reeves AP, San José Estépar R, Doucette JT, Liu X, Celedón JC, Nolan A: [2019] Increased pulmonary artery diameter is associated with reduced FEV₁ in former World Trade Center workers. *Clin Respir J* 13:614-623.
- de la Hoz RE, Liu X, Celedón JC, Doucette JT, Jeon Y, Reeves AP, San José Estépar R: [2019] Association of obesity with quantitative chest CT measured airway wall thickness in WTC workers with lower airway disease. *Lung* 197:517-522.
- Sigel KM, Xu D, Weber J, Wisnivesky JP, Celedón JC, de la Hoz RE: [2020] The prevalence of pulmonary nodules on computed tomography in World Trade Center rescue and recovery workers. *Ann Am Thorac Soc* 17:125-128.
- Weber J, Reeves AP, Doucette JT, Jeon Y, Sood A, San José Estépar R, Celedón JC, de la Hoz RE: [2020] Quantitative CT evidence of airway inflammation in World Trade Center workers and volunteers with low FVC spirometric pattern. *Lung* 198:555-563.
- Liu X, Reeves AP, Antoniak K, San José Estépar R, Doucette JT, Weber J, Jeon Y, Xu D, Celedón JC, de la Hoz RE: [2020] Association of quantitative CT lung density measurements with divergent FEV₁ trajectories in WTC workers. *Clin Respir J*

15:613-621. PMC7605357 DOI 10.1111/crj.13313.

- de la Hoz RE, Shapiro M, Nolan A, Celedón JC, Szeinuk J, Lucchini RG: [2020] Association of low FVC spirometric pattern with WTC occupational exposures. *Respir Med* 170:106058.

Abstracts presented (and corresponding †manuscripts in preparation):

- de la Hoz RE, Antoniak K, Liu X, Doucette JT, Weber J, Jeon Y. Chronic parenchymal lung disease radiological abnormalities and declining longitudinal FEV₁ trajectory in WTC workers and volunteers: [2019] *Am J Respir Crit Care Med* 199(IC):A1862. Abstracts of the 2019 American Thoracic Society meeting, Dallas, TX.
- Alruwaily A, Sood A, de la Hoz RE, Liu X, Doucette JT, Jeon Y, Celedón JC: [2020] Change in body mass index and expiratory flow in World Trade Center workers. *Eur Respir J* 56(suppl 64):3848. doi: 10.1183/13993003.congress-2020.3848. Oral poster presentation at the 2020 European Respiratory Society Congress.
- de la Hoz RE, Jeon Y, Doucette JT, Weber J, Celedón JC: [2021] Cluster analysis of the WTC-related lower airway diseases. DOI: 10.1183/13993003.congress-2021.PA3350. Abstract presented at the ERS 2021 Congress.
- de la Hoz RE, San José Estépar R, Reeves AP, Doucette JT, Jeon Y, Weber J, Celedón JC: [2021] Quantitative CT metrics of visceral adiposity are less predictive of adverse respiratory outcomes than body mass index among WTC workers.

Conclusions

Almost 20 years after the WTC disaster on September 11, 2001, the longitudinal surveillance of the WTC General Responders' Cohort demonstrated that the exposures at the disaster site were associated with the development of spirometrically defined low FVC (among men), COPD, and asthma COPD overlap, and our cluster analyses clearly identified those two phenotypes. The cumulative incidence of COPD remains modest (2.9%), compared to what is observed in the general population, and more than half of the cases also had lung function features (large bronchodilator response), that were suggestive of asthma, and thus asthma-COPD overlap. The importance of the latter finding, is that it is at least possible that some of the cases of fixed obstruction (and thus COPD) are seen in individuals with WTC-related asthma in earlier years. We documented steep declines in current smoking status since 2004, and that may have mitigated the incidence of COPD. Detailed clinical studies will be necessary to further study those trajectories towards COPD. Studies of longitudinal lung function trajectories demonstrated that proximal (segmental) bronchial wall thickness, presence of bronchodilator response and weight gain were all associated with accelerated FEV₁ decline. We showed, in turn, that obesity is associated with proximal (segmental) bronchial wall thickness in subjects with lower airway disease. Markers of visceral adiposity did not seem superior to body mass index (BMI) in predicting reduced lung function and accelerated lung function decline.

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Cumulative Inclusion Enrollment Table and Gender and Minority Study Subjects

See attached form PHS 2590.

Inclusion of Children

Not applicable.

Materials available for other investigators

This project utilized data from other projects, the WTC Pulmonary Evaluation Chest Imaging Archive and the WTC General Responders' Cohort Data Center, plus ancillary data bases. The first two are available under data user agreements with the respective principal investigators.