A. COVER PAGE

Project Title: Long-term effects of WTC exposure on respiratory and cardiovascular diseases using automated CT image analysis	
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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

In the aftermath of the 9/11 World Trade Center attack, toxic airborne dust particulates were inhaled by the many World Trade Center (WTC) responders working at the site. This dust exposure is associated with a wide variety of diseases, many of which have a long latency period of over 10 years, and in the case of asbestos-related diseases, latency periods of over 20 years. As we near the twentieth anniversary of the WTC attack, we can expect the number of WTC responders with toxic dust induced disease to increase. Beyond the asbestos fibers in the dust, there were other toxins. These toxins may affect multiple organs (e.g., lungs, heart) and may even have synergistic effects. Computed tomographic (CT) scans of the chest include the lungs and heart and up to half of the liver, most of the kidneys and the entire adrenal gland, thus allowing for early detection of various diseases. Many members of the WTC general responders cohort (GRC) have had at least one chest CT scan, and many have multiple scans obtained in the past 20 years. This provides a unique opportunity to examine the progression of disease.

The overall goal of this proposal is to understand the relationship between toxic dust exposure and respiratory and cardiovascular disease. Specifically, in this project, we will:

Aim 1. Apply developed automated image analysis tools to quantify emphysema, pleural thickening, interstitial lung disease, and coronary artery calcifications on all chest CT scans in the WTC GRC and a lung screening cohort.
In order to provide information on emphysema, pleural thickening, interstitial lung disease (ILD), and coronary artery calcifications (CAC), we will use the automated image analysis tools which we have developed for assessment of these abnormalities on chest CT scans. In addition, we will also use publicly available tools for emphysema, ILD, and CAC. These tools will be applied to two cohorts, WTC GRC responders enrolled at the Mount Sinai School of Medicine who have had chest CT scans performed at Mount Sinai, and an age- and sex--matched lung screening cohort undergoing CT screening for lung cancer at Mount Sinai. Both cohorts have serial chest CT scans over many years, allowing for measurement of the progression of disease over time. We will compare our tools with the publicly available tools to ascertain whether there are significant differences between the results.

Aim 2. Assess extent and progression of emphysema, pleural thickening, interstitial lung disease, and coronary artery calcifications in the WTC GRC compared with a lung screening cohort.
To better understand the effect of WTC dust exposure, we will compare the extent and progression of these four diseases between the WTC GRC and the non-WTC exposed lung screening cohort. We can determine which diseases occur more frequently and with greater progression with WTC exposure. This will allow us to identify which WTC GRC members have these diseases or early signs of these diseases.

Aim 3. Assess the relationship of extent and progression of emphysema, pleural thickening, interstitial lung disease, and coronary artery calcifications to the intensity of WTC dust exposure.
The relationship between the amount of WTC exposure and the extent and progression of these diseases is not yet known. By using the results of Aim 2 and the arrival time to the WTC site available from the WTC data center, we can determine the dose response relationship between WTC dust and the extent and progression of emphysema, pleural thickening, interstitial lung disease, and coronary artery calcification. If we find a strong relationship, this may lead to updated screening guidelines.

This proposed project will aid in the clinical care of members of the WTC GRC by identifying members with emphysema, pleural thickening, interstitial lung disease, and coronary artery calcifications. This has the potential to help a broader population of people with toxic dust exposure by providing information on the extent and progression of disease that may be used to update screening guidelines.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

B.2 (B2 Accomplishments Final merged.pdf)

List of Terms and Abbreviations

- CAC – coronary artery calcification
- CT – computed tomography
- GRC – General Responders Cohort
- HAA250 – percent volume of lung between -600 and -250 HU, a marker of interstitial lung disease
- ILD – Interstitial lung disease
- LAA950 – percent volume of lung below -950 HU, a marker of emphysema
- LDCT – low-dose CT
- PAratio – Pulmonary artery to aorta diameter ratio, a marker of pulmonary hypertension
- WTC – World Trade Center

Abstract

Responders to the World Trade Center (WTC) site in the aftermath of the 9/11 attacks were exposed to toxic dust, which has been linked to increased risk of respiratory and cardiovascular disease. The respiratory and cardiovascular effects of WTC dust exposure have been studied using pulmonary function tests and the number of cardiovascular events, but computed tomography (CT) scans provide an opportunity to see the early structural changes in the lungs and cardiovascular system before clinical symptoms appear. CT scans are used in the screening and evaluation of respiratory diseases such as lung cancer, interstitial lung disease, and chronic obstructive pulmonary disease, and to visualize coronary arteries and quantify the amount of coronary artery calcifications; in fact, it is possible to detect multiple diseases from a single chest CT scan. While manual evaluation by a radiologist is often the gold standard, automated image analysis tools can quickly and accurately quantify these diseases.

We identified non-contrast chest CT scans from members of the World Trade Center General Responders Cohort (WTC GRC) with slice thickness of 2.5 mm or less. We used the open-source Chest Imaging Platform software to compute measures of emphysema and interstitial lung disease and research software from Cornell University to compute measures of pulmonary hypertension and coronary artery calcification. We identified a sex, age (within 5 years), smoking status, one or more CT scans, and follow-up time -matched cohort of participants enrolled in the lung screening program at Mount Sinai. We compared disease measures from the WTC GRC group to the lung screening group to assess whether there was a difference in the extent and progression of disease. We also compared the extent and progression of disease in the WTC GRC according to the arrival time to the WTC site.

There were 4909 chest CT images of members of the WTC GRC that met our image quality criteria. There were 3855 members of the GRC for which we could obtain both chest CT images and clinical data. Of these, there were 2284 members for which we could obtain pulmonary disease measurements on at least one scan, 1246 members for which we could calculate cardiac measurements. The matched controls from the lung screening cohort consisted of 557 participants with 1122 chest CT images that met our image quality criteria and for which we obtained all four disease measures.

We compared members of the WTC GRC with matched participants from the lung screening program. One of the key findings is that after a median time of 11-13 years after 9/11, the WTC GRC group exhibited higher burdens of coronary artery calcification, emphysema, and interstitial lung disease compared with a matched control group of lung screening participants. The analysis of the progression of diseases was not conclusive and will require additional research. Similarly, we did not find an association between WTC dust exposure in terms of the arrival time to the WTC site and automated measures of respiratory and cardiac disease.

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Section 1

Our goal was to understand how toxic dust exposure from the World Trade Center (WTC) cleanup site affected both the incidence and progression of respiratory and cardiovascular disease in members of the WTC General Responders Cohort (GRC). To do so, we identified a matched cohort of lung screening participants for comparison. We applied existing automated image analysis tools that assessed the extent of these diseases from chest CT imaging, which allowed us to retrospectively analyze a larger number of CT scans than would otherwise have been possible with manual radiologist review.

Significant/key Findings

Aim 1 – Apply automated image analysis tools to quantify emphysema, interstitial lung disease (ILD), pulmonary hypertension, and coronary artery calcification on all chest CT scans in the WTC GRC and lung screening cohort.

In the WTC GRC, there were 4909 chest CT images that met our image slice thickness criteria of 2.5 mm or less. Of these 4909 chest CT scans, the emphysema and ILD analysis successfully completed on 4370 (89.0%) scans, while the coronary artery calcification was successful on 2122 (43.2%) scans, and both analyses were successful on 2023 scans (41.2%). There were 3855 members of the GRC for which we could obtain both chest CT images and clinical data. Of these, there were 2284 members for which we could obtain pulmonary disease measurements on at least one scan, 1246 members for which we could calculate cardiac measurements, and 1220 members for which we could successfully compute all four disease measures on at least one scan. We identified a sex, age (within 5 years), smoking status, one or more CT scans, and follow-up time -matched cohort of participants enrolled in the lung screening program at Mount Sinai.

The matched controls from the lung screening cohort consisted of 557 participants with 1122 chest CT images that met our image slice thickness criteria of 2.5 mm or less and for which we obtained all four disease measures.

One of the automated analyses we were not able to complete was the measurement of pleural thickening. The software was not validated by the end of the award period; instead, we included the pulmonary artery to aorta diameter ratio, which is a marker of pulmonary hypertension.

Aim 2 – Assess the relationship of extent and progression of emphysema, ILD, and coronary artery calcifications in the WTC GRC compared with a lung screening cohort.

We compared 557 members of the WTC GRC with matched participants from the lung screening program. One of the key findings is that after a median time of 10 years after 9/11, the WTC GRC group exhibited higher burdens of coronary artery calcification ($p < 0.001$), emphysema ($p < 0.001$), and interstitial lung disease ($p < 0.001$) compared with a control group of lung screening participants. This finding agrees with other published studies and suggests that WTC exposure is associated with coronary artery calcification, emphysema, and interstitial lung disease. The analysis of the progression of diseases was not conclusive and will require additional research.

Aim 3 – Assess the relationship of extent and progression of emphysema, ILD, and coronary artery calcifications to the intensity of WTC dust exposure.

The results of Aim 3 were inconclusive for determining a relationship between WTC dust exposure in terms of the arrival time to the WTC site and automated measures of respiratory and cardiac disease. One challenge was the lack of CT scans that met our inclusion criteria in the initial years after 9/11; the median time of the first CT scan in the WTC GRC cohort was 11-13 years after 9/11.

Translation of Findings

This grant was not specifically focused on translating the findings into practice; however, we are preparing to submit a paper and placed the current version into medrxiv.org.

Research Outcomes/Impact

In this study, we utilized automated measures of respiratory and cardiovascular disease, specifically emphysema, interstitial lung disease, coronary artery calcification, and pulmonary hypertension to quantify the burden of disease in all available chest CT scans of members in the WTC GRC. We investigated whether these measures of disease showed any difference between the WTC GRC and a matched cohort of lung screening participants for extent and progression, as well as whether these were affected by different levels of WTC dust exposure, defined as when each member arrived at the WTC site.

We successfully analyzed CT scans of 2284 members of the WTC GRC for pulmonary disease and 1246 members for cardiac disease. We established a matched cohort of 557 lung screening participants that were matched on sex, smoking status, one or more CT scans, follow-up time, and age.

Using this dataset, we found that there was a significant difference in the amount of emphysema, interstitial lung disease, and coronary artery calcifications on the first available CT between members of the WTC GRC and the matched lung screening cohort – the members of the WTC GRC had higher burden of these three diseases. Many of the first available CT scans were over 10 years after 9/11, which further suggests that the increased burden of these diseases remains even after a long period of time. This supports the need for long-term health monitoring and sustained surveillance programs for WTC GRC members. We did not find a significant difference in the marker of pulmonary hypertension. We also did not find evidence that the progression of these diseases differed between the two groups.

Similarly, we did not find a significant association between the arrival time to the WTC site and any of the four markers of disease. The lack of disease progression differences, may suggest that factors beyond initial exposure may play a more critical role in long-term disease trajectory. More research is needed to fully understand the long-term health impacts of WTC dust exposures and the factors influencing disease progression.

Section 2

Introduction

The 9/11 WTC attack exposed thousands of people to toxic dust; this exposure has been associated with many illnesses, many of which have a long latency period and remain undetected until reaching an advanced stage with symptoms that affect one's quality of life [1-4]. The WTC dust exposure affects many different organ systems; two of the most prominent are the respiratory and cardiovascular systems [1, 4-7]. Studies have shown that firefighters with WTC exposure had higher age-adjusted incident rates of cardiovascular disease [1] and reduction in pulmonary function [6], with visible lung abnormalities on chest CT [4] and lower airway disease [8]. A major component of the toxic dust exposure was asbestos, which was present in the fireproofing material used in the WTC [9, 10]. Asbestos exposure is associated with respiratory diseases such as lung cancer and asbestosis [11] and increased risk of cardiovascular disease [12].

Many respiratory and cardiovascular diseases can be identified and quantified on CT and low-dose chest CT (LDCT) scans used for lung cancer screening. CT scans provide an opportunity to identify and evaluate the presence of early disease prior to the onset of symptoms in the WTC general responders' cohort (GRC), as well as progression when multiple scans are obtained over time. Radiologists can visually and sometimes quantitatively assess diseases on CT scans, but these often have high variability, are time consuming to perform, or both [13-17]. With the increase in computing power and advances in image analysis and machine learning, automated tools have been developed to assess a wide variety of diseases on CT scans [18-22]. This automation is necessary to enable the retrospective analysis of all chest CT scans performed on WTC GRC members to date. To provide meaning to these quantitative measures, we have access to a large and unique lung screening cohort which we will use to compare the extent and progression versus the WTC GRC. This extensive screening database includes participants with a broad range of smoking histories, including never smokers, with long-term follow-up, and allows for matching with the WTC GRC to see if rates of progression are different between a non-exposed group to the exposed WTC group as well as determining how extent of exposure impacts prevalence and progression of these diseases.

We applied already developed and validated automated image analysis tools to identify and quantify respiratory and cardiovascular disease, specifically emphysema, interstitial lung disease, hypertension, and coronary artery calcifications. The earliest findings of these diseases are difficult to identify and measure, and little is known about how they progress in people with WTC exposures. The WTC GRC provides a unique opportunity where participants are monitored for many years and we now have many participants with several CT scans over time. Lung and pleural cancers and asbestos-related diseases have a long latency period of around 20 years [23], so we expect that early findings of these diseases can now be identified on CT scans of the WTC workers. The ability to quantify these diseases and assess the extent and progression over time allows for identification of the diseases at an early stage. Learning about how exposure to toxic dust relates to the progression of disease will enable improvements in treatment and management for not just WTC responders but all patients with occupational and environmental exposures.

Aim 1: Apply already developed and validated automated image analysis tools to quantify emphysema, interstitial lung disease (ILD), pulmonary hypertension, and coronary artery calcifications (CAC) on all chest CT scans in the WTC GRC and a comparably matched lung screening cohort.

We focused on the application of already developed and validated image analysis tools to quantify markers of respiratory and cardiovascular disease, specifically emphysema, ILD, pulmonary hypertension, and coronary artery calcifications. For emphysema and ILD, we used the Chest Imaging Platform, an open-source suite of lung image analysis tools funded by an NHLBI R01 grant (1R01HL116931-01) and used by the COPDGene project. For pulmonary hypertension and coronary artery calcification measurements, we used an internally developed suite of tools that has been previously published.

Data

The first task of Aim 1 was to obtain CT scans for members of the WTC GRC that were suitable for automated analysis. To ensure that the automated analysis tools would provide high quality results, we had to ensure the CT scans were not obtained with contrast and we used images with the thinnest slice thickness possible, with an upper bound of 2.5 mm. We requested from the WTC Health Program General Responder Data Center a list of WTC GRC members seen at the World Trade Center Health Program Clinical Center of Excellence at Mount Sinai who provided consent for their data to be used and for whom clinical information was available. We queried the Imaging and Research Warehouse at Mount Sinai using the following criteria: 1) a patient on

the list of WTC GRC members, 2) with at least one non-contrast CT scan of the chest, and 3) CT scan slice thickness of 2.5 mm or less.

The second task of Aim 1 was to create a matched set of controls from the cohort of lung screening participants at Mount Sinai. We matched on sex, age, smoking status, follow-up time, and whether there had one or two or more scans.

Methods

Automated analysis of chest CT scans

Having obtained all the CT images, we applied two different suites of software tools – the Chest Imaging Platform (CIP) (available from https://chestimagingplatform.org/), which provided measures of the lung parenchyma, including emphysema and interstitial lung disease (ILD) , and a research software suite from the Vision and Image Analysis (VIA) group at Cornell University for cardiac analysis, including aorta and pulmonary artery measurement and coronary artery calcification measurement [24-26]. For emphysema, we used the percentage of lung volume below -950 HU; for ILD, we used the percentage of lung volume above -250 HU. For the coronary artery calcification, we used the equivalent Agaston score and for hypertension, the pulmonary artery to aorta diameter ratios.

Automated measures of disease:

- Emphysema – LAA950% (low attenuation volume percent below -950 HU) – a lower value indicates less emphysema
- ILD – HAA250% (high attenuation volume percent above -250 HU) – a lower value indicates less fibrosis
- Pulmonary Hypertension – PA ratio (pulmonary artery to aorta ratio) – normal value is less than 1.0, 1.0 or higher indicates pulmonary hypertension
- Coronary artery calcification – Agaston score – values above 100 are considered moderate to severe and require further follow-up

Case control matching

Controls were selected for each case using a systematic matching algorithm to ensure comparability. WTC GRC members were matched to controls based on sex, smoking status, visit type (one vs. two or more), and within 5 years difference of age. In addition, controls were required to have a follow-up time at least as long as that of the corresponding case. In instances where multiple controls met the matching criteria, one was randomly selected from the eligible pool to minimize selection bias. The matching process was conducted iteratively without replacement.

Results

There was a total of 4909 chest CT scans of members of the WTC GRC meeting our criteria. Of these 4909 chest CT scans, the emphysema and ILD analysis successfully completed on 4370 (89.0%) scans, while the coronary artery calcification was successful on 2122 (43.2%) scans, and both analyses were successful on 2023 scans (41.2%). There were 3855 members of the GRC for which we could obtain both chest CT images and clinical data. Of these, there were 2284 members for which we could obtain pulmonary disease measurements on at least one scan, 1246 members for which we could calculate cardiac measurements, and 1220 members for which we could successfully compute all four disease measures on at least one scan. Table 1 lists the longitudinal scans available for each GRC member; Table 1a lists those members for which we were able to compute pulmonary measurements, and Table 1b lists those members for which we were able to compute cardiac measurements. Although most members had a single CT scan, there were a substantial number with two or more scans available for longitudinal analysis (1070 members with pulmonary measurements and 724 members with cardiac measurements).

We successfully identified eligible controls for 557 cases based on the pre-specified matching criteria. The demographic characteristics of the matched case-control groups are shown in Table 2. Of the 557 matched pairs, 457 (82%) of them were male and 18% female. The median age was 54 years, with an interquartile range of 48 to 60 years for the WTC GRC group and 49 to 60 years for the control lung screening group. Although matching was performed based on smoking history (whether individuals had ever smoked), current smoking status differed significantly between the groups ($P < .0001$). In the WTC GRC group, 23%

were current smokers, 30% were former smokers, and 47% were never smokers. In contrast, 34% of the control lung screening group were current smokers, 19% were former smokers, and 47% were never smokers.

Race distributions also varied significantly between the two groups (P < .0001). The WTC GRC group had a higher proportion of White participants (61%) compared to 55% in the control lung screening group. A higher proportion of Black or African American participants was observed in the control lung screening group (19%) compared to the WTC GRC group (9%). There were also notable differences in the representation of Asian participants (1% in WTC GRC vs. 13% in control). Among the 557 WTC GRC, arrival time for the WTC GRC group was recorded across various time points, with 17% exposed to the 9/11 Dust Cloud, 11% arriving after the dust cloud on 9/11, 30% arriving on 9/12 or 9/13, 30% arriving between 9/14 and the end of September, and 9% arriving in October or later.

Discussion

We successfully ran two different CT image analysis software suites on CT scans from the WTC GRC and participants in a lung screening program at Mount Sinai and established a set of matched controls from the lung screening cohort for each WTC GRC member. From the WTC GRC, we had measures of four different diseases on 1220 members, and from the matched lung screening control group, 557. While this is a small fraction of the over 20,000 WTC GRC members, most of the members did not have non-contrast chest CT scans meeting our slice thickness criteria. Furthermore, we encountered algorithm failures in the coronary analysis in over half of the CT scans. Both software for the emphysema/ILD measures and CAC measures utilized model-based methods as opposed to deep learning methods. There have been many advancements in deep-learning based methods in the past few years and newer methods may provide a higher success rate.

Challenges

Although this project did not develop any new automated algorithms, even setting up the database of images and running existing software presented some challenges. While there are a large number of members in the WTC GRC who visited Mount Sinai (over 27,000), only 4909 chest CT scans met our image quality criteria. Of these CT scans, a majority failed to be correctly analyzed by the Cornell cardiac analysis (56.8%). The lower success rate of the coronary artery analysis compared to the emphysema and ILD analyses is due to the higher difficulty of finding small calcium deposits in non-gated CT images – normally coronary artery calcifications are measured on gated CT imaging to eliminate artifacts caused by heart motion, but for this analysis, we are using chest CT images obtained for other purposes. The specific algorithm also requires the segmentation of a number of anatomical structures in the chest, including the lungs, airways, and ribs, which are more difficult than just segmenting the lungs. To try to improve the success rate, we attempted to use an open-source CAC measurement algorithm which we had identified at the time of the grant proposal; unfortunately, only the code was publicly available, not the trained model or annotated data used to train their model. We also started the process of obtaining commercial software for coronary artery calcification measurement, but this is still in progress as of the end of the grant.

Table 1. Breakdown of number of CT scans available for each WTC GRC member

(a) Among 2284 members with at least one scan with successful pulmonary measurements

Num CT scans	Num GRC members	Percent (%)
1	1214	53.2
2	520	22.8
3	279	12.2
4	135	5.9
5	66	2.9
6 or more	70	3.1
Total	2284	

(b) Among 1246 members with at least one scan with successful cardiac measurements

Num CT scans	Num GRC members	Percent (%)
1	522	41.9
2	302	24.2
3	194	15.6
4	105	8.4
5	56	4.5
6 or more	67	5.4
Total	1246	

Table 2. Demographics 557 members of WTC GRC and 557 members of the control lung screening cohort

Demographic characteristics	WTC GRC	Control Lung Screening	P-value
N	557	557	
Sex			
Male	457 (82%)	457 (82%)	1.00
Female	100 (18%)	100 (18%)	
Age*, y	54 (48, 60)	54 (49, 60)	
Smoking			
Current smoker	126 (23%)	189 (34%)	<.0001
Former smoker	169 (30%)	106 (19%)	
Never smoker	262 (47%)	262 (47%)	
Race			
American Indian/Alaska Native	1 (0%)	3 (1%)	<.0001
Asian	6 (1%)	74 (13%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	
Black or African America	50 (9%)	107 (19%)	
White	339 (61%)	308 (55%)	
More than One Race	124 (22%)	65 (12%)	
Unknown or Not Reported	37 (7%)	0 (0%)	
Arrival Time			
9/11 Dust Cloud	94 (17%)		
9/11 No Dust Cloud	62 (11%)		
9/12 & 9/13	168 (30%)		
9/14 - End of Sept	167 (30%)		
Oct and beyond	50 (9%)		
Unknown	16 (3%)		
Average length of follow-up (SD), year	3.61 (4.07)	1.79 (3.01)	<.0001

In the original grant, we proposed to use an automated algorithm to assess pleural thickening. However, we were unable to accomplish this due to the software still being in development. We replaced pleural thickening with measurement of pulmonary hypertension using the pulmonary artery to aorta diameter ratio (PAratio). Previous work has found that an elevated PAratio was associated with lung injury in exposed firefighters [7] and reduced lung function in former WTC workers [27].

Summary

The key outcomes of Aim 1 were: 1) the analysis of 4909 non-contrast chest CT scans from the WTC GRC to measure emphysema, interstitial lung disease, pulmonary hypertension, and coronary artery calcification, 2) establishing a set of 557 matched controls from a lung screening cohort, and 3) the analysis of 1122 CT scans of the matched control group.

Aim 2. Assess extent and progression of emphysema, interstitial lung disease, pulmonary hypertension, and coronary artery calcifications in the WTC GRC compared to a lung screening cohort.
For Aim 2, we utilized the datasets established in Aim 1 to compare the extent and progression of respiratory and cardiovascular disease between WTC responders and non-WTC participants in the lung screening cohort.

Data
From the dataset created in Aim 1, we selected members of the WTC GRC and lung screening cohort for which the pulmonary analysis and cardiac analyses were successful. We split up the analysis between the pulmonary (emphysema and ILD) and cardiac (pulmonary hypertension and CAC) due to differences in the number of cases that were successfully analyzed.

Methods
Continuous variables were summarized using median and interquartile range (IQR) and compared across groups using Kruskal-Wallis test. Categorical variables were summarized by frequency and percentages and compared using chi-squared test or Fisher's exact test as appropriate. All measures were assessed for normality and transformations were applied where necessary.

A linear mixed-effects model was employed to assess whether longitudinal changes in automated pulmonary and cardiovascular measurements derived from repeated CT scans differed between the WTC GRC and control lung screening groups. Follow-up time was defined as time since initial CT scan with adjustment for race and current smoking status. Random intercept and slope were used to account for within-subject correlation across repeated measures and between-subject heterogeneity in the rate of change over time. Using these models, we calculated the estimated marginal means of outcome measures for comparison between WTC GRC and control lung screening groups. Interaction terms between time and group (WTC GRC vs control lung screening) were explored to assess potential differences in the trajectory of these measures across groups. Separate models were fitted for each pulmonary (emphysema LAA950; interstitial lung disease HAA250) and cardiovascular (coronary artery calcification Agatston score; pulmonary hypertension PA ratio) outcome.

A two-sided p-value of < 0.05 was used to indicate statistical significance. All analyses were conducted using SAS (v9.4, SAS Institute, Cary, NC) and R (v4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

Results
<u>Extent of disease on initial CT scan</u>

Table 3 summarizes pulmonary and cardiac measures from the first CT scan for both the WTC GRC and control lung screening groups. Among the 184 participants with available cardiac findings, the median Agatston score, a measure of coronary artery calcification, was significantly higher on the first CT scan in the WTC GRC group (median: 68.70, IQR: 18.31, 258.92) compared to the control group (median: 8.65, IQR: 0.12, 120.04) ($p<0.001$). PA ratio, a measure of pulmonary hypertension, was similar between the WTC GRC group (median: 0.79, IQR: 0.73, 0.88) and the control group (median: 0.79, IQR: 0.72, 0.86) ($p=0.25$).
Among the 556 participants with available pulmonary findings, significant differences were observed for emphysema and interstitial lung diseases. The LAA950 score, which reflects the extent of emphysema, was significantly higher in the WTC GRC group (median: 0.09, IQR: 0.01, 0.19) compared to the control group (median: 0.03, IQR: 0.01, 0.09) ($p<0.001$), suggesting more extensive emphysema in the WTC GRC group. Similarly, the HAA250 score, a measure of interstitial lung disease, was also significantly higher in the WTC GRC group (median: 0.02, IQR: 0.02, 0.03) compared to the control group (median: 0.02, IQR: 0.01, 0.02) ($p<0.001$), indicating more extensive ILD among WTC GRC.

Overall, these results indicate that participants in the WTC GRC group exhibit a higher burden of coronary artery calcification, emphysema, and interstitial lung disease compared to those in the control group, while no significant difference was observed for pulmonary hypertension.

Table 3. Summary of cardiovascular and respiratory disease measurements on the WTC GRC members on the first available CT scan

Measures on first CT scan	WTC GRC	Non-WTC GRC	P-value
With available cardiac findings		184	
Coronary Artery Calcification			
Agatston score*	68.70 (18.31, 258.92)	8.65 (0.12, 120.04)	<0.001
Pulmonary Hypertension			
PA ratio*	0.79 (0.73, 0.88)	0.79 (0.72, 0.86)	0.249
With available pulmonary findings		556	
Emphysema			
LAA950*	0.09 (0.01, 0.19)	0.03 (0.01, 0.09)	<0.001
Interstitial lung diseases			
HAA250*	0.02 (0.02, 0.03)	0.02 (0.01, 0.02)	<0.001

*Median (IQR)

Progression of diseases

As shown in Table 4, at baseline, the average LAA950 was significantly higher in the WTC GRC group compared to the control lung screening group (0.12 vs. 0.075, P < 0.001), suggesting that WTC GRC had more extensive emphysema. Over time, the WTC GRC group showed a significant decrease in LAA950 score, with a yearly reduction of -0.011 (95% CI: -0.012, -0.009, P < 0.001). In contrast, the control group exhibited a slight but statistically significant increase in LAA950 over time, with a yearly increase of 0.0042 (95% CI: 0.0021, 0.0063, P < 0.001), indicating worsening of emphysema.

At baseline, the HAA250 score was also significantly higher in the WTC GRC group compared to the control group (0.027 vs. 0.019, P < 0.001). Figure 1 depicts the progression of the pulmonary disease measures over time for the WTC GRC group and control group. The WTC GRC group demonstrated a significant annual decrease in HAA250 (-0.0006, 95% CI: -0.0007, -0.0005, P < 0.001), while the control group did not exhibit any statistically significant change in HAA250 over time (-0.0001, 95% CI: -0.0004, 0.0001)..

At baseline, the PA ratio was similar between the WTC GRC and control groups (p=0.91). No significant differences were observed in the progression of pulmonary hypertension (PA ratio) between the groups (P = 0.85).

Agatston score was log-transformed prior to analysis due to the skewed distribution. The baseline log-transformed CAC Agatston score was significantly higher in the WTC GRC group compared to the control group (4.47 vs. 2.88, P = 0.045), indicating more extensive coronary artery calcification. Both groups showed significant increases in the CAC score over time, with the WTC GRC group showing an annual rate of increase of 0.09 (95% CI: 0.033, 0.14) and the control group showing a greater increase of 0.26 (95% CI: 0.19, 0.33). Figure 2 depicts the progression of the cardiac measures over time for the WTC GRC group and control group. The rate of progression was significantly different between the two groups (p<.001) with the control group showing faster progression.

Discussion

One of the key findings of this Aim is that members of the WTC GRC had elevated levels of coronary artery calcification, emphysema, and interstitial lung disease compared to the control lung screening group on the initial CT scan. The median time between 9/11 and the initial CT scan included in this study for the WTC GRC was about 10 years, which is a long enough time that any effect of WTC exposure on these diseases would already be seen. It also suggests that the burden of these diseases remains elevated even after 10 years; this supports the need for long-term health monitoring and sustained surveillance programs for WTC GRC members. A previous study by Weakley et al. showed that emphysema and COPD were more prevalent in the WTC-exposed fire fighters compared to the general population 5 years after 9/11, increasing or remaining

stable through year 8 [28]. While a previous study by Wanahita et al. did not find an increased prevalence of coronary artery disease in WTC-exposed police officers 5 years after 9/11, but the authors note that majority of the police officers were below 40 years of age [29]; however another study on WTC-exposed fire fighters by Cohen et al. found an association between WTC exposure and long-term cardiovascular disease risk [1].

The results on the progression of disease were negative – although there was a statistically significant decrease in emphysema and interstitial lung disease, we know that these diseases are not reversible. This is likely attributable to differences in CT scanners and acquisition protocols, Chen-Mayer et al. found that there were differences in lung density measurements across different scanners and protocols, which could be reduced by applying standardization procedures [30]. There was no significant difference observed between the WTC GRC group and the control group for the progression of hypertension which correlates with the denial of a petition to add hypertension as a WTC health condition [31]. While both the WTC GRC group and control group had increasing coronary artery calcification (CAC) over time, surprisingly the control group showed faster progression. This could again to attributable to differences in CT scanners and protocols; the lung screening group tended to have more recent CT scans with thinner slice thickness, which may be more sensitive for detection of CAC. Lastly, the etiology of pulmonary diseases may differ between the two groups due to the nature of exposure, potentially result in different clinical manifestations and progression of disease, complicating the comparative analysis.

Table 4. Extent and progression of respiratory and cardiovascular disease measures for members of the WTC GRC and the control group

a) Emphysema (LAA950)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.12	(0.11. 0.14)	<0.001	-0.011	(-0.012, -0.009)	<0.001
Control lung screening	0.075	(0.06, 0.09)		0.0042	(0.0021, 0.0063)	

b) Interstitial lung diseases (HAA250)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.027	(0.025, 0.028)	<0.001	-0.0006	(-0.0007, -0.0005)	<0.001
Control lung screening	0.019	(0.017, 0.021)		-0.0001	(-0.0004, 0.0001)	

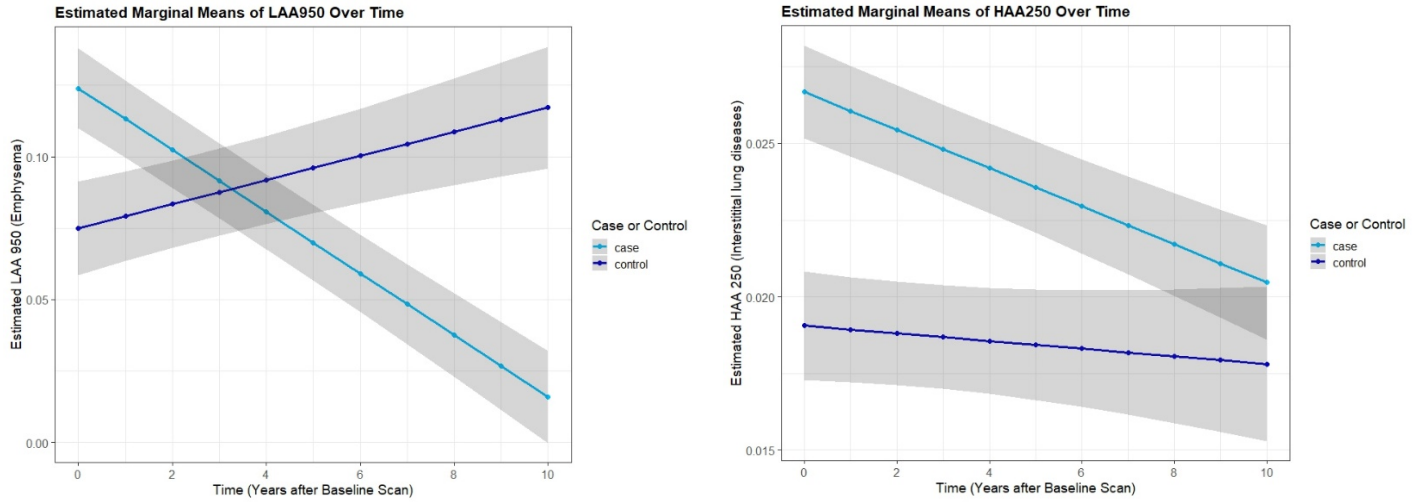
c) Pulmonary Hypertension (PA ratio)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.77	(0.72, 0.82)	0.91	-0.0002	(-0.0047, 0.0042)	0.85
Control lung screening	0.77	(0.71, 0.83)		-0.0009	(-0.0067, 0.0048)	

d) Log CAC Agatston score

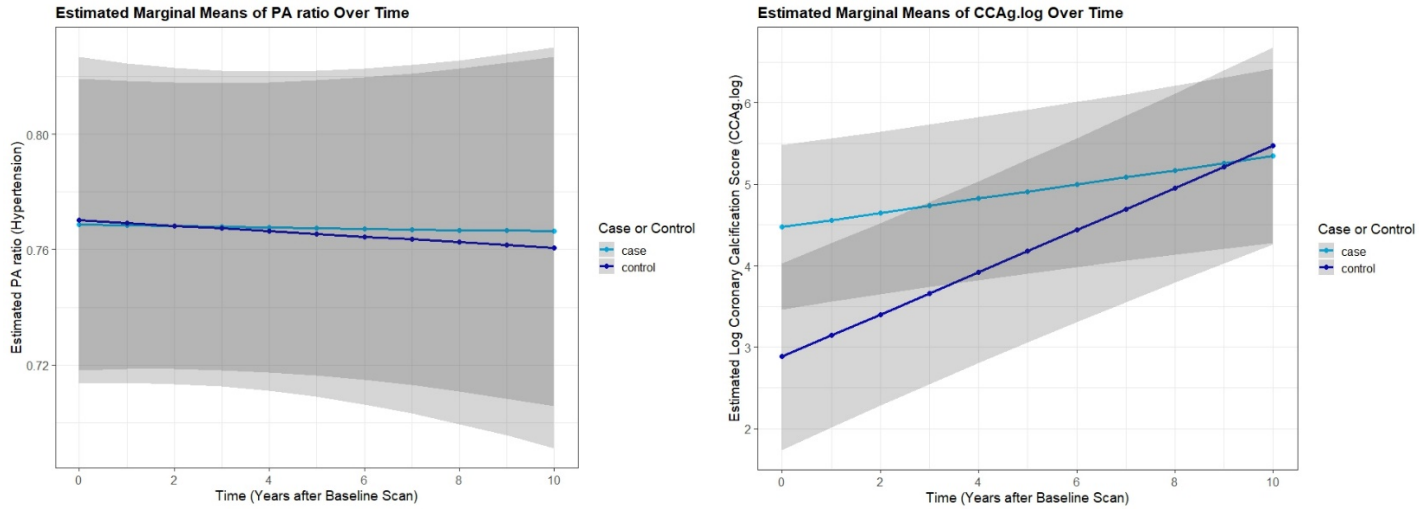
	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	4.47	(3.47, 5.48)	0.045	0.09	(0.033, 0.14)	<0.001
Control lung screening	2.88	(1.74, 4.03)		0.26	(0.19, 0.33)	

All models adjusted for race and current smoking status



(a) (b)

Figure 1. Respiratory measurements over time for the WTC GRC (Case) and lung screening control groups (control). a) Estimated mean emphysema score (LAA950) and b) Estimated mean interstitial lung disease measure (HAA250)



(a) (b)

Figure 2. Cardiac measurements for the WTC GRC group (Case) and control lung screening group (control) over time. a) Estimated mean pulmonary artery to aorta ratio (PA ratio) and b) log-transformed Agaston score.

Challenges

Perhaps the biggest challenge was the lack of early CT scans that met our quality criteria for members of the WTC GRC. The median time from 9/11 to the first CT scan was about 10 years, so we were not able to assess disease progression in those initial years where we may have seen more progression of disease.

We had a limited number of controls that met our matching criteria, CT image quality criteria, and were successfully analyzed by both software suites to generate the four disease measures. Of the three, we had the most trouble with successfully analyzing scans. This was due in part to the lung screening cohort using CT acquisition protocols with much thinner slice thickness, some as low as 0.4 mm; both software packages were developed for 1.0 and 1.25 mm slice thickness scans.

Summary

In summary, for Aim 2, one of the key findings is that after a median time of 11-13 years after 9/11, the WTC GRC group exhibited higher burdens of coronary artery calcification, emphysema, and interstitial lung disease compared with a control group of lung screening participants. This suggests that the burden of these diseases remains high even after a decade, which supports the need for continued surveillance of the WTC GRC members. The analysis of progression of disease was not conclusive and will require additional research.

Aim 3. Assess the relationship of extent and progression of emphysema, interstitial lung disease, hypertension, and coronary artery calcifications to the intensity of WTC dust exposure.
In Aim 3, we incorporated the intensity of WTC dust exposure in the analysis of disease measures computed from the chest CT images of members in the WTC GRC with the goal of assessing how dust exposure affected the extent and progression affected the diseases under study.

Data
From the dataset created in Aim 1, we selected members of the WTC GRC for which the pulmonary analysis and cardiac analyses were successful. We split up the analysis between the pulmonary (emphysema and ILD) and cardiac (hypertension and CAC) due to differences in the number of cases that were successfully analyzed.

Methods
Continuous variables were summarized using median and interquartile range(IQR) and compared across groups using Kruskal-Wallis test. Categorical variables were summarized by frequency and percentages and compared using chi-squared test or Fisher's exact test as appropriate. All measures were assessed for normality and transformations were applied where necessary.

Using a similar approach as Aim 2, linear mixed-effects model was employed to assess whether longitudinal changes in automated pulmonary and cardiovascular measurements derived from repeated CT scans differed across WTC dust exposure groups. Follow-up time was defined as time since September 11, 2001, with adjustments for sex, age, race and smoking status. Random intercepts and slopes were included to account for within-subject correlation across repeated measures and between-subject heterogeneity in the rate of change over time. Using these models, we calculated the estimated marginal means of outcome measures for comparison across the different WTC dust exposure groups. Interaction terms between time and exposure group (based on arrival time category) were explored to assess potential differences in the trajectory of these measures across exposure levels. Separate models were fitted for each pulmonary and cardiovascular outcome.

A two-sided p-value of < 0.05 was used to indicate statistical significance. All analyses were conducted using SAS (v9.4, SAS Institute, Cary, NC) and R (v4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

Results
Pulmonary measurements were available in 2284 participants and 724 (58.1%) had two or more CT scans. Demographics for these participants are presented in Table 5. Among these 724, the percentage of low-attenuation areas (LAA) below -950 HU on CT (LAA950), a measure of emphysema, was similar across all WTC dust exposure groups, with estimates ranging from 0.25 to 0.28. The 9/11 No Dust Cloud group had a slightly higher baseline LAA950 (0.28, 95% CI: 0.23, 0.34) compared to other groups, suggesting a slightly more severe emphysema on CT (Table 6). Figure 3 illustrates the trajectories from the linear mixed effects model, indicating the overall downward trend in emphysema over time. However, the rates of change per year (Δ/year) in LAA950 did not differ significantly across the groups (p=0.51, Figure 3). Specifically, the 9/11 Dust Cloud group had a decline of -0.025/year (95% CI: -0.031, -0.019), not statistically significantly different from other exposure groups 9/11 No Dust Cloud (-0.030/year, 95% CI: -0.037, -0.022), 9/12 and 9/13 (-0.026/year, 95% CI: -0.031, -0.021), 9/14 to end of Sept (-0.028/year, 95% CI: -0.033, -0.024), and October and beyond (-0.029/year, 95% CI: -0.039, -0.018) (p=0.86). Alternative measures of emphysema using LAA with 910 threshold, LAA with 856 threshold and threshold for 15% of lung volume were also examined and the overall trend were consistent with our findings using LAA with 950 threshold.

At baseline, the percentage of high attenuation area (HAA) between -600 and -250 HU on CT (HAA250), a measure of interstitial lung diseases, were consistent across all WTC dust exposure groups, with values ranging from 0.034 to 0.036 (Table 7). The 9/14 - End of September group had the highest baseline HAA250 value of 0.036 (95% CI: 0.033, 0.040) (indicating less ILD), while the 9/11 Dust Cloud group had a slightly lower HAA250 (0.034, 95% CI: 0.030, 0.039). Similar to emphysema, the rate of change (Δ/year) in HAA250 were similar across all groups, the 9/11 Dust Cloud group had a decline of -0.025 units/year (95% CI: -0.031, -0.019), while the 9/11 No Dust Cloud group showed a slightly larger decline of -0.030 units/year (95%

CI: -0.037, -0.022), 9/12 and 9/13 (-0.026/year, 95% CI: -0.031, -0.021), 9/14 to end of Sept (-0.028/year, 95% CI: -0.033, -0.024), and October and beyond (-0.029/year, 95% CI: -0.039, -0.018). All exposure groups exhibited negative rates of change, but the between group differences were not statistically significant (p=0.67) (Figure 4).

Cardiac measurements were available in 1246 participants and 1070 (46.8%) had two or more CT scans. Among these 1070, the pulmonary artery to aorta ratio (PA ratio), a measure of pulmonary hypertension, was generally higher in the 9/11 No Dust Cloud group (0.81, 95% CI: 0.73, 0.89) compared to the other groups at baseline. However, no statistically significant difference in PA ratio was found at baseline (p=0.97) (Table 8). PA ratio greater than 1.0 had been shown to be associated with pulmonary hypertension in prior studies. The slopes of PA ratio over time were relatively flat, with minimal longitudinal changes observed for all groups. The 9/11 Dust Cloud group had a negligible decline per year (-0.00047, 95% CI: -0.0052, 0.0043), while the 9/12 & 9/13 group showed a small increase per year (0.0015, 95% CI: -0.0021, 0.0051). Nonetheless, no statistically significant difference in rate of change per year between WTC dust exposure groups (p=0.46), suggesting that arrival time to the 9/11 event did not have a substantial impact on longitudinal changes in pulmonary hypertension (Figure 5).

Agatston score was log-transformed prior to analysis due to the skewed distribution. At baseline, Agatston score, a measure of coronary artery calcification, varied between 3.36 and 4.36 across the WTC dust exposure groups but these differences were not statistically significant (p=0.64) (Table 9). Over time, there was an overall annual increase in coronary artery calcification in most groups with the 9/11 Dust cloud group showing the highest rate of increase per year (0.10, 95% CI: 0.049, 0.15) (Figure 6). However, there were no statistically significant differences in the annual rate of change in Agatston score across the groups (p=0.28), suggesting that arrival time did not significantly impact the rate of coronary artery calcification progression.

Table 5. Demographics among 2284 members of WTC GRC with pulmonary findings

Demographic characteristics	Arrival Time							
	9/11 Dust Cloud	9/11 No Dust Cloud	9/12 & 9/13	9/14 - End of Sept	Oct and beyond	Missing	Overall	P-value
N	377	356	679	601	212	59	2284	
Sex								
Male	321 (85%)	297 (83%)	591 (87%)	457 (76%)	170 (80%)	52 (88%)	1888 (83%)	<.0001
Female	56 (15%)	59 (17%)	88 (13%)	144 (24%)	42 (20%)	7 (12%)	396 (17%)	
Age on 9/11*	43 (39, 48)	43 (39, 49)	45 (40, 51)	46 (40, 52)	47 (40, 52)	46 (42, 48)	42 (37, 48)	
Smoking								
Current smoker	68 (18%)	80 (22%)	145 (21%)	135 (22%)	44 (21%)	17 (29%)	489 (21%)	0.0828
Former smoker	96 (25%)	98 (28%)	218 (32%)	170 (28%)	73 (34%)	15 (25%)	670 (29%)	
Never smoker	213 (56%)	178 (50%)	316 (47%)	296 (49%)	95 (45%)	27 (46%)	1125 (49%)	
Race								
American Indian/Alaska Native	1 (0%)	0 (0%)	2 (0%)	1 (0%)	0 (0%)	0 (0%)	4 (0%)	<.0001
Asian	5 (1%)	6 (2%)	9 (1%)	4 (1%)	2 (1%)	0 (0%)	26 (1%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Black or African America	50 (13%)	44 (12%)	85 (13%)	52 (9%)	18 (8%)	7 (12%)	256 (11%)	
White	220 (58%)	226 (63%)	389 (57%)	299 (50%)	97 (46%)	33 (56%)	1264 (55%)	
More than One Race	76 (20%)	64 (18%)	141 (21%)	174 (29%)	76 (36%)	12 (20%)	543 (24%)	
Unknown or Not Reported	25 (7%)	16 (4%)	53 (8%)	71 (12%)	19 (9%)	7 (12%)	191 (8%)	
Time from Sept 11, 2001 to first CT, year*	11.09 (7.21, 14.89)	11.83 (7.43, 15.26)	10.01 (7.03, 14.82)	8.76 (6.00, 13.19)	8.87 (6.08, 12.95)	9.64 (6.35, 14.89)	9.93 (6.41, 14.80)	<.0001
Length of follow-up after Sept 11, 2001 (last CT-9/11), year*	12.85 (9.28, 15.80)	13.18 (9.32, 16.15)	12.82 (9.12, 15.74)	12.15 (8.42, 15.56)	12.34 (8.07, 15.28)	11.93 (8.48, 16.07)	12.68 (8.79, 15.72)	0.0012

Table 6. Emphysema measures (low attenuation area below -950HU, LAA950) by arrival time to WTC site category

		Emphysema (LAA950)					
		At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
Arrival Time	9/11 Dust Cloud	0.25	(0.22, 0.27)	0.53	-0.013	(-0.015, -0.011)	0.31
	9/11 No Dust Cloud	0.21	(0.18, 0.25)		-0.011	(-0.013, -0.010)	
	9/12 & 9/13	0.24	(0.22, 0.26)		-0.013	(-0.015, -0.012)	
	9/14 - End of Sept	0.25	(0.23,0.27)		-0.014	(-0.015, -0.012)	
	Oct and beyond	0.25	(0.21, 0.28)		-0.014	(-0.017, -0.012)	

*adjusted for sex, age, smoking status(yes/no) and race

Table 7. Interstitial lung disease measures (high attenuation area between -600 and -250 HU) by arrival time to WTC site category

		Interstitial lung diseases (HAA250)					
		At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
Arrival Time	9/11 Dust Cloud	0.035	(0.028, 0.041)	0.94	-0.001	(-0.0015, -0.0005)	0.19
	9/11 No Dust Cloud	0.038	(0.031, 0.045)		-0.0011	(-0.0017, -0.0007)	
	9/12 & 9/13	0.031	(0.026, 0.037)		-0.0005	(-0.0009, -0.0001)	
	9/14 - End of Sept	0.034	(0.029, 0.039)		-0.0009	(-0.0012, -0.0005)	
	Oct and beyond	0.036	(0.027, 0.045)		-0.0012	(-0.0019, -0.0005)	

*adjusted for sex, age, smoking status(yes/no) and race

Table 8. Pulmonary hypertension measure (pulmonary artery to aorta ratio, PAratio) by arrival time to WTC site category

		Pulmonary Hypertension (PA ratio)					
		At Baseline	**95% CI**	**p-value**	**Δ/year**	**95% CI**	**p-value**
Arrival Time	**9/11 Dust Cloud**	0.79	(0.72, 0.85)	0.84	-0.00039	(-0.0049, 0.0041)	0.4
	9/11 No Dust Cloud	0.82	(0.75, 0.90)		-0.0039	(-0.009, 0.0013)	
	9/12 & 9/13	0.76	(0.71, 0.81)		0.0016	(-0.0018, 0.0050)	
	9/14 - End of Sept	0.79	(0.74, 0.83)		-0.0006	(-0.004, 0.0028)	
	Oct and beyond	0.81	(0.71, 0.90)		-0.0039	(-0.011, 0.0032)	

*adjusted for sex, age, smoking status(yes/no) and race

Table 9.Coronary artery calcification measure, log-transformed Agaston score, by arrival time to WTC site category

		Log CAC Agatston score					
		At Baseline	**95% CI**	**p-value**	**Δ/year**	**95% CI**	**p-value**
Arrival Time	**9/11 Dust Cloud**	3.68	(2.95, 4.42)	0.51	0.94	(0.043, 0.14)	0.54
	9/11 No Dust Cloud	4.41	(3.57, 5.25)		0.032	(-0.027, 0.092)	
	9/12 & 9/13	4.15	(3.57, 4.73)		0.061	(0.023, 0.099)	
	9/14 - End of Sept	4.07	(3.49, 4.64)		0.061	(0.022, 0.10)	
	Oct and beyond	4.75	(3.67, 5.83)		0.029	(-0.055, 0.11)	

*adjusted for sex, age, smoking status(yes/no) and race

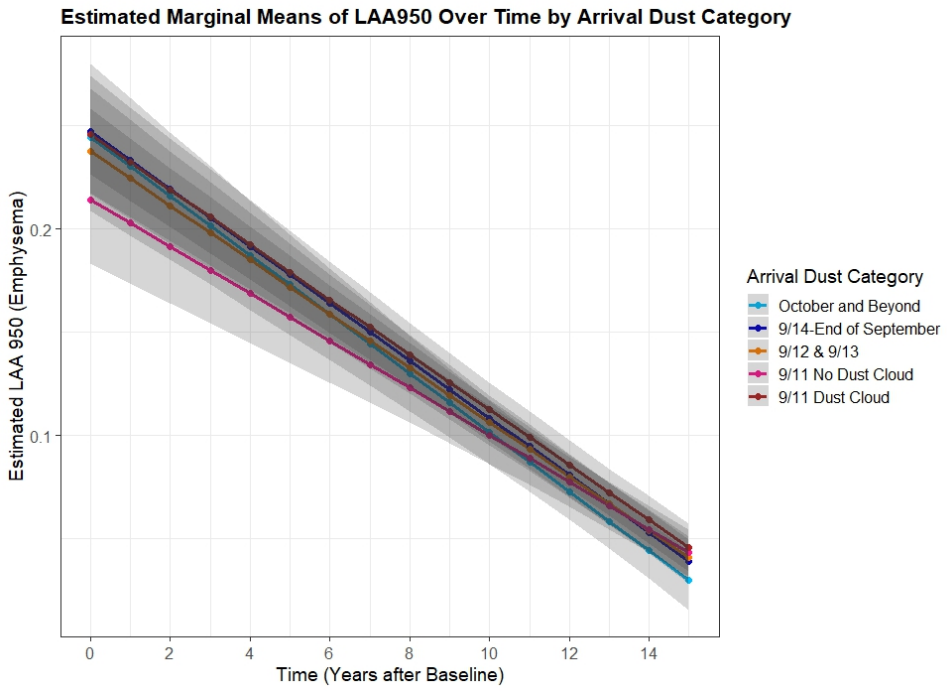


Figure 3. Marginal means of LAA950 over time by time of arrival at WTC site

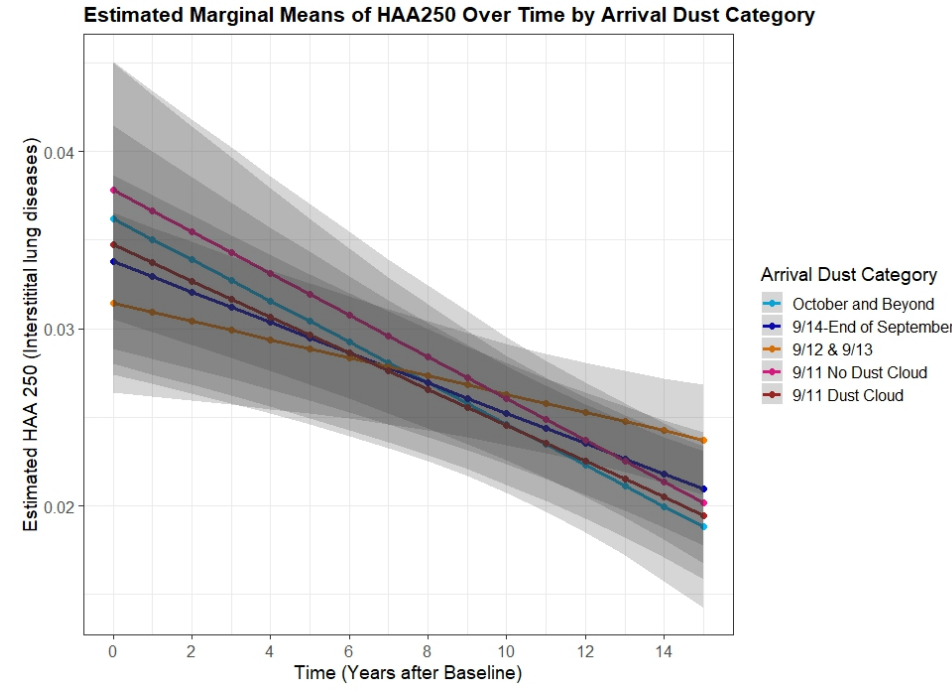


Figure 4.Marginal means of HAA950 over time by time of arrival at WTC site

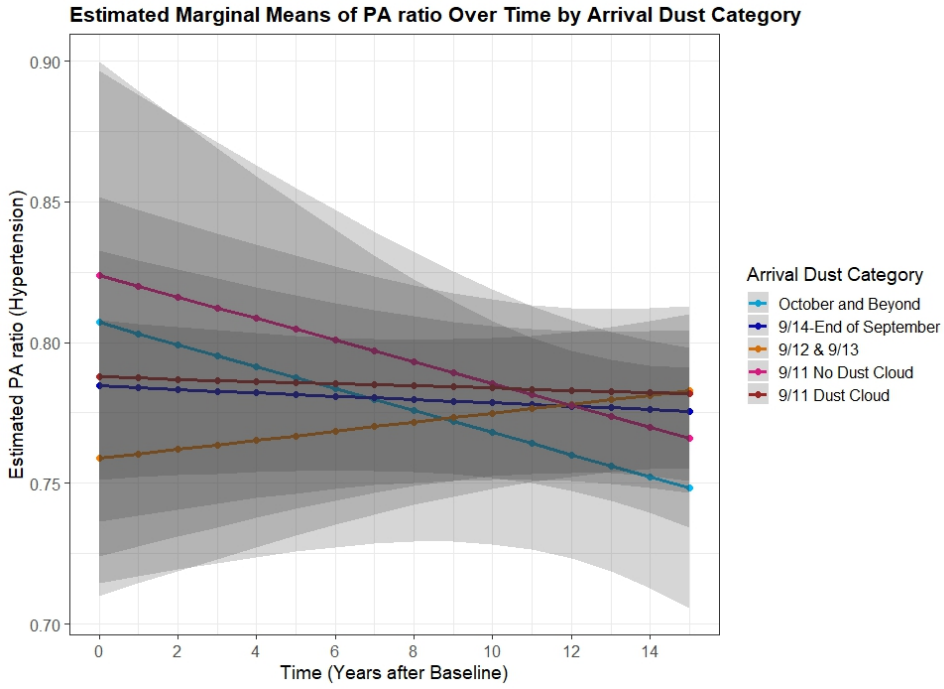


Figure 5. Marginal means of pulmonary artery to aorta diameter over time by time of arrival at WTC site

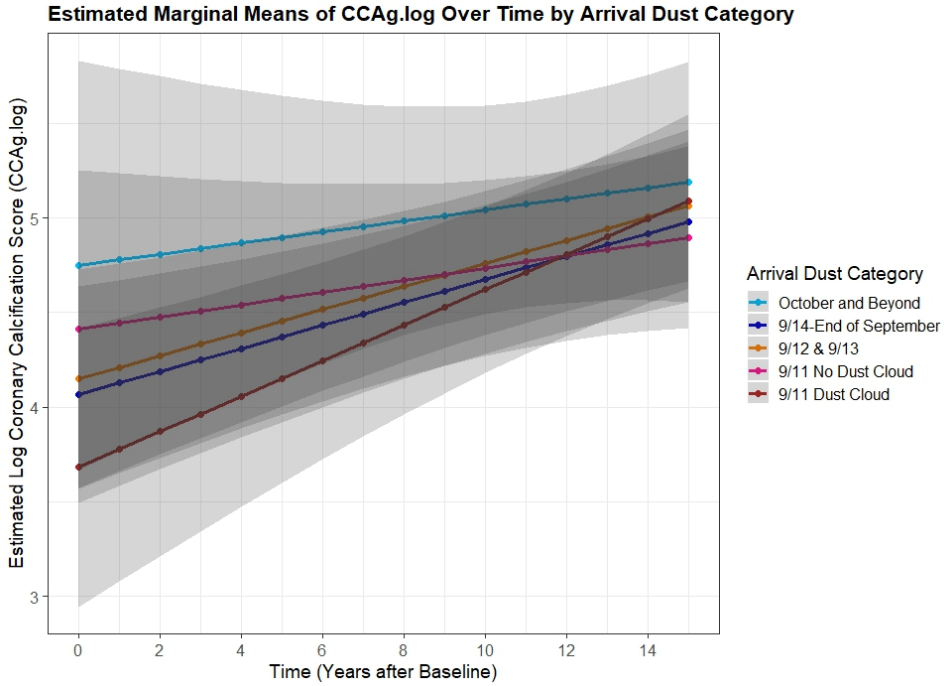


Figure 6. Marginal means of log-transformed Agaston score over time by time of arrival at WTC site

Discussion

The results indicate that arrival time to the 9/11 event was not significantly associated with longitudinal changes in emphysema, interstitial lung diseases, pulmonary hypertension, or coronary artery calcification over time. Although there were some differences in baseline values between the groups, none of the rates of change per year showed statistically significant differences, we did not find any significant dose-response effect of WTC dust exposure on these health outcomes after adjusting for age, sex, smoking status, and race. The lack of disease progression differences, may suggest that factors beyond initial exposure may play a more

critical role in long-term disease trajectory. More research is needed to fully understand the long-term health impacts of WTC dust exposures and the factors influencing disease progression.

Challenges

As in Aim 2, one of the largest challenges was a lack of CT scans that met our quality criteria in the initial years after 9/11 – the median time to the first CT scan of the WTC GRC members was about 10 years. Previous studies have found associations between arrival time and cardiovascular and respiratory diseases [1, 32, 33], though many of those studies analyzed data from the first 10 years after 9/11. There may be potential confounding factors that were not fully adjusted for in our models, such as pre-existing comorbidities, lifestyle factors, BMI, that could influence disease progression. Also, our study did not account for time-varying covariates which may help to elucidate these complex relationships.

Summary

The results of Aim 3 were inconclusive for determining a relationship between WTC dust exposure in terms of the arrival time to the WTC site and respiratory and cardiac disease.

Summary

We established a dataset of non-contrast chest CT scans for members of the WTC GRC and a matched cohort of lung screening participants with automated measurements of emphysema, interstitial lung disease, pulmonary hypertension, and coronary artery calcifications. We used this dataset to assess whether there were differences in the extent and progression of respiratory and cardiovascular diseases.

We found statistically significant differences on the initial CT scan between the two groups for emphysema, interstitial lung disease, and coronary artery calcification, with the WTC GRC members exhibiting higher measures, but no difference between the two groups for pulmonary hypertension. Since the initial CT scans of the WTC GRC members had a median follow-up time of about 11 years, this finding suggests that the elevated burden of these diseases remains high even after a decade, which supports the continued surveillance of the WTC GRC members.

The results comparing the progression of disease between the WTC GRC and control lung screening group did show statistically significant difference but were inconclusive. We examined the relationship between arrival time to the WTC site and the extent and progression of these diseases; again we did not find a statistically significant difference based on the arrival time to the WTC site. Aside from the possibility that WTC exposure does not impact these diseases, there are several factors that contribute to a lack of sensitivity to identifying these diseases. It may suggest that factors beyond initial exposure may play a more critical role in long-term disease trajectory. Also, the uncertainty introduced by the CT scanners is one of the largest factors; a recent study by Meyer et al found that most radiomic features are highly affected by CT acquisition and reconstruction settings [34]. Until recently, there has been little focus on ensuring CT scans present the best possible data for automated quantitation; efforts by such groups Radiological Society of North America have been studying this topic and provide recommendations on how to obtain high quality CT scans. We also noted that the median time to the first CT scan in the WTC GRC cohort in our dataset was about 10 years, so we are unable to capture the progression of early disease. Another possible factor is that the automated quantification measures utilized in this project are not sensitive to early disease and may not be able to identify small changes; with the explosion of AI-based tools in the medical imaging field, it is possible newer software might present a different result.

References

1. Cohen HW, Zeig-Owens R, Joe C, Hall CB, Webber MP, Weiden MD, Cleven KL, Jaber N, Skerker M, Yip J, Schwartz T, Prezant DJ. Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster. JAMA Netw Open. 2019;2(9):e199775. Epub 20190904. doi: 10.1001/jamanetworkopen.2019.9775. PubMed PMID: 31490535; PMCID: PMC6735414.
2. Singh A, Zeig-Owens R, Moir W, Hall CB, Schwartz T, Vossbrinck M, Jaber N, Webber MP, Kelly KJ, Ortiz V, Koffler E, Prezant DJ. Estimation of Future Cancer Burden Among Rescue and Recovery Workers Exposed to the World Trade Center Disaster. JAMA Oncol. 2018;4(6):828-31. doi: 10.1001/jamaoncol.2018.0504. PubMed PMID: 29710126; PMCID: PMC5933461.
3. Wisnivesky J, Teitelbaum S, Todd A, Boffetta P, Crane M, Crowley L, de la Hoz R, Dellenbaugh C, Harrison D, Herbert R, Kim H, Jeon Y, Kaplan J, Katz C, Levin S, Luft B, Markowitz S, Moline J, Ozbay F, Pietrzak R, Shapiro M, Sharma V, Skloot G, Southwick S, Stevenson L, Udasin I, Wallenstein S, Landrigan P. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. Lancet. 2011;378(9794):888-97. Epub 2011/09/06. doi: 10.1016/s0140-6736(11)61180-x. PubMed PMID: 21890053.
4. Liu C, Putman B, Singh A, Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen HW, Fazzari MJ, Prezant DJ, Weiden MD. Abnormalities on Chest Computed Tomography and Lung Function Following an Intense Dust Exposure: A 17-Year Longitudinal Study. International journal of environmental research and public health. 2019;16(9). Epub 2019/05/16. doi: 10.3390/ijerph16091655. PubMed PMID: 31085989; PMCID: PMC6540073.
5. Banauch GI, Alleyne D, Sanchez R, Olender K, Cohen HW, Weiden M, Kelly KJ, Prezant DJ. Persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center. American journal of respiratory and critical care medicine. 2003;168(1):54-62. Epub 2003/02/25. doi: 10.1164/rccm.200211-1329OC. PubMed PMID: 12615613.
6. Banauch GI, Hall C, Weiden M, Cohen HW, Aldrich TK, Christodoulou V, Arcentales N, Kelly KJ, Prezant DJ. Pulmonary function after exposure to the World Trade Center collapse in the New York City Fire Department. American journal of respiratory and critical care medicine. 2006;174(3):312-9. Epub 2006/04/27. doi: 10.1164/rccm.200511-1736OC. PubMed PMID: 16645172; PMCID: PMC2648115.
7. Schenck EJ, Echevarria GC, Girvin FG, Kwon S, Comfort AL, Rom WN, Prezant DJ, Weiden MD, Nolan A. Enlarged pulmonary artery is predicted by vascular injury biomarkers and is associated with WTC-Lung Injury in exposed fire fighters: a case-control study. BMJ Open. 2014;4(9):e005575. Epub 20140929. doi: 10.1136/bmjopen-2014-005575. PubMed PMID: 25270856; PMCID: PMC4179411.
8. de la Hoz RE. Occupational lower airway disease in relation to World Trade Center inhalation exposure. Current opinion in allergy and clinical immunology. 2011;11(2):97-102. Epub 2011/02/18. doi: 10.1097/ACI.0b013e3283449063. PubMed PMID: 21325944.
9. Swayze GA, Clark RN, Sutley SJ, Hoefen TM, Plumlee GS, Meeker GP, Brownfield IK, Livo KE, Morath LC. Spectroscopic and X-ray Diffraction Analyses of Asbestos in the World Trade Center Dust: Asbestos Content of the Settled Dust. Urban Aerosols and Their Impacts: American Chemical Society; 2005. p. 40-65.
10. Meeker GP, Sutley SJ, Brownfield IK, Lowers HA, Bern AM, Swayze GA, Hoefen TM, Plumlee GS, Clark RN, Gent CA. Materials Characterization of Dusts Generated by the Collapse of the World Trade Center. Urban Aerosols and Their Impacts: American Chemical Society; 2005. p. 84-102.
11. Mossman BT, Gee JB. Asbestos-related diseases. The New England journal of medicine. 1989;320(26):1721-30. Epub 1989/06/29. doi: 10.1056/NEJM198906293202604. PubMed PMID: 2659987.
12. Rong Y, Luo X, Zhang Z, Cui X, Liu Y, Chen W. Occupational exposure to asbestos and cardiovascular related diseases: A meta-analysis. Prev Med Rep. 2015;2:920-6. Epub 2016/02/05. doi: 10.1016/j.pmedr.2015.10.005. PubMed PMID: 26844169; PMCID: PMC4721368.
13. Armato SG, 3rd, McNitt-Gray MF, Reeves AP, Meyer CR, McLennan G, Aberle DR, Kazerooni EA, MacMahon H, van Beek EJ, Yankelevitz D, Hoffman EA, Henschke CI, Roberts RY, Brown MS, Engelmann RM, Pais RC, Piker CW, Qing D, Kocherginsky M, Croft BY, Clarke LP. The Lung Image Database Consortium (LIDC): an evaluation of radiologist variability in the identification of lung nodules on CT scans. Academic radiology. 2007;14(11):1409-21. doi: 10.1016/j.acra.2007.07.008. PubMed PMID: 17964464; PMCID: 2290739.
14. Haga A, Takahashi W, Aoki S, Nawa K, Yamashita H, Abe O, Nakagawa K. Classification of early stage non-small cell lung cancers on computed tomographic images into histological types using radiomic features:

interobserver delineation variability analysis. Radiological physics and technology. 2018;11(1):27-35. Epub 2017/12/07. doi: 10.1007/s12194-017-0433-2. PubMed PMID: 29209915.
15. Heuvelmans M, Han DW, Vliegenthart R, De Jonge G, Walter J, Van Ooijen P, De Koning H, Oudkerk M. Influence of Nodule Morphology on Inter-Reader Variability of Volume and Diameter Measurements in CT Lung Cancer Screening. Journal of Thoracic Oncology. 2017;12(1):S345-S6. PubMed PMID: WOS:000413055800361.
16. Pompe E, de Jong PA, de Jong WU, Takx RAP, Eikendal ALM, Willemink MJ, Oudkerk M, Budde RPJ, Lammers JWJ, Hoesein F. Inter-observer and inter-examination variability of manual vertebral bone attenuation measurements on computed tomography. European radiology. 2016;26(9):3046-53. doi: 10.1007/s00330-015-4145-x. PubMed PMID: WOS:000381122400021.
17. van Hamersvelt RW, Willemink MJ, Takx RAP, Eikendal ALM, Budde RPJ, Leiner T, Mol CP, Isgum I, de Jong PA. Cardiac valve calcifications on low-dose unenhanced ungated chest computed tomography: inter-observer and inter-examination reliability, agreement and variability. European radiology. 2014;24(7):1557-64. doi: 10.1007/s00330-014-3191-0. PubMed PMID: WOS:000337041900015.
18. Ardila D, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng L, Tse D, Etemadi M, Ye W, Corrado G, Naidich DP, Shetty S. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nature medicine. 2019. doi: 10.1038/s41591-019-0447-x.
19. Liu S, Xie Y, Jirapatnakul A, Reeves AP. Pulmonary nodule classification in lung cancer screening with three-dimensional convolutional neural networks. J Med Imaging (Bellingham). 2017;4(4):041308. doi: 10.1117/1.JMI.4.4.041308. PubMed PMID: 29181428; PMCID: PMC5685809.
20. Humphries SM, Notary AM, Centeno JP, Strand MJ, Crapo JD, Silverman EK, Lynch DA, Genetic Epidemiology of CI. Deep Learning Enables Automatic Classification of Emphysema Pattern at CT. Radiology. 2019:191022. Epub 2019/12/04. doi: 10.1148/radiol.2019191022. PubMed PMID: 31793851.
21. Shin KE, Chung MJ, Jung MP, Choe BK, Lee KS. Quantitative computed tomographic indexes in diffuse interstitial lung disease: correlation with physiologic tests and computed tomography visual scores. Journal of computer assisted tomography. 2011;35(2):266-71. Epub 2011/03/18. doi: 10.1097/RCT.0b013e31820ccf18. PubMed PMID: 21412102.
22. Jirapatnakul A, Reeves AP, Lewis S, Chen X, Ma T, Yip R, Chin X, Liu S, Perumalswami PV, Yankelevitz DF, Crane M, Branch AD, Henschke CI. Automated measurement of liver attenuation to identify moderate-to-severe hepatic steatosis from chest CT scans. European journal of radiology. 2020;122:108723. Epub 2019/11/30. doi: 10.1016/j.ejrad.2019.108723. PubMed PMID: 31778964; PMCID: PMC7179816.
23. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. Cancer. 1980;46(12):2736-40. doi: 10.1002/1097-0142(19801215)46:12<2736::Aid-cncr2820461233>3.0.Co;2-l.
24. Reeves AP, Xie Y, Liu S. Large-scale image region documentation for fully automated image biomarker algorithm development and evaluation. J Med Imaging (Bellingham). 2017;4(2):024505. doi: 10.1117/1.JMI.4.2.024505. PubMed PMID: 28612037; PMCID: PMC5462336.
25. Xie Y, Cham MD, Henschke CI, Yankelevitz DF, Reeves AP. Automated coronary artery calcification detection on low-dose chest CT images. SPIE International Symposium on Medical Imaging 2014; San Diego, CA: SPIE; 2014. p. 9035-14.
26. Xie Y, Liu S, Miller A, Miller JA, Markowitz S, Akhund A, Reeves AP. Coronary artery calcification identification and labeling in low-dose chest CT images. In: Armato III SG, Petrick N, editors. Medical Imaging 2017: Computer-aided Diagnosis: SPIE; 2017. p. 101340L.
27. de la Hoz RE, Jeon Y, Reeves AP, San Jose Estepar R, Liu X, Doucette JT, Celedon JC, Nolan A. Increased pulmonary artery diameter is associated with reduced FEV(1) in former World Trade Center workers. Clin Respir J. 2019;13(10):614-23. Epub 20190819. doi: 10.1111/crj.13067. PubMed PMID: 31347281; PMCID: PMC6783324.
28. Weakley J, Webber MP, Gustave J, Kelly K, Cohen HW, Hall CB, Prezant DJ. Trends in respiratory diagnoses and symptoms of firefighters exposed to the World Trade Center disaster: 2005-2010. Preventive medicine. 2011;53(6):364-9. Epub 20110910. doi: 10.1016/j.ypmed.2011.09.001. PubMed PMID: 21930151.
29. Wanahita N, See JL, Giedd KN, Friedmann P, Somekh NN, Bergmann SR. No evidence of increased prevalence of premature coronary artery disease in New York City police officers as predicted by coronary artery calcium scoring. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2010;52(6):661-5. doi: 10.1097/JOM.0b013e3181e36457. PubMed PMID: 20523232.

30. Chen-Mayer HH, Fuld MK, Hoppel B, Judy PF, Sieren JP, Guo J, Lynch DA, Possolo A, Fain SB. Standardizing CT lung density measure across scanner manufacturers. Medical physics. 2017;44(3):974-85. Epub 20170221. doi: 10.1002/mp.12087. PubMed PMID: 28060414; PMCID: PMC6276120.
31. Centers for Disease Control and Prevention HHS. World Trade Center Health Program; Petition 018-Hypertension; Finding of Insufficient Evidence. 2018. p. 17783-7.
32. Sloan NL, Shapiro MZ, Sabra A, Dasaro CR, Crane MA, Harrison DJ, Luft BJ, Moline JM, Udasin IG, Todd AC, Teitelbaum SL. Cardiovascular disease in the World Trade Center Health Program General Responder Cohort. American journal of industrial medicine. 2021;64(2):97-107. Epub 2020/12/15. doi: 10.1002/ajim.23207. PubMed PMID: 33315266.
33. Li J, Cone JE, Brackbill RM, Giesinger I, Yung J, Farfel MR. Pulmonary Fibrosis among World Trade Center Responders: Results from the WTC Health Registry Cohort. Int J Environ Res Public Health. 2019;16(5). Epub 20190307. doi: 10.3390/ijerph16050825. PubMed PMID: 30866415; PMCID: PMC6427469.
34. Meyer M, Ronald J, Vernuccio F, Nelson RC, Ramirez-Giraldo JC, Solomon J, Patel BN, Samei E, Marin D. Reproducibility of CT Radiomic Features within the Same Patient: Influence of Radiation Dose and CT Reconstruction Settings. Radiology. 2019;293(3):583-91. Epub 20191001. doi: 10.1148/radiol.2019190928. PubMed PMID: 31573400; PMCID: PMC10860741.

B.2 (B2 Accomplishments Final merged.pdf)

Publications

We have placed a preprint of a paper “Comparison of the extent and progression of respiratory and cardiovascular disease in World Trade Center responders to lung screening participants” on medxriv.org.

Inclusions

Cumulative Inclusion Enrollment Table

	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
Racial categories	Female	Male	Unknown	Female	Male	Unknown	Female	Male	Unknown	Total
American Indian/Alaska Native	0	5	0	0	1	0	0	1	0	7
Asian	29	59	0	0	4	0	0	8	0	100
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African America	64	275	0	1	8	0	2	13	0	363
White	158	1241	0	11	37	0	20	123	0	1590
More than One Race	4	34	0	167	376	0	5	28	0	614
Unknown or Not Reported	2	5	0	32	126	0	4	24	0	193
Total	257	1619	0	211	552	0	31	197	0	2867

Gender and minority subjects

This was a retrospective analysis of already collected data, so the distribution of gender and race were fixed.

Children

No people under the age of 18 were included in this study.

Materials available to other investigators

The automated computer measurements are available to other investigators upon written request to the PI in accordance with the latest NIH guidelines to ensure the privacy and confidentiality of the included research participants.

Comparison of the extent and progression of respiratory and cardiovascular disease in World Trade Center responders to lung screening participants

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Abstract

Responders to the World Trade Center (WTC) site in the aftermath of the 9/11 attacks were exposed to toxic dust, which has been linked to increased risk of respiratory and cardiovascular disease. The respiratory and cardiovascular effects of WTC dust exposure have been studied using pulmonary function tests and the number of cardiovascular events, but computed tomography (CT) scans provide an opportunity to see the early structural changes in the lungs and cardiovascular system before clinical symptoms appear. CT scans are used in the screening and evaluation of respiratory diseases such as lung cancer, interstitial lung disease, and chronic obstructive pulmonary disease, and to visualize coronary arteries and quantify the amount of coronary artery calcifications; in fact, it is possible to detect multiple diseases from a single chest CT scan. While manual evaluation by a radiologist is often the gold standard, automated image analysis tools can quickly and accurately quantify these diseases.

We identified non-contrast chest CT scans from members of the World Trade Center General Responders Cohort (WTC GRC) with slice thickness of 2.5 mm or less. We used the open-source Chest Imaging Platform software to compute measures of emphysema and interstitial lung disease and research software from Cornell University to compute measures of pulmonary hypertension and coronary artery calcification. We identified a sex, age (within 5 years), smoking status, one or more CT scans, and follow-up time -matched cohort of participants enrolled in the lung screening program at Mount Sinai. We compared disease measures from the WTC GRC group to the lung screening group to assess whether there was a difference in the extent and progression of disease.

There were 4909 chest CT images of members of the WTC GRC that met our image quality criteria. There were 3855 members of the GRC for which we could obtain both chest CT images and clinical data. Of these, there were 2284 members for which we could obtain pulmonary disease measurements on at least one scan, 1246 members for which we could calculate cardiac measurements. The matched controls from the lung screening cohort consisted of 557 participants with 1122 chest CT images that met our image quality criteria and for which we obtained all four disease measures.

We compared members of the WTC GRC with matched participants from the lung screening program. One of the key findings is that after a median time of 11-13 years after 9/11, the WTC GRC group exhibited higher burdens of coronary artery calcification, emphysema, and interstitial lung disease compared with a matched control group of lung screening participants. This supports the continued surveillance of WTC responders.

Introduction

The 9/11 World Trade Center (WTC) attack exposed thousands of people to toxic dust; this exposure has been associated with many illnesses, many of which have a long latency period and remain undetected until reaching an advanced stage with symptoms that affect one's quality of life (1-4). A major component of the toxic dust exposure was asbestos, which was present in the fireproofing material used in the WTC (5,6). Asbestos exposure is associated with respiratory diseases such as lung cancer and asbestosis (7) and increased risk of cardiovascular disease (8).

The WTC dust exposure affects many different organ systems; two of the most prominent are the respiratory and cardiovascular systems (1,4,9-11). Studies have shown that firefighters with WTC exposure had higher age-adjusted incident rates of cardiovascular disease (1) and reduction in pulmonary function (10), with visible lung abnormalities on chest CT (4) and lower airway disease (12). A variety of abnormalities of the lung have been seen in firefighters with WTC exposure, including emphysema (5.9% of participants), pleural thickening (3.0%), and to a lesser extent pulmonary fibrosis (0.6%) (4). A more recent study of WTC responders found pleural abnormalities in 21% of the cohort (13). There was an increased risk of adverse cardiovascular events in firefighters with WTC exposure (1), although another study of police officers with WTC exposure found no increase of CAC after 5 years (14). CAC and aortic valve calcification (AVC) have both been shown to be independent prognostic risk factors of cardiovascular events and mortality (15) and can be measured on LDCT scans (16,17). A key question of WTC-related research is whether the amount of WTC dust exposure is related to the development and progression of disease. Previous WTC-related studies have found preliminary relationships between the amount of WTC exposure and various diseases. A study of firefighters found a linear relationship between the arrival time at the WTC site and decline in lung function measured by spirometry (10), and a later study found that high-intensity WTC exposure is associated with increased risks of air trapping, emphysema, and bronchial wall thickening (4). Another study on the WTC GRC found no association between WTC exposure duration or early arrival time at the WTC with pleural abnormalities on CT scans on a sub-cohort of 1453 members of the WTC GRC, from 2003-2012 (13), but another study found that reduced lung function from spirometry was lower in those who arrived early at the WTC and was associated with proximal airway disease (18). A recent study of firefighters showed an association between arrival time and duration at the WTC site with risk of cardiovascular disease (1). Male workers who arrived on the WTC site on 9/11 had a higher risk of heart disease compared to those who arrived after 9/18 (19), but this was not significant. A later study using a dust exposure questionnaire reported similar results (20). A study of workers in Italy exposed to asbestos reported an increase in all-cause mortality, and specifically lung and pleural cancers (21).

Many respiratory and cardiovascular diseases can be identified and quantified on CT and low-dose chest CT (LDCT) scans used for lung cancer screening. Emphysema has been quantified from CT scans by computing the percentage of lung volume below a set threshold (22), typically -910 HU. ILD has been automatically quantified by analyzing the texture of the lung parenchyma (23,24); one algorithm, CALIPER, used texture analysis of volumes of interest in the lung to classify regions into one of five different characteristic CT patterns (25). There are preliminary automated tools to quantify pleural thickening (26-28). Automated software for measuring CAC from chest CT has also been developed and showed good agreement with the current reference standard, Agatston scoring (29,30).

CT scans provide an opportunity to identify and evaluate the presence of early disease prior to the onset of symptoms in the WTC general responders' cohort (GRC), as well as progression when multiple scans are obtained over time. Radiologists can visually and sometimes quantitatively assess diseases on CT scans, but these often have high variability, are time consuming to perform, or both (31-35). With the increase in computing power and advances in image analysis and machine learning, automated tools have been developed to assess a wide variety of diseases on CT scans (36-40).

In this work, we applied automated methods to quantify two respiratory diseases, emphysema ad interstitial lung disease, and two cardiovascular conditions, hypertension and coronary artery calcifications, in a cohort of WTC responders and a matched cohort of lung screening participants, to assess whether WTC exposure impacted the incidence rate or progression of these diseases.

Methods

Data

This study was approved by our institutional review board (IRB) and was HIPAA-compliant. We obtained a list of members of the WTC General Responders Cohort (GRC) from the WTC Data Center who received care at our institution through 2021. We queried our institution's imaging archive for CT scans meeting the following criteria: 1) a patient on the list of WTC GRC members, 2) a CT scan that was non-contrast of the chest, and 3) slice thickness of 2.5 mm or less. The requirement for non-contrast CT scans with a slice thickness of 2.5 mm or less was to meet the image quality requirements of the automated software tools.

We curated a dataset of participants enrolled in the lung screening program at our institution that were matched on age, smoking status, follow-up time, and whether the participant had one or more CT scans to members of the WTC GRC for whom we had CT scans meeting the criteria above.

Automated analysis

For pulmonary analyses, we used the open-source Chest Imaging Platform (CIP)[1], an evolution of Airway Inspector. This software was developed primarily for quantitative CT analysis of lung disease, particularly chronic obstructive pulmonary disease (COPD). This is available as a docker container and ran on a workstation with an AMD Ryzen Threadripper PRO 5955WX with 128 GB of RAM. For cardiac analyses, we used research software developed by Cornell University (41,42) which we ran on a computer with an Intel Xeon Gold 6134 with 384gb of RAM. Images were converted from DICOM to the required image format for both software tools.

Statistical analyses

Continuous variables were summarized using median and interquartile range(IQR) and compared across groups using Kruskal-Wallis test. Categorical variables were summarized by frequency and percentages and compared using chi-squared test or Fisher's exact test as appropriate. All measures were assessed for normality and transformations were applied where necessary.

Controls were selected for each case using a systematic matching algorithm to ensure comparability. Cases were matched to controls based on sex, smoking status, visit type (one vs. two or more), and within 5 years difference of age. In addition, controls were required to have a follow-up time at least as long as that of the corresponding case. In instances where multiple controls met the matching criteria, one was randomly selected from the eligible pool to minimize selection bias. The matching process was conducted iteratively without replacement.

A linear mixed-effects model was employed to assess whether longitudinal changes in automated pulmonary and cardiovascular measurements derived from repeated CT scans differed between the WTC GRC and lung screening groups. Follow-up time was defined as time since initial CT scan with adjustment for race and current smoking status. Random intercept and slope were used to account for within-subject correlation across repeated measures and between-subject heterogeneity in the rate of change over time. Using these models, we calculated the estimated marginal means of outcome measures for comparison between WTC GRC and lung screening groups. Interaction terms between time and group (WTC GRC vs lung screening) were explored to assess potential differences in the trajectory of these measures across groups. Separate models were fitted for each pulmonary (emphysema LAA950; interstitial lung disease HAA250) and cardiovascular outcome (coronary artery calcification Agatston score; pulmonary hypertension PA ratio).

A two-sided p-value of < 0.05 was used to indicate statistical significance. All analyses were conducted using SAS (v9.4, SAS Institute, Cary, NC) and R (v4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

[1] Available from https://chestimagingplatform.org/index.htm

There was a total of 4909 chest CT scans of members of the WTC GRC meeting our criteria. Of these 4909 chest CT scans, the emphysema and ILD analysis successfully completed on 4370 (89.0%) scans, while the coronary artery calcification was successful on 2122 (43.2%) scans, and both analyses were successful on 2023 scans (41.2%). There were 3855 members of the GRC for which we could obtain both chest CT images and clinical data. Of these, there were 2284 members for which we could obtain pulmonary disease measurements on at least one scan, 1246 members for which we could calculate cardiac measurements, and 1220 members for which we could successfully compute all four disease measures on at least one scan. Table 1 lists the longitudinal scans available for each GRC member; Table 1a lists those members for which we were able to compute pulmonary measurements, and Table 1b lists those members for which we were able to compute cardiac measurements. Although most members had a single CT scan, there were a substantial number with two or more scans available for longitudinal analysis (1070 members with pulmonary measurements and 724 members with cardiac measurements).

We successfully identified eligible controls for 557 cases based on the pre-specified matching criteria. The demographic characteristics of the matched case-control groups are shown in Table 2. Of the 557 matched pairs, 457 (82%) of them were male and 18% female. The median age was 54 years, with an interquartile range of 48 to 60 years for the WTC GRC group and 49 to 60 years for the control lung screening group. Although matching was performed based on smoking history (whether individuals had ever smoked), current smoking status differed significantly between the groups (P < .0001). In the WTC GRC group, 23% were current smokers, 30% were former smokers, and 47% were never smokers. In contrast, 34% of the control lung screening group were current smokers, 19% were former smokers, and 47% were never smokers.

Table 1. Breakdown of number of CT scans available for each WTC GRC member

(a) Among 2284 members with at least one scan with successful pulmonary measurements

Num CT scans	Num GRC members	Percent (%)
1	1214	53.2
2	520	22.8
3	279	12.2
4	135	5.9
5	66	2.9
6 or more	70	3.1
Total	2284	

(b) Among 1246 members with at least one scan with successful cardiac measurements

Num CT scans	Num GRC members	Percent (%)
1	522	41.9
2	302	24.2
3	194	15.6
4	105	8.4
5	56	4.5
6 or more	67	5.4
Total	1246	

Race distributions also varied significantly between the two groups (P < .0001). The WTC GRC group had a higher proportion of White participants (61%) compared to 55% in the control lung screening group. A higher proportion of Black or African American participants was observed in the control lung screening group (19%) compared to the WTC GRC group (9%). There were also notable differences in the representation of Asian participants (1% in WTC GRC vs. 13% in control). Among the 557 WTC GRC, arrival time for the WTC GRC group was recorded across various time points, with 17% exposed to the 9/11 Dust Cloud, 11% arriving after the dust cloud on 9/11, 30% arriving on 9/12 or 9/13, 30% arriving between 9/14 and the end of September, and 9% arriving in October or later.

Extent of disease on initial CT scan

Table 3 summarizes pulmonary and cardiac measures from the first CT scan for both the WTC GRC and control lung screening groups. Among the 184 participants with available cardiac findings, the median Agatston score, a measure of coronary artery calcification, was significantly higher on the first CT scan in the WTC GRC group (median: 68.70, IQR: 18.31, 258.92) compared to the control group (median: 8.65, IQR: 0.12, 120.04) (p<0.001). PA ratio, a measure of pulmonary hypertension, was similar between the WTC GRC group (median: 0.79, IQR: 0.73, 0.88) and the control group (median: 0.79, IQR: 0.72, 0.86) (p=0.25).
Among the 556 participants with available pulmonary findings, significant differences were observed for emphysema and interstitial lung diseases. The LAA950 score, which reflects the extent of emphysema, was significantly higher in the WTC GRC group (median: 0.09, IQR: 0.01, 0.19) compared to the control group (median: 0.03, IQR: 0.01, 0.09) (p<0.001), suggesting more extensive emphysema in the WTC GRC group.

Similarly, the HAA250 score, a measure of interstitial lung disease, was also significantly higher in the WTC GRC group (median: 0.02, IQR: 0.02, 0.03) compared to the control group (median: 0.02, IQR: 0.01, 0.02) ($p<0.001$), indicating more extensive ILD among WTC GRC.

Overall, these results indicate that participants in the WTC GRC group exhibit a higher burden of coronary artery calcification, emphysema, and interstitial lung disease compared to those in the control group, while no significant difference was observed for pulmonary hypertension.

Table 2. Demographics 557 members of WTC GRC and 557 members of the control lung screening cohort

Demographic characteristics	WTC GRC	Control Lung Screening	P-value
N	557	557	
Sex			
Male	457 (82%)	457 (82%)	1.00
Female	100 (18%)	100 (18%)	
Age*, y	54 (48, 60)	54 (49, 60)	
Smoking			
Current smoker	126 (23%)	189 (34%)	<.0001
Former smoker	169 (30%)	106 (19%)	
Never smoker	262 (47%)	262 (47%)	
Race			
American Indian/Alaska Native	1 (0%)	3 (1%)	<.0001
Asian	6 (1%)	74 (13%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	
Black or African America	50 (9%)	107 (19%)	
White	339 (61%)	308 (55%)	
More than One Race	124 (22%)	65 (12%)	
Unknown or Not Reported	37 (7%)	0 (0%)	
Arrival Time			
9/11 Dust Cloud	94 (17%)		
9/11 No Dust Cloud	62 (11%)		
9/12 & 9/13	168 (30%)		
9/14 - End of Sept	167 (30%)		
Oct and beyond	50 (9%)		
Unknown	16 (3%)		
Average length of follow-up (SD), year	3.61 (4.07)	1.79 (3.01)	<.0001

Progression of diseases

As shown in Table 4, at baseline, the average LAA950 was significantly higher in the WTC GRC group compared to the control lung screening group (0.12 vs. 0.075, $P < 0.001$), suggesting that WTC GRC had more extensive emphysema. Over time, the WTC GRC group showed a significant decrease in LAA950 score, with a yearly reduction of -0.011 (95% CI: -0.012, -0.009, $P < 0.001$). In contrast, the control group exhibited a slight but statistically significant increase in LAA950 over time, with a yearly increase of 0.0042 (95% CI: 0.0021, 0.0063, $P < 0.001$), indicating worsening of emphysema.

At baseline, the HAA250 score was also significantly higher in the WTC GRC group compared to the control group (0.027 vs. 0.019, $P < 0.001$). Figure 1 depicts the progression of the pulmonary disease measures over time for the WTC GRC group and control group. The WTC GRC group demonstrated a significant annual decrease in HAA250 (-0.0006, 95% CI: -0.0007, -0.0005, $P < 0.001$), while the control group did not exhibit any statistically significant change in HAA250 over time (-0.0001, 95% CI: -0.0004, 0.0001).

Table 3. Summary of cardiovascular and respiratory disease measurements on the WTC GRC members on the first available CT scan

Measures on first CT scan	WTC GRC	Non-WTC GRC	P-value
With available cardiac findings		184	
Coronary Artery Calcification			
Agatston score*	68.70 (18.31, 258.92)	8.65 (0.12, 120.04)	<0.001
Pulmonary Hypertension			
PA ratio*	0.79 (0.73, 0.88)	0.79 (0.72, 0.86)	0.249
With available pulmonary findings		556	
Emphysema			
LAA950*	0.09 (0.01, 0.19)	0.03 (0.01, 0.09)	<0.001
Interstitial lung diseases			
HAA250*	0.02 (0.02, 0.03)	0.02 (0.01, 0.02)	<0.001

*Median (IQR)

At baseline, the PA ratio was similar between the WTC GRC and control groups (p=0.91). No significant differences were observed in the progression of pulmonary hypertension (PA ratio) between the groups (P = 0.85).

Agatston score was log-transformed prior to analysis due to the skewed distribution. The baseline log-transformed CAC Agatston score was significantly higher in the WTC GRC group compared to the control group (4.47 vs. 2.88, P = 0.045), indicating more extensive coronary artery calcification. Both groups showed significant increases in the CAC score over time, with the WTC GRC group showing an annual rate of increase of 0.09 (95% CI: 0.033, 0.14) and the control group showing a greater increase of 0.26 (95% CI: 0.19, 0.33). Figure 2 depicts the progression of the cardiac measures over time for the WTC GRC group and control group. The rate of progression was significantly different between the two groups (p<.001) with the control group showing faster progression.

Discussion

This analysis showed that members of the WTC GRC had elevated levels of coronary artery calcification, emphysema, and interstitial lung disease compared to the lung screening control group on the initial CT scan. The median time between 9/11 and the initial CT scan included in this study for the WTC GRC was about 10 years, which is a long enough time that any effect of WTC exposure on these diseases would already be seen. It also suggests that the burden of these diseases remains elevated even after 10 years; this supports the need for long-term health monitoring and sustained surveillance programs for WTC GRC members. A previous study by Weakley et al. showed that emphysema and COPD were more prevalent in the WTC-exposed fire fighters compared to the general population 5 years after 9/11, increasing or remaining stable through year 8 (43). While a previous study by Wanahita et al. did not find an increased prevalence of coronary artery disease in WTC-exposed police officers 5 years after 9/11, but the authors note that majority of the police officers were below 40 years of age (14); however another study on WTC-exposed fire fighters by Cohen et al. found an association between WTC exposure and long-term cardiovascular disease risk (1).

The results on the progression of disease were negative – although there was a statistically significant decrease in emphysema and interstitial lung disease, we know that these diseases are not reversible. This is likely attributable to differences in CT scanners and acquisition protocols, Chen-Mayer et al. found that there were differences in lung density measurements across different scanners and protocols, which could be reduced by applying standardization procedures (44). There was no significant difference observed between the WTC GRC group and the control group for the progression of hypertension which correlates with the denial of a petition to add hypertension as a WTC health condition (45). While both the WTC GRC group and control

group had increasing coronary artery calcification (CAC) over time, surprisingly the control group showed faster progression. This could again to attributable to differences in CT scanners and protocols; the lung screening group tended to have more recent CT scans with thinner slice thickness, which may be more sensitive for detection of CAC. Lastly, the etiology of pulmonary diseases may differ between the two groups due to the nature of exposure, potentially result in different clinical manifestations and progression of disease, complicating the comparative analysis.

In computing the automated disease measures, we encountered algorithm failures in the coronary analysis in over half of the CT scans. The lower success rate of the coronary artery analysis compared to the emphysema and ILD analyses is due to the higher difficulty of finding small calcium deposits in non-gated CT images – normally coronary artery calcifications are measured on gated CT imaging to eliminate artifacts caused by heart motion, but for this analysis, we are using chest CT images obtained for other purposes. The specific algorithm also requires the segmentation of a number of anatomical structures in the chest, including the lungs, airways, and ribs, which are more difficult than just segmenting the lungs. Both software for the emphysema/ILD measures and CAC measures utilized model-based methods as opposed to deep learning methods. There have been many advancements in deep-learning based methods in the past few years and newer methods may provide a higher success rate.

Table 4. Extent and progression of respiratory and cardiovascular disease measures for members of the WTC GRC and the control group

a) Emphysema (LAA950)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.12	(0.11. 0.14)	<0.001	-0.011	(-0.012, -0.009)	<0.001
Control lung screening	0.075	(0.06, 0.09)		0.0042	(0.0021, 0.0063)	

b) Interstitial lung diseases (HAA250)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.027	(0.025, 0.028)	<0.001	-0.0006	(-0.0007, -0.0005)	<0.001
Control lung screening	0.019	(0.017, 0.021)		-0.0001	(-0.0004, 0.0001)	

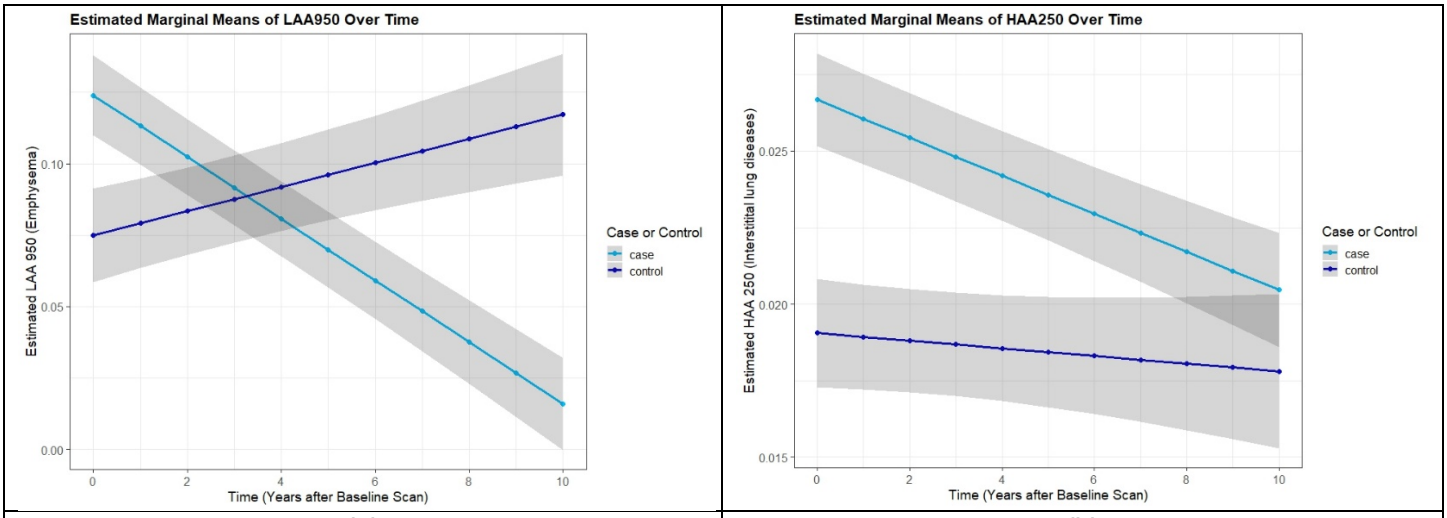
c) Pulmonary Hypertension (PA ratio)

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	0.77	(0.72, 0.82)	0.91	-0.0002	(-0.0047, 0.0042)	0.85
Control lung screening	0.77	(0.71, 0.83)		-0.0009	(-0.0067, 0.0048)	

d) Log CAC Agatston score

	At Baseline	95% CI	p-value	Δ/year	95% CI	p-value
WTC GRC	4.47	(3.47, 5.48)	0.045	0.09	(0.033, 0.14)	<0.001
Control lung screening	2.88	(1.74, 4.03)		0.26	(0.19, 0.33)	

All models adjusted for race and current smoking status



(a) (b)

Figure 1. Respiratory measurements over time for the WTC GRC (Case) and lung screening control groups (control). a) Estimated mean emphysema score (LAA950) and b) Estimated mean interstitial lung disease measure (HAA250)

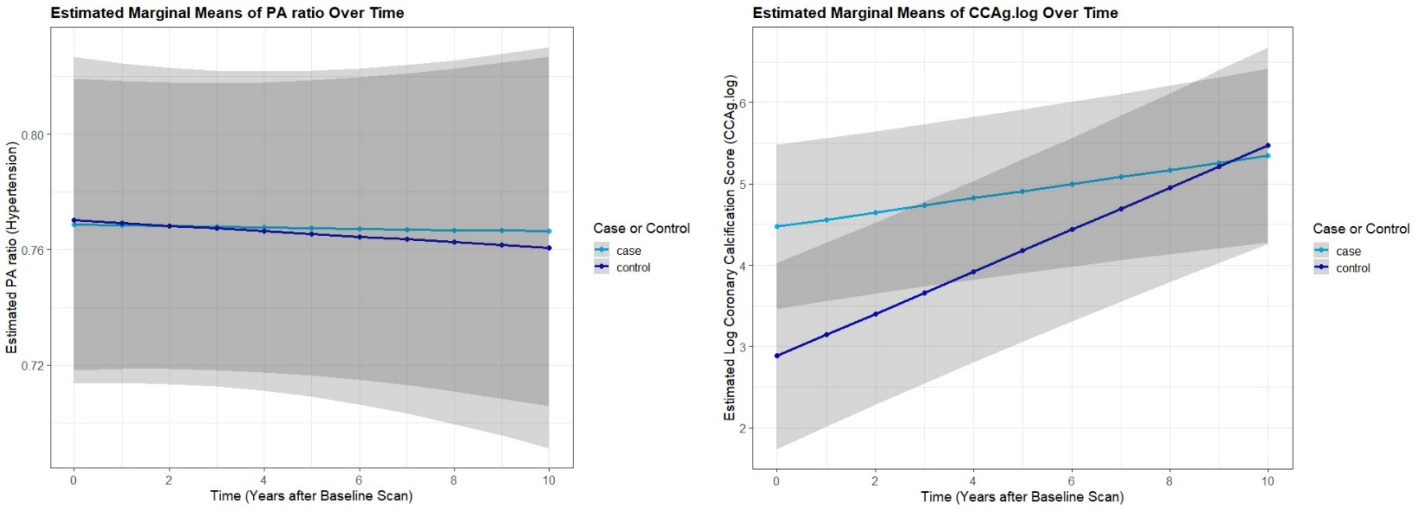


Figure 2. Cardiac measurements for the WTC GRC group (Case) and control lung screening group (control) over time. a) Estimated mean pulmonary artery to aorta ratio (PA ratio) and b) log-transformed Agaston score.

Acknowledgements

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References

1. Cohen HW, Zeig-Owens R, Joe C, Hall CB, Webber MP, Weiden MD, Cleven KL, Jaber N, Skerker M, Yip J, Schwartz T, Prezant DJ. Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster. JAMA Netw Open 2019;2:e199775.
2. Singh A, Zeig-Owens R, Moir W, Hall CB, Schwartz T, Vossbrinck M, Jaber N, Webber MP, Kelly KJ, Ortiz V, Koffler E, Prezant DJ. Estimation of Future Cancer Burden Among Rescue and Recovery Workers Exposed to the World Trade Center Disaster. JAMA Oncol 2018;4:828-31.
3. Wisnivesky J, Teitelbaum S, Todd A, Boffetta P, Crane M, Crowley L, de la Hoz R, Dellenbaugh C, Harrison D, Herbert R, Kim H, Jeon Y, Kaplan J, Katz C, Levin S, Luft B, Markowitz S, Moline J, Ozbay F, Pietrzak R, Shapiro M, Sharma V, Skloot G, Southwick S, Stevenson L, Udasin I, Wallenstein S, Landrigan P. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. Lancet 2011;378:888-97.
4. Liu C, Putman B, Singh A, Zeig-Owens R, Hall CB, Schwartz T, Webber MP, Cohen HW, Fazzari MJ, Prezant DJ, Weiden MD. Abnormalities on Chest Computed Tomography and Lung Function Following an Intense Dust Exposure: A 17-Year Longitudinal Study. Int J Environ Res Public Health 2019;16.
5. Swayze GA, Clark RN, Sutley SJ, Hoefen TM, Plumlee GS, Meeker GP, Brownfield IK, Livo KE, Morath LC. Spectroscopic and X-ray Diffraction Analyses of Asbestos in the World Trade Center Dust: Asbestos Content of the Settled Dust. Urban Aerosols and Their Impacts. ACS Symposium Series, vol 919: American Chemical Society; 2005. p. 40-65.
6. Meeker GP, Sutley SJ, Brownfield IK, Lowers HA, Bern AM, Swayze GA, Hoefen TM, Plumlee GS, Clark RN, Gent CA. Materials Characterization of Dusts Generated by the Collapse of the World Trade Center. Urban Aerosols and Their Impacts. ACS Symposium Series, vol 919: American Chemical Society; 2005. p. 84-102.
7. Mossman BT, Gee JB. Asbestos-related diseases. N Engl J Med 1989;320:1721-30.
8. Rong Y, Luo X, Zhang Z, Cui X, Liu Y, Chen W. Occupational exposure to asbestos and cardiovascular related diseases: A meta-analysis. Prev Med Rep 2015;2:920-6.
9. Banauch GI, Alleyne D, Sanchez R, Olender K, Cohen HW, Weiden M, Kelly KJ, Prezant DJ. Persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center. Am J Respir Crit Care Med 2003;168:54-62.
10. Banauch GI, Hall C, Weiden M, Cohen HW, Aldrich TK, Christodoulou V, Arcentales N, Kelly KJ, Prezant DJ. Pulmonary function after exposure to the World Trade Center collapse in the New York City Fire Department. Am J Respir Crit Care Med 2006;174:312-9.

11. Schenck EJ, Echevarria GC, Girvin FG, Kwon S, Comfort AL, Rom WN, Prezant DJ, Weiden MD, Nolan A. Enlarged pulmonary artery is predicted by vascular injury biomarkers and is associated with WTC-Lung Injury in exposed fire fighters: a case-control study. BMJ Open 2014;4:e005575.
12. de la Hoz RE. Occupational lower airway disease in relation to World Trade Center inhalation exposure. Curr Opin Allergy Clin Immunol 2011;11:97-102.
13. de la Hoz RE, Weber J, Xu D, Doucette JT, Liu X, Carson DA, Celedon JC. Chest CT scan findings in World Trade Center workers. Arch Environ Occup Health 2019;74:263-70.
14. Wanahita N, See JL, Giedd KN, Friedmann P, Somekh NN, Bergmann SR. No evidence of increased prevalence of premature coronary artery disease in New York City police officers as predicted by coronary artery calcium scoring. J Occup Environ Med 2010;52:661-5.
15. Hoffmann U, Massaro JM, D'Agostino RB, Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular Event Prediction and Risk Reclassification by Coronary, Aortic, and Valvular Calcification in the Framingham Heart Study. J Am Heart Assoc 2016;5.
16. Shemesh J, Henschke C, Shaham D, Yip R, Farooqi A, Cham M, McCauley D, Chen M, Smith J, Libby D, Pasmantier M, Yankelevitz D. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. Radiology 2010;257:541-8.
17. Zhu Y, Wang Y, Gioia WE, Yip R, Jirapatnakul AC, Chung MS, Yankelevitz DF, Henschke CI. Visual scoring of aortic valve calcifications on low-dose CT in lung cancer screening. Eur Radiol 2020;30:2658-68.
18. Weber J, Reeves AP, Doucette JT, Jeon Y, Sood A, San Jose Estepar R, Celedon JC, de la Hoz RE. Quantitative CT Evidence of Airway Inflammation in WTC Workers and Volunteers with Low FVC Spirometric Pattern. Lung 2020;198:555-63.
19. Jordan HT, Miller-Archie SA, Cone JE, Morabia A, Stellman SD. Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: results from the World Trade Center Health Registry. Prev Med 2011;53:370-6.
20. Jordan HT, Stellman SD, Morabia A, Miller-Archie SA, Alper H, Laskaris Z, Brackbill RM, Cone JE. Cardiovascular disease hospitalizations in relation to exposure to the September 11, 2001 World Trade Center disaster and posttraumatic stress disorder. J Am Heart Assoc 2013;2:e000431.
21. Luberto F, Ferrante D, Silvestri S, Angelini A, Cuccaro F, Nannavecchia AM, Oddone E, Vicentini M, Barone-Adesi F, Cena T, Mirabelli D, Mangone L, Roncaglia F, Sala O, Menegozzo S, Pirastu R, Azzolina D, Tunesi S, Chellini E, Miligi L, Perticaroli P, Pettinari A, Bressan V, Merler E, Girardi P, Bisceglia L, Marinaccio A, Massari S, Magnani C, working g. Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy. Environ Health 2019;18:71.
22. Archer DC, Coblentz CL, deKemp RA, Nahmias C, Norman G. Automated in vivo quantification of emphysema. Radiology 1993;188:835-8.
23. Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, Hartman TE, Bartholmai BJ, Robb RA, Ryu JH. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J 2014;43:204-12.
24. Humphries SM, Yagihashi K, Huckleberry J, Rho BH, Schroeder JD, Strand M, Schwarz MI, Flaherty KR, Kazerooni EA, van Beek EJR, Lynch DA. Idiopathic Pulmonary Fibrosis: Data-driven Textural Analysis of Extent of Fibrosis at Baseline and 15-Month Follow-up. Radiology 2017;285:270-8.
25. Bartholmai BJ, Raghunath S, Karwoski RA, Moua T, Rajagopalan S, Maldonado F, Decker PA, Robb RA. Quantitative Computed Tomography Imaging of Interstitial Lung Diseases. J Thorac Imaging 2013;28:298-307.
26. Chaisaowong K, Knepper A, Kraus T, Aach T. Application of supervised range-constrained thresholding to extract lung pleura for automated detection of pleural thickenings from thoracic CT images. Medical Imaging. SPIE; 2007.
27. Rudrapatna M, Mai V, Sowmya A, Wilson P, editors. Knowledge-Driven Automated Detection of Pleural Plaques and Thickening in High Resolution CT of the Lung2005; Berlin, Heidelberg: Springer Berlin Heidelberg.
28. Gudmundsson E, Straus CM, Armato SG, 3rd. Deep convolutional neural networks for the automated segmentation of malignant pleural mesothelioma on computed tomography scans. J Med Imaging (Bellingham) 2018;5:034503.
29. Takx RAP, de Jong PA, Leiner T, Oudkerk M, de Koning HJ, Mol CP, Viergever MA, Isgum I. Automated Coronary Artery Calcification Scoring in Non-Gated Chest CT: Agreement and Reliability. Plos One 2014;9:6.

30. Xie Y, Cham MD, Henschke C, Yankelevitz D, Reeves AP, editors. Automated coronary artery calcification detection on low-dose chest CT images. SPIE International Symposium on Medical Imaging; 2014.
31. Armato SG, 3rd, McNitt-Gray MF, Reeves AP, Meyer CR, McLennan G, Aberle DR, Kazerooni EA, MacMahon H, van Beek EJ, Yankelevitz D, Hoffman EA, Henschke CI, Roberts RY, Brown MS, Engelmann RM, Pais RC, Piker CW, Qing D, Kocherginsky M, Croft BY, Clarke LP. The Lung Image Database Consortium (LIDC): an evaluation of radiologist variability in the identification of lung nodules on CT scans. Acad Radiol 2007;14:1409-21.
32. Haga A, Takahashi W, Aoki S, Nawa K, Yamashita H, Abe O, Nakagawa K. Classification of early stage non-small cell lung cancers on computed tomographic images into histological types using radiomic features: interobserver delineation variability analysis. Radiol Phys Technol 2018;11:27-35.
33. Heuvelmans M, Han DW, Vliegenthart R, De Jonge G, Walter J, Van Ooijen P, De Koning H, Oudkerk M. Influence of Nodule Morphology on Inter-Reader Variability of Volume and Diameter Measurements in CT Lung Cancer Screening. Journal of Thoracic Oncology 2017;12:S345-S6.
34. Pompe E, de Jong PA, de Jong WU, Takx RAP, Eikendal ALM, Willemink MJ, Oudkerk M, Budde RPJ, Lammers JWJ, Hoesein F. Inter-observer and inter-examination variability of manual vertebral bone attenuation measurements on computed tomography. European Radiology 2016;26:3046-53.
35. van Hamersvelt RW, Willemink MJ, Takx RAP, Eikendal ALM, Budde RPJ, Leiner T, Mol CP, Isgum I, de Jong PA. Cardiac valve calcifications on low-dose unenhanced ungated chest computed tomography: inter-observer and inter-examination reliability, agreement and variability. European Radiology 2014;24:1557-64.
36. Ardila D, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng L, Tse D, Etemadi M, Ye W, Corrado G, Naidich DP, Shetty S. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nature Medicine 2019.
37. Liu S, Xie Y, Jirapatnakul A, Reeves AP. Pulmonary nodule classification in lung cancer screening with three-dimensional convolutional neural networks. J Med Imaging (Bellingham) 2017;4:041308.
38. Humphries SM, Notary AM, Centeno JP, Strand MJ, Crapo JD, Silverman EK, Lynch DA, Genetic Epidemiology of CI. Deep Learning Enables Automatic Classification of Emphysema Pattern at CT. Radiology 2019:191022.
39. Shin KE, Chung MJ, Jung MP, Choe BK, Lee KS. Quantitative computed tomographic indexes in diffuse interstitial lung disease: correlation with physiologic tests and computed tomography visual scores. J Comput Assist Tomogr 2011;35:266-71.
40. Jirapatnakul A, Reeves AP, Lewis S, Chen X, Ma T, Yip R, Chin X, Liu S, Perumalswami PV, Yankelevitz DF, Crane M, Branch AD, Henschke CI. Automated measurement of liver attenuation to identify moderate-to-severe hepatic steatosis from chest CT scans. Eur J Radiol 2020;122:108723.
41. Reeves AP, Xie Y, Liu S. Large-scale image region documentation for fully automated image biomarker algorithm development and evaluation. J Med Imaging (Bellingham) 2017;4:024505.
42. Xie Y, Liu S, Miller A, Miller JA, Markowitz S, Akhund A, Reeves AP. Coronary artery calcification identification and labeling in low-dose chest CT images. In: Armato III SG, Petrick N, editors. Medical Imaging 2017: Computer-aided Diagnosis: SPIE; 2017. p. 101340L.
43. Weakley J, Webber MP, Gustave J, Kelly K, Cohen HW, Hall CB, Prezant DJ. Trends in respiratory diagnoses and symptoms of firefighters exposed to the World Trade Center disaster: 2005-2010. Prev Med 2011;53:364-9.
44. Chen-Mayer HH, Fuld MK, Hoppel B, Judy PF, Sieren JP, Guo J, Lynch DA, Possolo A, Fain SB. Standardizing CT lung density measure across scanner manufacturers. Med Phys 2017;44:974-85.
45. Centers for Disease Control and Prevention HHS. World Trade Center Health Program; Petition 018-Hypertension; Finding of Insufficient Evidence. 2018. p. 17783-7.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Jirapatnakul A, Yip R, Branch AD, Yankelevitz DF, Henschke CI. Comparison of the extent and progression of respiratory and cardiovascular disease in World Trade Center responders to lung screening participants. medRxiv : the preprint server for health sciences. 2024.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	Sr/Key	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
AJIRAPATNAKUL	Y	Jirapatnakul, Artit	BS,MS,PHD	PD/PI	3.0	0.0	0.0			NA
CHENSCHKE	N	HENSCHKE, CLAUDIA	MD,PHD	Co-Investigator	0.6	0.0	0.0			NA
DYANKELEVITZ	N	YANKELEVITZ, DAVID F	MD	Co-Investigator	0.6	0.0	0.0			NA
ANDREA_D_BRANCH	N	BRANCH, ANDREA D.	PHD,MS	Co-Investigator	0.6	0.0	0.0			NA
JAGATNARULA	N	NARULA, JAGAT	MD,PHD	Co-Investigator	0.3	0.0	0.0			NA
YIP0001	N	Yip, Rowena	MPH	Statistician	3.0	0.0	0.0			NA
	N	Zhang, Jiafang	MS	Statistician	3.0	0.0	0.0			NA

Glossary of acronyms:
Sr/Key - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

We found that WTC responders have elevated measures of emphysema, interstitial lung disease, and coronary artery calcification on their initial CT scans compared to participants in a lung screening program. These scans were obtained a median time of 11 years after 9/11. The continued higher burden of disease supports the continued surveillance of WTC responders.

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND NOTICE OF FUNDING OPPORTUNITIES REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
CumulativeInclusionEnrollmentReport.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Long-term effects of WTC exposure on respiratory and cardiovascular diseases using automated CT imageanalysis

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	5	0	0	1	0	0	1	0	**7**
Asian	29	59	0	0	4	0	0	8	0	**100**
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	**0**
Black or African American	64	275	0	1	8	0	2	13	0	**363**
White	158	1,241	0	11	37	0	20	123	0	**1,590**
More Than One Race	4	34	0	167	376	0	5	28	0	**614**
Unknown or Not Reported	2	5	0	32	126	0	4	24	0	**193**
Total	**257**	**1,619**	**0**	**211**	**552**	**0**	**31**	**197**	**0**	**2,867**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015)

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OMB No. 0925-0001/0002
Cumulative Inclusion Enrollment Report

I. OUTCOMES

I.1 What were the outcomes of the award?

In this study, we utilized automated measures of respiratory and cardiovascular disease, specifically emphysema, interstitial lung disease, coronary artery calcification, and pulmonary hypertension to quantify the burden of disease in all available chest CT scans of members in the WTC GRC. We investigated whether these measures of disease showed any difference between the WTC GRC and a matched cohort of lung screening participants for extent and progression, as well as whether these were affected by different levels of WTC dust exposure, defined as when each member arrived at the WTC site.
We successfully analyzed CT scans of 2284 members of the WTC GRC for pulmonary disease and 1246 members for cardiac disease. We established a matched cohort of 557 lung screening participants that were matched on sex, smoking status, one or more CT scans, follow-up time, and age.

Using this dataset, we found that there was a significant difference in the amount of emphysema, interstitial lung disease, and coronary artery calcifications on the first available CT between members of the WTC GRC and the matched lung screening cohort – the members of the WTC GRC had higher burden of these three diseases. Many of the first available CT scans were over 10 years after 9/11, which further suggests that the increased burden of these diseases remains even after a long period of time. This supports the need for long-term health monitoring and sustained surveillance programs for WTC GRC members. We did not find a significant difference in the marker of pulmonary hypertension. We also did not find evidence that the progression of these diseases differed between the two groups.

Similarly, we did not find a significant association between the arrival time to the WTC site and any of the four markers of disease. The lack of disease progression differences, may suggest that factors beyond initial exposure may play a more critical role in long-term disease trajectory. More research is needed to fully understand the long-term health impacts of WTC dust exposures and the factors influencing disease progression.