A. OVERALL COVER PAGE

Project Title: Hepatotoxic Exposures, Progressive Fatty Liver Disease (NASH), and Liver Cancer Risk in the World Trade Center Health Program General Responder Cohort	
Grant Number: 5U01OH011489-04	**Project/Grant Period:** 07/01/2017 - 06/30/2021
Reporting Period: 07/01/2020 - 06/30/2021	**Requested Budget Period:** 07/01/2020 - 06/30/2021
Report Term Frequency: Final	**Date Submitted:** 11/17/2022
Program Director/Principal Investigator Information: ANDREA D BRANCH , PHD MS **Phone Number:** (212) 659-8371 **Email:** andrea.branch@mssm.edu	**Recipient Organization:** ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI 1 GUSTAVE L. LEVY PL NEW YORK, NY 100296574 **DUNS:** 078861598 **UEI:** C8H9CNG1VBD9 **EIN:** 1136171197A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: AMANDA AMESCUA One Gustave L. Levy Place, Box 1075 New York, NY 100296574 **Phone number:** 646-605-8659 **Email:** amanda.amescua@mssm.edu	**Signing Official:** AMANDA AMESCUA One Gustave L. Levy Place, Box 1075 New York, NY 100296574 **Phone number:** 646-605-8659 **Email:** amanda.amescua@mssm.edu
Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

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

SPECIFIC AIMS: Hepatotoxic Exposures, Progressive Fatty Liver Disease (NASH), and Liver Cancer Risk in the World Trade Center Health Program General Responder Cohort

Premise: Little is known about liver disease among responders to the World Trade Center (WTC) attack, although many were heavily exposed to dust, airborne particulate matter, and chemicals known to cause liver toxicity in other populations. Hepatotoxic exposures and hepatotoxins include particulate matter, air pollution, close proximity to major roadways and to toxic waste sites, exposure to active and passive smoking, and to volatile chemicals. Studies in animals confirm the hepatotoxic effects of airborne particulate matter (PM2.5) and chemicals. Toxic exposures provoke a series of intrahepatic changes. Injured hepatocytes and other liver cells release liver enzymes and proinflammatory cytokines; hepatocytes accumulate excess fat, leading to steatosis and oxidative stress; finally, hepatic stellate cells and other myofibroblasts increase collagen synthesis, producing scar (fibrosis). These changes can culminate in non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) that can lead to liver failure and liver cancer. Obesity, diabetes, smoking, exposure to air pollution, chemicals, and roadway toxins are risk factors for NAFLD/NASH. Importantly, about half of the patients with NASH who develop liver cancer do not have cirrhosis, which distinguishes them from patients with hepatitis C virus (HCV), for example, in whom liver cancer rarely develops in the absence of cirrhosis. Thus, WTC responders may face the life-threatening consequences of progressive fatty liver disease even if they do not have liver cirrhosis. This project addresses the need for a greater understanding of NASH and other progressive liver diseases in WTC responders.

Significance: Our Preliminary Results suggest that WTC exposure is a risk factor for liver steatosis. We discovered a high prevalence of excess liver fat serendipitously: Currently, WTC responders are not screened for liver disease, even though a previous study of WTC-exposed firefighters found NAFLD in 22%. The central premise of this project is that it is essential to screen for liver disease proactively among WTC responders because liver disease is often a silent killer that remains undiagnosed until irreversible damage has occurred. During the early and curable stages, many liver diseases are asymptomatic. Advanced liver disease can present catastrophically as metastatic liver cancer. This project provides the first systematic investigation of liver disease in the WTC general responder cohort (GRC). We expect to find that the WTC attack exposed responders to hepatotoxins and caused steatosis and scarring. Uncovering previously-unrecognized liver disease will allow WTC responders to be counseled and treated. Our project will also yield two innovative digital technologies, one to automate the calculation of liver fat; the other to efficiently analyze medical record data and identify liver disease, enhancing care by bringing (silent/unrecognized) liver disease to the attention of providers.

Aim I: The goal is to test the hypothesis that WTC exposure is a risk factor for liver disease by comparing GRC members (n=400) to a control group of non-responders (n=400) using multivariable linear regression to analyze liver fat (SubAim 1) and liver fibrosis (SubAim 2). Liver fat will be estimated using FibroScan-CAP scores and CT attenuation values; the correlation between these two methodologies will be analyzed (SubAim 3). The study has 90% power to detect a difference in the liver fat content between the two groups. WTC providers will be notified of high risk patients (those with both elevated fat and fibrosis), enhancing care.

Aim II: The goal is to develop innovative enabling technology to computationally estimate liver fat content from low-dose non-contrast chest CT images (SubAim 1), to apply this technology to existing images of 5000 GRC members (SubAim 2), and to use general linear models with pairwise comparisons to test the hypothesis that there is a linear dose-response relationship between the intensity of WTC exposure and liver fat (SubAim3).

Aim III: The goals are to determine the prevalence of and risk factors for advanced fibrosis/cirrhosis in the GRC (SubAim 1), to develop advanced medical informatics tools to computationally identify patients with NASH, HCV, and/or alcoholic liver disease (SubAim 2), to combine these tools with manual chart review to detect and analyze liver diseases, including liver cancer, among the estimated 2000 GRC members with in-depth medical, pharmaceutical, and claims data; and to provide feedback to providers, enhancing care (SubAim3). In response to recommendations by the review panel, the project will also include in vitro mechanistic studies of hepatotoxic exposures.

Impact: The project will yield unprecedented data about WTC exposure and liver disease; it will also generate enabling technology; and it is likely to uncover liver disease that has been overlooked, improving care.

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?

File Uploaded : 5U01OH011489 Accomphishments Final Report.pdf

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?

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

Findings were published in three peer-reviewed studies and at national and international meetings

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

Not Applicable

Abstract

This project is the first systematic investigation of liver disease in the Mount Sinai World Trade Center (WTC) General Responder Cohort (GRC). Currently, General Responders enrolled in the Mount Sinai WTC health program (WTCHP) are not screened for liver diseases, although they were heavily exposed to dust, airborne particulate matter, and chemicals known to cause liver toxicity in other populations. Studies in animals confirm the hepatotoxic effects of airborne particulate matter (PM2.5) and chemicals. Toxic exposures have been associated with non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) that can lead to liver failure and liver cancer. Toxicant-associated fatty liver disease (TAFLD) is an important type of NAFLD that is often associated with work place exposures to chemicals. This project addresses the need for a greater understanding of susceptibility factors for NASH and other progressive liver diseases in WTC General Responders. Because liver disease is often a silent killer that remains undiagnosed until irreversible damage has occurred, it is essential to screen for liver disease proactively. During the early and curable stages, many liver diseases are asymptomatic. Advanced liver disease can present catastrophically as metastatic liver cancer and/or liver failure. To achieve our long term goal of reducing liver-related morbidity and mortality among people exposed to the WTC attack, in this project, we developed and then applied two sets of innovative diagnostic tools, a computer algorithm to automatically detect hepatitis steatosis (excess liver fat) in chest CT images and a series of phenotyping algorithms to detect NASH/TAFLD, primary liver cancer, and hepatitis C virus infection based on electronic health record (EMR) data. We had five major findings: [1] The odds ratio for moderate-to-severe hepatic steatosis was 3.4-fold higher in members of the WTC GRC than in non-WTC participants in a propensity score analysis that used inverse probability weighting; [2] The novel automated method for measuring liver attenuation and thereby detecting hepatic steatosis was highly accurate and had almost perfect agreement with manual methods, validating its use in clinical care and research; [3] The phenotyping algorithms accurately identified patients with fatty liver disease, liver cancer, and hepatitis C virus infection and was successfully used to increase linkage to care; [4] The number of WTC GRC members with primary liver cancer is rising steeply, as expected in a population with a high prevalence of NAFLD/TAFLD and other liver diseases, heightening concern about the lack of systematic liver disease screening; and [5] There is a dose-response relationship between the intensity of exposure to the WTC dust cloud and the prevalence of hepatitis steatosis. This project produced valuable new diagnostic tools and revealed that liver disease is highly prevalent among WTC responders, paving the way for improved liver disease management in the future.

Section 1
Significant and Key Findings

Aim I: Determine whether exposure to the WTC dust cloud is a liver disease risk factor

To determine whether exposure to the WTC dust cloud is a liver disease risk factor, we determined the prevalence of moderate-to-severe hepatic steatosis (HS) and associated risk factors in members of the World Trade Center (WTC) General Responder Cohort (GRC) who qualified for low-dose non-contrast computed tomography for lung cancer screening and compared them to non-WTC participants in the same screening program. All participants gave written informed consent. Clinical variables and laboratory values were recorded. Hepatic attenuation in Hounsfield units (HU) was measured on low-dose computed tomography (LDCT) and a threshold attenuation value <40 HU indicated moderate-to-severe HS. Bivariate and multivariable linear and logistic regression analyses were performed. Propensity scores (PS) were calculated and inverse probability weighting (IPW) was used to adjust for potential confounders when comparing the WTC with non-WTC participants. The prevalence of moderate-to-severe HS was 16.2% among 154 WTC participants compared to 5.3% among 170 non-WTC participants. In WTC members, moderate-to-severe HS was associated with higher BMI, higher serum levels of liver enzymes, and former smoking status. Using PS analysis and IPW to account for potential confounders, the odds ratio for moderate-to-severe HS was 3.4-fold higher (95% confidence interval: 1.7–6.7) in the WTC participants compared with non-WTC participants. Moderate-to-severe HS was also associated with higher BMI and former smoker status. **Conclusion**: The prevalence of moderate-to-severe HS was over 3-fold higher in the WTC-GRC group than in other participants.

Aim II: Develop innovative technology a) to automatically detect liver steatosis in chest CT scans and b) to automatically identify fatty liver disease and liver cancer based on medical record data and information from the Mount Sinai WTCHP General Responder Data Center

a) In order to detect liver steatosis using digital data in chest CT scans, we developed a computer program that automatically identifies a region below the right lung within the liver and uses statistical sampling techniques to exclude non-liver parenchyma. Agreement between the manual and automated CT methods, the manual MRI method, and pathology for determining moderate-to-severe HS was assessed using Cohen's Kappa by applying a 40 HU threshold to the CT method and 17.4% fat fraction to MRI. Agreement between the manual and automated CT methods was assessed using the intraclass correlation coefficient (ICC). Variability was assessed using Bland-Altman limits of agreement (LoA). The automated method for detecting liver steatosis was validated in a step-wise manner. First, the manual and automated CT methods were compared to each other and found to have almost perfect agreement (ICC = 0.97, $\kappa = 1.00$) with LoA of −7.6 to 4.7 HU. Then both manual and automated CT methods were compared to manual MRI and found to have almost perfect agreement with MRI ($\kappa = 0.90$) and substantial agreement with pathology ($\kappa = 0.77$), indicating that automated measurements of liver attenuation from LDCT scans can be used to identify moderate-to severe hepatic steatosis in chest CT scans.

b) In order to identify WTC responders with fatty liver, liver cancer, and chronic HCV infection based on medical record data, we developed phenotyping algorithms. The algorithm for NASH/TAFLD identified patients with liver disease based on persistent ALT elevation or ICD codes for chronic non-specific or non-alcoholic liver disease (ICD-9: 571.5, 571.8, 571.9; ICD-10: K75.81, K76.0, K76.9). Persistent ALT elevation was defined as two or more instances of ALT ≥ 40 IU/mL for men, or ≥ 31 IU/mL for women in the ambulatory setting, more than six months apart. Then, we excluded patients with viral hepatitis, alcoholic liver disease, or other chronic liver disease. These conditions were identified via ICD codes, as enumerated in the eMerge algorithm. Next, we excluded patients on steatogenic medications (defined in eMerge). Finally, patients with evidence of hepatic steatosis on imaging, biopsy, or documented in a clinical note were identified using natural language processing (NLP) to identify reports of hepatic steatosis and related terms. The algorithm for primary liver cancer used a combination of ICD-9 or ICD-10 codes for primary liver cancer and also identified patients with terms related to liver cancer in clinical notes, radiology reports, or pathology reports. NPL steps are used to remove negative cases (e.g., "absence of liver cancer"). To identify patients from whom liver tissue was removed (as a result of either biopsy or surgery), pathology reports are automatically parsed for terms related to liver specimens by using SQL queries to find this information in an Oracle EHR database. We used this algorithm to identify liver cancer cases among the WTC GRC. The digital phenotyping algorithm for hepatitis C infection uses Java and structured query language (SQL). The algorithm recognizes all U.S. Food and Drug Administration–approved HCV-RNA tests recorded in Mount Sinai's EPIC and/or Soft Computer Corporation (SCC) clinical laboratory records, all drugs used to treat HCV, and all International Classification of Diseases

(ICD)-9/10 codes for HCV infection (B17.10, B17.11, B18.2, B19.10, B19.20, B19.21, K73.2, K74.60, K74.69, R76.8, and Z86.19). It uses natural language processing, accesses the Mount Sinai death registry, calculates Fibrosis-4 (FIB-4) scores, and infers HCV status using serial alanine aminotransferase (ALT) measurements. The algorithm's positive and negative predictive values were 88% and 97%, respectively, for identifying and correctly classifying patients whose medical record contained information about HCV status, as determined by manual review of 500 EMRs. **Conclusion**: The excellent performance characteristic of the two new sets of diagnostic tools validate their use in clinical care and in research.

Aim III: Determine the prevalence of liver fibrosis in WTC GRC members and identify risk factors:

To identify risk factors for liver disease in WTC GRC members, we first evaluated the dose-response relationship between WTC dust exposure and hepatic steatosis. All low dose non-contract CT scans of the chest performed on the WTC GRC between September 11, 2001 and December 31st, 2018, collected as part of the WTCHP, were reviewed. The intensity of WTC dust exposure was categorized into five groups based on WTC arrival time. We analyzed the earliest low-dose chest CT scans performed on WTC GRC members (2003-2018) as part of the WTCHP who had laboratory test data. CT liver attenuation was determined using the computer algorithm described in Aim II, which was developed as part of this project. The dose-response relationship between the intensity of exposure to WTC dust and the risk of moderate-to-severe liver steatosis was evaluated using linear regression, Janckheere-Terpstra, Cochran-Armitage or Cochran-Mantel-Haenszel trend tests. General linear models were used to compare the mean liver attenuation between exposure groups, adjusting for sex, age on September 11, race, smoking status, BMI, alcohol use, diabetes, GERD and forced expiratory volume in 1 second (FEV_1).

Of the1788 WTC responders, 258 (14.4%) had liver attenuation HU < 40 on their earliest CT. Median time after 9/11/01 and the earliest available CT was 11.3 years (IQR: 8.0-14.9 years). The prevalence of liver attenuation < 40 HU was 17.0% for arrivals on 9/11/01, 16.0% for arrivals on (9/12/01 or 9/13/01), 10.9% for arrivals on 9/14/01-9/30/01, and 9.0% for arrivals on 10/1/01 or later (p=0.0015). A statistically significant trend of increasing liver steatosis was observed with earlier arrival times (p<0.0001). WTC arrival time remained a significant independent factor for decreased liver attenuation after controlling for other covariates. **Conclusion**: Early arrival at the WTC site was significantly associated with increasing hepatic steatosis.

To further investigate risk factors for liver fibrosis in WTC GRC members, we selected a group of 7493 members of the WTC GRC who could be matched 1:1 to members of the National Health and Nutrition Evaluation Survey (NHANES), a nationally-representative cohort, on age, sex, and race/ethnicity. Advanced liver fibrosis was defined as a Fibrosis-4 (FIB-4) score ≥ 2.67 and an ALT value above the upper limit of normal. The prevalence of advanced liver fibrosis in WTC responders was 1.4%. In a multivariable logistic regression analysis, advanced liver fibrosis among WTC responders was associated with older age, male sex, missing data about alcohol consumption and reduced pulmonary function. There was a strong trend toward higher risk for non-Hispanic Black persons compared to non-Hispanic White persons (odds ratio = 1.65, p = 0.06). Diabetes was not a risk factor. Among the NHANES cohort, advanced liver fibrosis was associated with older age, male sex, alcohol use, diabetes, and non-Mexican American Hispanic ethnicity; however, reduced pulmonary function was not a risk factor. **Conclusion**: These findings suggest that exposure to WTC dust, by impairing pulmonary function, may contribute to liver injury particularly in non-Hispanic Black persons.

Translation of Findings: This project increased awareness of the liver disease risk associated with exposure to the WTC attack. The WTCHP is initiating a program to flag General Responders with elevated FIB-4 scores.

Research Outcomes/Impact

The project established that liver disease is highly prevalent among the WTC General Responder cohort and provided two new sets of tools for detecting liver disease. This project raised awareness of the liver disease risk associated with exposure to the WTC dust cloud and GRC responders are now being screened for liver fibrosis using the FIB-4 score. Fifty-three cases of liver cancer were found in GRC responders and the number of cases is expected to rise. As part of a subsequent NIOSH project, these cases are being investigated in detail. In Summary: This project produced valuable new diagnostic tools and revealed that liver disease is highly prevalent among WTC responders, paving the way for improved liver disease management in the future.

Background:

This project is the first systematic investigation of liver disease in the World Trade Center (WTC) general responder cohort (GRC). Currently, WTC responders are not screened for liver diseases, although they were heavily exposed to dust, airborne particulate matter, and chemicals known to cause liver toxicity in other populations. Studies in animals confirm the hepatotoxic effects of airborne particulate matter (PM2.5) and chemicals. Toxic exposures have been associated with non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) that can lead to liver failure and liver cancer. Toxicant-associated fatty liver disease (TAFLD) is an important type of NAFLD. This project addresses the need for a greater understanding of NASH and other progressive liver diseases in WTC responders. Because liver disease is often a silent killer that remains undiagnosed until irreversible damage has occurred, it is essential to screen for liver disease proactively. During the early and curable stages, many liver diseases are asymptomatic. Advanced liver disease can present catastrophically as metastatic liver cancer. We expect to find that the WTC attack exposed responders to hepatotoxins and caused steatosis and fibrosis. Uncovering previously unrecognized liver disease will allow WTC responders to be diagnosed and treated.

Methods:

To detect liver steatosis using digital data in chest CT scans, we developed a computer program that identifies a region below the right lung within the liver and uses statistical sampling techniques to exclude non-liver parenchyma. Agreement between the manual and automated CT methods, the manual MRI method, and pathology for determining moderate-to-severe HS was assessed using Cohen's Kappa by applying a 40 HU threshold to the CT method and 17.4% fat fraction to MRI. Agreement between the manual and automated CT methods was assessed using the intraclass correlation coefficient (ICC). Variability was assessed using Bland-Altman limits of agreement (LoA).

In order to identify WTC responders with fatty liver and liver cancer based on medical record data, we developed phenotyping algorithms. The algorithm identified patients with liver disease based on persistent ALT elevation or ICD codes for chronic non-specific or non-alcoholic liver disease (ICD-9: 571.5, 571.8, 571.9; ICD-10: K75.81, K76.0, K76.9). Persistent ALT elevation was defined as two or more instances of ALT ≥ 40 IU/mL for men, or ≥ 31 IU/mL for women in the ambulatory setting, more than six months apart. Then, we excluded patients with viral hepatitis, alcoholic liver disease, or other chronic liver disease. These conditions were identified via ICD codes, as enumerated in the eMerge algorithm. Viral hepatitis cases were also identified using lab values (HBV surface antigen, HCV RNA). Next, we excluded patients on steatogenic medications (defined in eMerge). Finally, patients with evidence of hepatic steatosis on imaging, biopsy, or documented in a clinical note were identified using natural language processing (NLP) to identify reports of hepatic steatosis and related terms and/or reports of liver cancer.

To determine the dose-response relationship between WTC dust exposure and hepatic steatosis, all low dose non-contract CT scans of the chest performed on the WTC GRC between September 11, 2001 and December 31st, 2018, collected as part of the World Trade Center Health Program (WTCHP), were reviewed. WTC dust exposure was categorized into 5 groups based on WTC arrival time. CT liver density was estimated using an automated algorithm developed as part of this project. The relationship between the intensity of WTC dust exposure and risk of hepatic steatosis was examined using univariate and multivariable regression analyses.

To determine the prevalence of advanced liver fibrosis and the factors associated with advanced liver fibrosis, data were obtained from the National Health and Nutrition Evaluation Survey (NHANES) for nationally-representative data and from the WTC data collection and Mount Sinai electronic medical records (EMRs) for WTC-specific information. Advanced liver fibrosis was defined as a Fibrosis-4 (FIB-4) score ≥ 2.67.

Results:

The automated method for detecting liver steatosis was validated in a step-wise manner. First, the manual and automated CT methods were compared to each other and found to have almost perfect agreement (ICC = 0.97, κ = 1.00) with LoA of −7.6 to 4.7 HU. Then both manual and automated CT methods were compared to manual MRI and found to have almost perfect agreement with MRI (κ = 0.90) and substantial agreement with pathology (κ = 0.77), leading to the conclusion that automated measurements of liver attenuation from LDCT scans can be used to identify moderate-to severe hepatic steatosis in chest CT scans

Of the 1788 WTC responders, 258 (14.4%) had liver attenuation HU < 40 on their earliest CT. Median time after 9/11/01 and the earliest available CT was 11.3 years (IQR: 8.0-14.9 years). The prevalence of liver attenuation < 40 HU was 17.0% for arrivals on 9/11/01, 16.0% for arrivals on (9/12/01 or 9/13/01), 10.9% for arrivals on 9/14/01-9/30/01, and 9.0% for arrivals on 10/1/01 or later (p=0.0015). A statistically significant trend of increasing liver steatosis was observed with earlier arrival times (p<0.0001). WTC arrival time remained a significant independent factor for decreased liver attenuation after controlling for other covariates.

The phenotyping algorithm for liver cancer identified 38 cases for review. Of these, 26 were confirmed: 23 were hepatocellular carcinoma (HCC) and three were intrahepatic cholangiocarcinoma. The other 12 were mostly non-liver cancer cases that were picked up by the algorithm because of mis-coding. The Mount Sinai Cancer registry identified two additional cases. With funding from U01 OH012263, the verified cases of primary liver cancer (and additional cases identified through up-dated searches) will be analyzed by Dr. M-Isabel Fiel, the study pathologist. She will use the modified Knodell/Ishak system to evaluate necroinflammation [histology activity index (HAI)] (scale, 0-18) and fibrosis stage (scale, 0-6); the Brunt system will be used to score steatosis and steatohepatitis (scales, 0-3). Additional features, e.g., sinusoidal dilatation, will be recorded. Immunohistochemistry will be used to identify cell types and proteins. Quantitative morphometry will be performed using computerized Life Science morphometry system (BIOQUANT) on 10 or 20 images per specimen. Both tumor and non-tumor tissues will be examined. Dr. Fiel will use her extensive experience to compare the WTC specimens to those of patients with other known liver diseases.

A group of 7493 members of the WTC GRC were identified who could be matched 1:1 to members of the NHANES cohort on age, sex, and race/ethnicity. Among this group, the prevalence of advanced liver fibrosis in WTC responders was 1.4%. In a multivariable logistic regression analysis, advanced liver fibrosis among WTC responders was associated with older age, male sex, missing data about alcohol consumption and reduced pulmonary function. There was a strong trend toward higher risk for non-Hispanic Black persons compared to non-Hispanic White persons (odds ratio = 1.65, p = 0.06). Diabetes was not a risk factor. Among the NHANES cohort, advanced liver fibrosis was associated with older age, male sex, alcohol use, diabetes, and non-Mexican American Hispanic ethnicity; however, reduced pulmonary function was not a

risk factor. These findings suggest that exposure to WTC dust, by impairing pulmonary function, may contribute to liver injury particularly in non-Hispanic Black persons

The research led to five publications in peer-reviewed journals

1. 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* (2019), doi: https://doi.org/10.1016/j.ejrad.2019.108723 [Epub ahead of print]

2. Chen X, Ma T, Yip R, Perumalswami PV, Branch AD, Lewis S, Crane M, Yankelevitz DF and Henschke CI. Elevated prevalence of moderate-to-severe hepatic steatosis in World Trade Center General Responder Cohort in a program of CT lung screening. *Clinical Imaging*.
2019. https://doi.org/10.1016/j.clinimag.2019.12.009

3. Vandromme M, Jun T, Perumalswami PV, Dudley JT, Branch AD, Li L. Automated phenotyping of patients with non-alcoholic fatty liver disease reveals clinically relevant disease subtypes. *Pacific Symposium on Biocomputing* (PSB 2020). 91-102 (2019), https://doi.org/10.1142/9789811215636_0009

4. Artit Jirapatnakul, Rowena Yip, Andrea.D Bracnh, Sara Lewis, Michael Crane, David F. Yankelevitz, Claudia Henschle, “Dose-response relationship between World Trade Center dust exposure and hepatic steatosis”.american Journal of Industrial Medicine, 20121

5. Brooke Wyatt, Ponni V. Perumalswami, Anna Mageras, Mark Miller,Alyson Harty, Ning Ma, Chip A. Bowman, Francina Collado, Jihae Jeon, Lismeiry Paulino, Amreen Dinani, Douglas Dieterich, Li Li, Maxence Vandromme and Andrea D. Branch, “A Digital Case-Finding Algorithm for Diagnosed but Untreated Hepatitis C: A Tool for Increasing Linkage to Treatment and Care,” Hepatology,74 2974-2987.

Findings were presented at four national and international meetings

1. 4/2019: “Hepatotoxic Exposures, Progressive Fatty Liver Disease, and Liver Cancer Risk in the WTC Health Program General Responder Cohort,” American Occupational Health Conference 2019, Anaheim, CA

2. 9/2019: “Opportunistic Findings in Low-dose Non-contrast Chest CT Images,” 2019 World Conference on Lung Cancer, Barceloma, Spain

3. 11/2019: AD Branch, Rowena Yip, **Maxence Vandromme**, Brooke Wyatt, Ms. Clara Rodriguez Rivas, Leore Lavin, Mark Miller, **Amreen M Dinani**, Amon Asharpour, Priya Grewal, Thomas D Schiano, M. Isabel Fiel, Myron E Schwartz, Douglas T Dieterich, David F. Yankelevitz, Anthony Reeves, Joel Dudley, Li Li, Michael Crane, Sara Lewis, Artit

Jirapatnakul, Ponni V Perumalswami and Claudia Henschke, "Evidence of toxicant-associated fatty liver disease in responders to the world trade center attack, American Association for the Study of Liver Disease, Boston, MA.

4. 7/2022: "A Digital Case-Finding Algorithm for Diagnosed but Untreated Hepatitis C: A Tool for Increasing Linkage to Treatment and Care," 2022 EASL Conference London England

Opportunities for Development
Graduate Students:
IDPs are mandatory for all graduate students (PhDs). All second and fourth year students are expected to fill out an IDP as a prelude to discussing their career plans in a formal graduate school setting as well as with their advisor.

C. OVERALL 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, Lewis S, Crane M, Yankelevitz DF, Henschke CI. Dose-response relationship between World Trade Center dust exposure and hepatic steatosis. American journal of industrial medicine. 2021 October;64(10):837-844. PubMed PMID: 34328231; DOI: 10.1002/ajim.23269.
N/A: Not NIH Funded	Wyatt B, Perumalswami PV, Mageras A, Miller M, Harty A, Ma N, Bowman CA, Collado F, Jeon J, Paulino L, Dinani A, Dieterich D, Li L, Vandromme M, Branch AD. A Digital Case-Finding Algorithm for Diagnosed but Untreated Hepatitis C: A Tool for Increasing Linkage to Treatment and Cure. Hepatology (Baltimore, Md.). 2021 December;74(6):2974-2987. PubMed PMID: 34333777; PubMed Central PMCID: PMC9299620; DOI: 10.1002/hep.32086.

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. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
ANDREA_D_BRANCH	Y	BRANCH, ANDREA D.	MS,PHD	PD/PI	6.0	0.0	0.0			NA
EDOYLE01	N	Doyle, Erin	BA,PHD	Graduate Student (research assistant)	12.0	0.0	0.0			NA
AJIRAPATNAKUL	N	Jirapatnakul, Artit	PHD,MS,BS	Co-Investigator	1.0	0.0	0.0			NA
LI___LI	N	LI, LI	MD/PhD	Co-Investigator	1.0	0.0	0.0			NA
SARALEWIS	N	Lewis, Sara Ann	PHD,BS	Co-Investigator	1.0	0.0	0.0			NA
	N	Yip, Rowena	MS	Statistician	2.0	0.0	0.0			NA
	N	Miller, Mark	RN	Coordinator	2.0	0.0	0.0			NA

Glossary of acronyms:
S/K - 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. OVERALL 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?

NOTHING TO REPORT

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. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT 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

NOTHING TO REPORT

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

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

Background:
This project is the first systematic investigation of liver disease in the World Trade Center (WTC) general responder cohort (GRC). Currently, WTC responders are not screened for liver diseases, although they were heavily exposed to dust, airborne particulate matter, and chemicals known to cause liver toxicity in other populations. Studies in animals confirm the hepatotoxic effects of airborne particulate matter (PM2.5) and chemicals. Toxic exposures have been associated with non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) that can lead to liver failure and liver cancer. Toxicant-associated fatty liver disease (TAFLD) is an important type of NAFLD. This project addresses the need for a greater understanding of NASH and other progressive liver diseases in WTC responders. Because liver disease is often a silent killer that remains undiagnosed until irreversible damage has occurred, it is essential to screen for liver disease proactively. During the early and curable stages, many liver diseases are asymptomatic. Advanced liver disease can present catastrophically as metastatic liver cancer. We expect to find that the WTC attack exposed responders to hepatotoxins and caused steatosis and fibrosis. Uncovering previously unrecognized liver disease will allow WTC responders to be diagnosed and treated.

Methods:
To detect liver steatosis using digital data in chest CT scans, we developed a computer program that identifies a region below the right lung within the liver and uses statistical sampling techniques to exclude non-liver parenchyma. Agreement between the manual and automated CT methods, the manual MRI method, and pathology for determining moderate-to-severe HS was assessed using Cohen's Kappa by applying a 40 HU threshold to the CT method and 17.4% fat fraction to MRI. Agreement between the manual and automated CT methods was assessed using the intraclass correlation coefficient (ICC). Variability was assessed using Bland-Altman limits of agreement (LoA).

In order to identify WTC responders with fatty liver and liver cancer based on medical record data, we developed phenotyping algorithms. The algorithm identified patients with liver disease based on persistent ALT elevation or ICD codes for chronic non-specific or non-alcoholic liver disease (ICD-9: 571.5, 571.8, 571.9; ICD-10: K75.81, K76.0, K76.9). Persistent ALT elevation was defined as two or more instances of ALT ≥ 40 IU/mL for men, or ≥ 31 IU/mL for women in the ambulatory setting, more than six months apart. Then, we excluded patients with viral hepatitis, alcoholic liver disease, or other chronic liver disease. These conditions were identified via ICD codes, as enumerated in the eMerge algorithm. Viral hepatitis cases were also identified using lab values (HBV surface antigen, HCV RNA). Next, we excluded patients on steatogenic medications (defined in eMerge). Finally, patients with evidence of hepatic steatosis on imaging, biopsy, or documented in a clinical note were identified using natural language processing (NLP) to identify reports of hepatic steatosis and related terms and/or reports of liver cancer.

To determine the dose-response relationship between WTC dust exposure and hepatic steatosis, all low dose non-contract CT scans of the chest performed on the WTC GRC between September 11, 2001 and December 31st, 2018, collected as part of the World Trade Center Health Program (WTCHP), were reviewed. WTC dust exposure was categorized into 5 groups based on WTC arrival time. CT liver density was estimated using an automated algorithm developed as part of this project. The relationship between the intensity of WTC dust exposure and risk of hepatic steatosis was examined using univariate and multivariable regression analyses.

To determine the prevalence of advanced liver fibrosis and the factors associated with advanced liver fibrosis, data were obtained from the National Health and Nutrition Evaluation Survey (NHANES) for nationally-representative data and from the WTC data collection and Mount Sinai electronic medical records (EMRs) for WTC-specific information. Advanced liver fibrosis was defined as a Fibrosis-4 (FIB-4) score ≥ 2.67.

Results:

The automated method for detecting liver steatosis was validated in a step-wise manner. First, the manual and automated CT methods were compared to each other and found to have almost perfect agreement (ICC = 0.97, κ = 1.00) with LoA of −7.6 to 4.7 HU. Then both manual and automated CT methods were compared to manual MRI and found to have almost perfect agreement with MRI (κ = 0.90) and substantial agreement with pathology (κ = 0.77), leading to the conclusion that automated measurements of liver attenuation from LDCT scans can be used to identify moderate-to severe hepatic steatosis in chest CT scans

Of the 1788 WTC responders, 258 (14.4%) had liver attenuation HU < 40 on their earliest CT. Median time after 9/11/01 and the earliest available CT was 11.3 years (IQR: 8.0-14.9 years). The prevalence of liver attenuation < 40 HU was 17.0% for arrivals on 9/11/01, 16.0% for arrivals on (9/12/01 or 9/13/01), 10.9% for arrivals on 9/14/01-9/30/01, and 9.0% for arrivals on 10/1/01 or later (p=0.0015). A statistically significant trend of increasing liver steatosis was observed with earlier arrival times (p<0.0001). WTC arrival time remained a significant independent factor for decreased liver attenuation after controlling for other covariates.

The phenotyping algorithm for liver cancer identified 38 cases for review. Of these, 26 were confirmed: 23 were hepatocellular carcinoma (HCC) and three were intrahepatic cholangiocarcinoma. The other 12 were mostly non-liver cancer cases that were picked up by the algorithm because of mis-coding. The Mount Sinai Cancer registry identified two additional cases. With funding from U01 OH012263, the verified cases of primary liver cancer (and additional cases identified through up-dated searches) will be analyzed by Dr. M-Isabel Fiel, the study pathologist. She will use the modified Knodell/Ishak system to evaluate necroinflammation [histology activity index (HAI)] (scale, 0-18) and fibrosis stage (scale, 0-6); the Brunt system will be used to score steatosis and steatohepatitis (scales, 0-3). Additional features, e.g., sinusoidal dilatation, will be recorded. Immunohistochemistry will be used to identify cell types and proteins. Quantitative morphometry will be performed using computerized Life Science morphometry system (BIOQUANT) on 10 or 20 images per specimen. Both tumor and non-tumor tissues will be examined. Dr. Fiel will use her extensive experience to compare the WTC specimens to those of patients with other known liver diseases.

A group of 7493 members of the WTC GRC were identified who could be matched 1:1 to members of the NHANES cohort on age, sex, and race/ethnicity. Among this group, the prevalence of advanced liver fibrosis in WTC responders was 1.4%. In a multivariable logistic regression analysis, advanced liver fibrosis among WTC responders was associated with older age, male sex, missing data about alcohol consumption and reduced pulmonary function. There was a strong trend toward higher risk for non-Hispanic Black persons compared to non-Hispanic White persons (odds ratio = 1.65, p = 0.06). Diabetes was not a risk factor. Among the NHANES cohort, advanced liver fibrosis was associated with older age, male sex, alcohol use, diabetes, and non-Mexican American Hispanic ethnicity; however, reduced pulmonary function was not a risk factor. These findings suggest that exposure to WTC dust, by impairing pulmonary function, may contribute to liver injury particularly in non-Hispanic Black persons