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# Elevated Prevalence of Moderate-to-Severe Hepatic Steatosis in World Trade Center General Responder Cohort in a Program of CT Lung Screening

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a) conception or design of the work: XC, CH, DY
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Potential conflict of interest:
• Dr. Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. He is also an equity owner in Accumetra, a privately held technology company committed to improving the science and practice of image-based decision making (7 Corporate Drive, Clifton Park, NY 12065; Tel: 518-280-7530; http://accumetra.com/). Dr. Yankelevitz also serves on the advisory board of GRAIL (1525 O'Brien Drive, Menlo Park, CA 94025; Tel: 650-542-0372; https://grail.com/).
• Dr. Henschke is the President and serves on the board of the Early Diagnosis and Treatment Research Foundation. She receives no compensation from the Foundation. The Foundation is established to provide grants for projects, conferences, and public databases for research on early diagnosis and treatment of diseases. Dr. Claudia Henschke is also a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest which are owned by Cornell Research Foundation (CRF). Since 2009, Dr. Henschke does not accept any financial benefit from these patents including royalties and any other proceeds related to the patents or patent applications owned by CRF.

**Institution and Ethics approval and informed consent:** This work was performed at the Icahn School of Medicine at Mount Sinai in New York, NY. We reviewed baseline LDCT scans of the chest of all WTC participants who qualified for and participated in the National Institute of Occupational Safety and Health (NIOSH)-approved early lung cancer screening program between Feb 2016-Jan 2017. Written informed consent was obtained according to a HIPAA-compliant protocol approved by the Icahn School of Medicine at Mount Sinai IRB.

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## Abstract

**Background and aims—**To determine 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 qualify for low-dose non-contrast computed tomography for lung cancer screening and compare them to non-WTC participants in the same screening program.

**Methods—**All participants gave written informed consent before participating in this IRB-approved study. Clinical variables and laboratory values were recorded. Hepatic attenuation measurement (Hounsfield unit; HU) was measured on low-dose computed tomography (LDCT) and a threshold attenuation value <40HU 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.

**Results—**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 laboratory liver function tests, 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—**Prevalence of moderate-to-severe HS was more than 3-fold higher in the WTC-GRC group than in other participants.



### Keywords

liver attenuation; CT screening; liver disease; airborne particulate matter


## Introduction

Liver disease can be a silent killer that produces few early symptoms. A common cause of liver disease worldwide is nonalcoholic fatty liver disease (NAFLD). In the US, prevalence estimates that are expected to rise through 2030 [1]. NAFLD spans the spectrum of simple hepatic steatosis (HS) to steatohepatitis, and can result in the development of liver fibrosis, cirrhosis and hepatocellular carcinoma [2]. Computed tomography (CT) has a high sensitivity and specificity for detecting moderate-to-severe HS [3], defined histologically by the presence of macrovesicular fat affecting at least 30% of hepatocytes. By reporting HS, radiologists can significantly increase the likelihood that a patient will receive follow-up testing for liver disease [4].

Fat reduces the attenuation value of the liver on CT, as measured by Hounsfield Unit (HU), with a threshold value of 40HU commonly used to detect HS [5–7]. Using this threshold value, 6.2% of individuals in a colon cancer screening program had moderate-to-severe HS [8]. A recent study of 170 individuals in a low-dose CT (LDCT) lung screening program in New York City, using the same threshold value, reported that 5.3% of participants had moderate-to-severe HS [9].

The World Trade Center (WTC) attack resulted in the exposure of over 20,000 responders to dust, airborne particulate matter, and chemicals known to cause hepatotoxicity [10–14]. A previous study of WTC-exposed firefighters found moderate-to-severe steatosis in 22% [15]. Because CT screening is approved for WTC General Responder Cohort (GRC) participants who meet the age and smoking history criteria, there was a two-fold purpose for this study: 1) to determine the prevalence of moderate-to-severe HS and associated risk factors in members of the WTC undergoing LDCT screening for lung cancer in a National Institute of Occupational Health(NIOSH)-approved program and 2) to compare the prevalence of HS in the WTC to non-WTC participants in the same screening program.

## Materials and Methods

### Participants

We reviewed baseline LDCT scans of the chest of all WTC participants who qualified for and participated in the National Institute of Occupational Safety and Health (NIOSH)-approved early lung cancer screening program between 2/2016–1/2017. Written informed consent was obtained according to a HIPAA-compliant protocol approved by the Mount Sinai IRB. Entry criteria were 55 to 77 years of age, a smoking history of ≥30 pack-years, and being either current smokers or quit within the last 15 years. The participants were interviewed at the time of the CT scan by a coordinator who obtained data on demographics, smoking history, height, weight, and body mass index (BMI) data. Self-reported medical comorbidities of diabetes, chronic obstructive pulmonary disease(COPD)/emphysema, and hypertension were recorded. Clinical laboratory values of aspartate aminotransferase(AST), alanine aminotransferase(ALT), and platelets were obtained from the WTC data center. The date of these tests ranged from 11 months before CT to one month after CT. The Fibrosis-4 (FIB-4) score, an indicator of hepatic fibrosis stage that takes into account age, AST, ALT and platelet levels, was calculated [16].

The prevalence of HS in the WTC participants was compared to the previously reported prevalence of 170 non-WTC current and former smokers who had participated in the same screening program between 8/2011–4/2016, had the same documentation of their background information, but different entry criteria [9]. The non-WTC participants were asymptomatic ever-smokers, aged 40 or older while the WTC participants were asymptomatic ever-smokers, aged 55 to 78 with at least 30 pack-years of smoking who were currently smoking or had quit within the 15 years of enrollment. Considerations of the differences in entry criteria is addressed in the statistical analysis paragraph.

### CT imaging acquisition

All WTC and non-WTC participants underwent LDCT in the supine position in a single breath-hold without intravenous contrast. The scanning field of view spanned from the lung apices to the level of the adrenal glands. 148 WTC participants had CT performed on

Siemens Somatom Definition Flash CT (120 kVp, 35–85mA, images reconstructed at 0.5-mm and 3.0-mm axial slice thickness) and 6 WTC participants were scanned on GE Medical Systems Revolution CT (120kVp, 52–58mA, images reconstructed at 0.625-mm and 2.5-mm axial slice thickness).

## Liver CT attenuation measurement

Using the same accepted methodology previously described [9,17], liver attenuation(HU) was measured at the level of the portal vein in four sectors as defined by the Couinaud system (Figure 1) [17]. In each sector, a 1.0cm$^2$ region of interest(ROI) was selected, avoiding lesions and large blood vessels. Using standard window settings (width 350HU; level 25HU) [9], the average liver attenuation, standard deviation(SD) and quartile measurements were calculated.

## Other CT-derived data

The presence of emphysema was documented on each CT scan [18]. The Ordinal Score for coronary artery calcifications(CAC) was determined [19] and a total Ordinal CAC Score(0 to 12), representing the sum of the CAC scores for each of the coronary arteries, was calculated. The Ordinal CAC Scores were divided into three categories of increasing disease severity(0, 1–3, and 4–12), as these were predictive of death from cardiovascular disease [19,20].

## Statistical analysis of the WTC participants

Frequencies and descriptive statistics were obtained for all the variables. For continuous variables, histograms and Kolmogorov-Smirnov test were used to test for violation of the normality assumption. Bivariate and multivariable linear regression analyses were used to explore the relationship between liver attenuation and risk factors such as age, gender, diabetes, hypertension, COPD, cardiovascular diseases (CVD), and baseline CT findings of CAC and emphysema. Only factors with P-values≤0.10 in the bivariate model were retained in the multivariable model. Pairwise correlations among variables were computed using Pearson correlations coefficients(r) and multicollinearity was assessed with variance inflation factors(VIF). Potential two-way interactions between smoking, gender, and BMI on CT attenuation of the liver were assessed. Interactions were assessed by adding the interaction terms to the regression model with main effects and covariates, interaction term with p-value<0.05 was considered as significant. Coefficient estimates with and without the interaction term were compared and interaction plots were also used to visualize the presence or absence of interactions among independent variables. Presence of a significant interaction indicates that the effect of one covariate on HS is different at different values of the other covariate. Probability and residual plots were used to detect violation of normality, homoscedasticity and independent errors assumptions. Liver attenuation values were then classified into one of two categories (liver attenuation <40HU or ≥40HU). The difference in the distribution of demographic and clinical characteristics was evaluated by t-test or nonparametric Kruskal Wallis test. For categorical variables, Chi-squared and Fisher's exact test were used.

### Statistical comparison of WTC and non-WTC participants

To address the differences of the WTC and non-WTC participants, propensity score(PS) were calculated for each participant. For this comparison, PS was calculated using multiple logistic regression with the cohort assignment as the dependent variable (1 for WTC-GRC; 0 for non-WTC). The explanatory variables were all measured covariates available for both groups [age, gender, smoking status, pack-years, race, BMI, self-reported comorbidities of diabetes, hypertension, COPD]. The PS represents the probability of being a member of the WTC cohort, conditional on all the covariates used in the PS analysis. Covariate balance was examined by weighted Wilcoxon rank sum and weighted chi-square test. Inverse probability weighting(IPW) was then performed. To investigate the effect of cohort membership on liver attenuation, IPW adjusted odds ratio(OR) for the risk of liver attenuation<40HU in the WTC cohort as compared with the comparison group was calculated using a multiple logistic regression in the weighted sample, additionally controlling for CAC score and presence of emphysema on CT. In a separate analysis, multivariable logistic regression was used to identify factors significantly associated with liver attenuation<40HU in the WTC cohort, as described above. All statistical analyses were performed using SAS (Statistical Analysis System, version 9.4, Cary, NC).

## Results

### WTC participants

Of the 154 WTC participants, 85.7% (n=132) were men and 66% (n=102) were Caucasian (Table 1). Diabetes, COPD and hypertension were self-reported by 29 (20%), 41 (30%) and 81 (57%) subjects. Liver attenuation values ranged from 17.6–68.2 HU (Figure 2), with a mean±standard deviation (SD) of 52.7±11.1 HU. The prevalence of moderate-to-severe HS, using the cutoff of <40 HU, was 16.2% (25/154). The participants with <40HU had a higher percentage of former smokers, a lower percentage with CT-confirmed emphysema, higher BMI, AST, ALT, and higher percentage with transaminase values above the ULN (Upper limit normal). Bivariate linear regression showed that lower liver CT attenuation was associated with being a former smoker (p=0.047), more pack-years of smoking(p=0.003), higher BMI (p<0.0001), self-reported diabetes (p=0.047) and hypertension(p=0.03), higher CAC score (p=0.02) and the absence of emphysema (p=0.01) (Table 2). When these variables were considered simultaneously in the multivariable linear regression, lower liver CT attenuation was independently associated with higher BMI(p<0.0001) and higher CAC score(p=0.01) while the other variables (emphysema, smoking status, pack-years of smoking, and self-reported diabetes and hypertension) were no longer significant. Multivariable logistic regression analysis showed that no variable other than CAC score (p = 0.03) were significant discriminators between those below and above 40HU.

Of the 154 WTC participants, 148(96%) had available laboratory test results. The median time between the baseline CT scan and these tests was −0.6 (IQR: −1.2 to −0.2) months. Comparison of the six participants without clinical laboratory test results to the 148 with these results revealed no significant differences. Among the 148 participants, the 25 with liver attenuation <40HU had significantly higher transaminase levels than the 129 with liver attenuation ≥40HU: median AST values were 26.5 IU/L vs. 20.0 IU/L (p = 0.001), median ALT values were 34.0 IU/L vs. 21.0 IU/L (p <0.0001).

### Comparison of WTC (n = 159) and non-WTC (n = 170) participants

As shown in Table 3, the WTC participants had a higher percentage of men (85.7% vs. 45.3%, p < 0.0001), were slightly younger (61.1 vs. 62 years of age, p=0.04), had more participants whose race/ethnicity was "other" (multi-racial or unknown) (24.0% vs. 1.8%, p=0.04), higher BMI (29.5 vs. 27.0, p<0.0001), current smokers (53.2% vs. 32.9%, p=0.0002), higher pack-years of smoking (47.6 vs. 29.1, p<0.0001), individuals with self-reported hypertension (56.6% vs. 27.6%, p<0.0001), and COPD (29.7% vs. 13.5%, p=0.0005) (Table 3). Self-reported diabetes was higher in the WTC participants compared with the non-WTC participants (20.3% vs. 12.4%, p=0.06). Because clinical laboratory values were available for only 76 (45%), non-WTC participants, these factors were not compared between the two groups. To adjust for the differences of the WTC and non-WTC participants, PS analyses were used for further analyses. The PS adjustment successfully balanced the baseline characteristics between two groups as there were no longer significant differences in the PS-adjusted comparisons shown in Table 3.

Table 4 shows the comparison of the WTC and non-WTC participants. The prevalence of moderate-to-severe HS (<40HU) was 16.2% for the WTC participants while it was 5.3% for the non-WTC participants, a more than 3-fold higher (16.2% vs. 5.3%). The unadjusted odds ratio (OR) of having moderate-to severe hepatic steatosis in the WTC compared to the non-WTC participants was 3.5 (95% CI: 1.6–7.7).

The final adjusted OR needed to consider all significant variables included in Table 3 (gender, age, pack-years of smoking, BMI) as well as the LDCT findings of CAC and presence of emphysema. The average CAC score was: 2.0 vs. 1.5, p=0.02, and the presence of emphysema was: 58% vs. 56%, p=0.37, respectively for the WTC and non-WTC participants. The final adjusted OR for moderate-to severe hepatic steatosis in the WTC participants was 3.4 (95% CI: 1.7 −6.7), even after adjustment for all these variables (Table 4).

Using an alternative approach, multiple logistic regression revealed that liver attenuation <40HU was positively associated with being part of the WTC (OR=2.9, 95% CI:1.03–8.17), higher BMI (OR=1.10 per kg/M$^2$) and it was negatively associated with being a current smoker (OR=0.41, 95% CI:0.17–0.99). The model adjusted for gender, pack years of smoking, self-reported diabetes, hypertension, and CAC score (Table 5). Although smoking is generally associated with lower BMI, we did not observe an interaction between smoking and BMI in this study.

## Discussion

The most important results of our study were that the odds of having moderate-to-severe hepatic steatosis, defined by CT liver attenuation <40HU, was over 3-fold higher among WTC screening participants than among non-WTC participants enrolled in the same LDCT screening program with different entry criteria, before and after adjustment for all significant covariates.

The WTC cohort is a unique patient population whose clinical data have been recorded until the present time as part of the World Trade Center (WTC) Health Program. Numerous adverse health effects have been described in this patient population, findings in keeping with other studies, suggesting the significant epidemiologic link between the exposure to airborne particulates and adverse health effects. A longitudinal study of a large cohort of WTC rescue and recovery workers demonstrated a substantial burden of health problems, including a 9-year cumulative occurrence of asthma (27.6%), sinusitis(42.3%), and gastroesophageal reflux disease (39.3%) [21]. Multiple studies have demonstrated lung function abnormalities in individuals exposed at the WTC disaster and in pre-clinical models [22,23]. Hepatotoxic exposures are reported to continue for years after exposure to the toxin has stopped [24].

Studies have also shown that ambient particular matter (PM) exposure to lung is closely associated with pathogenesis of metabolic syndrome affecting non-pulmonary organs including the cardiovascular system, adipose tissue and liver. Inhaled particulates can enter the systemic circulation and concentrate in the liver, which serves as a major site of detoxification. Hepatotoxic exposures include particulate matter [11], air pollution [12], close proximity to major roadways [25] and to toxic waste sites [13], exposure to active and passive smoking [14], and to volatile chemicals [11]. Animal studies confirm the hepatotoxic effects of airborne particulate matter ($PM_{2.5}$) and chemicals [26,27]. Toxic exposures not only provoke a series of intrahepatic changes that can lead to liver failure and liver cancer, but have been shown to induce NAFLD [12]. The differential associations with lung dysfunction and NAFLD may reflect distinct but overlapping pathophysiologic mechanisms of lung and liver disease after PM exposure. In a more general sense, ambient PM is known to induce systemic inflammation, oxidative stress response and vascular dysfunction, ultimately affecting multiple organs including liver and lungs.

Elevated BMI and obesity are more prevalent in the WTC responders compared to the general US population, with an obesity prevalence of 42–48.6% [28]. A greater number of responders were overweight compared to the general US population (43% vs. 33%, respectively)[28]. Obesity was shown to be a major risk factor for liver steatosis due to the increased delivery of free fatty acids to the liver and an increase in hepatic lipogenesis associated with hyperinsulemia [29]. A significant, yet small, association between weight gain and decline in lung function in the longitudinal follow up study in WTC responders was also shown [22]. Polycyclic aromatic hydrocarbon(PAH), a toxic exposure recognized at the WTC site [30], was also related to obesity and the expression of a number of obesity-related cardiometabolic health risk factors [31]. We also found that BMI was significantly higher in the WTC cohort than in the non-WTC participants.

Our results are especially meaningful as we also found that liver function tests results were significantly higher in WTC participants with CT liver density measurement <40HU, suggesting that moderate-to-severe HS may be accompanied by increased hepatocyte injury. A recent analysis of the National Health and Nutrition Examination Survey (NHANES) data showed that FIB-4>1.3(intermediate elevation) and/or >2.67(high elevation) were both significantly associated with increased liver-related mortality [32]. These findings underscore the importance of providing additional work up for possible liver disease. Because the attenuation threshold used in this study excludes cases with milder degrees of HS of questionable clinical relevance, liver density measurement of <40HU may represent a useful diagnostic cutoff value for screening.

We acknowledge several limitations of our study. First, the sample size was limited and we lacked pathologic confirmation of HS. While non-contrast CT is valuable for detecting moderate-to-severe steatosis, detection of mild HS [33], is limited. The frequency of HS in the WTC cohort was compared to the non-WTC cohort, both enrolled in the same screening program at the same institution. To account for differences in the age and smoking history, PS methods were used to create groups with similar characteristics so that the effect of WTC exposure on HS could be compared. Assumption for PS analysis is that all covariates relevant to HS that differ between the two cohorts are accounted for, so that the analysis is limited by its inability to control for unmeasured confounders and measurement errors. Although WTC participants had significantly higher BMI and more likely to have diabetes compared to non-WTC participants, tests and diagnostics confirmed that our model balances the covariates and the two groups were comparable. Alcohol consumption [34,35] and steroid use have been shown to increase risk of HS [36,37], but data on alcohol consumption and steroid use was not available for either cohort. With the higher prevalence of COPD among WTC participants and steroids being one of most commonly prescribed medications for people with COPD, differential steroid use between the two cohorts may bias our results. As a result, there might be residual confounding due to the unaccounted effect of both alcohol consumption and steroid use. Future studies including alcohol and steroid use data are necessary to further examine the effect of hepatotoxic exposures in the WTC attack area.

In summary, members of the WTC General Responder Cohort have been affected by number of chronic health conditions; however, they have not been evaluated for liver disease. This is the first study to assess HS among the WTC general responder participants and to compare them to non-WTC participants in the same LDCT lung screening program. We have demonstrated that WTC participants have a significantly higher rate of HS. Overlapping pathophysiologic mechanisms of lung and liver disease after particulate matter exposure, smoking and obesity likely contribute to the development and higher rates of hepatic steatosis in this population. Further work is necessary to further elucidate the pathophysiologic mechanism behind the development of HS in this unique patient population and to investigate the long-term effects and potential for the development of liver disease. Based on these preliminary results, we suggest that WTC general responders with liver attenuation values <40HU should be referred to a hepatologist for further evaluation.

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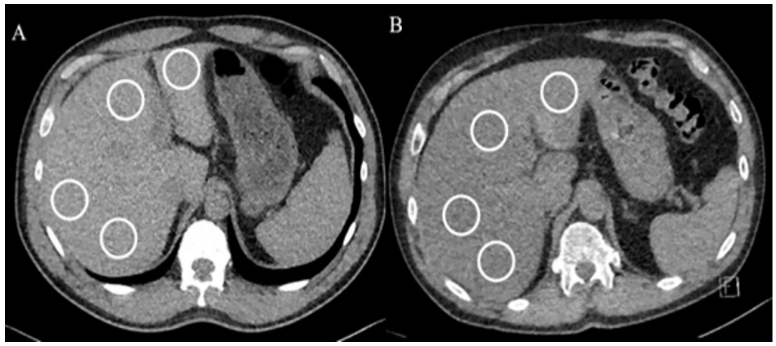


**Figure 1.**

Liver density measurements on non-contrast chest CT in WTC participants. Averaged normal liver attenuation (59.5 HU) was noted in a 56-year-old male (A) and averaged lower liver attenuation (25 HU) was noted in a 57-year-old male (B), consistent with hepatic steatosis. Region of interest (ROIs, white circles) measurements were placed in the right posterior, right anterior, left medial and left lateral segments of the liver to determine liver attenuation, avoiding lesions and vessels.

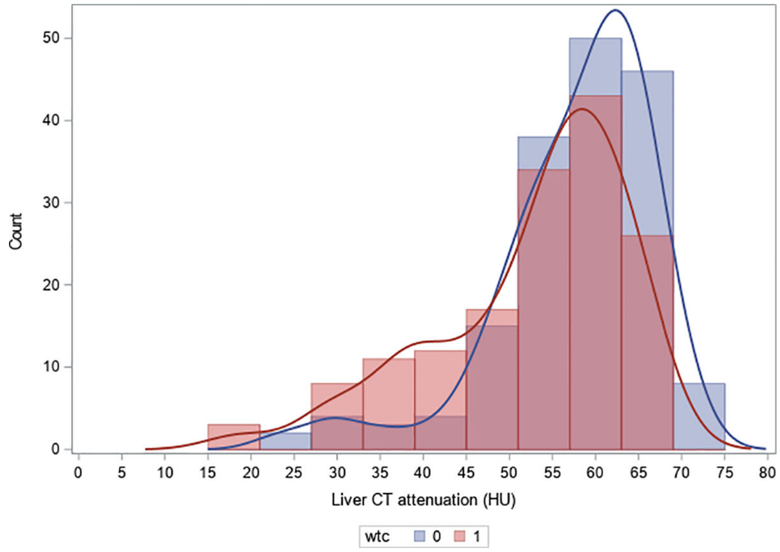


**Figure 2.**

Histogram and distribution curve of liver attenuation based on CT measurements of 154 members of the WTC cohort (pink bars/lines) and 170 members of the non-WTC cohort (blue bars/lines).

**Table 1.**

Characteristics of the 154 individuals in the WTC cohort comparing those with liver attenuation <40 or ≥40 HU).

| | <40 HU n | (n=25) (%) | ≥40 HU n | (n=129) (%) | Total n | (n=154) (%) | <40 HU vs. ≥40 HU P-value |
|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | |
| Male | 22 | (88%) | 110 | (85%) | 132 | (86%) | 1.00 |
| Female | 3 | (12%) | 19 | (15%) | 22 | (14%) | |
| **Age, years (mean ± SD)** | 60.4 ± 3.9 | | 61.2 ± 4.8 | | 61.1 ± 4.7 | | 0.51 |
| **Ethnicity** | | | | | | | |
| Caucasian | 19 | (76%) | 83 | (64%) | 102 | (66%) | 0.44 |
| African American | 1 | (4%) | 14 | (11%) | 15 | (10%) | |
| Other | 5 | (20%) | 32 | (25%) | 37 | (24%) | |
| **Smoking Status** | | | | | | | |
| Current smoker | 8 | (32%) | 74 | (57%) | 82 | (53%) | 0.02 |
| Former smoker | 17 | (68%) | 55 | (43%) | 72 | (47%) | |
| **Pack-years of smoking** | | | | | | | |
| **Mean ± SD** | 55.4 ± 39.3 | | 46.1 ± 21.3 | | 47.6 ± 25.2 | | 0.54 |
| **BMI (Mean ± SD)** | 32.2 ± 4.7 | | 29.0 ± 5.1 | | 29.5 ± 5.1 | | 0.002 |
| **Comorbidity** | | | | | | | |
| Diabetes | 6 | (26%) | 23 | (19%) | 29 | (20%) | 0.57 |
| Hypertension | 14 | (61%) | 67 | (56%) | 81 | (57%) | 0.66 |
| COPD | 6 | (26%) | 35 | (30%) | 41 | (30%) | 0.68 |
| **CAC Score on CT** | | | | | | | |
| None | 3 | (12%) | 40 | (31%) | 43 | (28%) | 0.06 |
| 1–3 | 14 | (56%) | 68 | (53%) | 82 | (53%) | |
| 4–12 | 8 | (32%) | 21 | (16%) | 29 | (19%) | |
| **Emphysema on CT** | 5 | (20%) | 53 | (41%) | 58 | (38%) | 0.05 |
| **Clinical laboratory testing** | | | | | | | |
| Available | 24 | (96%) | 124 | (96%) | 148 | (96%) | 1.00 |
| AST, median (IQR) | 26.5 | (21.5–40.0) | 20.0 | (17.0–25.0) | 21.0 | (17.0–26.0) | 0.001 |
| AST<35 | 18 | (72%) | 118 | (91%) | 136 | (88%) | 0.012 |
| AST≥35 | 7 | (28%) | 11 | (9%) | 18 | (12%) | |
| ALT, median (IQR) | 34.0 | (27.0–59.5) | 21.0 | (16.0–28.0) | 22.0 | (17.0–31.0) | <.0001 |
| ALT<45 | 15 | (60%) | 121 | (94%) | 136 | (88%) | <.0001 |
| ALT≥45 | 10 | (40%) | 8 | (6%) | 18 | (12%) | |
| Platelets, median (IQR) | 227.0 | (178.0–255.0) | 232.0 | (194.0–277.0) | 230.0 | (194.0–274.0) | 0.72 |
| Platelets < 150 | 2 | (8%) | 14 | (11%) | 16 | (10%) | 1.00 |
| Platelets ≥ 150 | 23 | (92%) | 115 | (89%) | 138 | (90%) | |
| FIB 4, median (IQR) | 1.1 | (0.8–1.7) | 1.2 | (0.9–1.7) | 1.2 | (0.9–1.7) | 0.54 |
| FIB4<1.3 | 15 | (60%) | 73 | (57%) | 88 | (57%) | 0.75 |
| FIB4≥1.3 | 10 | (40%) | 56 | (43%) | 66 | (43%) | |

*SD-Standard deviation; IQR-Interquartile range; HU-Hounsfield unit; BMI-Body mass index; CAC-Coronary artery calcification; AST- Aspartate Aminotransferase (Upper limit normal ULN=35); ALT- Alanine Aminotransferase (ULN=45); Platelets ULN=150; FIB-4 Fibrosis-4 Score= (Age x AST)/(Platelet x √ALT).

**Table 2.**

Bivariate and multivariable regression model of liver CT attenuation (HU) in CT scans of 154 members of the WTC GRC

| | Linear Regression | | | | | | | Logistic Regression* | |
|---|---|---|---|---|---|---|---|---|---|
| | Bivariate | | | | Multivariable ▱ | | | Multivariable ⊿ | |
| | Estimates | SE | p-value | $R^2$ | Estimates | SE | p-value | OR | p-value |
| **Male gender** | −2.53 | 2.56 | 0.33 | 0.006 | | | | | |
| **Age (years)** | 0.24 | 0.19 | 0.22 | 0.010 | | | | | |
| **Current Smoker** | 3.55 | 1.78 | 0.047 | 0.026 | 1.33 | 1.71 | 0.44 | 0.46 (0.16–1.27) | 0.13 |
| **Pack years** | −0.10 | 0.03 | 0.003 | 0.06 | −0.05 | 0.03 | 0.13 | | |
| **BMI** | −1.00 | 0.16 | <.0001 | 0.21 | −0.88 | 0.18 | <.0001 | 1.09 (0.99–1.19) | 0.07 |
| **Comorbidity** | | | | | | | | | |
| Diabetes | −4.66 | 2.32 | 0.047 | 0.03 | −1.47 | 2.22 | 0.51 | | |
| Hypertension | −4.23 | 1.88 | 0.03 | 0.03 | −0.97 | 1.84 | 0.60 | | |
| COPD | −1.25 | 2.12 | 0.56 | 0.003 | | | | | |
| **CAC Score** | −1.04 | 0.43 | 0.02 | 0.04 | −1.08 | 0.42 | 0.01 | 1.26 (1.02–1.54) | 0.03 |
| **Emphysema on CT** | 4.97 | 1.81 | 0.01 | 0.05 | 2.99 | 1.72 | 0.09 | 0.39 (0.13–1.15) | 0.09 |

SE-Standard Error; BMI-Body mass index; CAC-Coronary artery calcification

*Logistic regression models the risk of liver attenuation <40 HU.

▱R2 for the multivariable linear regression is 0.30

⊿only variables with p-value<0.10 in the bivariate analysis were included

**Table 3.**

Demographic characteristics and self-reported comorbidities of WTC GRC and non-WTC

| | WTC GRC (N=154) | | non-WTC (N=170) | | P-value | |
|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **Unadjusted** | **PS-Adjusted*** |
| **Male gender** | 132 | (85.7%) | 77 | (45.3%) | <0.0001 | 0.70 |
| **Age (years), Mean (SD)** | 61.1 | (4.7) | 62.0 | (8.7) | 0.04 | 0.97 |
| **Ethnicity** | | | | | | |
| Caucasian | 102 | (66.2%) | 138 | (81.2%) | 0.0022 | 0.95 |
| African American | 15 | (9.7%) | 29 | (17.1%) | 0.05 | 0.96 |
| Other | 37 | (24.0%) | 3 | (1.8%) | Ref. | |
| **BMI, Mean (SD)** | 29.5 | (5.1) | 27.0 | (5.0) | <0.0001 | 0.87 |
| **Smoking Status** | | | | | | |
| Current smoker | 82 | (53.2%) | 56 | (32.9%) | 0.0002 | 0.89 |
| Former smoker | 72 | (46.8%) | 114 | (67.1%) | Ref. | |
| **Pack-years, Mean (SD)** | 47.6 | (25.2) | 29.1 | (25.3) | <0.0001 | 0.78 |
| **Comorbidity** | | | | | | |
| Diabetes | 29 | (20.3%) | 21 | (12.4%) | 0.06 | 0.95 |
| Hypertension | 81 | (56.6%) | 47 | (27.6%) | <.0001 | 0.85 |
| COPD | 41 | (29.7%) | 23 | (13.5%) | 0.0005 | 0.90 |

*The propensity score was calculated for each participant using logistic regression analysis (1 assigned to WTC and 0 to non-WTC) based on each participant's gender, age, race, pack-years of smoking, smoking status (current or former smokers), self-reported comorbidities (diabetes, COPD and hypertension) and BMI. P-value after adjusted for propensity score was calculated for each participant using logistic regression analysis (1 assigned to WTC and 0 to non-WTC) based on each participant's gender, age, ethnicity, pack-years of smoking, smoking status (current or former smokers), self-reported comorbidities (diabetes, COPD, hypertension) and BMI.

## Table 4.

Propensity Score Analysis*: Comparison of risk of liver attenuation <40 HU between 154 WTC and 170 non-WTC participants ▱.

| | WTC-GRC (n=154) | | non-WTC (n=170) | | |
|---|---|---|---|---|---|
| **Liver attenuation** | **n** | **(%)** | **n** | **(%)** | **P-value** |
| **Mean (SD)** | 52.7 | (11.1) | 57.6 | (9.3) | <0.0001 |
| **<40 HU** | 25 | (16.2%) | 9 | (5.3%) | 0.001 |
| **≥40 HU** | 129 | (83.8%) | 161 | (94.7%) | |
| **Prevalence of liver attenuation <40 HU*** | | | | | |
| Unadjusted Odds Ratio | | | 3.5 (95% CI: 1.6–7.7) | | P = 0.0022 |
| Inverse probability weighted Odds Ratio | | | 3.4 (95% CI: 1.7–6.7) | | P = 0.0007 |

▱Data of the non-WTC cohort were previously reported in Chen et al. Hepatic steatosis in participants in a program of low-dose CT screening for lung cancer. Eur J Radiol. 2017 Sep;94:174–179.

CI = confidence interval

*The odds ratio represents the risk of liver attenuation<40 HU of a participant in the WTC-exposed cohort compared with a participant in the non-WTC screening cohort. Inverse probability weighted model was also adjusted for gender, age, pack-years, BMI, CAC score and presence of emphysema

**Table 5.**

Multivariable logistic regression analysis of factors associated with liver attenuation <40 HU, indicating moderate-to-severe HS, in members of the WTC and non-WTC participants

| | Univariate | | | Multiple | | |
|---|---|---|---|---|---|---|
| | **Odds Ratio (OR)** | **95% CI** | **P-value** | **Odds Ratio (OR)** | **95% CI** | **P-value** |
| Male gender | 2.16 | (0.90–5.17) | 0.08 | 1.01 | (0.35,2.90) | 0.99 |
| Age (years) | 0.98 | (0.93–1.03) | 0.45 | | | |
| Ethnicity | | | | | | |
| Caucasian | Ref. | | | | | |
| African American | 0.62 | (0.18–2.17) | 0.46 | | | |
| Other | 1.19 | (0.39–3.67) | 0.76 | | | |
| BMI | 1.15 | (1.07–1.22) | <.0001 | 1.10 | (1.02,1.19) | 0.02 |
| Smoking Status | | | | | | |
| Current smoker | 0.51 | (0.23–1.14) | 0.10 | 0.41 | (0.17,0.99) | 0.05 |
| Former smoker | Ref. | | | | | |
| Pack-years | 1.02 | (1.01–1.03) | 0.01 | 1.01 | (0.99,1.02) | 0.30 |
| Comorbidity | | | | | | |
| Diabetes | 2.76 | (1.22–6.28) | 0.02 | 1.69 | (0.63,4.50) | 0.30 |
| Hypertension | 2.00 | (0.96–4.19) | 0.07 | 0.75 | (0.3,1.87) | 0.54 |
| COPD | 1.31 | (0.56–3.07) | 0.54 | | | |
| CAC Score | 1.23 | (1.04–1.44) | 0.01 | 1.19 | (0.99,1.44) | 0.07 |
| Emphysema on CT | 0.60 | (0.26–1.38) | 0.23 | | | |
| **Membership in the WTC** | **3.58** | **(1.60–8.02)** | **0.002** | **2.90** | **(1.03,8.17)** | **0.04** |