Cardiovascular Disease Biomarkers Predict Susceptibility or Resistance to Lung Injury in World Trade Center Dust Exposed Firefighters

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Abstract

Pulmonary vascular loss is an early feature of chronic obstructive pulmonary disease. Biomarkers of inflammation and of metabolic syndrome, predicts loss of lung function in World Trade Center Lung Injury (WTC-LI). We investigated if other cardiovascular disease (CVD) biomarkers also predicted WTC-LI.

This nested case-cohort study used 801 never smoker, WTC exposed firefighters with normal pre-9/11 lung function presenting for subspecialty pulmonary evaluation (SPE) before March, 2008. A representative sub-cohort of 124/801 with serum drawn within six months of 9/11 defined CVD biomarker distribution. Post-9/11/01 FEV_1 at subspecialty exam defined cases: susceptible WTC-LI cases with FEV_1 77% predicted (66/801) and resistant WTC-LI cases with FEV_1 107% (68/801). All models were adjusted for WTC exposure intensity, BMI at SPE, age at 9/11, and pre-9/11 FEV_1.

Susceptible WTC-LI cases had higher levels of Apo-AII, CRP, and MIP-4 with significant RRs of 3.85, 3.93, and 0.26 respectively with an area under the curve (AUC) of 0.858. Resistant WTC-LI cases had significantly higher sVCAM and lower MPO with RRs of 2.24, and 2.89 respectively; AUC 0.830.

Biomarkers of CVD in serum six-month post-9/11 predicted either susceptibility or resistance to WTC-LI. These biomarkers may define pathways producing or protecting subjects from pulmonary vascular disease and associated loss of lung function after an irritant exposure.

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Keywords

Airway Inflammation; Cytokines; Pulmonary Funtion Testing

Introduction

One of the hallmarks of particulate matter (PM) exposure is systemic inflammation, endothelial dysfunction, and subsequent end-organ damage. (1–5) Epidemiologic investigation has documented associations between increased ambient PM, lung disease, and cardiovascular disease (CVD). (6–12) Inflammation and remodeling are key features of airflow obstruction in asthma and chronic obstructive pulmonary disease (COPD). (13, 14) High ambient PM exposures significantly decrease forced expiratory volume in one second (FEV_1) even after five to seven days. (15–17) Systemic inflammation produces vascular endothelial injury and subsequent CVD. (18–20) Recent studies associate systemic vascular involvement with lung disease (21, 22) and prospective studies have demonstrated an association between impaired lung function and central arterial stiffness even before the development of CVD, with systemic inflammation contributing to this association. (23–25)

Recently, we have shown that biomarkers of inflammation (GM-CSF, MDC) and of the metabolic syndrome, observed in serum drawn within six months of WTC exposure, predict the post-9/11 decline in FEV_1 in this cohort of WTC-exposed FDNY firefighters. (3, 17) Utilizing a nested case-cohort design, the goal of this study is to investigate if CVD serum biomarkers drawn within six months of 9/11/01 can predict WTC-LI in this longitudinal well phenotyped cohort of FDNY firefighters. We hypothesized that individuals exposed to WTC particulates who went on to develop persistent WTC-LI, would express different levels of CVD biomarkers than those similarly exposed individuals who were resistant to developing WTC-LI.

The collapse of the WTC exposed tens of thousands of people to extremely high PM concentrations. Several cohorts of WTC-exposed individuals have been longitudinally followed. Among exposed workers, volunteers, and lower Manhattan residents, abnormal spirometry has been a common finding. (26) In rescue/recovery workers from the Fire Department of the City of New York (FDNY), WTC exposure led to WTC lung injury (WTC-LI) as evidenced by substantial declines in pulmonary function in the first six months after 9/11 (at a rate twelve times greater than that found prior to 9/11) (27, 28) and these findings persisted over the next 6.5 years. (29)

Pulmonary vascular injury occurs early in smoking related chronic obstructive lung disease (COPD) with pulmonary perfusion abnormalities and reduced blood return to the heart observed prior to development of abnormal FEV_1. (30, 31) Similar pathophysiology likely occurs in irritant induced COPD. Pulmonary arteriopathy was present in 58% of lung biopsies from non-FDNY WTC exposed individuals and in 74% with constrictive bronchiolitis after inhalational exposures during military service in Iraq and Afghanistan. (32, 33)

Methods

Study Participants

WTC exposed FDNY firefighters entered the FDNY-Medical Monitoring and Treatment Program (MMTP) and had spirometry at medical monitoring entry (MME). (34, 35) Briefly, FDNY Spirometry was performed according to American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines using Portascreen Spirometry (S&M

Instruments, Doylestown, PA). (36) In order to provide three acceptable spirograms, seated workers wearing nose clips performed up to 8 forced expiratory maneuvers per testing session. Subspecialty pulmonary examination (SPE) pulmonary function tests (PFTs) were performed according to ATS/ERS guidelines using a Jaeger Masterscreen PFT System (Viasys Healthcare, Yorba Linda, CA). All acceptable measures were expressed in absolute values (liters) and as percent predicted of normal

The study cohort was derived from symptomatic subjects referred for SPE (N=1720) between 10/1/2001 and 3/10/2008. (37) The baseline cohort consisted of never-smokers (consistently reported not smoking on all health screens), male, had reliable National Health and Nutrition Examination Survey (NHANES) normative data for predicted FEV_1, had post-9/11 FDNY PFTs within 200 days of 9/11/01 and had pre-9/11 FEV_1 >75% predicted (801/1720, 47%). All subjects signed informed Institutional Review Board approved consent at the time of enrollment allowing analysis of their information and samples for research (Montefiore Medical Center; #07-09-320 and New York University; #11-00439).

Cases were defined by their FEV_1% Predicted at SPE using NHANES III criteria. Those resistant to WTC-LI, were defined as being within one standard deviation (SD) of the highest FEV_1% predicted of the study cohort (N=100) had an FEV_1 107%. Those susceptible to WTC-LI were similarly defined as being within one SD of the lowest FEV_1% predicted of the cohort (N=100), which was an FEV_1 77%. The sub-cohort controls (N=171) were randomly selected from the study cohort after stratification based on BMI and FEV_1% Predicted at MME. Serum biomarkers were available for N=124/171 of the sub-cohort controls, N=68/100 resistant cases, and 66/100 susceptible cases.

Demographics

Age, gender, and years of service at FDNY were obtained from the FDNY-WTC-monitoring database. BMIs were calculated from height and weight measured at the time of MME and SPE. Degree of exposure was self-reported at the first FDNY-WTC-monitoring and was categorized using the FDNY-WTC Exposure Intensity Index (Arrival Time): i. Present on the morning of 9/11/2001 ii. Arrived after noon on 9/11/2001 iii. Arrived on 9/12/2001. Those arriving after day three were excluded from analysis as a result of their low numbers in this sample. (3, 17)

Serum Sampling and Analysis

Blood was drawn at MME, from 10/29/2001-1/312002 for the subjects in this analysis. Samples were allowed to stand for one hour at room temperature before being centrifuged at 1,800 g for ten minutes. Serum was stored at −80°C (Bio-Reference Laboratories, Inc. Elmwood Park, NJ). Serum was thawed once at four degrees and assayed using CVD-1 (HCVD1-67AK), Apolipoproteins (APO-62K), and Neurodegenerative (HNDG2-36K) panels according to manufacturer's instructions (Millipore, Billerica, MA) on a Luminex 200IS (Luminex Corporation, Austin, TX). Data analyzed with MasterPlex QT software (Version 1.2; MiraiBio, Inc.). Each batch of samples processed contained controls and cases in an approximate 12/7 ratio.

Statistical Analysis

SPSS 19 (IBM, Armonk, NY) used for all database management and statistics. Demographic information and analyte levels were compared by Mann-Whitney U or Kruskal-Wallis where appropriate. We used logistic regression analysis to estimate the CVD biomarkers relative risks for crude and single analyte models adjusted for the confounders of age at 9/11, BMI at SPE, exposure group, and pre-9/11 FEV_1% predicted, Table 4. Relative risk was calculated by binary logistic regression. Cases (WTC-LI susceptible or resistant) were

compared to the sub-cohort controls as the dichotomous outcome variable and cutpoints of analytes were used as the predictors. MPO <25th percentile, MIP-4 ⩾ 50th percentile, CRP ⩾ 2.45 mg/dl, and Apo-AII, sVCAM ⩾ 75th were defined as cutpoints. (3, 38, 39) Models were adjusted for potential confounders; BMI at SPE, exposure group as categorical variable, age on 9/11, and FEV$_1$% Predicted prior to 9/11 as a continuous variable. Hosmer-Lemeshow goodness-of-fit statistic was used as a statistical test of model adequacy. Receiver operator characteristic area under the curve (ROC AUC) was also quantified for each final model. For all statistical tests significance was assessed by p <0.05.

Results

Demographics

We developed a sub-cohort control to represent the full spectrum of lung function response of the baseline cohort and two case definitions represented extremes of response to WTC dust and smoke (Figure 1). The demographics of all groups with serum available are summarized in Table 1. The control and case groups had similar WTC exposure; time from 9/11 to MME, time from 9/11 to SPE, years of service, and age at 9/11. BMI of susceptible cases was higher than controls or resistant cases at MME and SPE.

Lung Function

Susceptible cases had lower FEV$_1$ and this correlated with DLCO and measures of airflow obstruction, including methacholine and bronchodilator response, Table 2. Lung function in resistant cases and sub-cohort controls increased from the MME to SPE (105% to 113% and 92% to 95% respectively) while the FEV$_1$% predicted of affected cases continued to decline between the two pulmonary function tests (79% to 72%; p<0.001 all comparisons).

CVD Biomarkers

We measured CVD serum biomarkers expressed within six months of 9/11/2001. Compared to sub-cohort controls, cases susceptible to WTC-LI had significant elevations of Apolipoprotein (Apo) AI (4273.98 vs. 2569.94, p=0.003), Apo AII (1830.96 vs. 845.12, p=0.002), Apo CII (305.80 vs. 203.18, p=0.006), Apo CIII (973.58 v 600.91, p=0.005), and Apo E (257.43 vs. 140.71, p=0.001), and significantly lower levels of Macrophage InflammatoryProtein-4 (MIP-4) (145.28 vs. 184.68, p=0.015), Table 3A. Whereas resistant WTC-LI cases had significantly decreased levels of Myeloperoxidase (MPO) (117.94 vs. 143.56, p=0.016) compared to sub-cohort controls, Table 3B (median concentration in ng/ml except for CRP is in mg/dL).

Resistant WTC-LI Cases: Development of Relative Risk Models

Univariate Model—We found that MPO <25th%, sVCAM ⩾ 75th% predicted cases resistant to WTC-LI in both crude and confounder adjusted models. *Multivariate Model.* In a multivariate model that combined sVCAM ⩾ 1568.65 and MPO ⩾ 105.26 both stayed significant predictors of resistance to WTC-LI RR=2.24 (95% CI 1.07–4.70) and RR=2.89 (95% CI 1.37–7.47) respectively, Table 4. The final model for resistance to lung injury had an AUC of 0.830 (0.774–0.887).

Susceptible WTC-LI Cases: Development of Relative Risk Models

Univariate Analysis—We found that CRP ⩾ 2.45, ApoAI, ApoAII, ApoCII, ApoCIII, and ApoE 75th% and MIP-4 50% as crude value, all significantly predicted the risk of having an FEV$_1$ ⩽ 77% at SPE in individuals who were exposed to WTC dust. CVD biomarkers predicted the risk of WTC-LI at SPE in both crude and confounder adjusted models, Table 4.

Multivariate Model—We then assessed the biomarkers ability in the final logistic regression model to predict case status after adjusting for confounders. We found that a three analyte model combining Apo AII, CRP, and MIP-4 optimally predicted the susceptible cases with ApoAII 1772.87 RR=3.85 (95% CI, 1.79–8.26), CRP 2.45 mg/dL, RR=3.93 (95% CI, 1.43–10.79), and MIP-4>194.90 ng/mL, RR=0.26 (95% CI, 0.11–0.59). The final model produced a receiver operator characteristic area under the curve (AUC) of 0.858 (0.79–0.919), Table 4. Apo-AII was used in the final model because it consistently produced the highest RR of any Apo when combined with another Apo and ApoAII made the other Apolipoproteins insignificant when combined together.

Discussion

We observed serum biomarkers classically associated with CVD to predict lung function after exposure to dust and smoke at the WTC site in FDNY non-smoking firefighters with normal pre-9/11 lung function. Firefighters with elevated sVCAM and low MPO levels within six months of 9/11/2001 recovered lung function returning to pre-9/11 values after an acute decline. Alternately, individuals with elevated ApoAII and CRP levels within six months of 9/11 had significantly increased risk of developing decreased lung function over the subsequent six years while elevated MIP-4 reduced the risk of susceptibility to decreased lung function.

Our observation that risk factors for vascular injury are also predictors of lung dysfunction is consistent with recent reports that perfusion abnormalities and reduced pulmonary blood flow occur prior to development of abnormal FEV_1 in smokers at risk for COPD. In other WTC exposed cohorts pulmonary vasculopathy is a prominent feature. Vascular injury may be a prominent feature of irritant exposure since soldiers exposed to sand and products of combustion also had vasculopathy on pathology. CRP is known a marker of acute systemic inflammation and CVD. (40, 41) It is biologically plausible that processes that injure systemic arteries could also injure pulmonary arteries. There is an inverse relationship between serum CRP and FEV_1. (42) CRP levels were elevated in individuals with COPD independent of any CVD risks. (43) Pulmonary hypertension another disease of the pulmonary vasculature is associated with CVD biomarkers. (44) This parallels our prior observation that dyslipidemia predicts poor outcome after WTC dust exposure. MIP-4 (CCL18) is an early promoter of regulatory T cell differentiation and may generate an anti-inflammatory counter-regulatory response. (45, 46) Our data demonstrate that low levels of MPO demonstrate less neutrophil activation in patients resistant to the damaging effects of WTC dust exposure. Neutrophil activation is an important mediator of PM induced the pulmonary and cardiovascular vascular injury. (1, 47) Taken together, the data in this and other recent reports emphasize the need to better understand the mechanisms by which inhaled irritants damage pulmonary vessels.

This Case-cohort study design was utilized to assess the predictive abilities of CVD biomarkers in determining the relative risk (RR) of either being protected from or developing WTC-LI. (48–50) Sub-cohort controls, susceptible and resistant cases were all drawn from the larger baseline cohort. The sub-cohort controls contain an overlapping population of those who also met case definitions. The odds ratios approximate the RR of the biomarker-disease relationship of the larger cohort. In addition, case-cohort studies have several advantages. First, comparing multiple case definitions to the same sub-cohort control group facilitates the identification of biomarkers of susceptibility and resistance to WTC-LI. Second, the case-cohort studies are cost-effective and logistically efficient since biomarkers only needed to be assayed for a sample of the entire cohort. Lastly, the study design minimized batch bias and freeze-thaw problems associated with biomarker discovery. (48)

The study cohort was nested within a larger intensively evaluated, longitudinally followed symptomatic firefighters who presented for subspecialty pulmonary evaluation prior to March 2008. We chose to exclude ever-smokers to eliminate the confounding effect of smoking on lung function and CVD risk. We narrowed the baseline cohort of 801 to produce a sub-cohort control of 136 patients with serum available, a group large enough to be representative of the baseline cohort but small enough to allow cost effective measurement of biomarker expression. Since the control group represented the larger cohort, comparing biomarkers expression in cases to that in the sub cohort control permitted relative risk measures produced by the biomarkers. We used FEV_1 for case definition because it is the best single measure of lung function available on the entire FDNY cohort at each point of interest. Cases resistant to WTC-LI were defined by FEV_1 in the top 12.5 percentile while susceptible cases were defined by FEV_1 in the lowest 12.5 percentile at SPE. This cohort had serial pulmonary function pre- and post-9/11/2001 thereby allowing us to define resistance or susceptibility to WTC-LI after a severe irritant exposure. Another unique aspect of the study is biomarker expression was measured within six months after 9/11/01 and prior to recovery from injury or the development of persistent WTC-LI.

Cases susceptible or resistant to WTC-LI and the sub-cohort controls experienced similar exposure to smoke and dust, which led to declines in their FEV_1 within six months post 9/11. This suggests a similar response to acute irritant exposure. However, protected cases and cohort controls maintained normal lung function while affected cases developed abnormal FEV_1 by SPE. One explanation for this may be that the WTC-LI cases had significantly lower pre-9/11 FEV_1. Cases therefore needed a smaller relative decline to drop below 77% post-9/11. We adjusted for this potential confounder by adding pre-9/11 FEV_1 to all models. Predictors of resistance and susceptibility were not strongly affected by pre-9/11 FEV_1 demonstrating the serum biomarker effect was independent of the pre-exposure lung function. Similarly, increased BMI is well known to be associated with reduced FEV_1, but adjusting for this potential confounder did not alter the ability of the serum biomarkers to predict recovery or decline in lung function. This demonstrates an inflammatory process in susceptible lung injury cases that produces persistent loss of lung function for years after the insult. On the other hand, resistant cases showed long-term protection from WTC-LI.

There are several limitations to this study. It's a single unique cohort of FDNY firefighters with serum samples available from **10/29/2001-1/31/2002**. This limits the generalizability of these finding to other WTC exposed cohorts who likely include individuals with pre-existing lung disease or other risk factors such as smoking. Definitions of susceptible and resistant cases were based on FEV_1 measured at SPE. We believe that low FEV_1 is the single best outcome measure to define lung injury in the FDNY cohort because FEV_1 has been longitudinally measured starting three years prior to 9/11/2001 and continues to be performed at every FDNY-WTC-MMTP. However, using FEV_1 as a single measure of lung function could lead to non-differential misclassification. Since FEV_1 is reduced in both restriction and obstruction low FEV_1 doesn't distinguish between the two. In prior investigation, we have observed that obstruction caused the vast majority of abnormal FEV_1 in WTC exposed fire fighters. (37) In addition, patients with accelerated decline in FEV_1 who will progress to disease but currently have a normal FEV_1 will be misclassified as controls. While misclassification may occur when using $FEV_1 < 77\%$ as a single measure of abnormal lung function, heterogeneity of disease(s) produced by this single measure will bias the results toward the null. In spite of the potential for non-differential information bias, using low FEV_1 has yielded strong biomarkers-disease associations. (3, 39) Since all the FDNY firefighters were exposed to WTC dust, we do not have unexposed control group to compare and therefore we cannot determine if WTC exposure is necessary for the observed effect. Replication of these findings in other longitudinally followed populations with and without PM exposure will be important to demonstrate the generalizability of these findings.

Utilizing a nested case-cohort design, we were able to identify CVD serum biomarkers drawn within six months of 9/11/01 that predicted if an exposed individual was likely to recover lung function or progress to lung disease. These biomarkers were expressed during disease evolution and so reflect processes leading to WTC-LI susceptibility or resistance. The observation that CVD biomarkers predict changes in lung function is consistent with a growing body of evidence that pulmonary vascular disease occurs early in COPD. This study emphasizes the utility of serum stored in the aftermath of a disaster. This insight on protein expression may guide future mechanistic and therapeutic studies designed to blunt the impact of the world wide COPD epidemic.

Acknowledgments

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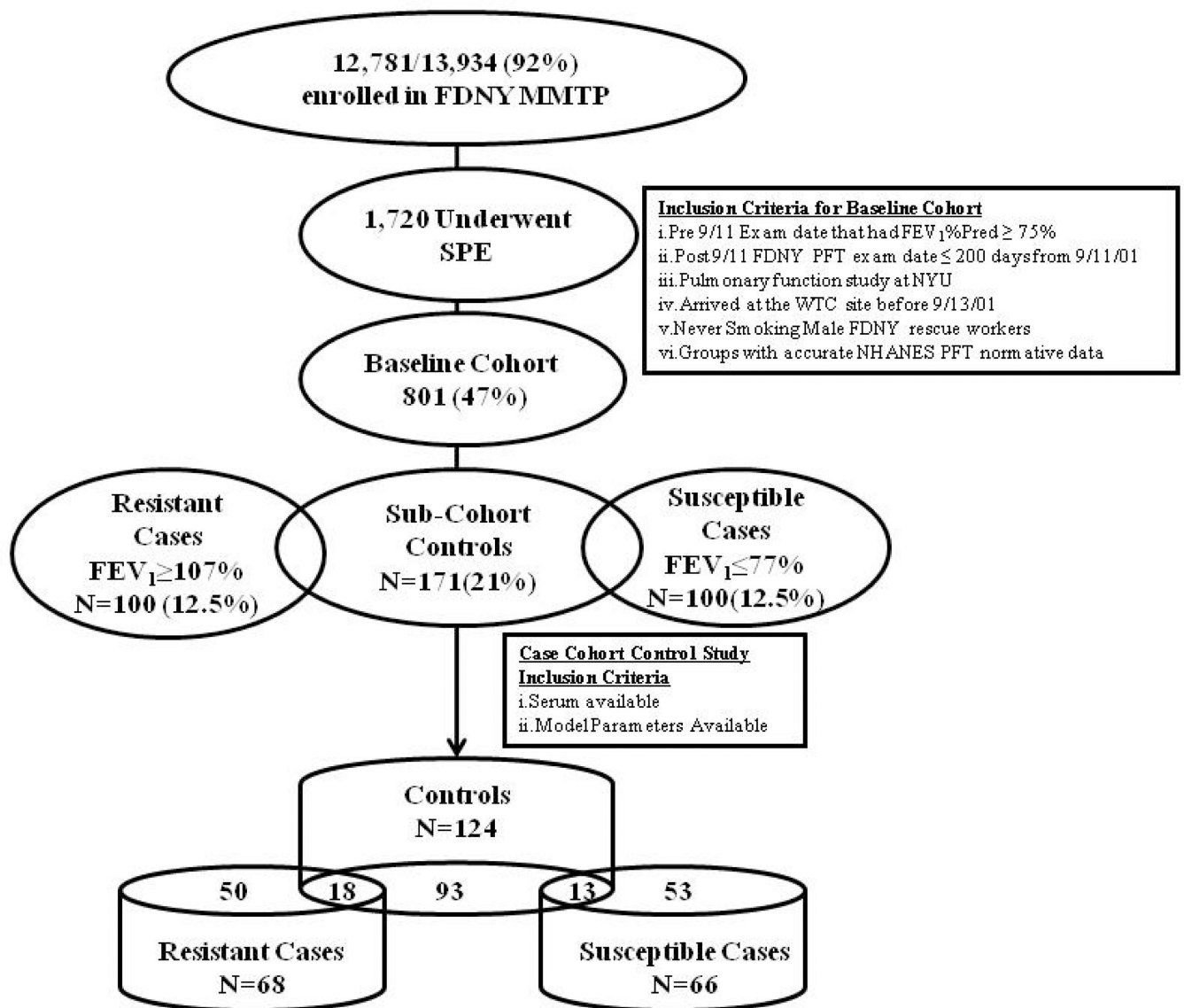
Figure 1.
Study Design

Table 1

Demographics and FEV$_1$ of Subspecialty Pulmonary Evaluation Cohorts

Characteristic		Baseline Cohort N=801	Resistant[+] N=68	Controls[+] N=124	Susceptible[+] N=66
WTC Arrival Time[#]	Morning 9/11	197 (25)	13(19)	21(17)	18 (27)
	Afternoon 9/11	498 (62)	48(71)	88(71)	36 (55)
	Anytime 9/12	106 (13)	7(10)	15 (12)	12(18)
9/11 to Study, Months[¶]	MME	2.7 (2–3.8)	2.0(2–3)	2.5 (2–3)	2.0 (2–3)
	SPE	33.8 (25–57)	33.0(27–53)	33.3 (25–55)	32.0 (21–52)
BMI, kg/m²[¶§]	MME	28.0 (26–30)	27.3(26–29)	28.0(26–30)	29.1 (27–32)
	SPE	28.9 (27–31)	27.6(26–30)	29.0(27–31)	30.3 (28–34)
Years of Service at 9/11[¶ƒ]		18.3(11–23)	18.7(10–24)	18.0 (11–22)	18.8(14–23)
Age at 9/11[¶]		40.0 (36–45)	42.0(38–46)	42.0 (37–46)	40.5(36–46)

[#]Expressed as N (%);

[¶]Expressed as Median (Inter Quartile Range);

[+]p<0.05 by one-way ANOVA Kruskal Wallis between Susceptible, Resistant Cases, and Controls

[§]BMI at MME: Resistant N=67

[ƒ]Years of Service: Controls: N=68; Resistant N=26; Susceptible: N=51

Abbreviation Dictionary: Medical Monitoring Entry (MME); Subspecialty Pulmonary Exam (SPE)

Table 2

Pulmonary Function Testing[#]

		Resistant	Controls	Susceptible	p[f]
Pre 9/11 FEV$_1$		117(107–124)	102(92–112)	89(82–96)	<0.001
MME FEV$_1$		105(96–113)	92(82–99)	79(72–89)	<0.001
	FEV$_1$	113(109–118)	95(84–103)	72(67–75)	<0.001
	MCT Slope[¶]	0.039(0.02–0.07)	0.048(0.03–0.12)	0.15(0.05–1.8)	<0.001
SPE	**DLCO % Predicted**[+]	119(108–135)	106(99–116)	95(84–107)	<0.001
	BD Response[§]	4(2–8)	5(2–10)	15(7–28)	<0.001

[#]Values Expressed as Median (Inter Quartile Range)

[¶]MCT Slope: Controls N=94; Resistant Cases N=57; Susceptible Cases N=32

[+]DLCO % Predicted: Controls N=59; Resistant Cases N=24; Susceptible Cases N=44

[§]BD Response : Controls N=64; Resistant Cases N=26; Susceptible Cases=48

[f]Significance assessed by one-way ANOVA Kruskal Wallis between Resistant, Susceptible Cases and Controls

Abbreviation Dictionary: MCT: Methacholine Challenge Test; BD: Bronchodilator; DLCO: Diffusion Capacity of the Lung for Carbon Monoxide; FEV$_1$, Forced Expiratory Capacity in 1 second

Table 3

A: Values of Significant Serum Analytes in Single logistic Regression Model

Analyte[#][¶]	Susceptible (N=66)	Controls (N=124)	p[+]
CRP	6.28(3.28–13.16)	5.10(1.99–11.19)	0.151
MIP-4	145.28(106.56–211.25)	184.68(109.68–948.20)	0.008
Apo AI	4273.98(2039.29–6333.55)	2569.94(1833.34–4198.31)	0.003
Apo AII	1830.96(570.65–2594.51)	845.12(428.00–1730.77)	0.002
Apo CII	263.82(11.59–1794.55)	165.01(LLOD-757.13)	0.007
Apo CIII	305.80(157.92–646.63)	203.18(112.44–398.44)	0.005
Apo E	973.58(454.16–1749.37)	600.91(311.08–1058.87)	0.001

B: Values of Significant Serum Analytes in Single logistic Regression Model

Analyte[#][¶]	Resistant (N=68)	Controls (N=124)	p[+]
MPO	117.94(68.01–176.91)	143.56(105.26–212.31)	0.016
sVCAM	1500.83(1126.57–1808.16)	1349.97(1126.57–1568.65)	0.103

[#]Expressed as Median(Inter Quartile Range);

[¶]MIP-4 in ng/mL, CRP in μg/dL, Apolipoproteins in μg/mL

[+]p<0.05 by Mann-Whitney U-test between Susceptible Cases and Controls

Abbreviation Dictionary: CRP: C-Reactive Protein; MIP-4: Macrophage Inhibitory Proten-4; Apo: Apolipoprotein; LLOD: Lower Limit of Detection

[#]Expressed as Median(Inter Quartile Range);

[¶]Expressed in ng/mL

[+]p<0.05 by Mann-Whitney U-test between Resistant Cases and Controls

Abbreviation Dictionary: MPO: Myeloperoxidase; sVCAM: soluble Intracellular Adhesion Molecule

Table 4

Relative Risk Models Predicting Resistance or Susceptibility to World Trade Center-Lung Injury

	Analyte	Cutpoint#¶	Sample Fraction		Relative Risk(95% CI)	
			Cases	Controls	Crude[+]	Adjusted §
RESISTANT						
Single Analyte	MPO	105.26	31/68	31/124	2.37(1.26–4.44)	2.92(1.40–6.08)
	sVCAM	1568.65	30/68	31/124	2.51(1.34–4.71)	2.26(1.10–4.64)
Multi-Analyte	MPO	105.26	31/68	31/124	2.39(1.26–4.56)	2.89(1.37–6.10)
	sVCAM	1568.65	30/68	31/124	2.53(1.34–4.82)	2.24(1.07–4.70)
				AUC	0.647(0.564–0.731)	0.830(0.774–0.887)
	CRP	2.45	58/66	85/124	3.33(1.45–7.63)	3.00(1.20–7.47)
	MIP-4	194.90	18/66	59/124	0.45(0.24–0.84)	0.37(0.18–0.77)
	Apo AI	4220.87	33/66	30/124	3.13(1.66–5.91)	3.61(1.72–7.61)
Single Analyte	Apo AII	1772.87	36/66	30/124	3.76(1.99–7.10)	4.04(1.94–8.40)
	Apo CII	398.44	29/66	31/124	2.35(1.25–4.43)	2.69(1.29–5.62)
SUSCEPTIBLE	Apo CIII	1058.87	29/66	31/124	2.35(1.25–4.43)	2.71(1.29–5.70)
	Apo E	268.71	33/66	31/124	3.00(1.60–5.64)	3.03(1.46–6.30)
	Apo AII	1772.87	36/66	30/124	3.51(1.80–6.87)	3.85(1.79–8.26)
Multi-Analyte	CRP	2.45	58/66	85/124	4.01(1.65–9.79)	3.93(1.43–10.79)
	MIP-4	194.90	18/66	59/124	0.33(0.16–0.66)	0.26(0.11–0.59)
				AUC	0.767(0.692–0.842)	0.858(0.796–0.919)

MIP-4, sVCAM, and MPO in ng/mL, CRP in mg/dL, Apolipoproteins in µg/mL

¶ Cutpoints were based on the 75th percentile of the Controls for all analytes except MPO (25th percentile) and CRP 2.45

[+] Crude represents the risk without adjusting for any confounders

§ Adjusted: age at 9/11, BMI at SPE, exposure group and pre-9/11 FEV1 % Predicted

Abbreviation Dictionary: Area Under the Curve(AUC)