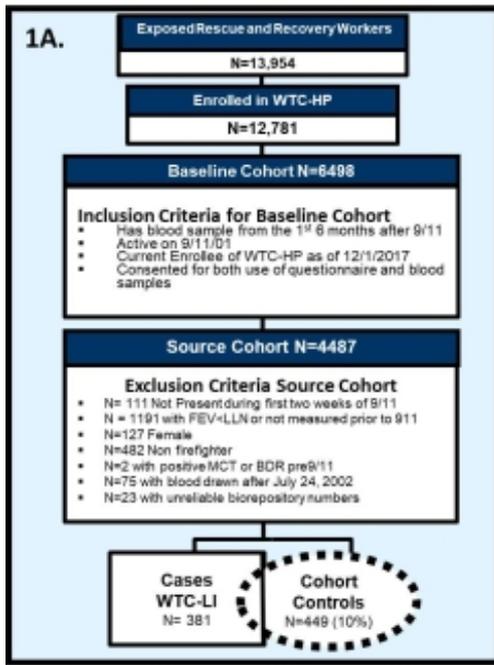# Validation of Biomarkers of World Trade Center (WTC) Lung Injury: Design of a Case Cohort Control

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RATIONALE World Trade Center Exposed (WTC) Fire Department of New York (FDNY) responders suffered symptomatic loss of FEV_1<lower limit of normal (LLN), defined as WTC-Lung Injury (WTC-LI). We have identified serum biomarkers predictive of WTC-LI in a select group of never smoking, symptomatic male firefighters. We now aim to validate metabolomics biomarkers to predict WTC-LI in the entire FDNY-WTC-responder cohort with a case-cohort design to determine clinically relevant disease modifiers. METHODS Subjects enrolled in the WTC-Health Program (WTC-HP)(n=12,781), were included in the baseline cohort(n=6,498) if they were current participants of the WTC-HP who consented and had a blood sample within 6 months from 9/11/2001, Figure-1A. The source cohort(n=4,487) were male firefighters present during the first two weeks of 9/11 with normal measured lung function prior to 9/11 ($FEV_1 \geq$LLN and negative MCT/BDR), and reliable bioprepository samples banked by 7/24/2002, the closure of the WTC site. Cases of WTC-LI, defined as having>one post-9/11 FEV_1<LLN without resolution(N=381), were compared to cohort-controls(N=449), a randomly drawn 10% of the source cohort. Clinical parameters available from the FDNY database were compared between cases and cohort-controls (N=794, N=36 overlap) by Chi-square/Student's t-test as appropriate. RESULTS. There were no significant differences between cohort controls and the source cohort in age, BMI, smoking, race, exposure, or clinical parameters, Figure-1B. Case and Cohort Controls. Age, BMI, race, and 9/11 exposure, baseline blood pressures, glucose, and lipids were not statistically significant between groups. Preliminary analyses show that cases had a higher percentage of smoking history and lower but normal FEV_1 prior to 9/11 compared to cohort controls (40% vs 32%, p=0.015; 94% vs 106%, p<0.001) respectively. There was no clinically significant reduction in FEV_1/FVC ratios between cases and cohort-controls. CONCLUSIONS Completion of this study will validate potentially modifiable biomarkers of WTC-LI. Obtaining the metabolomic profile of this case cohort will identify targets associated with disease severity and progression of WTC-LI. We will monitor the effect of dietary modification on these biomarkers (FIREHOUSE TRIAL www.clinicaltrials.gov,#NCT03581006) and examine their utility in prognosticating WTC-LI sequelae using Cox regression models. Global metabolomics will be acquired on case-cohort and used to augment understanding the impact of risk factors such as smoking, obesity, and diet on WTC-LI. Qualified bio-signatures from this cohort can be expanded

to other cohorts with metabolic syndromes and heavy particulate exposure.

1A.

Exposed Rescue and Recovery Workers
N=13,954

Enrolled in WTC-HP
N=12,781

Baseline Cohort N=6498

Inclusion Criteria for Baseline Cohort
- Has blood sample from the 1st 6 months after 9/11
- Active on 9/11/01
- Current Enrollee of WTC-HP as of 12/1/2017
- Consented for both use of questionnaire and blood samples

Source Cohort N=4487

Exclusion Criteria Source Cohort
- N= 111 Not Present during first two weeks of 9/11
- N = 1191 with FEV<LLN or not measured prior to 911
- N=127 Female
- N=482 Non firefighter
- N=2 with positive MCT or BDR pre9/11
- N=75 with blood drawn after July 24, 2002
- N=23 with unreliable biorepository numbers

Cases WTC-LI N= 381 | Cohort Controls N=449 (10%)

1B: Clinical Measures

Measure	Baseline Cohort N=4487	Cohort Ctrls N=449	Cases N=381	P
Age on 9/11 (yrs)	39.7(7.5)	40.1(7.5)	39.5(7.8)	0.298
BMI (at WTC-HP Entry)	29.1(3.22)	29.2(3.22)	29.4(3.71)	0.293
Ever Smokers	1417(32%)	143(32%)	152(40%)	0.015
Caucasian Race	4216(94%)	427(95%)	354(93%)	0.616
Exposure Group — AM of 9/11	751(16%)	85(19%)	67(18%)	
Exposure Group — PM of 9/11	2412(54%)	235(52%)	194(43%)	0.667
Exposure Group — 9/12 or later	1324(30%)	129(29%)	120(31%)	
Duration (months)	3.76(2.7)	3.68(2.7)	3.51(2.7)	0.357
Systolic BP	116.7(12.3)	117.2(13.3)	117.9(13)	0.482
Diastolic BP	73.2(8.3)	73.5(8.7)	74.1(8.8)	0.291
Glucose	93.3(18.2)	93.9(18.4)	94.5(20.5)	0.653
Triglyceride	184.1(135)	183.9(127)	196.6(142)	0.176
HDL	48.3(12)	48.4(13)	48.3(13)	0.952
LDL	125.2(35)	126(34)	122(36)	0.103
Cholesterol (total)	210.3(38)	211.1(36)	209.6(39)	0.563
Pre-9/11 — $FEV_{1 \%pred}$	106.4(13)	105.7(13)	93.3(8)	<0.001
Pre-9/11 — FEV_1/FVC	85(5)	85(5)	83(6)	<0.001
WTC-HP Entry — $FEV_{1 \%pred}$	98(13)	98.3(14)	84.6(10)	<0.001
WTC-HP Entry — FEV_1/FVC	84(5)	84(5)	81(6)	<0.001

Values are in Mean(SD) or N(%) as indicated; P calculated by t-test or Chi-Square as appropriate; No significant difference between any of the clinical measures in baseline cohort vs cohort control. P significant <0.05 between cases and baseline cohort by t-test or Chi-square as appropriate highlighted in red.
BMI kg/m²; BPs mmHg; Glucose dL/mL; Lipids mg/dL; $FEV_{1\%pred}$ based on $FEV_{1patient}/FEV_{1population}$ based on age/sex/height.

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