# Metabolomics of WTC-Lung Injury (WTC-LI): A Validation Study

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RATIONALE In our earlier metabolomics pilot, cases exposed to PM that later developed WTC-LI, those resistant to WTC-LI, and cohort controls express distinct metabolomes. We used random forests models to detect metabolites relevant to exposure and WTC-LI, and integrated the metabolome into predictive models of WTC-LI to improve discriminative abilities. We now aim to validate these findings and discover new relevant metabolites in a larger cohort. Given the size of the dataset generated, this process includes unique data pre-processing and analysis challenges, and is an opportune application for previously piloted analysis methods. METHODS Perform hypothesis-generating metabolomic profiling in collaboration with the Eastern Regional Comprehensive Metabolomics Resource Core on serum sampled within 6 months of 9/11/2001. Demographic/clinical data was obtained from the WTC-Health Program, Fig-1A. Symptomatic subjects referred for subspecialty pulmonary examination(SPE) underwent pulmonary function testing. Cases defined by their $FEV_{1\%predicted}$ of normal at SPE (NHANES III). Subjects resistant to WTC-LI (n=50), had $FEV_1$% predicted within one standard deviation (SD) of the highest $FEV_{1\%predicted}$ of the study cohort. Subjects susceptible (n=50) to WTC-LI had $FEV_{1\%predicted}$ within one SD of the lowest $FEV_{1\%predicted}$ of the cohort. The cohort controls (n=100) were randomly selected from the study cohort after stratification based on BMI and $FEV_{1\%predicted}$(n=100), Fig-1B. Metabolic profiling was performed using ultra-performance liquid chromatography coupled to time-of-flight mass spectrometry. Signals will be matched to in-house retention time mass libraries and public mass databases, mapping the matched signals to biochemical pathways. RESULTS 5,623 distinct peak intensities were identified in the 200 samples. Data was filtered so that peak intensities in the study pools were nonzero. Peak intensities were normalized and median-centered to account for day-to-day variations in measurement. We will perform validation of pilot random forests metabolomics models on this new subject pool, as well as a new analysis. Exploratory tools will include neural-nets, decision trees, support-vector machine, as well as unsupervised clustering and dimension reduction. We predict models of bioactive lipids, polyunsaturated fatty acids, as well as acetylated/acylated, aliphatic, and branched-chain amino acids will identify subjects most and least at risk for developing WTC-LI. Integration of metabolomic findings with previously identified biomarkers will

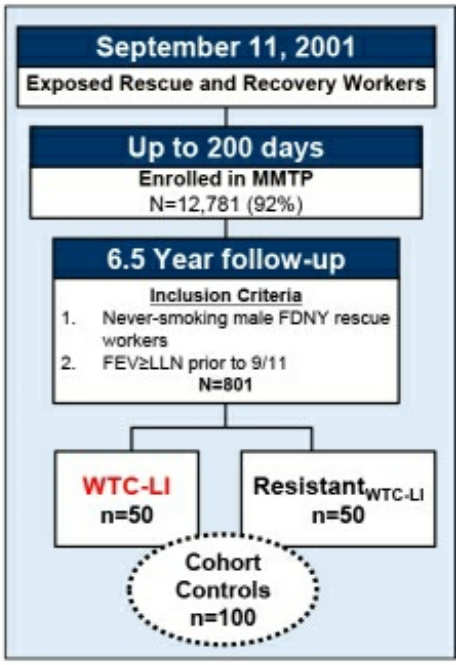
improve the discriminative abilities of predictive models. CONCLUSIONS We expect to validate the performance of previously identified metabolite, chemokine, cytokine, clinical, and environmental biomarkers in this group of 200 individuals. We also aim to support and gain insight into hypotheses on mechanistic relationships between our biomarkers using unsupervised exploratory analysis.

**A. Clinical Measures**

| Measure | | Metabolomics Subcohort | | |
|---|---|---|---|---|
| | | Controls n=100 | WTC-LI n=50 | Resistant$_{WTC-LI}$ n=50 |
| PFT at SPE | $FEV_{1\%Pred}$ | 93(85-98) | 73(68-76) | 114(109-121) |
| | $FVC_{\%Pred}$ | 96(90-103) | 80(75-85) | 111(107-120) |
| | $FEV_1/FVC$ | 76(73-80) | 71(65-77) | 81(78-84) |
| BMI ($kg/m^2$) | WTC-HP Entry [a] | 28(26-31) | 29(27-31) | 27(26-29) |
| | SPE | 29(27-31) | 29(27-33) | 28(26-30) |
| Age on 9/11 (years) | | 41(36-44) | 41(36-45) | 42(38-45) |
| Exposure N(%) | Low | 10(10%) | 11(22%) | 5(10%) |
| | Intermediate | 71(71%) | 28(56%) | 35(70%) |
| | High | 19(19%) | 11(22%) | 10(20%) |
| Duration (months) [d] | | 3(1-5) | 1(1-4) | 3(1-7) |
| Lipids (mg/dL) | Trig | 168(105-246) | 185(113-271) | 123(97-185) |
| | HDL | 47(40-55) | 42(36-52) | 46(40-55) |
| | LDL | 131(105-158) | 134(110-161) | 135(108-154) |
| Heart Rate [c] | | 72(66-76) | 74(72-80) | 72(67-76) |
| BP (mmHg) | SBP[a] | 116(108-124) | 120(110-128) | 118(110-122) |
| | DBP[a] | 72(70-80) | 72(69-82) | 70(69-80) |

[a] - data available for 49 subcohort resistant$_{WTC-LI}$ cases; [b] - data available for 48 subcohort resistant$_{WTC-LI}$ cases; [c] - data available for 47 subcohort resistant$_{WTC-LI}$ cases; [d] - data available for 46 subcohort resistant$_{WTC-LI}$ cases

**B.**

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