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RESEARCH ARTICLE

Lysophosphatidic acid and apolipoprotein A1 predict increased risk of developing World Trade Center-lung injury: a nested case-control study

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Abstract

Rationale: Metabolic syndrome, inflammatory and vascular injury markers measured in serum after World Trade Center (WTC) exposures predict abnormal FEV_1. We hypothesized that elevated LPA levels predict $FEV_1 < LLN$.
Methods: Nested case-control study of WTC-exposed firefighters. Cases had $FEV_1 < LLN$. Controls derived from the baseline cohort. Demographics, pulmonary function, serum lipids, LPA and ApoA1 were measured.
Results: LPA and ApoA1 levels were higher in cases than controls and predictive of case status. LPA increased the odds by 13% while ApoA1 increased the odds by 29% of an $FEV_1 < LLN$ in a multivariable model.
Conclusions: Elevated LPA and ApoA1 are predictive of a significantly increased risk of developing an $FEV_1 < LLN$.

Keywords

Biomarkers, dyslipidemia and occupational exposure, World Trade Center

History

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Introduction

The destruction of the World Trade Center (WTC) complex led to the exposure of thousands of subjects to particulates and the products of combustion. The intense particulate matter (PM) exposure at the WTC site overwhelmed the lung's normal protective defenses. Respiratory compromise after WTC-PM exposure has been documented in FDNY rescue workers (Aldrich et al., 2010; Banauch et al., 2003, 2005, 2006; Feldman et al., 2004; Felipe et al., 2011; Prezant et al., 2002) other exposed workers (Herbert et al., 2006) and lower Manhattan residents (Reibman et al., 2005). Some individuals subsequently developed abnormal lung function while others improved. It is this dichotomous outcome and identifying predictive biomarkers that has been the focus of our recent work.

Our group has published that mediators of metabolic syndrome, inflammation and vascular injury in early serum samples are predictive of lung function outcome in a longitudinally followed never smoking WTC-exposed FDNY cohort (Nolan et al., 2012). Development of lung dysfunction following particulate exposure is a major health concern worldwide. The prevalence of metabolic syndrome is high in industrialized nations and is rapidly increasing in developing nations where high ambient particulates are also a tremendous health concern (Chen & Schwartz, 2008). The interaction of these two disorders is a topic of considerable importance.

Nearly half of chronic obstructive pulmonary disease (COPD) patients demonstrate the presence of one or more components of metabolic derangement. Lipids are key components of metabolic syndrome and their metabolites have been linked to pulmonary inflammation and subsequent airflow obstruction (Tiengo et al., 2008). We also know that statin therapy-reduced airspace inflammatory cells and Th2 cytokine production in murine allergic asthma (McKay et al., 2004; Yeh & Huang, 2004). Simvastatin inhibited lung parenchymal destruction and peribronchial and perivascular inflammatory cell infiltration in a murine model of smoking-induced emphysema (Lee et al., 2005). In asthmatics, statin therapy is associated with reduced leukocytes

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and leukotrienes in sputum and improvement in FEV_1 (Cowan et al., 2010; Hothersall et al., 2008). Subjects with COPD treated with statins had reduced FEV_1 decline, decreased intubations and decreased mortality (Blamoun et al., 2008; Soyseth et al., 2007). There are also data that suggest a relationship between serum total and non-high-density lipoprotein (HDL) cholesterol and having asthma (Fessler et al., 2009). Therefore, not only are lipids biologically active in the development of lung disease but they are also plausible therapeutic targets. However, the systemic inflammatory effects of lipids, their subsequent end-organ effects and the mechanism of lipid-induced pulmonary inflammation are poorly understood.

Low-density lipoprotein (LDL), HDL and triglycerides (Trig) are routinely available biomarkers of vascular disease and are components of metabolic syndrome. Our group has recently shown that dyslipidemia is a predictor of developing WTC-lung injury (WTC-LI). As a logical extension of our earlier work we therefore turned our attention to the biological active lipids, LPA (an LDL derivative) and ApoA1 (a component of HDL). We hypothesized that LPA and ApoA1, a known mediator of LPA, predict the development of WTC-LI. In a nested case-control study we show that increased serum LPA and ApoA1 levels predict the development of an abnormal FEV_1 in our WTC-PM-exposed firefighters. Some of the results of these studies have been previously reported in the form of an abstract (Cho et al., 2013).

Methods

Study design

As part of the first medical monitoring exam (MME) post-9/11, all participants received pulmonary function testing and serum samples were collected and banked in a biorepository. Firefighters who presented with pulmonary symptoms were referred to subspecialty pulmonary evaluation (SPE) between 9/12/2001 and 3/10/2008. The baseline cohort was derived from the 1720 exposed symptomatic workers who needed SPE and treatment within 6.5 years of 9/11/2001 (Naveed et al., 2012; Weiden et al., 2012). We performed a nested case-control study on a homogeneous baseline cohort of 801 subjects without prior lung disease and without tobacco use as a lung disease confounder. We specifically excluded all subjects who ever reported smoking on any of their yearly monitoring visits. Cases and controls were both drawn from this baseline cohort. *Cases* of WTC-LI were identified as the 100 (62 of whom had all final model parameters) that had the lowest FEV_1 at the time of SPE. Specifically, cases were defined as being in the bottom octile of FEV_1% predicted at SPE. The FEV_1% predicted of the cases was below the lower limit of normal (LLN) as calculated by NHANES III. The cohort control ($N = 171$) was randomly selected from the baseline cohort after stratification on BMI and FEV1 at MME. The *controls* are all individuals in the random sample cohort control who did not meet criteria to be a WTC-LI case ($n = 153$). Controls with all final model parameters were 111/153. All subjects signed informed Institutional Review Board-approved consent at the time of enrollment allowing analysis of their information and samples for research. This study has been approved by the Institutional Review Boards of Montefiore Medical Center (#07-09-320 and New York University; #11-00439).

Demographics

Age, race 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): (1) present on the morning of 9/11/2001; (2) Arrived between afternoon on 9/11/2001 and 9/12/2001 (Weiden et al., 2010). Those arriving after day three were excluded from analysis as a result of their low numbers in this sample (Longo et al., 2011). In addition, medication histories were obtained by reviewing clinical and electronic medication records. Subject were considered to have received pulmonary specific treatment if they had ever received either a short acting beta-agonist, long acting beta-agonist or inhaled corticosteroid. In addition, we considered a subject to have received lipid-lowering therapy if they were on any statin at any time.

Serum sampling

Blood drawn at the first post-9/11 FDNY-WTC-monitoring exam was allowed to stand for 1 h at room temperature before being centrifuged at 1800 *g* for 10 min. Serum was stored at −80 °C (Bio-Reference Laboratories, Inc., Elmwood Park, NJ). Serum was thawed once at 4 °C and assayed using LPA Elisa (Echelon, Salt Lake City, UT) and Apolipoprotein Plex (Millipore, Billerica, MA) according to manufacturer's instructions on a Luminex 200IS (Luminex Corporation, Austin, TX). Data were analyzed using Graphpad Prism V (San Diego, CA) and $MasterPlex_{QT}$ (MiraiBio Group, San Francisco, CA). Other measures of inflammation such as white blood cell count (WBC) and differential were obtained from the medical records at the time of MME serum sampling.

Statistical analysis

We tested normality using the Shapiro–Wilk test and Q–Q plots. Data are expressed as median (interquartile range, IQR) or odds ratio (95% confidence interval), unless otherwise stated. A two-sided p value less than 0.05 were considered significant. All analyses were performed with STATA/SE version 12.1 (StataCorp LP, College Station, TX) and SPSS version 20 (IBM, Armonk, NY). We used Wilcoxon rank sum test for between group comparisons, as appropriate. Chi-squared test was used to determine significance of categorical variable.

Lipid predictors of WTC-LI model building and validation

Given the dichotomous outcome of normal and abnormal FEV_1 we tested if serum biomarkers predicted airflow obstruction using logistic regression. Variables identified as potential confounders and those with a p value <0.2 in univariable analysis were included in the multivariable logistic regression model. The Hosmer–Lemeshow goodness-of-fit test was used to assess calibration of the final

model. The model discrimination was evaluated using the receiver operating characteristic area under the curve. Bootstrap was used to internally validate and confirm the robustness of the classification performance using 10 000 samples of equal size to the original data set used to develop the final model (Steyerberg et al., 2001).

Results

Nested case-control design

FEV_1 was measured starting three years prior to 9/11/2001. FEV_1 is still performed at every FDNY-WTC-Medical Monitoring and Treatment Program (MMTP) visit, giving a comprehensive measure of changing lung function over time. The baseline cohort was derived from the symptomatic subjects enrolled in the SPE cohort if they met the inclusion criteria as outlined in Figure 1 and as previously described. Derivation of 801 baseline cohort, 62 cases, and 111 controls from the SPE cohort with final model characteristics available is described in Figure 1.

Demographics of both the SPE cohort and baseline cohort were similar to sub-cohort controls, as previously described (Nolan et al., 2012). Cases and controls had statistically similar time from 9/11 to MME and SPE, years of service and age at 9/11. Cases had a similar percentage of subjects that arrived at the site on the morning of 9/11 as arrived on the afternoon of 9/11 till 9/12. BMI of the cases was only significantly elevated compared with controls at SPE (Table 1).

Lung function and computed tomography (CT)-scan phenotyping

Lung function

Controls had similar FEV_1, forced vital capacity (FVC) and FEV_1/FVC compared with the SPE cohort ($N = 1720$) and baseline cohort ($N = 801$) (data not shown). Cases had lower FEV_1, FVC and FEV_1/FVC, total lung capacity (TLC), alveolar volume (VA), carbon monoxide diffusing capacity (DLCO) and DLCO/VA when compared with controls at all-time points. Measures of airflow obstruction, including methacholine slope and bronchodilator response was statistically increased in the cases when compared with controls (Table 2). Lung function in sub-cohort controls increased from the MME to SPE (93–97%) while the FEV_1% predicted (FEV_1%pred) of affected cases continued to decline between the two pulmonary function tests (78–72%; $p < 0.0001$ all comparisons). Despite these significant differences in lung function, we found that 57/62 (92%) of cases and 91/111 (82%) of controls were receiving some pulmonary specific treatment (Pearson's χ^2 3.188, $p = 0.074$).

CT-scan phenotype

CT scans had been done on 38/62 cases and 61/111 controls. Cases had similar measures of air trapping and bronchial wall thickening as controls.

Clinical biomarkers of inflammation and lipid derangement in cases and controls

We used logistic regression as a tool to analyze our data (binary outcome), we indeed checked the linear relationship between the logit (log-odds) and the continuous variables following the steps described by Hosmer and Lemeshow (Hosmer & Lemeshow, 1989). No transformations of the data were needed.

Univariable regression was used to identify potential predictors and confounders of case status. Based on the analysis, LPA, ApoA1 and, as previously showed, dyslipidemia were significant predictors of case status. On the other hand, HDL, LDL, triglycerides, WBC and cell differential were not (Table 3). LPA, ApoA1, dyslipidemia,

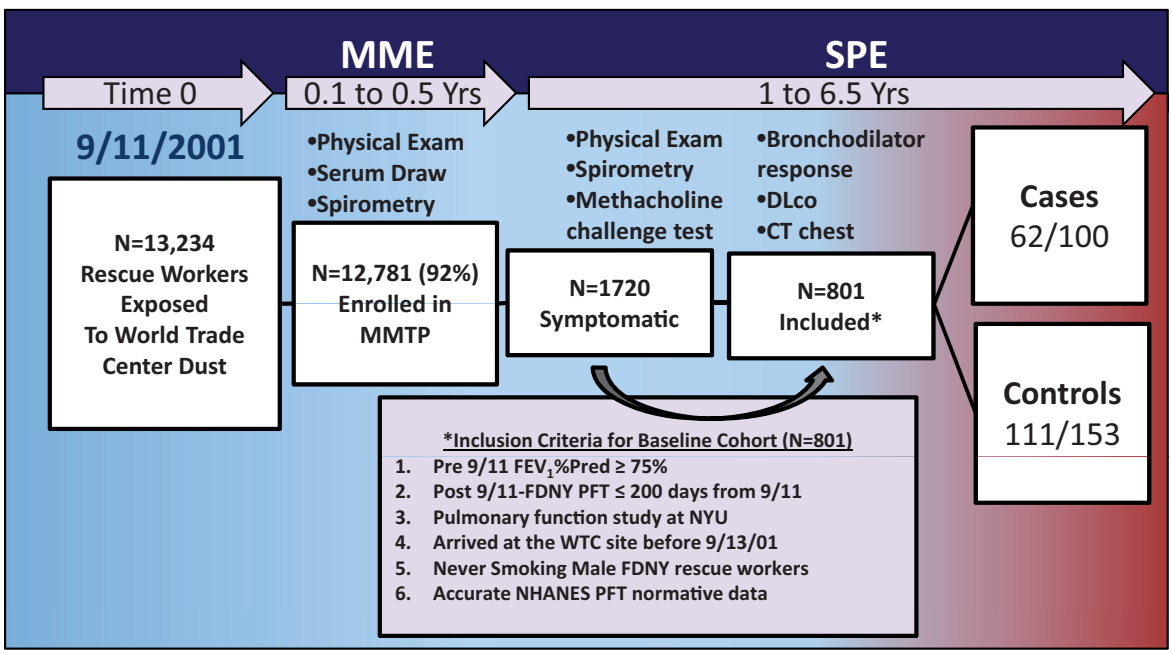

Figure 1. Study design/timeline. Symptomatic subjects in the FDNY MME presented for SPE. Subjects underwent outlined studies at MME and SPE, respectively. Baseline cohort met the listed inclusion criteria. Cases ($N = 62$) and Controls ($N = 111$) had all final model variables available.

Table 1. Demographics.

Characteristics	Baseline cohort	Cases	Controls	p‡
WTC arrival[a]				
Morning 9/11	197 (25)	17 (24)	18 (16)	0.079
Afternoon 9/11–9/12	604 (75)	45 (76)	93 (84)	
9/11 to study, months[b]				
MME	2.7 (2–4)	2.7 (2–4)	2.5 (2–3)	0.170
SPE	33.8 (25–57)	32.7 (21–53)	33.8 (26–56)	0.472
BMI kg/m^2[b]				
MME	28.0 (26–30)	29.1 (27–31)	27.9 (26–31)	0.077
SPE	28.9 (27–31)	30.0 (28–34)	29.0 (27–31)	0.006
Years of Service at 9/11[b]	13 (7–19)	15 (9–18)	14 (8–18)	0.977
Age at 9/11[b]	40.0 (36–45)	40 (36–46)	42 (37–46)	0.666

Definition of abbreviations: MME, medical monitoring entry; SPE, subspecialty pulmonary evaluation; BMI, body mass index.
[a]Expressed as N(%).
[b]Expressed as median (inter quartile range).
‡Significance assessed by the Wilcoxon Rank sum test and chi-squared test.

Table 2. Pulmonary function testing and CT phenotype.

	Cases	Controls	p‡
Pre 9/11[a]			
FEV_1	88 (82–96)	104 (92–113)	<0.001
FVC	87 (80–96)	97 (88–108)	<0.001
FEV_1/FVC	82 (78–86)	85 (81–88)	0.001
MME[a]			
FEV_1	78 (71–88)	93 (85–100)	<0.001
FVC	79 (72–88)	89 (82–95)	<0.001
FEV_1/FVC	82 (76–86)	84 (80–87)	0.021
SPE[a]			
FEV_1	72 (68–74)	97 (88–104)	<0.001
FVC	79 (75–85)	98 (93–106)	<0.001
FEV_1/FVC	71 (65–77)	77 (74–81)	<0.001
TLC	96 (83–105)	103 (98–109)	0.001
VA	83 (76–90)	94 (88–101)	<0.001
DLCO %[b]	96 (86–107)	107 (101–116)	0.001
DLCO/VA	121 (113–132)	117 (103–122)	0.044
MCT slope[c]	0.148 (0.05–1.09)	0.04 (0.02–0.10)	0.005
BD response[d]	15 (8–25)	5 (2–8)	<0.001
CT Findings[e]			
Air trapping	22/38 (58)	25/61 (41)	0.147
BWT	13/38 (34)	22/61 (36)	1.000

Definition of abbreviations: MME, medical monitoring entry; SPE, subspecialty pulmonary evaluation; MCT, methacholine challenge test; BD, bronchodilator response; BWT, bronchial wall thickening.
[a]Values Expressed as Median (Inter Quartile Range).
[b]DLCO % predicted: controls $N = 50$; cases $N = 42$.
[c]MCT slope: controls $N = 90$; cases $N = 30$.
[d]BD response: controls $N = 54$; cases $= 46$.
[e]Expressed as N (%).
‡Significance assessed by the Wilcoxon Rank sum test or chi-squared test.

polymorphonuclear (PMN) all had a p value <0.2 and were included in the multivariable logistic regression model. Even though the medians of LPA levels were similar between cases and controls, the same magnitude of increment (10 μM) does not behave the same in terms of LI prediction. In the univariable and multivariable logistic analyses per every 10 μM increased in LPA the odd of developing LI was estimated to be 1.12 and 1.13 times larger, respectively.

Despite platelet count not being significant in univariate analysis we chose to include it in multivariable analysis, since it is a known potential confounder of vascular disease and a source of LPA (Boucharaba et al., 2004). In addition, review of their electronic medical record showed that 16/111 (15%) of the control patients and 11/62 (18%) of the cases were taking a statin (Pearson's χ^2 0.336; $p = 0.56$).

Inflammatory and dyslipidemic biomarkers predict decline in lung function

To assess the relationship between LPA and ApoA1 with the outcome of being a susceptible case, we fitted a multivariable logistic model adjusted for BMI at SPE, exposure intensity, pre-9/11 FEV_1% predicted, age on 9/11, and WTC arrival time, dyslipidemia, platelet and PMN count (Table 4). In the adjusted model, a 10 μM increase in LPA was associated with a 14% increase in the odds of having WTC-LI while an increase of 1 mg/mL of ApoA1 increased the odds of developing WTC-LI by 29% (Table 4). The interaction term was not significant. The change in BMI was also adjusted for in this same model and a 10μM increase in LPA was associated with a 12% increase in the odds of having WTC-LI while an increase of 1 mg/mL of ApoA1 increased the odds of developing WTC-LI by 29%.

Model validation

Since there is no external cohort that can be used to validate this model, we chose bootstrapping as an internal method to validate the models classification performance. We chose to use bootstrapping since it outperforms jackknife (Steyerberg et al., 2001). For LPA the calculated bias was 0.0019022 (coefficient $p = 0.045$) and for ApoA1 of 0.0342232 (coefficient $p = 0.007$). Therefore, these results internally confirm the classification performances of the model developed above.

The effect of LPA and ApoA1 level on the probability of developing WTC-LI

To better understand the effect of LPA and ApoA1 on the probability of developing WTC-LI, we utilized a three-dimensional (3D) surface plot of the 25th and 75th percentiles of both LPA and ApoA1 (Figure 2). The chance of developing WTC-LI is shown as a probability isopleth. LPA and ApoA1 both show that with increasing serum levels, the probability of WTC-LI is increased. Specifically, LPA axis: the probability of developing WTC-LI goes from 43% to 51%, when

Table 3. Biomarkers and crude OR predicting WTC-LI.

Analyte	Cases[a]	Controls[a]	Crude OR[b]	*p*
LPA (μM)	11.4 (5.6–42.8)	11.5 (4.0–24.2)	1.123 (1.020–1.237)[c]	0.018
Apo AI (mg/mL)	4.36 (2.06–6.32)	2.55 (1.83–3.79)	1.237 (1.085–1.409)	0.001
HDL (mg/dL)	43 (38–54)	48 (41–55)	0.985 (0.958–1.013)	0.288
LDL (mg/dL)[d]	133 (115–153)	131 (106–158)	1.001 (0.992–1.010)	0.852
TG (mg/dL)	142 (106–226)	144 (97–246)	1.000 (0.997–1.002)	0.929
Dyslipidemia (N%)[e]	18 (29)	17 (15)	2.262 (1.065–4.805)	0.034
WBC ($x10^3$)	6.3 (5.1–7.2)	6.2 (5.5–7.4)	0.926 (0.764–1.124)	0.437
PMN ($x10^3$)	3.5 (2.8–4.3)	3.6 (3.0–4.4)	0.787 (0.597–1.040)	0.092
Lymphocyte (Abs)	1686 (1512–2200)	1760 (1508–2208)	1.000 (1.000–1.001)	0.395
Platelets	230 (219–263)	239 (206–265)	1.000 (0.993–1.007)	0.920

Definition of abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; WBC, white blood cell; PMN, polymorphonuclear cell; OR, odds ratio.
[a]Expressed as median (inter quartile range) except for dyslipidemia.
[b]OR (95%CI).
[c]Per 10 μM.
[d]LDL Cases ($n = 57$), controls ($n = 103$).
[e]Dyslipidemia, HDL < 40 mg/dL and Trig > 150 mg/dL, reference is no dyslipidemia.

Table 4. Models predicting susceptibility to WTC–LI.

	Analyte	OR (95% CI)[a]	*p*
Single analyte	LPA, μM per 10	1.134 (1.020–1.261)	0.020
	Apo AI, mg/mL	1.290 (1.090–1.527)	0.003
	Dyslipidemia (N (%))	1.618 (0.660–3.968)	0.293
	PMN (x 10^3)	0.727 (0.521–1.015)	0.061
	Platelets	1.005 (0.996–1.014)	0.318
Multi-analytes	LPA (μM per 10)	1.139 (1.020–1.272)	0.021
	Apo AI (mg/mL)	1.288 (1.089–1.522)	0.003

Definition of abbreviations: PMN, polymorphonuclear cell count; OR, odds ratio.
[a]Adjusted for Plt count, BMI at SPE, exposure intensity, pre-9/11 FEV_1% predicted, PMN count, and the presence of dyslipidemia (HDL < 40 mg/dL and Trig > 150 mg/dL); χ^2 (8) = 69.34, $p < 0.001$; Hosmer-Lemeshow (Goodness-of-Fit) $p = 0.184$; AUC = 0.848 (0.786–0.910).

ApoA1 = 1.94, and from 61% to 68% when ApoA1 = 4.76, where 1.94 and 4.76 are ApoA1 IQR. ApoA1 axis: the probability of developing WTC-LI goes from 43% to 61%, when LPA = 4.3, and from 51% to 68% when LPA = 27.7 (Figure 2).

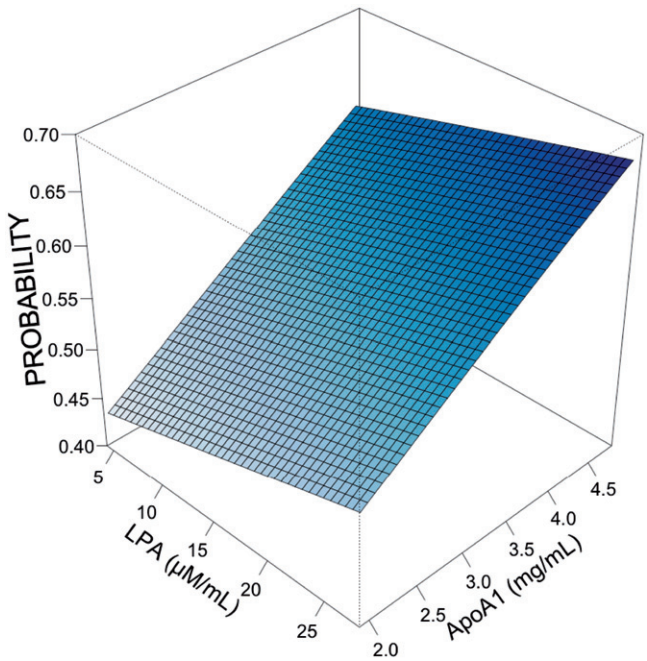

Figure 2. Multi-analyte model as 3D plot. Probability of developing WTC-LI of both LPA and ApoA1 are represented when adjusting for the covariates of exposure, BMI at SPE, pre-9/11 FEV_1% predicted, dyslipidemia, platelet and PMN count. Plots express probability isopleths for the development of WTC-LI with all other covariates held constant.

Discussion

In this report, we find that increased levels of LPA and ApoA1 in serum sampled within 6 months of 9/11 are associated with eventual loss of FEV_1 to less than LLN in the WTC-exposed FDNY firefighter cohort. These analytes were significant predictors when adjusted for exposure (9/11 arrival time), dyslipidemia, BMI at SPE, Pre-911 FEV_1% predicted, platelet and PMN counts. These findings suggest that the LPA and ApoA1 are biomarkers of WTC-PM associated loss of FEV_1.

Development of ventilatory dysfunction following particulate exposure is a major health concern worldwide. In addition, lipid derangement has also become a major health concern in both first and in emerging nations. Both diseases place a tremendous burden on the world's health resources. PM exposure and lipid derangements cause systemic inflammation, endothelial dysfunction and subsequent end-organ damage (Gan et al., 2004; Gosker et al., 2006; Mills et al., 2007; Tornqvist et al., 2007).

This study focuses on cases defined by their decline in FEV_1 to less than LLN at the time of symptomatic presentation. We believe that $FEV_1 <$ LLN is the single best outcome measure to define LI in the FDNY cohort. FEV_1 has been longitudinally measured starting three years prior to 9/11/2001 and continues to be performed at every FDNY-WTC-MMTP with quality controls that meet ATS criteria. This measurement has proven to be robust and reproducible. $FEV_1 <$ LLN is widely used as an outcome in the pulmonary literature so using it in the WTC-exposed FDNY cohort improves generalizability of our findings. Using FEV_1 as single measure of lung function could lead to non-differential misclassification since FEV_1 is reduced in both restriction and

obstruction. In prior investigation, we have observed that obstruction caused the vast majority of abnormal FEV_1 in WTC-exposed firefighters (Weiden et al., 2010). While misclassification may occur when using $FEV_1 < LLN$ 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 $FEV_1 < LLN$ has yielded strong biomarkers-disease associations (Weiden et al., 2013). Furthermore, our cases and controls had similar exposure as defined by WTC arrival time, age at the time of exposure and normal FEV_1 pre-911, relative to LLN. Finally, we had previously shown that our cohort had similar prevalence of lipid derangements as the larger population that it was drawn from.

Elevated LPA was observed to predict loss of FEV_1 in cases of WTC-LI. LPA is an oxidative product of LDL (Siess et al., 1999). LPA is a phospholipid and is soluble in both cell membranes and in aqueous fluid. LPA activates pathways involved in vascular injury (Lin et al., 2010; Moolenaar et al., 2004; Murph & Mills, 2007; Smyth et al., 2008). In addition, receptors of LPA are found in the lung. Specifically, the receptor for advanced glycation end-products (RAGE) has recently been identified as a novel mediator of LPA signaling (Rai et al., 2012). In the lung, RAGE is expressed at the highest baseline level of any other organ (Buckley & Ehrhardt, 2010). Pulmonary vascular injury occurs early in smoking-related COPD with pulmonary perfusion abnormalities and reduced blood return to the heart observed prior to development of abnormal FEV_1 (Liebow, 1959; Rodriguez-Roisin et al., 2009). Similar pathophysiology likely occurs in irritant-induced COPD. Pulmonary arteriopathy was also present in over 50% of lung biopsies from non-FDNY WTC-PM exposed individuals and in over 70% with constrictive bronchiolitis after inhalational exposures during military service (Caplan-Shaw et al., 2011; King et al., 2011). Aberrant LPA signaling is implicated in numerous pathologies, including vascular injury and tumorigenesis and the pathways involved are potential therapeutic targets.

ApoA1 was also found to predict the loss of FEV_1 as in our prior study (Weiden et al., 2013). Our current study is the first to show an association between elevated ApoA1 and lung function loss in particulate exposure in a multianalyte model, including other lipid mediators. ApoA1 is a mediator of LPA and a major protein in HDL and therefore their association with PM-induced LI is of particular interest. ApoA1 is known to bind pro-inflammatory phospholipids such as LPA. In a murine cancer model, overexpression of ApoA1 not only led to increased survival but also to reduced levels of LPA (Su et al., 2010). We know that mice with a genetic deletion of ApoA1 have increased airway resistance, inflammatory cell recruitment and airway collagen deposition in the steady state (Wang et al., 2010). In contrast, ApoA1 is involved in the activation of protein kinase C which is involved in the activation of vascular and bronchial smooth muscles (Hu et al., 1994; Mukherjee et al., 2013). In our analysis, the interaction term for LPA and ApoA1 was not significant, suggesting that the odds for developing an abnormal FEV_1 due to an elevation of both biomarkers are likely additive, not synergistic.

This study has several limitations. Our FDNY firefighter cohort is unique as they had massive acute exposure to WTC-PM dusts. This limits the generalizability of these findings to other study populations with the lower level PM exposure produced by ambient air pollution. We did not have an unexposed control group to compare and therefore we could not determine the direct effect of WTC-PM exposure on LPA or ApoA1 levels. Replication of these findings in other longitudinally followed populations with and without PM exposure will be important to demonstrate the generalizability of these findings.

This investigation shows that elevated serum LPA and ApoA1 in serum sampled within six months of 9/11 predict eventual loss of FEV_1 on average six years later. These results suggest that these biologically active lipid mediators are involved in the pathogenesis of WTC-PM-mediated LI. Further investigation is required to define the mechanistic underpinning of LPA as a mediator of lung function loss after PM exposure. This finding could place LPA and ApoA1 in the center of a lipid-driven inflammatory cascade.

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Declaration of interest

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