Accelerated Spirometric Decline In Alpha-1 Antitrypsin Deficient New York City Firefighters

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_Chest_; Prepublished online July 15, 2010; DOI 10.1378/chest.10-0187

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Accelerated Spirometric Decline In Alpha-1 Antitrypsin Deficient New York City Firefighters

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5 - Bureau of Health Services, New York City Fire Department, Brooklyn

Institutions At Which Work Was Performed:
Montefiore Medical Center and New York City Fire Department (Bureau of Health Services)
Financial Support:

D. J. Prezant received funding from the Centers for Disease Control and Prevention [U1Q/CCU221158] and the National Institute of Occupational Safety and Health [U10-OH008243 and U10-OH008242]. G. I. Banauch received funding from the NCRR 5K12RR017672. G. Izbicki was supported by the Jesselon Einstein-Shaare Zedeck Fellowship Program. M. D. Weiden received funding from the National Institutes of Health [M01 00096, K23HL084191, K24A1080298, R01HL057879]. M. Brantly received support from the Alpha One Foundation.

Conflict of Interest Notification:

None of the authors had any conflicts of interest.

Dr. Hall received salary support from the National Institute of Occupational Safety and Health through the New York City Fire Department and Montefiore Medical Center. Dr. Prezant is the principal investigator for this grant funded clinical research study. Funding source is NIOSH - CDC
Abstract

Background: On 9/11/2001 the World Trade Center (WTC) collapse caused massive air pollution, producing variable amounts of lung function reduction in the New York City Fire Department (FDNY) rescue workforce. Alpha-1 antitrypsin (AAT) deficiency is a risk factor for obstructive airway disease.

Methods: This prospective, longitudinal cohort study investigated influence of AAT deficiency on adjusted longitudinal spirometric change (forced expiratory volume during the first second [FEV1]) in 90 WTC-exposed FDNY rescue workers over the first 4 years post-9/11/2001. Workers with protease inhibitor (Pi) Z heterozygosity were considered moderately AAT-deficient; PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity was mildly deficient, and PiM homozygosity was normal. Alternately, workers had low AAT levels if serum AAT was ≤20 µmol/l.

Results: In addition to normal aging-related decline (37 ml/year), significant FEV1 decline accelerations developed with increasing AAT deficiency severity (110 ml/year and 32 ml/year for moderate and mild deficiency) or with low AAT serum levels (49 ml/year). Spirometric rates pre-9/11/2001 did not show accelerations with AAT deficiency. Among workers with low AAT levels, cough persisted in a significant number of individuals to 4 years post-9/11/2001.

Conclusions: AAT-deficient FDNY rescue workers had significant spirometric decline accelerations and persistent airway symptoms during the first 4 years after the WTC exposure. This represents a novel gene-by-environment interaction. Clinically meaningful decline acceleration occurred even with the mild serum AAT level reductions associated with PiS heterozygosity (without concomitant PiZ heterozygosity).
Abbreviations:

AAT      - Alpha-1 antitrypsin
ANOVA    - Analysis of variance
ATS      - American Thoracic Society
EMS      - Emergency medical services
FDNY     - Fire Department of the City of New York
FEV1     - Forced expiratory volume during the first second
FVC      - Forced vital capacity
MMP      - Medical monitoring program
SD       - Standard deviation
SPSS     - Statistical Package for the Social Sciences
WTC      - World Trade Center
Introduction

New York City’s World Trade Center (WTC) collapse on September 11, 2001, produced significant exposures to respirable particulates and combustion by-products. In rescue and recovery workers and residents, new respiratory symptoms have emerged. Rescue workers (firefighters and emergency medical services [EMS] personnel) from the Fire Department of the City of New York (FDNY) received intensive post-exposure follow up as part of the FDNY WTC Medical Monitoring Program (FDNY-WTC-MMP). In a longitudinal spirometric study of 12,079 FDNY workers, adjusted average pulmonary function (forced expiratory volume during the first second [FEV1] and forced vital capacity [FVC]) was substantially reduced during the first year post-9/11/01, with an exposure-response gradient. Resolution of symptoms and airflow obstruction has been variable, pointing toward an individual predisposition for the persistence of airway inflammation.

Alpha-1 antitrypsin (AAT) is a key inflammatory regulator in the human airway. It belongs to the serine protease superfamily, members of which act as proteinase regulators especially in inflammatory pathways. Deficient individuals are predisposed to chronic airflow obstruction and hyperreactivity. Tests for AAT serum levels and deficiency protein phenotypes are well validated, and a clinical diagnosis of AAT deficiency requires both low serum concentrations and a deficient AAT phenotype (performed with protease inhibitor [Pi] typing). Given the variability of airflow obstruction/hyperreactivity in WTC-exposed FDNY workers and the known link between AAT deficiency and airway disease, we analyzed the influence of AAT expression on longitudinal spirometric change in 90 WTC-exposed FDNY workers over the first 4 years post-9/11/2001.
Materials and Methods

Study Design and Timeline

This prospective cohort study compared longitudinal spirometric decline rates among 3 AAT phenotype combination categories of highly/moderately WTC-exposed FDNY workers over the first 4 years post-9/11/2001. Spirometry was obtained at 1-3 and 6 months, and 1, 2, and 4 years post-9/11/2001. AAT testing was offered only 4 years post-9/11/2001.

WTC Exposure Groups

Exposure intensity was self-reported (FDNY-WTC-MMP questionnaire, confirmatory interviews). Exposure intensity was categorized according to workers’ first WTC site arrival time: high intensity if arrival preceded collapse of North and/or South towers (morning of 9/11/2001); intermediate intensity if arrival followed the collapse and occurred on 9/11/2001 or 09/12/2001; low intensity if arrival occurred after 09/12/2001.

Enrollment and Exclusion Criteria:

Study enrollment took place 1 and 3 months post-09/11/2001 during the FDNY-WTC-MMP examination (10/2001-12/2002). None of the 1,546 eligible subjects (hereafter referred to as the source population) were on medical leave. One month post-09/11/2001, every second highly or moderately exposed worker registering for WTC Medical Monitoring who met study eligibility criteria was approached for enrollment. Three months post-09/11/2001, due the strain on resources from larger numbers of workers registering for the medical monitoring examination at that time, every 20th highly or moderately exposed worker who met study eligibility criteria was approached for enrollment. Exclusion criteria included: current smoking, allergies, FEV1 <65% predicted or low intensity WTC exposure.
Follow-Up Visits:

Study participation was voluntary. Each study visit required informed consent approved by Montefiore Medical Center’s Institutional Review Board (protocol # 01-12-299). Longitudinal participation is shown in figure 1. At final follow-up, 4 years post-9/11/2001, no participant reported new or recurrent tobacco use, and two refused AAT testing. Thus, the current cohort comprised 90 WTC-exposed FDNY workers (60% retention). All follow-ups included a self-administered questionnaire assessing respiratory symptoms, and spirometry. All symptoms were recorded prior to disclosing AAT status.

Spirometry:

Spirometry was performed according to American Thoracic Society (ATS) guidelines. Spirometers were calibrated daily and testing was performed seated, wearing noseclips, with up to 8 forced expiratory maneuvers per session to maximize quality. To allow calculation of separate spirometric rates for time periods pre-09/11/2001 and post-9/11/2001 as well as to allow for more precise modeling post-9/11/2001, spirometric measurements obtained from the FDNY-WTC-MMP pre9/11/2001 (Portascreen, S&M Instruments, Doylestown, PA) and post-9/11/2001 (EasyOne, NDD Medical Technologies, Andover, MA) were included with those obtained on study dates (KoKo spirometers, PDS Instrumentation, Louisville, CO). Each spirogram was reviewed by a board certified pulmonologist (blinded to patient identifier, exposure status, AAT phenotype and serum level) to determine that strict quality assurance guidelines were adhered to. Spirograms were accepted if they (1) did not show artifacts such as (a) cough or glottis closure during the first second of exhalation, (b) early termination, (c) variable effort, (d) leak, and (e) obstructed mouthpiece; (2) had good starts with back-extrapolated volume not exceeding 5% of FVC or 150ml (whichever was larger), (3) had
satisfactory exhalation length (at least 6 seconds or a plateau in the volume/time curve). Spirometric measurements were considered reproducible if the best and second best FVC or FEV1 measurements were within 200ml of each other. The largest FVC and FEV1 from among all acceptable spirograms were selected for electronic archiving. Pre-09/11/2001, 142 spirograms were acceptable for inclusion in the database; the median number per study participant was 2 (range, 0-3) and 77 of 90 study participants (86%) had at least one spirogram. Post-09/11/2001, 221 spirograms from the FDNY monitoring program and 299 from the study visits were acceptable for inclusion, for a total of 520 spirograms; the median number per study participant was 6 (range, 2-8). Nine spirometric measurements were rejected.

**Alpha-1 Antitrypsin Testing**

On the final visit, before spirometry, participants were phlebotomized. Seventeen ml of unheparinized venous blood coagulated for 20 min, then centrifuged for 6 min at 3300 rpm, room temperature. Serum was stored at -80°C. Protease inhibitor phenotyping used high resolution gel isoelectric focusing (pH 4-5). Serum AAT concentrations were determined using rate limited nephelometry (purified AAT standard).

**AAT Deficiency Categories**

Two different methods were used to categorize AAT deficiency severity. The main categorization used AAT Pi phenotype combinations; the alternate categorization used serum AAT level. For the main categorization, workers with PiZ heterozygosity were considered moderately deficient; workers with PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity were considered mildly deficient, and workers with PiM homozygosity were normal. For the alternate categorization, workers had low serum AAT levels if level was ≤20 µmol/l.
Demographic, Clinical and Spirometric Comparisons – Univariate Analyses

FDNY work assignment on 09/11/2001 (firefighter vs. EMS), FDNY tenure, age, race, height, gender and smoking status were extracted from the FDNY-WTC-MMP database. Gender, race, ex-smoking status, work assignment, WTC exposure intensity, and upper or lower respiratory symptoms were compared at enrollment between the following groups: source population and study cohort; AAT phenotype combination categories; and low vs. normal serum AAT categories (chi square; Fisher’s exact test).

Four years post-9/11/2001, upper or lower respiratory symptoms were compared between AAT phenotype combinations, and low vs. normal serum AAT levels (chi square; Fisher’s exact test). Symptom persistence from enrollment to final visit was explored within each AAT phenotype combination, and within low vs. normal serum levels (McNemar’s test). Percentages of AAT deficiency phenotypes were compared between low vs. normal serum levels (Fisher’s exact test). Mean serum AAT levels were compared between AAT phenotype combinations (Mann-Whitney U, Kruskal-Wallis test).

Spirometric measurements, measured pre-9/11/2001, at enrollment, and 4 years post-9/11/2001, as well as AAT levels, age, and FDNY tenure were compared between the same groups detailed above (t-test, one-way analysis of variance [ANOVA], Mann-Whitney U, Kruskal-Wallis test).

Clinical and Spirometric Comparisons – Multivariate Analyses

Indicators for clinical symptoms 1-3 months post-9/11/2001 were compared between source population and study cohort adjusting for the following factors: age, FDNY tenure, WTC exposure intensity, work assignment, and ex-smoker percentage). Indicators for clinical symptoms 4 years post-9/11/2001 were compared between AAT phenotype combinations, and
between workers with low vs. normal serum AAT levels adjusted for the same factors using logistic regression. Spirometric measurements 1-3 months post-9/11/2001 (adjusted for the same factors plus gender and height) were compared between source population and study cohort, between the different AAT phenotype combinations, and between workers with low vs. normal serum AAT levels using linear regression.

**Spirometric Decline Rates - Mixed Linear Random Effect Models**

We analyzed differences in average spirometric change rates (FVC or FEV1) during 3 years pre-09/11/2001 and during 4 years post-9/11/2001, and whether AAT deficiency combinations influenced spirometric change rates during 4 years post-9/11/2001 using mixed linear random effects modeling. Separate models were run for FEV1 and FVC as dependent variables. Workers contributed 2-10 observations. The primary predictor of interest was the interaction between spirometric change rate during 4 years post-9/11/2001 and AAT deficiency combinations (based on either phenotype combinations or serum levels). AAT deficiency severity was modeled both as nominal predictor and as ordinal predictor (to test for linear trend) in separate models. Separate spirometric change rates and separate interaction terms between spirometric change and AAT categories were included for 3 years pre-9/11/2001 and for 4 years post-9/11/2001. In addition, models allowed a spirometry decrement post-9/11/2001, because this was previously observed in longitudinal spirometric analysis of this workforce. Additional predictors were included as confounders: age, gender, height, race, smoking status, work assignment (firefighter, EMS), FDNY tenure, WTC exposure intensity, and interaction between AAT deficiency and tobacco history. All predictors were fixed effects. A random intercept was used to reflect across subject heterogeneity and correlation induced by having repeated same-subject observations. To eliminate nonlinear confounding due to the known interaction of
smoking with AAT deficiency,\textsuperscript{35} we modeled spirometric change rates both in the study cohort that included ex- and never-smokers (N=90) and in the subcohort of never smokers (N=75). Statistical Package for the Social Sciences (SPSS) version 12.0 was used for all analyses.

**Results**

**Study Cohort and Source Population**

The study cohort consisted of 90 source population members (highly/moderately WTC-exposed FDNY workers, non-allergic, ex-/never-smokers, with FEV\textsubscript{1}≥65\% predicted measured during FDNY-WTC-MMP 1-3 months post-9/11/2001) who agreed to participate in and completed this longitudinal 4-year study (figure 1). Demographic and symptom information of source population and study cohort are in table 1. No significant difference in gender, age and ex-smoker percentage between study cohort and source population was found. The study cohort included significantly more highly WTC-exposed workers and, to a lesser extent, significantly more non-Caucasians and EMS workers. Compared to the source population, study participants at enrollment, 1-3 months post-9/11/2001, were more symptomatic with increased prevalence of nocturnal respiratory symptoms and nasal drip/congestion.

Source population and study cohort spirometric measurements are in table 2. Pre-09/11/201, study participants had significantly lower mean spirometric measurements than the source population, but these differences were not significant when normalized as percent predicted values. At enrollment 1-3 months post-9/11/2001, lower spirometric measurements in study participants was consistent with the larger number of highly WTC-exposed workers in the study cohort, compared to the source population.\textsuperscript{3,4}
AAT Phenotype Distributions and AAT Deficiency Combinations

For analysis, workers were grouped according to AAT phenotype combination deficiency severity: 4 workers with PiZ heterozygosity were considered moderately deficient (2 with M1Z, 1 with M3Z and 1 with SZ phenotype); 7 workers with PiS homo-/heterozygosity without concomitant PiZ heterozygosity were considered mildly deficient (3 with M1S, 2 with M2S, 1 with M3S, and 1 with SS phenotype), and 79 workers with PiM homozygosity were considered normal (38 with M1M1, 28 with M1M2, 11 with M1M3 and 2 with M3M3). Significant differences in mean serum AAT levels were observed among the three AAT deficiency combinations (table 3). Alternatively, 13 workers were categorized as having low AAT serum levels (<20 µmol/l; table 4), and significant differences in percentages of AAT deficiency combinations were observed between workers with low vs. normal serum AAT levels.

Symptoms by AAT Combination

There were no significant differences in gender, age, race, ex-smoking, work assignment, WTC exposure intensity, pre-9/11/01 FEV1 or FVC values between the three AAT phenotype combinations (table 3) or between those with low vs. normal serum AAT levels. Among workers with low serum AAT levels, cough persisted in a significant number of individuals from 1-3 months to 4 years post-9/11/2001.

Spirometric Decline Rates by AAT Phenotype Combination Category

We compared adjusted FEV1 decline rates during the 4 years post-9/11/2001 among AAT phenotype combinations, and among workers with low vs. normal serum AAT levels. Significant accelerations in FEV1 decline were evident with increasing AAT deficiency severity (figure 2A), or with decreasing AAT serum levels (figure 2B). These decline rate accelerations occurred even though models allowed for a spirometric decrement immediately post-9/11/2001.
The magnitude of this immediate decrement (370 ml) equaled 10 times the cohort’s yearly adjusted longitudinal aging-related decline rate of 37 ml/year. After accounting for both aging-related and the immediate post-09/11/2001 decrement, moderately AAT-deficient workers had an additional 110 ml/year FEV1 decline rate acceleration, while mildly AAT-deficient workers had an additional 32 ml/year FEV1 decline rate acceleration during the 4 years post-09/11/2001. The magnitude of AAT deficiency-related, adjusted FEV1 decline rate acceleration thus equaled nearly triple the cohort’s yearly adjusted aging-related decline rate for moderately AAT-deficient workers, and almost equaled the yearly adjusted aging-related decline rate for mildly AAT-deficient workers (figure 3). This was true regardless of whether smokers were included, or whether the single individual with a PiSZ phenotype combination was included. Furthermore, after accounting for aging-related decline and the 370 ml immediate decrement, workers with low AAT serum levels had an additional 49 ml/year decline rate acceleration compared to those with normal levels during the 4 years post-9/11/2001. For workers with low serum AAT levels, the magnitude of adjusted AAT deficiency-related decline rate acceleration thus exceeded the cohort’s yearly adjusted aging-related decline rate (figure 3). This was true regardless of whether ex-smokers were included. Similar results were obtained for adjusted FVC decline rate accelerations (data not shown). When adjusted spirometric decline rates pre-9/11/2001 were compared to rates post-9/11/2001, no decline rate acceleration attributable to AAT deficiency was observed for the 3 year period preceding the WTC exposure (figure 2).
Discussion

In this prospective longitudinal cohort study, we showed that AAT-deficient FDNY rescuers developed significant spirometric decline accelerations during the first 4 years post-09/11/2001 even though such deficiency did not affect spirometric declines pre-9/11/2001. A gene-by-environment interaction exists when disease risk among individuals exposed to both genotype and environmental exposure is greater than predicted from either genotype or exposure alone. \(^{36}\) Accelerated lung function decline developed in AAT-deficient individuals after the intense inflammatory stimulus of WTC inhalation injury,\(^ {37-39}\) representing a novel gene-by-environment interaction. Clinically meaningful and statistically significant lung function loss developed even with only the mild serum AAT level reduction associated with PiS heterozygosity (without concomitant PiZ heterozygosity).

It is now well accepted that respirable pollutants after the WTC attack caused inhalation injury.\(^ {2-14}\) Biochemical,\(^ {38,39}\) physiologic\(^ {2-10,12}\) and clinical\(^ {2-16,40,41}\) correlates of airway inflammation due to this exposure have been described in multiple cohorts including FDNY rescue workers.\(^ {7}\) Subacutely, during study initiation 1-3 months post-9/11/2001, irritative respiratory symptoms and physiologic correlates (e.g., decreased spirometric measurements) were associated with WTC exposure intensity.\(^ {2-5}\) This association was no longer detectable at final follow-up, 4 years post-9/11/2001. Instead, AAT deficiency severity emerged as a determinant of both persistent symptoms and spirometric decline acceleration, highlighting its role in lung injury/repair. While AAT deficiency has repeatedly been implicated in the development of airflow obstruction over chronic time periods,\(^ {42,43}\) this study revealed development of AAT deficiency-related spirometric decline acceleration during a much shorter period (i.e., 4 years), thus highlighting how quickly AAT deficiency can produce clinical disease.
and airflow obstruction. WTC-derived airborne pollution was a complex mixture of particulates and chemicals.\textsuperscript{1,7} To date severe deteriorations in pulmonary function are well-described for AAT deficient individuals following bacterial infections\textsuperscript{44,45}, but have not been described following exposures to particulates, chemicals or mixtures. In addition, no such gene-by-environment interactions for pulmonary disease have previously been described for mild/moderate AAT deficiency due to PiS heterozygosity without concomitant PiZ heterozygosity. This interesting, novel finding might be due to the strength of the inhalational inflammatory stimulus sustained by FDNY rescue workers at the WTC site.

It is important to note our investigation’s limitations. First and most importantly, sample size was moderate. However, this moderate-sized study cohort represented the FDNY source population quite well in key demographic and spirometric aspects. Second, FDNY rescuers sustained extremely high intensity exposures, which might be qualitatively different, compared to other rescue/recovery workers or residents. For these reasons, caution is certainly prudent when extrapolating our current findings. Third, the missing AAT characterization of the initially enrolled subjects who did not participate in the 4-year follow-up exam has the potential to bias our results. Specifically, study results would falsely favor an association between AAT deficiency and accelerated FEV1 decline if a disproportionate number of individuals with PiM homozygosity did not participate in follow-up and at the same time did have accelerated airflow obstruction. The fact that the prevalence of deficiency phenotype carriers in our current cohort (12\%) is close to the prevalence of deficiency phenotype carriers in the general North American population (9\%)\textsuperscript{46} suggests that our results were likely not substantially affected by incomplete follow-up.
We partitioned participants into three AAT phenotype combinations, considering those with PiZ heterozygosity moderately deficient, those with PiS homozygosity or with PiS heterozygosity without concomitant PiZ heterozygosity mildly deficient, and those with PiM homozygosity normal. Statistically significant differences in mean serum AAT levels between the three phenotype combinations supported this categorization. With this categorization, we demonstrated significant, clinically meaningful spirometric decline rate accelerations even for mildly abnormal PiS carriers – a unique finding in the literature.

Magnitude of AAT deficiency-related spirometric decline rate acceleration was both clinically and statistically significant, equaling almost triple this cohort’s aging-related spirometric decline rate for moderately AAT-deficient workers, despite allowing for a one-time decrement in spirometric measurements post-9/11/2001. When we reported this one-time spirometric decrement 1 year post-09/11/2001, we speculated whether the acute inflammatory response and pulmonary function decrement would be transient and reversible. However, in our current study, which includes spirometric measurements obtained as long as 4 years post-9/11/2001, we still observed a decrement of almost equal magnitude as that observed during the first year post-09/11/2001 (370 ml FEV1 decline). This one-time decrement persisted in addition to the AAT-related decline rate acceleration post-9/11/2001, and persistence of this decrement has also been reported in the entire FDNY workforce. These findings argue strongly against a transient, reversible WTC-related loss of pulmonary function.

In conclusion, we demonstrated significant associations between spirometric decline rate acceleration and AAT deficiency severity in the FDNY workforce during the first 4 years after WTC-related inhalation injury. These decline rate accelerations represent a novel gene-by-environment interaction; are both clinically and statistically significant; and occurred even in PiS
heterozygous workers, who had only mild reductions in serum AAT levels. This finding of accelerated pulmonary function decline despite modest sample size, milder degrees of AAT deficiency, and only 4 years of follow-up, allows inferences about the key anti-inflammatory role of AAT in the lower airways, and about the strength of the WTC-related inhalation injury in FDNY workers.

**Acknowledgements:**

Gisela I. Banauch designed the study, performed data acquisition, analyzed and interpreted the data, drafted and revised the manuscript, and prepared the final version of the manuscript. Mark Brantly performed data acquisition, laboratory measurements and contributed to and revised the manuscript. Gabriel Izbicki performed data acquisition, contributed to and revised the manuscript, and contributed to the final version of the manuscript. Charles Hall analyzed and interpreted the data, contributed to and revised the manuscript, and contributed to the final version of the manuscript. Alan Shanske contributed to the study design, contributed to and revised the manuscript, and contributed to the final version of the manuscript. Robert Chavko performed data acquisition, and contributed to and revised the manuscript. Ganesha Santhyadka performed data acquisition, and contributed to and revised the manuscript. Vasilios Christodoulou performed data acquisition, and contributed to the manuscript. Michael D. Weiden contributed to and revised the manuscript. David J. Prezant contributed to the study design, drafted and revised the manuscript, and contributed to the final version of the manuscript.
References:


46. De Serres FJ. Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. Environ Health Perspect 2003;111:1851-4.
Figure Legends:

Figure 1.

Source population, study cohort and study time course. Recruitment from the source population, numbers for follow-up testing at each time point, and workers who consented to AAT testing are shown. AAT testing was offered only at the final follow-up visit.

Figure 2.

Time course of average adjusted FEV1 pre- and post-9/11/2001 for the 3 AAT phenotype combination deficiency categories (panel A); time course of average adjusted FEV1 pre- and post-9/11/2001 for low vs. normal AAT serum levels (panel B). Significant acceleration in average adjusted spirometric declines according to AAT phenotype combination category (110 ml FEV1/yr for moderately AAT-deficient workers, 32 ml FEV1/yr for mildly AAT-deficient workers; p=0.003, test for trend) occurred during the 4 years post-9/11/2001, but not during the 3 years pre-9/11/2001. Spirometric measurements for a Caucasian male never-smoking, highly WTC-exposed FDNY firefighter of mean age and height and with median FDNY tenure length are depicted. Workers with PiZ heterozygosity were categorized as moderately AAT-deficient (N=4), workers with PiS homo- or heterozygosity (without concomitant PiZ heterozygosity) were categorized as mildly AAT-deficient (N=7), and workers with PiM homozygosity were categorized as normal (N=79; panel A). Workers with serum AAT levels ≤20µmol/l were categorized as having low levels (N=13), and those with serum AAT levels >20µmol/l were categorized as having normal levels (N=77; panel B). Spirometric decline rates were adjusted for gender, race, age, height, ex-smoking status, work assignment on 09/11/2001, length of FDNY tenure, WTC exposure intensity, and the interaction of smoking with AAT deficiency. The
statistical models allowed for a decrement in spirometric measurements post-9/11/2001 because this had previously been observed in the FDNY workforce\(^3\).

**Figure 3.**

Magnitude of average adjusted FEV\(_1\) decline rates post-9/11/2001 for the 2 AAT deficiency combinations and for low serum AAT levels. Normal aging-related decline rates for the cohort provide a clinically meaningful comparison. Decline rate magnitudes due to AAT deficiency and due to aging, and standard errors are shown. AAT-related accelerations in decline rate equaled nearly triple the cohort’s adjusted aging-related decline rate for moderately AAT-deficient workers, and almost equaled the cohort’s adjusted aging-related decline rate for mildly AAT-deficient workers (p=0.011), with statistically significant trend for decline rate acceleration by AAT phenotype combination deficiency category (p=0.003). In addition, AAT-related accelerations in decline rate for low AAT serum levels exceeded the cohort’s yearly adjusted aging-related decline rate (p=0.027). The rightmost data point represents the FEV\(_1\) decline rate due to aging alone, which subjects with normal AAT phenotypes experienced, since they did not experience any additional decline rate acceleration due to AAT deficiency. Decline rates for a Caucasian male never-smoking, highly WTC-exposed FDNY firefighter of mean age and height and with median FDNY tenure length are depicted. Moderate AAT deficiency was defined as PiZ heterozygosity (N=4); mild AAT deficiency was defined as PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity (N=7). Low serum AAT level was defined as \(\leq 20\mu\text{mol/l}\). Decline rates were adjusted for gender, race, age, height, ex-smoking status, work assignment on 09/11/2001, length of FDNY tenure, WTC exposure intensity, and the interaction of smoking with AAT deficiency.
### Tables:

Table 1 – Demographic and Clinical Characteristics of Study Cohort And Source Population At Enrollment

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**Demographic Characteristics**

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<tr>
<td>(% EMS)</td>
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<td>(% highly exposed; i.e. arrived at WTC site morning of 09/11/2001)</td>
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**Clinical Characteristics**

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<thead>
<tr>
<th>Upper Respiratory Symptoms (%)</th>
<th>Source Population*</th>
<th>Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Drip/Congestion</td>
<td>44†</td>
<td>56</td>
</tr>
<tr>
<td>Sore/Hoarse Throat</td>
<td>60</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower Respiratory Symptoms (%)</th>
<th>Source Population*</th>
<th>Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Cough</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>Wheezing</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Chest Tightness/Pain</td>
<td>25†</td>
<td>37</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>27†</td>
<td>41</td>
</tr>
<tr>
<td>Nocturnal Respiratory Symptoms Interfering With Sleep</td>
<td>27‡</td>
<td>41</td>
</tr>
</tbody>
</table>
* - includes those workers who enrolled at study initiation 1-3 months post-9/11/2001 but did not participate in follow-up testing 4 years post-9/11/2001, and those workers who did not consent to AAT testing during the follow-up visit 4 years post-9/11/2001

† - p<0.005, chi square; difference in symptoms was no longer significant after adjustment for age, length of FDNY tenure, WTC exposure intensity, work assignment, and percentage of ex-smokers

‡ - p<0.005, chi square; difference in symptoms remained significant after adjustment for age, length of FDNY tenure, WTC exposure intensity, work assignment, and percentage of ex-smokers

§ - p<0.05, Fisher’s exact test

‖ - p<0.001, chi square
Table 2 – Spirometric Characteristics of Study Cohort and Source Population Prior To and During Enrollment

<table>
<thead>
<tr>
<th></th>
<th>Source Population*</th>
<th>Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior To 09/11/2001†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>4.37 ± 0.71§</td>
<td>4.19 ± 0.68</td>
</tr>
<tr>
<td>Percent Predicted</td>
<td>103 ± 14</td>
<td>101 ± 15</td>
</tr>
<tr>
<td>FVC (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>5.16 ± 0.85§</td>
<td>4.91 ± 0.82</td>
</tr>
<tr>
<td>Percent Predicted</td>
<td>100 ± 14</td>
<td>98 ± 14</td>
</tr>
<tr>
<td><strong>1-3 Months Post-9/11/2001‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>4.08 ± 0.71‖</td>
<td>3.90 ± 0.64</td>
</tr>
<tr>
<td>Percent Predicted</td>
<td>96 ± 15</td>
<td>94 ± 15</td>
</tr>
<tr>
<td>FVC (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>4.86 ± 0.84‖</td>
<td>4.64 ± 0.83</td>
</tr>
<tr>
<td>Percent Predicted</td>
<td>94 ± 14</td>
<td>92 ± 15</td>
</tr>
</tbody>
</table>

* - includes those workers who enrolled at study initiation 1-3 months post-9/11/2001 but did not participate in follow-up testing 4 years post-9/11/2001, and those workers who did not consent to AAT testing during the follow-up visit 4 years post-9/11/2001

† - last spirometric measurement prior to 09/11/2001 obtained during routine occupational health surveillance at FDNY; available for 83% of source population and 86% of study cohort
‡ - obtained during enrollment 1-3 months post-9/11/2001

§ - p<0.05, t-test for independent samples

‖ – p<0.05, t-test for independent samples; these spirometric differences were no longer statistically significant after adjusting for differences in WTC exposure intensity between study cohort and source population
Table 3 – Clinical and Biochemical Characteristics of Study Cohort by AAT Deficiency Category

<table>
<thead>
<tr>
<th>AAT Phenotype Combination Deficiency Category</th>
<th>Moderately Deficient</th>
<th>Mildly Deficient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Number</strong></td>
<td>4</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td><strong>AAT Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAT Phenotype Combinations</td>
<td>MZ, SZ</td>
<td>MS, SS</td>
<td>MM</td>
</tr>
<tr>
<td>Serum AAT Level (µmol/l; mean ± SD)</td>
<td>14.9 ± 3.2*</td>
<td>18.4 ± 2.6</td>
<td>23.9 ± 3.0</td>
</tr>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>100</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>100</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Age (years; mean ± SD)</td>
<td>46.1 ± 6.1</td>
<td>38.7 ± 4.4</td>
<td>40.2 ± 7.3</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>25</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Work Assignment on 09/11/2001 (% EMS)</td>
<td>0</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>WTC Exposure Intensity</td>
<td>75</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>(% highly exposed; i.e., arrived at WTC site morning of 09/11/2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDNY Tenure Length on 09/11/2001 (years; mean ± SD)</td>
<td>20.0 ± 6.4⁺</td>
<td>11.5 ± 4.9</td>
<td>10.9 ± 8.4</td>
</tr>
</tbody>
</table>

* - p<0.001, Kruskal-Wallis test

⁺ - p<0.05, comparing normal and mildly AAT-deficient workers to moderately deficient workers, t-test
Table 4 – Alpha-1 Antitrypsin Values (Micromoles per Liter; Mean ± Standard Deviation) and AAT Phenotype Combinations of Study Cohort by AAT Deficiency Category and AAT Serum Level

<table>
<thead>
<tr>
<th>AAT Phenotype Combination</th>
<th>AAT Serum Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>24.55 ± 2.81</td>
</tr>
<tr>
<td></td>
<td>75 PiMM</td>
</tr>
<tr>
<td>Mildly Deficient</td>
<td>21.70 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>2 PiMS</td>
</tr>
<tr>
<td>Moderately Deficient</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* - p<0.001 comparing mean serum AAT levels among AAT phenotype categories, Kruskal-Wallis test

† - p<0.001 comparing AAT deficiency phenotype combinations among workers with low vs normal AAT serum levels, Mann-Whitney U
Figure 1:
10,116 surviving FDNY WTC rescue workers evaluated during FDNY WTC medical monitoring exam

2,059 rescue workers evaluated during study enrollment period

513 not eligible for enrollment

1,546 eligible for enrollment; 215 approached for enrollment

64 did not agree to enrollment

151 enrolled

59 did not complete 4-year follow-up; 2 did not agree to Alpha-1 antitrypsin (AAT) testing

90 completed 4-year follow-up

<table>
<thead>
<tr>
<th>Enrollment Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Moderately AAT Deficient</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Mildly AAT Deficient</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>Normal AAT Phenotype</td>
</tr>
<tr>
<td>79</td>
</tr>
<tr>
<td>Total Number Tested During Each Time Period</td>
</tr>
<tr>
<td>90</td>
</tr>
</tbody>
</table>
Figure 2 - Panel A

Adjusted FEV1 (liters)

Normal AAT phenotype
- - -
Moderately AAT deficient
- -
Mildly AAT deficient

Years before/after 09/11/2001

Figure 2 - Panel B

Adjusted FEV1 (liters)

Normal AAT serum level
- -
Low AAT serum level
- - - - -

Years before/after 09/11/2001
10,116 surviving FDNY WTC rescue workers evaluated during FDNY WTC Medical Monitoring Exam

2,059 rescue workers evaluated during study enrollment period

513 not eligible for enrollment

1,546 eligible for enrollment; 215 approached for enrollment

64 did not agree to enrollment

149 enrolled

57 did not complete 4-year follow-up; 2 did not agree to Alpha 1 antitrypsin (AAT) testing

90 completed 4-year follow-up

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<th>Enrollment</th>
<th>Follow-Up</th>
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<td>Normal AAT Phenotype</td>
<td>79</td>
</tr>
<tr>
<td>Total Number Tested During Each Time Period</td>
<td>90</td>
</tr>
</tbody>
</table>
Figure 2B

Adjusted FEV1 (liters)

- - - - - Normal AAT serum level

- - - - - Low AAT serum level

Years before/after 09/11/2001

Adjustments for FEV1 are plotted for two serum levels of α1-antitrypsin (AAT): normal and low. The graph shows a decrease in Adjusted FEV1 over the years before and after 09/11/2001, with the low AAT serum level experiencing a more pronounced decrease compared to the normal AAT level.
Figure 3

Average Adjusted FEV1 Decline (ml/yr)

-200 -175 -150 -125 -100 -75 -50 -25 0 1 2 3 4 5 6 7

Moderate AAT Deficiency
Mild AAT Deficiency
Low AAT Serum Level
Normal
Accelerated Spirometric Decline In Alpha-1 Antitrypsin Deficient New York City Firefighters
Gisela I. Banauch, Mark Brantly, Gabriel Izbicki, Charles Hall, Alan Shanske, Robert Chavko, Ganesha Santhyadka, Vasilios Christodoulou, Michael D. Weiden and David J. Prezant
Chest; Prepublished online July 15, 2010; DOI 10.1378/chest.10-0187

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