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Respiratory health outcomes in community members exposed to environmental toxins: lessons learned from the WTC disaster

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Goals

- Disclosures
    - None

Goals

- Overview of WTC toxin exposure to community members
- Challenges with assessment of respiratory symptoms in community members with WTC exposures
    - Physiologic measures
    - Pathology studies
    - Imaging
    - (Blood biomarkers)

WTC destruction as an environmental disaster

- Civilian community at risk for WTC dust/fume exposure

Brackbill et al. MMWR 55:No. SS-2; 2006

- 300,000 local workers/office workers, commuters, teachers
- 60,000 residents south of Canal Street
- 15,000 students

Lioy et al. Env Health Perspect 2002

The cloud in Lower Manhattan, south of Chambers Street.

What were the respiratory hazards: Characteristics of settled WTC dust

- ~10 million tons of material
- Most of settled dust was large - Mass median aerodynamic diameter of 23 μm
- 1-2% of outdoor dust consisted of particles <2.5 μm
- Alkaline (pH 9-11)
- Construction materials
  - Concrete (calcium hydroxide)
  - Gypsum wallboard (calcium sulfate)
  - Synthetic vitreous fibers (fibrous glass, gypsum fibers, chrysotile asbestos)

Landrigan et al. Env Health Perspectives 2004;112: 731
Banauch et al. Curr. Opinion Pulm Med 2005; 11:160
USGS Environmental Studies of WTC
Lippman, Cohn, Chen Crit Rev Toxicol 2015; 45: 492
Lee 2014

Chemical components of WTC dust

- Combustion products
  - Jet fuel
  - Building materials (plastics, metals, woods, insulation, fluorescent lights, computers)
- Construction debris

- Particulate matter
  - Organic compounds
    - PAH
    - Polychlorinated biphenols,
    - Polychlorinated dibenzodioxins
    - Benzene
    - Phthalate esters
  - Asbestos
  - Heavy metals
    - Lead

Lioy et al. 2002; 110:703
Banauch et al. Curr. Opinion Pulm Med 2005, 11:160-168
Lippman et al. Crit Rev Toxic 2015; 45:492

WTC Dust characteristics

- Easily resuspended – 10 – 10,000 times more than that of ordinary office building dust
- Aerosolized WTC dust contained significant quantities of respirable hazardous substances
- Problems with WTC-related air quality monitoring
    - Issues with early protocols
    - Location of sampled sites
    - Methods of measurement

EPA actions

- Ground Zero not declared a hazardous waste site or Superfund site
  - allowed for reduced protection requirements
  - diminished pressure for building owners to remediate their buildings

- No legal responsibility for assessing or addressing indoor environmental contamination until 1 year later
  - Commercial and residential tenants left to contend with their private spaces
  - NYCDOHMH advice – damp mop

How to characterize exposures in WTC community members

Acute exposures - Dust cloud(s) on 9/11

Chronic exposures from resuspended dust

Local workers returned to work September 17, 2001

Chronic exposure from indoor dust

- Dust resuspended during cleaning and from incompletely cleaned ventilation systems
- Similar in composition to outdoor dust
- Greater percentage of mass < 53 μm compared to outdoor samples
- Few residents were evacuated

Yiin et al. J Air Waste Manag Assoc 2004

Chronic exposures: Gases and fumes

- Fires burned through December 2001

Pertinence to Gulf War exposures

- Mixed exposures
- Delay in toxicant characterization
- Difficulties with characterizing dose

Health assessment in the civilian community

- Adverse health effects reported in responders
- Adverse health effects in the WTC community members
- Focus on lower respiratory effects

WTC Residents Respiratory Health Study

- Collaborative effort with NYS DOH and local community
- Cross-sectional study of sampled “exposed” and “control” residential population
- Study completed within 16 months after 9/11/01

Reibman et al., Environ Health Perspectives 113: 406;2005

Lin S. et al., Amer J Epidemiol 162:499;2005

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New-onset respiratory symptoms increased in previously normal exposed residents

Symptom, %	Exposed (n=2410)	Control (n=271)	Crude Incidence ratio (95% CI)*
Cough	16.0	4.0	4.0 (2.2-7.4)
Shortness of breath (SOB)	10.6	3.6	2.9 (1.5-5.7)
Wheeze	10.5	1.6	6.5 (2.4-17.3)
Chest tightness	8.4	1.6	5.2 (2.0-13.9)
Exertional dyspnea	7.4	1.7	4.5 (1.7-11.9)
Any of the above	26.4	7.5	3.5 (2.3-5.5)

[b]Symptom frequency ≥ 2 days per week in the past 4 weeks.

* Effect still statistically significant after adjusting for age, gender, education, smoking and race.

Reibman et al., Environ Health Perspectives 113: 406;2005

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Increase in medical consultation and asthma medicine use in previously normal residents

	Exposed (n=2410)	Control (n=271)	Crude IR (95% CI)*
Unplanned Medical Visits (in the past 12 months)	13.7%	7.8%	1.8 (1.2-2.7)*
Fast Relief Med Use (in the past 4 weeks)	8.0%	3.3%	2.4 (1.3-4.7)*
Controller Med Use (in the past 4 weeks)	8.6%	3.7%	2.3 (1.3-4.3)*

No diagnosis of asthma, chronic obstructive pulmonary disease, chronic bronchitis, or other lung disease before 9/11/2001.

* Effect still statistically significant after adjusting for age, gender, education, and race.

Lin S. et al., Amer J Epidemiol 162:499;2005

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NYC DOH WTC Health Registry

- NYC Department of Health WTC Registry (n = >71,000 individuals) initiated in 2003
- Remains on ongoing closed cohort for those exposed on 9/11 and below Chambers street
- Confirmed adverse respiratory health effects in community
  - Brackbill et al. MMMWR Surveill Summ 2006;55:1-18
  - Farfel et al. J Urban Health 2008;85:880-909

Both acute and chronic exposures associated with lower respiratory symptoms

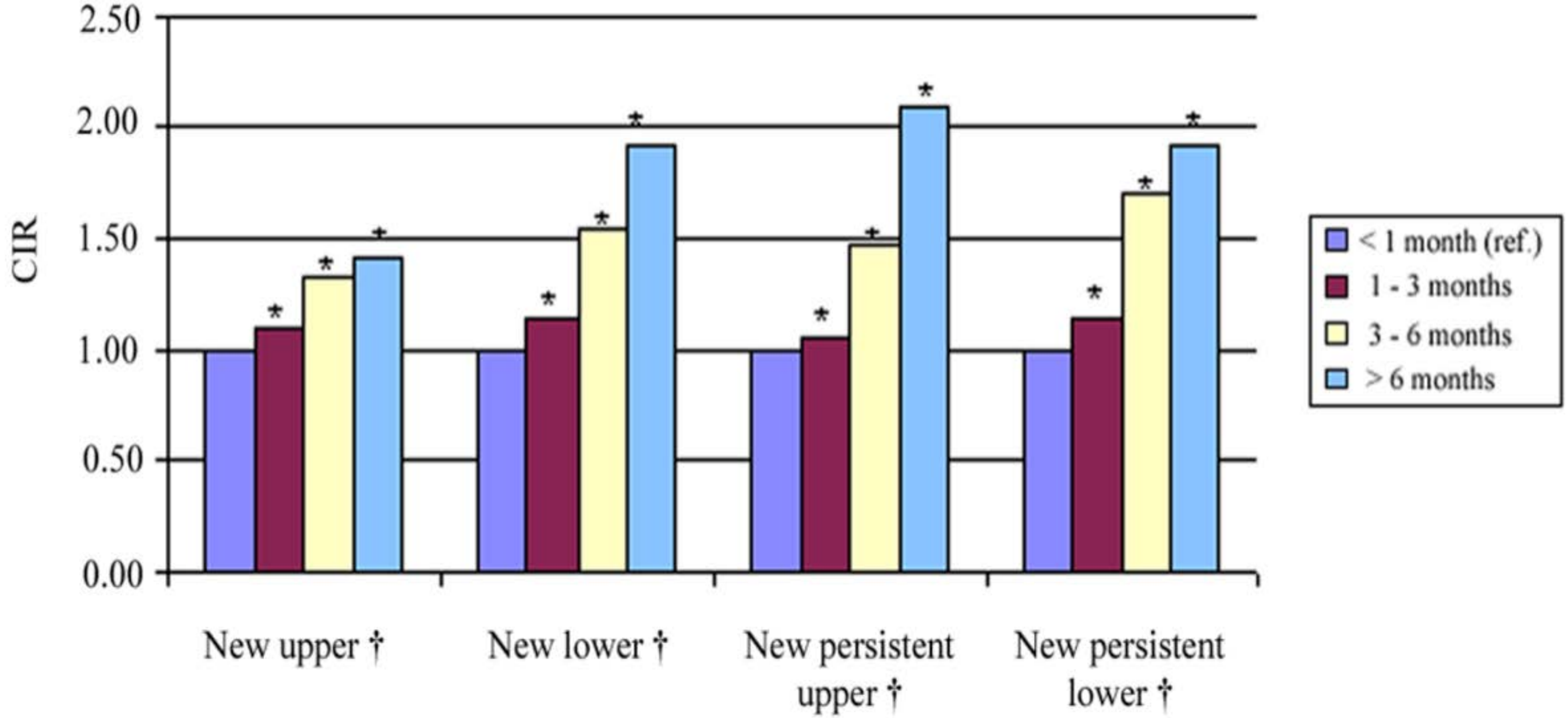
TABLE 4—Composite Exposure Scales Following September 11, 2001, and Their Association With Case Status Among New York World Trade Center–Area Residents and Workers

		All Participants (n = 785)			Residents[d] (n = 479)			Area Workers[d] (n = 422)	
Composite Exposure Scale and Component Variables	α[a]	OR[b] (95% CI)	AOR[c] (95% CI)	α[a]	OR[b] (95% CI)	AOR[c] (95% CI)	α[a]	OR[b] (95% CI)	AOR[c] (95% CI)
Acute Exposure									
Dust cloud: density	0.95	1.9 (1.6, 2.3)	1.7 (1.3, 2.2)	0.96	1.9 (1.5, 2.4)	1.5 (1.1, 2.1)	0.94	2.1 (1.7, 2.7)	1.8 (1.2, 2.7)
Personal appearance after thickest part of cloud									
Visibility in thickest part of cloud									
Time first caught, relative to World Trade Center collapses									
Dust cloud: time	0.93	1.3 (1.1, 1.5)	1.0 (0.8, 1.4)	0.92	1.3 (1.1, 1.5)	1.0 (0.7, 1.3)	0.93	1.2 (1.0, 1.5)	1.1 (0.8, 1.7)
Duration of time in dust cloud									
Proportion of time in thickest part of cloud									
Chronic Exposure									
Dust: home/workplace	0.92	1.7 (1.4, 2.0)	2.1 (1.5, 2.8)	0.89	1.6 (1.3, 2.0)	1.8 (1.2, 2.8)	0.94	1.8 (1.4, 2.2)	2.6 (1.7, 4.2)
Extent of dust coverage at home or workplace									
Depth of thickest dust layer at home or workplace									
Proportion of home or workplace most affected									
Smoke: home/workplace	0.92	1.3 (1.1, 1.5)	1.8 (1.3, 2.6)	0.86	1.3 (1.0, 1.6)	1.5 (0.9, 2.4)	0.95	1.3 (1.0, 1.5)	2.5 (1.4, 4.2)
Smelled smoke inside, outside, both									
Duration of time during which smelled smoke									
Time: home/workplace	0.85	0.9 (0.8, 1.0)	1.2 (0.9, 1.6)	0.82	0.8 (0.7, 1.0)	0.9 (0.6, 1.3)	0.86	1.0 (0.8, 1.2)	1.4 (0.9, 2.3)
Time at home or workplace									
Month first at home or workplace after 9/11									
Cleaning: home/workplace	0.94	1.6 (1.4, 1.9)	1.0 (0.7, 1.3)	0.92	1.7 (1.4, 2.1)	1.3 (0.9, 1.9)	0.97	1.6 (1.3, 2.0)	0.8 (0.5, 1.3)
Participated in cleaning of home or workplace									
Number of items cleaned by participant[a]									
Time spent cleaning home									

Note. AOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio.

Maslow et al. Amer J Public Health 102: 1186, 2012

New onset symptoms associated with persistence of dust or odors in home



Lin et al. J. Asthma 2007

WTC Environmental Health Center

- Multidisciplinary treatment program for community members with presumed WTC-related illness
- Target population - local residents, local workers, students, clean-up workers
  - 2002 community collaborative program in the Bellevue Hospital Asthma Clinic
  - 2005 American Red Cross Liberty Disaster Relief Fund
  - 2006 City of New York
  - 2008 CDC-NIOSH
  - 2010 James Zadroga 9/11 Health and Compensation Act

WTC Environmental Health Center

- Self-selected population
- Patients have to have aerodigestive or mental health <u>symptoms</u> in order to enroll
- Cancers included in 2011
- All patients undergo standardized questionnaires including exposure assessment, PFT, mental health screening
- Multidisciplinary treatment program
- > 11,000 patients enrolled

Problem: How to characterize objective findings in a large population reporting lower respiratory symptoms?

- Physiologic assessment
- Pathologic findings
- Imaging
- (Biomarkers)

Can spirometry be used to explain lower respiratory symptoms (LRS)

Spirometry

- Forced vital capacity (FVC)
- Forced expiratory volume (FEV_1)
- Spirometry pattern

- Firefighters had decline in lung function
  - Pre-existing measures
  - Decline in lung function
  - Importantly, most values remained normal limits

No pre-existing measures available for this community population

Most patients with LRS had preserved spirometry measures at baseline evaluation

	No LRS (n = 102)	Mild LRS (n = 137)	Severe LRS (n = 559)	*P*-value
Sex, N (%)				
Female	46 (45)	64 (47)	297 (53)	0.18
Male	56 (56)	73 (53)	262 (47)	
Age, year				
Mean (SD)	48 (12)	47 (12)	52 (10)	<0.0001
Race/ethnicity, N (%)				
Hispanic	39 (38)	70 (51)	200 (36)	0.02
Caught in WTC dust cloud, N (%)*	16 (16)	23 (17)	136 (24)	
No	55 (54)	72 (53)	230 (41)	0.008
Yes	47 (46)	64 (47)	326 (59)	
Exposure category, N (%)*				
Clean-up worker	10 (10)	38 (28)	95 (17)	0.0002
Local worker	51 (50)	64 (47)	326 (59)	
Rescue/recovery/other	14 (14)	16 (12)	40 (7)	
Resident	27 (26)	19 (14)	96 (17)	
Body mass index, N (%)				
Normal	42 (41)	35 (26)	135 (24)	0.009
Overweight	33 (32)	55 (40)	215 (38)	
Obese	27 (26)	47 (34)	209 (37)	
Spirometry pattern, N (%) V1				
Normal	77 (75)	99 (72)	367 (66)	0.25
Low FVC	14 (14)	20 (15)	85 (15)	
Obstructed	9 (9)	15 (11)	78 (14)	
Low VC/obstructed	2 (2)	3 (2)	29 (5)	

Caplan-Shaw et al. Am J of Instrial Med 59:777 2016

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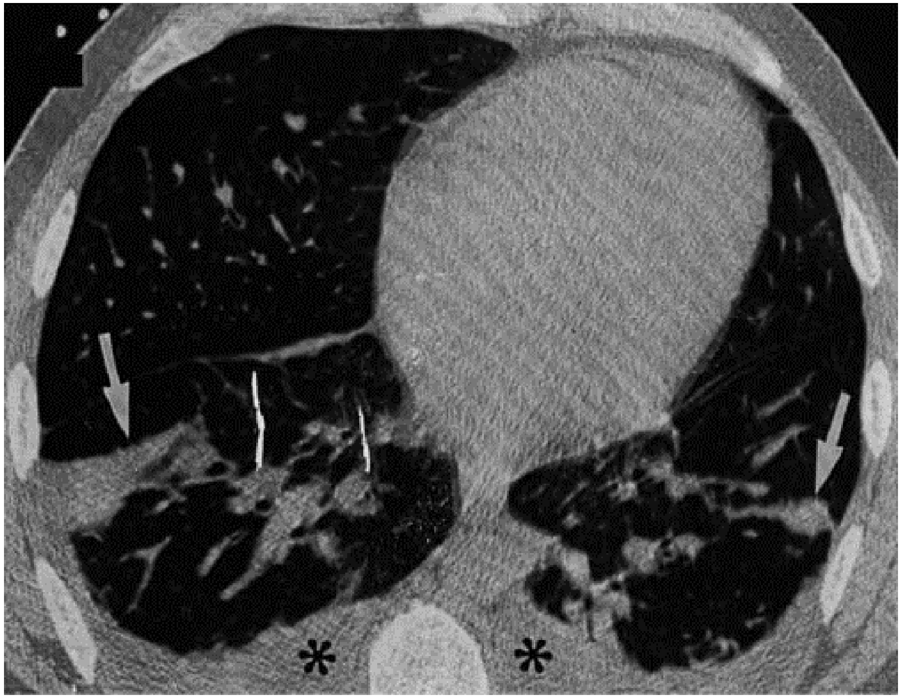
Additional assessments of lung function – airway hyper-responsiveness

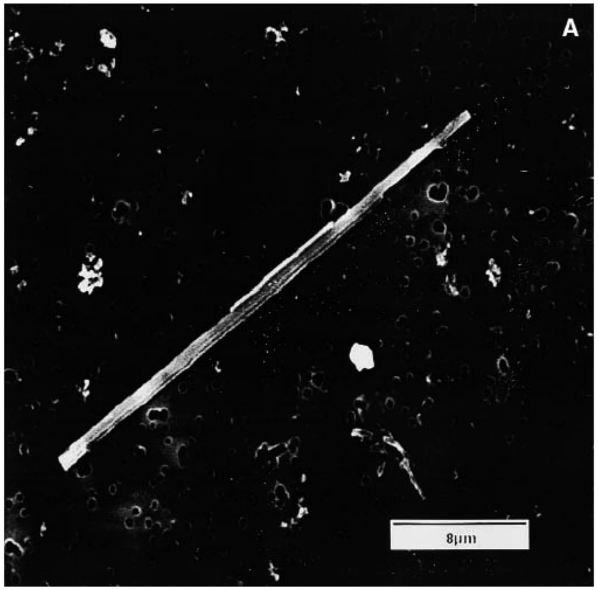
- Methacholine challenge
- Cumbersome
- ~50% positive at < 8 mg methacholine in sampled groups

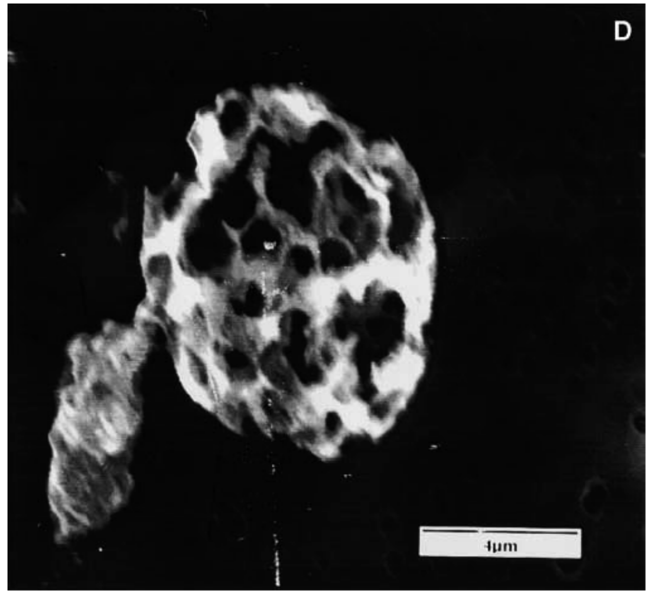
Acute pneumonia in a firefighter after WTC exposure – 2 weeks after 9/11

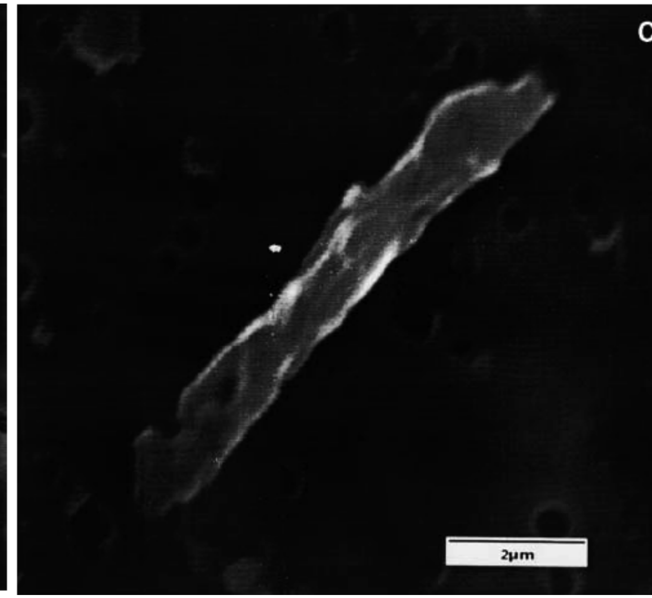


Rom et al. Am J Respir Crit Care Med 2002

Mineralogic analysis of bronchoalveolar lavage from firefighter







(*A*) Amosite asbestos fiber (uncoated)

(B) Fly ash particle

(*C*) Degraded fibrous glass.

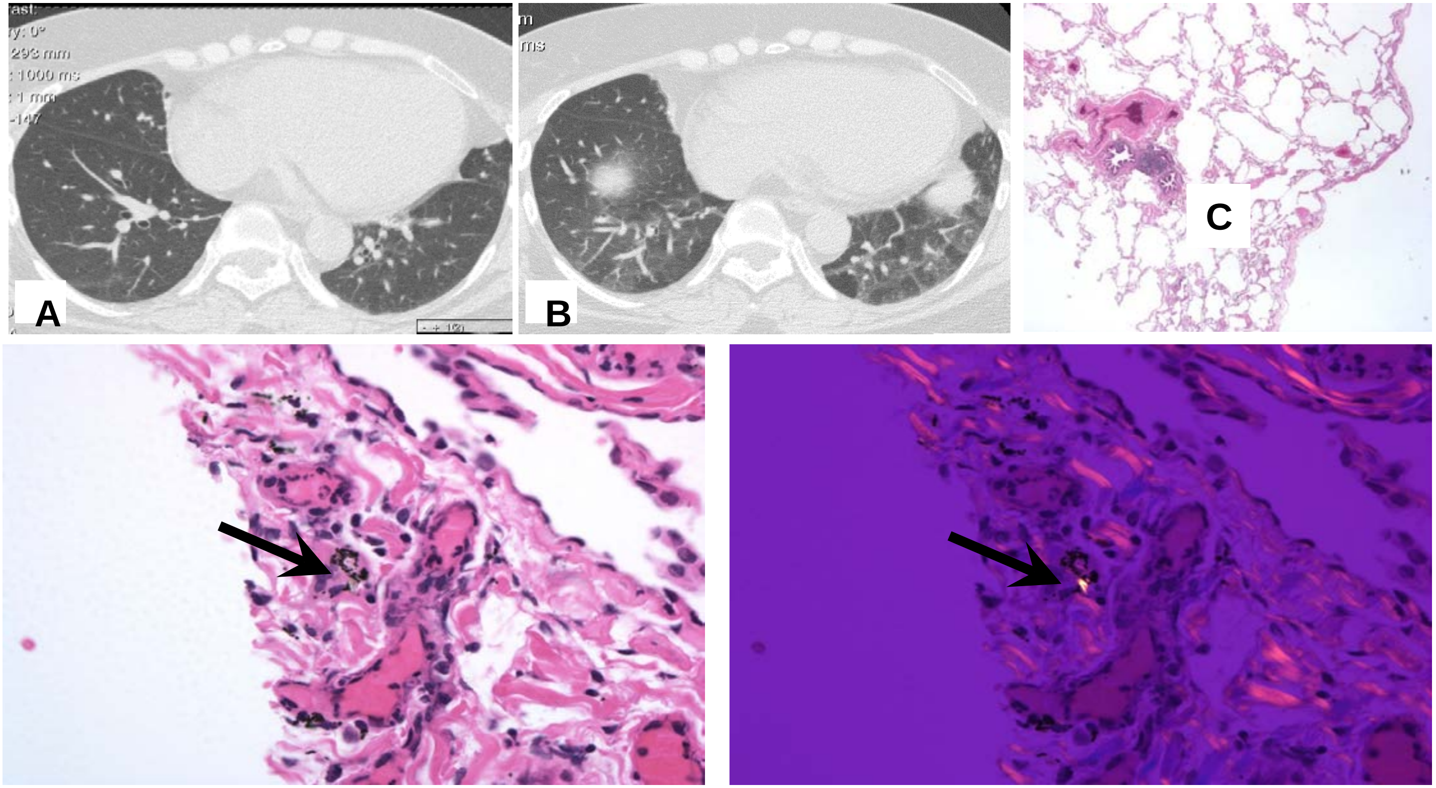
- Diverse environmental particles in the lung
- **Large particles capable of reaching deep in the lung**

Rom et al. Am J Respir Crit Care Med 2002

Can pathologic evaluations of symptomatic patients in the WTC EHC help reveal disease process

- The most common abnormality in lung function was a reduced vital capacity
- Evaluated lung biopsy specimens (VATS) in patients (n= 6) without evidence of CT parenchymal abnormalities.

Pathologic findings in community member with WTC exposure



D E

- CT with air trapping
- Rare visible airways – most were normal
- Loss of alveolar attachments -?emphysema
- Rare inflammation
- Birefringent particles

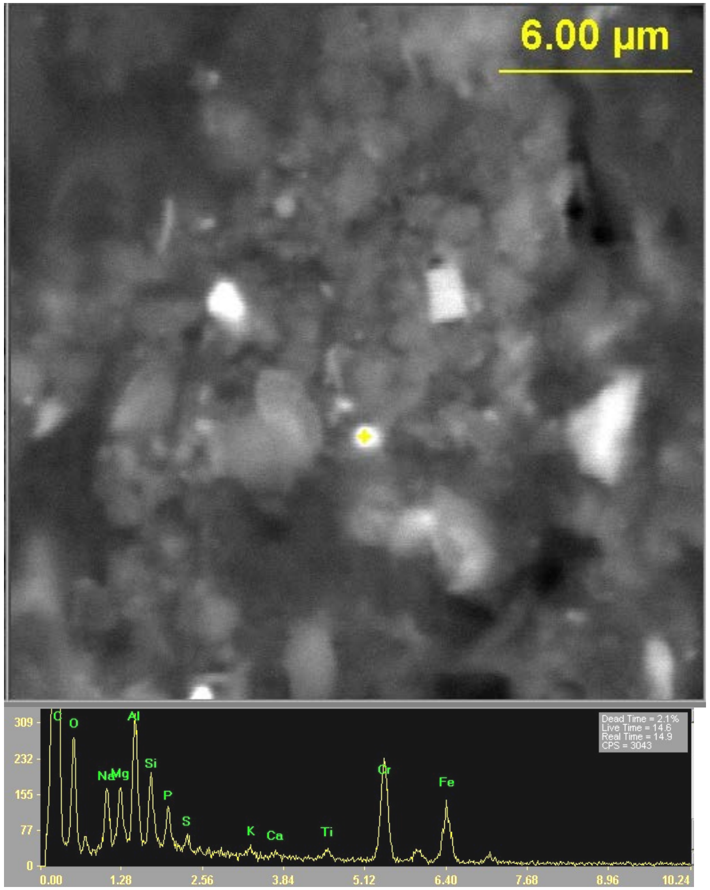
Caplan-Shaw et al. J Occup Environ Med. 53: 981, 2011

Particle analysis of lung biopsy specimens

Scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM-EDS) performed on 5 samples

- Silica
- Aluminum silicate
- Titanium
- Talc
- Metals – steel, copper, chromium

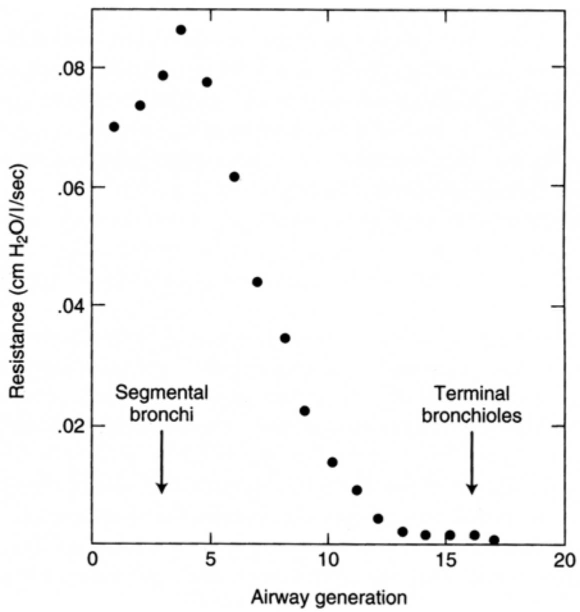
Analysis suggested unusual material and material in distal lung



Caplan-Shaw et al. J Occup Environ Med. 53: 981, 2011

Suggestion of involvement of small airways –Problem with spirometry for assessment of small airways

- Spirometry measures airflow (resistance)
- Small airways (75% of the lung) have low resistance due to multiple branching
- Resistance in these airways is not detected by spirometry (Quiet zone)



Pedley et. at. Respir Physiol 1970; 9:387

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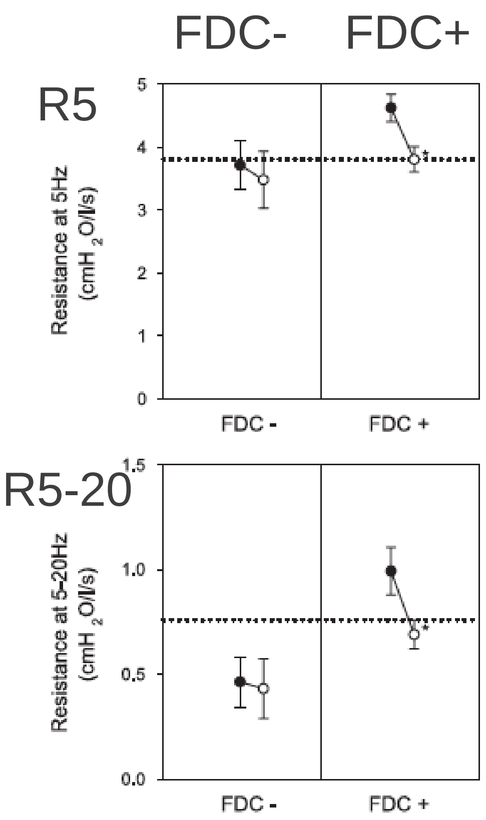
Forced oscillation technique

- Commercially available equipment– Impulse Oscillometer
- Noninvasive, simple maneuver at tidal breathing
- Measures resistance directly by measuring the relationship between pressure and flow at different oscillating frequencies by sound waves applied externally to the respiratory system
- Assessment at multiple oscillation frequencies allows identification of non-uniformities in airflow distribution – a hallmark of small airway dysfunction.
- R5 (resistance at oscillating frequency at 5 Hertz) (Airway resistance)
- R5-20 (frequency dependence of resistance)(Small airway resistance)
- Other measures also available (Ax)

Do forced oscillation measures reflect small airway abnormalities in the WTC population?

- Frequency dependence of compliance (FDC) (employs esophageal manometry, gold standard for measure of small airway abnormalities)
- Compared IOS measures with frequency dependence of compliance (FDC)
- IOS measures (R5, R5-20) were elevated (abnormal) in those with small airway abnormalities as determined by FDC+
- The IOS response to bronchodilator reinforced that it was an airway process



Oppenheimer et al. Chest 2007;132(4):1275

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Forced oscillation measures in the WTC EHC

- Routinely incorporated IOS measures in all lung function evaluations in the WTC EHC
- Rapid, effort independent, and relatively easy to perform

- Problem –
- Most patients had lower respiratory symptoms
- Most patients had abnormal FOT (IOS) measurements
- Findings not interpretable without a control population.

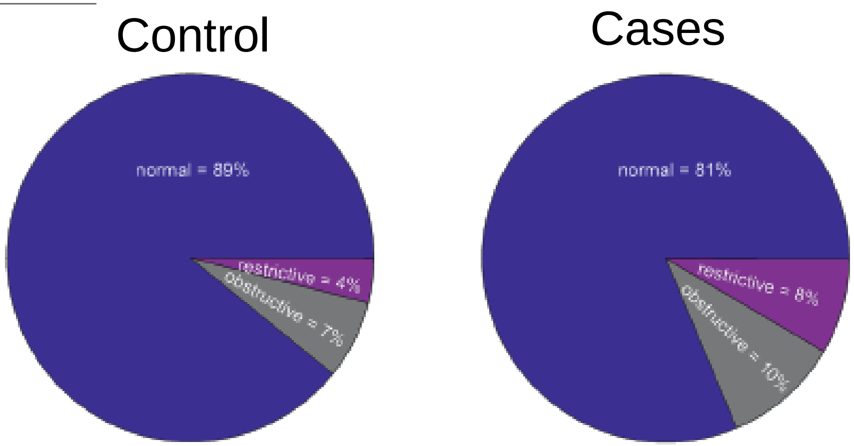
Collaboration with the NYC DOHMH WTC Registry: Case-Control Study

- NYC DOHMH WTC Registry
- Field study of DOHMH WTC Registry participants
    - Symptomatic Cases - symptoms at repeated surveys
    - Controls - no symptoms at any survey
- Performed spirometry and IOS in the field
- Compared lung function (spirometry and FOT;IOS) between Symptomatic Cases and Controls

NYC DOH WTC Registry: Case-Control Study

- Most Controls and Cases had normal spirometry (Blue)

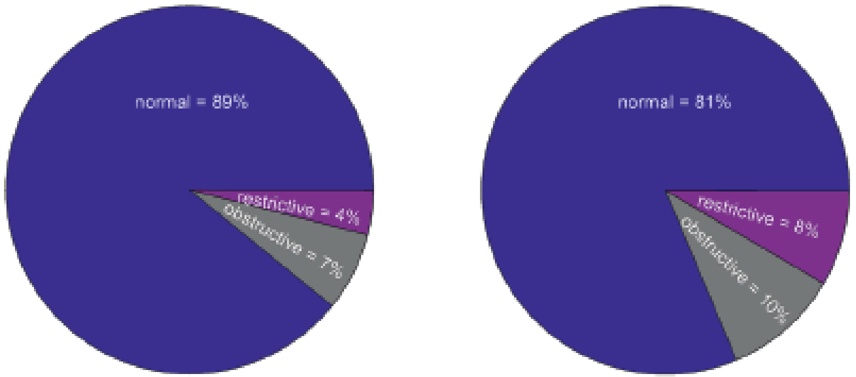
Spirometry analysis



Symptomatic cases had abnormal IOS (FOT)

Spirometry analysis

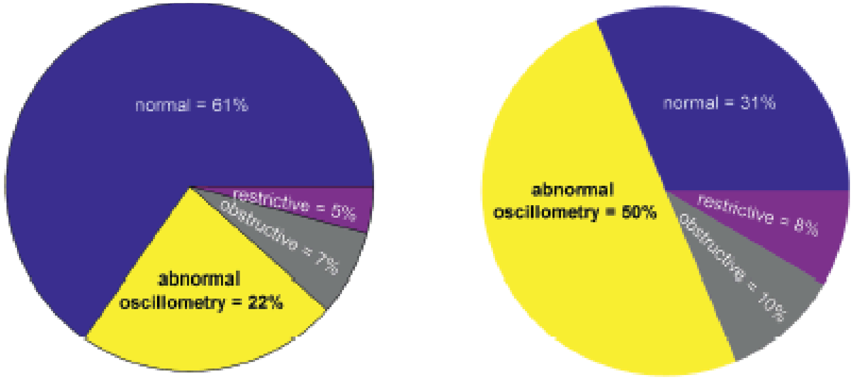
Control Cases



- Most Cases with normal spirometry, had abnormal IOS (yellow)

Oscillometry analysis

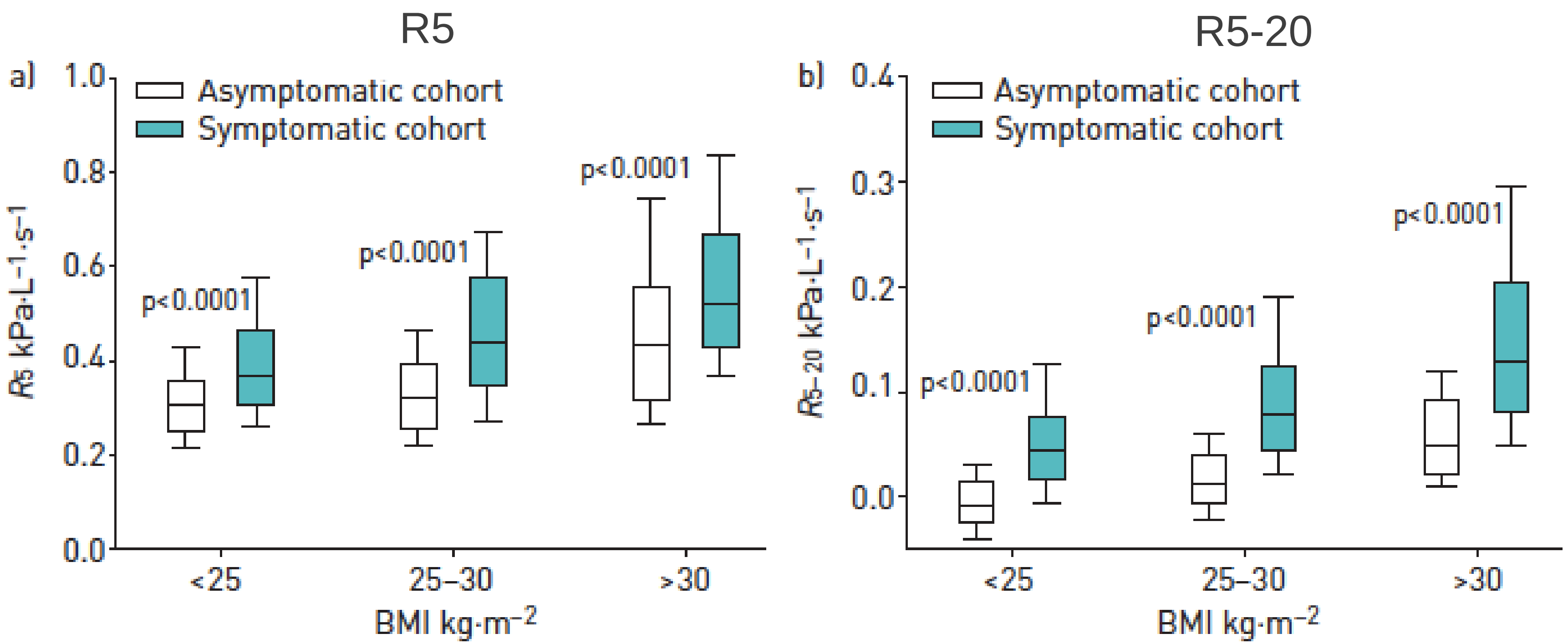
Control Cases



- IOS measures were associated with WTC exposures (data not shown)

Friedman et al. Am J Resp Crit Care Med 185:582 2011

IOS measures in symptomatic patients in the WTC EHC were elevated (abnormal) compared to asymptomatic cohort



- IOS measures elevated in symptomatic patients
- Differences in IOS measures remain significant within BMI categories

Berger et al. ERJ Open Res 2015; 1:00043-2015

Increase in IOS measures associated with increase in symptoms in the WTC EHC

TABLE 4 Severity and frequency of wheeze and impulse oscillometry for the symptomatic cohort

	Subjects n	R_5 kPa·L^{-1}·s^{-1}	R_{5-20} kPa·L^{-1}·s^{-1}
Wheeze severity			
None	502	0.447 (0.212)	0.074 (0.087)
Mild	137	0.458 (0.260)	0.085 (0.123)
Moderate	128	0.473 (0.233)	0.102 (0.121)
Severe	67	0.503 (0.301)	0.113 (0.129)
p-value#		0.001	<0.0001
Wheeze frequency days per week			
0–1	524	0.441 (0.220)	0.076 (0.088)
2–6	194	0.461 (0.218)	0.086 (0.117)
7	100	0.510 (0.278)	0.126 (0.122)
p-value#		<0.01	0.0001

Data are presented as median (interquartile range) unless otherwise stated. R_5: resistance at an oscillating frequency of 5 Hz; R_{5-20}: difference in resistances measured at 5 and 20 Hz. #: Jonckheere–Terpstra test.

Similar findings in those with normal spirometry (data not shown)

Berger et al. ERJ Open Res 2015; 1:00043-2015

Summary of FOT/IOS experience

- FOT/IOS could be performed easily in clinic/field
- Useful tool as adjunct to standard lung function measures for assessment of LRS symptoms, particularly in those with normal spirometry
    - Pros
        - Relatively easy, effort independent
        - Normative data available (Oostveen et al. ,Eur Respir J 2013;42:1513, Berger in preparation)
    - Cons
        - Interpretation confounded by BMI
        - Doesn’t reveal source of abnormality – chest wall, parenchymal, pleural as well as airway

Can imaging studies help characterize small airway disease in an exposed population?

Early imaging studies in responders suggested air trapping noted on expiratory high resolution CT imaging

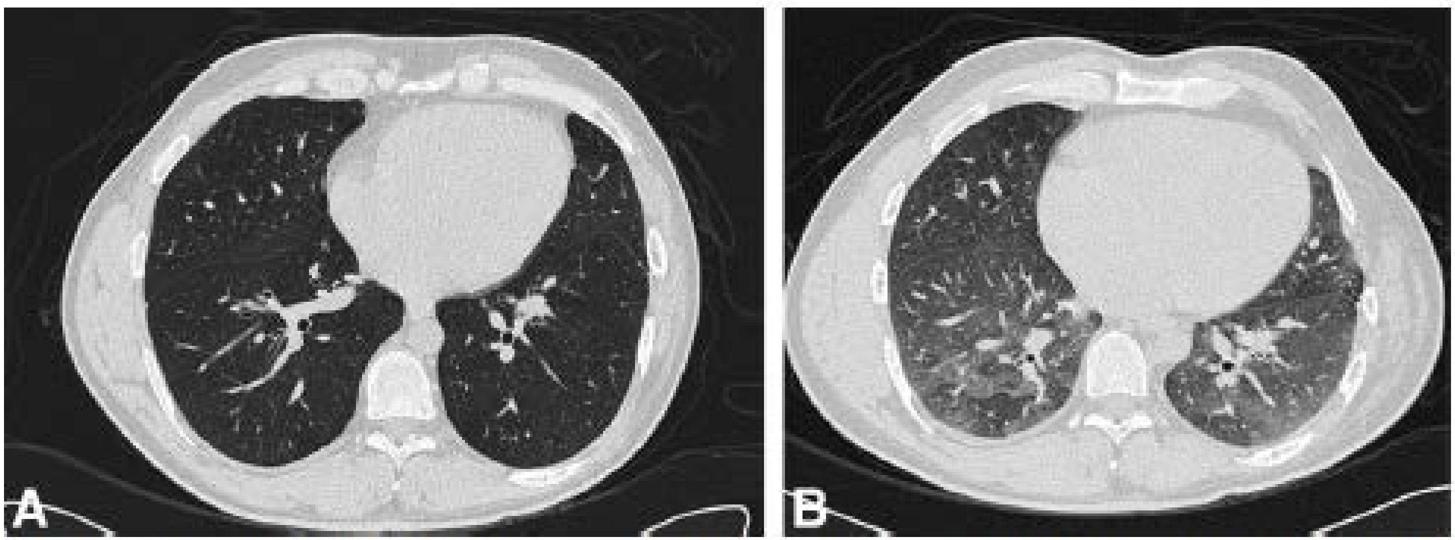


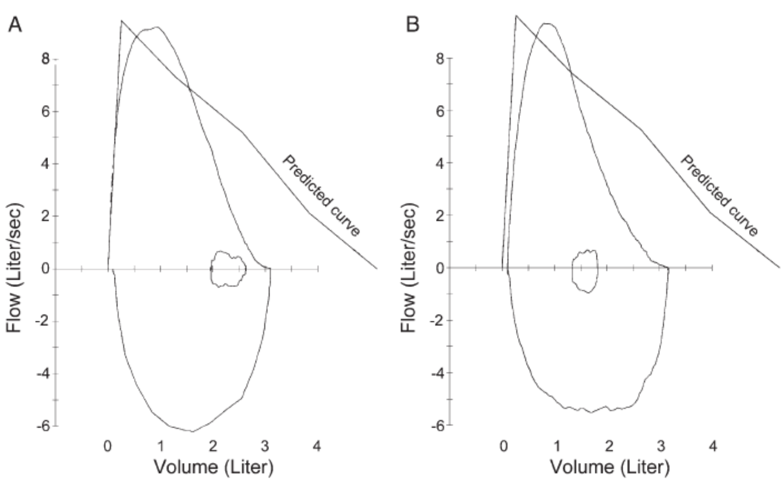
Fig. 1. Patient with an AT score of 20 (maximum possible score of 24). Figure 1A demonstrates a section of the lower zone from the end-inpiratory CT, and Figure 1B is a similar level from the end-exspiratory examination. The mosaic pattern can be noted on the end expiratory portion of the examination. The same level appears normal on the inspiratory image. This combination is indicative of AT.

Mendelson et al.J Occup Environ Med 2007;49:840

Imaging and lung function studies in a WTC EHC group with reduced Vital Capacity on spirometry

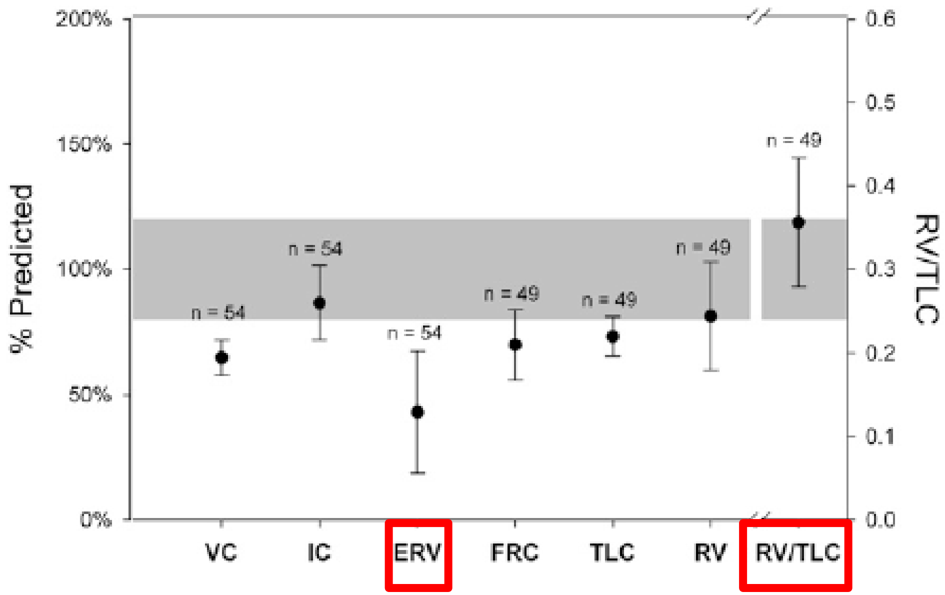
- Most common abnormality in the WTC EHC (and responder) population was a reduction in VC

WTC patient ILD patient



Berger et al. Chest 2013; 144:249

Reduced VC consistent with small airway abnormalities in the WTC EHC



- ERV (Expiratory Reserve Volume) reduced (differs from patients with interstitial lung disease)
- Elevated RV/TLC
- Slightly reduced TLC
- Compliance studies not consistent with ILD
- Imaging studies c/w airway disease (air trapping) and not parenchymal disease

New methods in CT evaluation

Large airway measures

- Quantification of airway wall thickness

Small Airway disease

- % of gas trapping – Hounsfield units at RV
- Parametric response mapping of functional small-airway abnormality (PRM fSAD)
  - paired inspiratory and expiratory CTs can identify and quantify the extent of small-airway abnormalities
  - commercially available software application (Imbio Lung Density Analysis)

PRM fSAD shows CT changes in tobacco smokers with preserved spirometry - GOLD 0 (Spiromics)

PRM fSAD abnormal in patients with long term exposure to Vapors/Gas/Dust/Fumes (Spiromics)

- Paulin et al. Ann Am Thoracic Soc 2018;15:1411.

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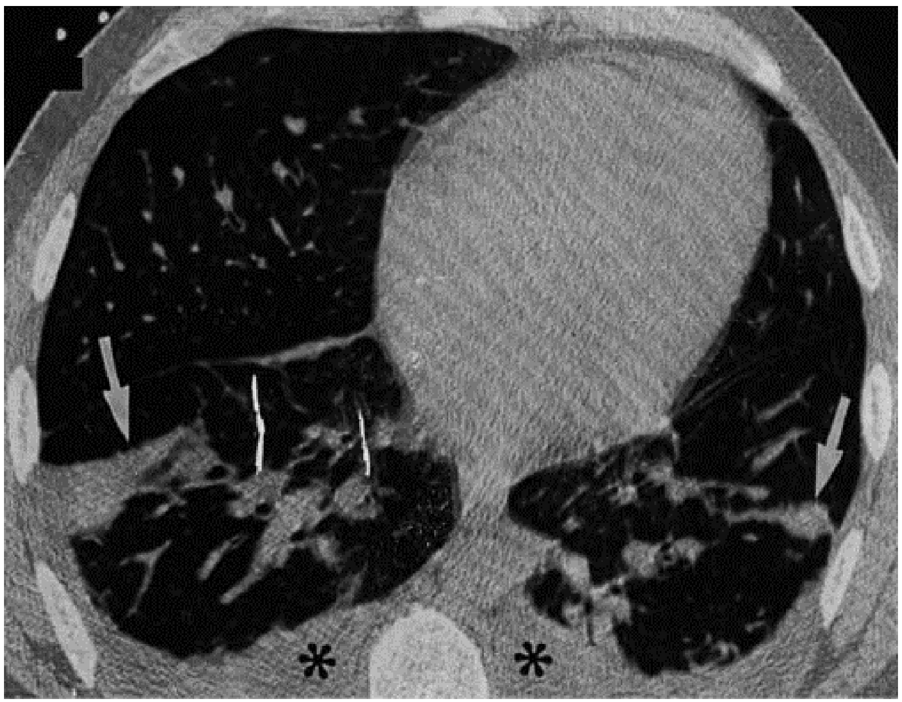
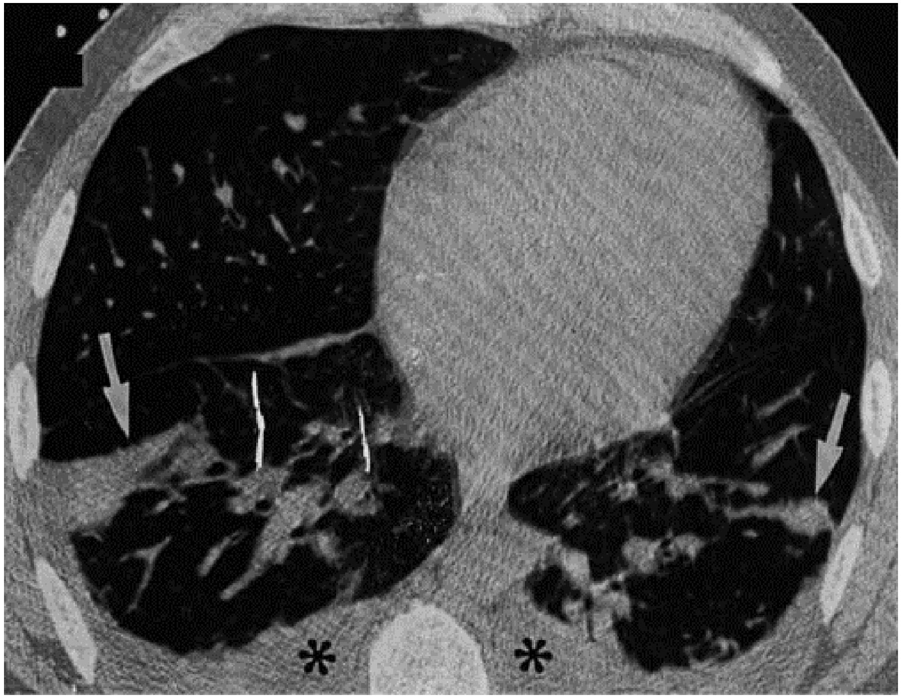
Do blood biomarkers reflect lower respiratory symptoms in the WTC EHC?

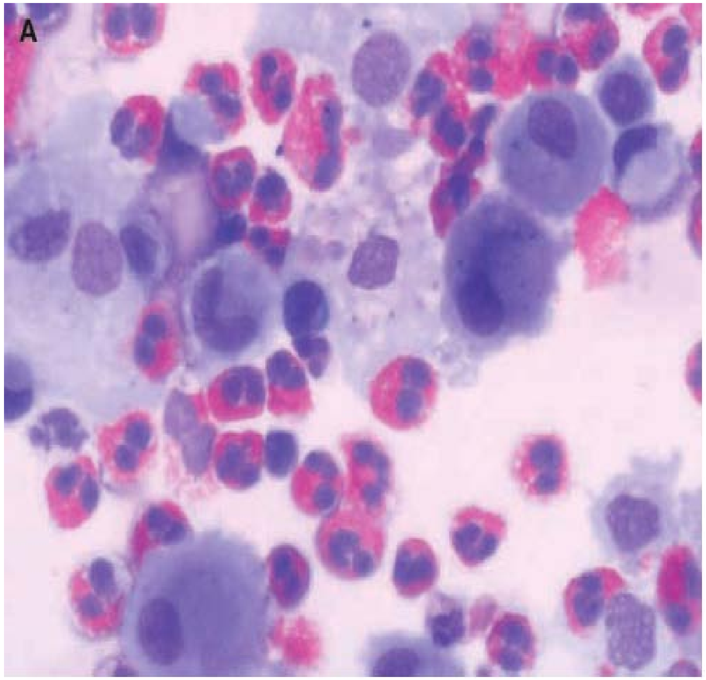
Acute pneumonia in a firefighter



Rom et al. Am J Respir Crit Care Med 2002

Acute eosinophilic pneumonia in a firefighter





Rom et al. Am J Respir Crit Care Med 2002

Peripheral eosinophils associated with wheeze and airway obstruction

Category	**High Eos** N = 176	**Low Eos** N = 964	OR[†]	P value
Spirometry pattern, n (%)				
Normal	117 (66)	735 (76)	1	
Obstructed [a]	27 (16)	70 (7)	2.42	0.0002
Low FVC [b]	32 (18)	159 (17)	1.27	NS

Kazeros et al. J Asthma. 2013; 1 :25-32

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Systemic inflammation – C-reactive protein

Spirometry pattern, n(%)	High CRP	Low CRP	OR*	P value
Normal	161(30)	367(70)	1	
Obstructed [a]	22(29)	54(71)	1.39	0.28
Low FVC [b]	65(52)	59(48)	2.58	<0.001
Low FVC/Obstructed [c]	13(50)	13(50)	1.99	0.13

- Elevated CRP associated with lower respiratory symptoms and low FVC
- Elevated CRP associated with abnormal small airway measures (FOT:IOS)

Kazeros et al, J. Occ Environ Med 2013

Summary

- Many community members with WTC dust exposure had lower respiratory symptoms
- Lower respiratory symptoms out of proportion to screening spirometry
- Heterogeneity in lung function and diagnoses (asthma, ?, ILD)
- Bronchoalveolar lavage and pathology studies suggested ability of WTC particles to reach the distal lung (small airways, parenchyma)
- Lung function findings (reduced VC), forced oscillation findings, and air trapping on CT, consistent with abnormalities in small airways, even in those with normal spirometry
- Common blood biomarkers, were associated with subtypes of disease but T2 patterns (elevated eosinophils, FeNO) uncommon

Challenges with assessment of environmental lung injury pertinent to Gulf War

- Variability in individual clinical response
- Standard measures of lung function may not be adequate
- Need consideration of additional techniques
  - Measures of airway hyper-responsiveness
  - Measures of small airway function
    - Physiologic
      - IOS/FOT simple, provides supportive information for small airway involvement
    - Imaging
      - Parametric response mapping of functional small-airway abnormality (PRM fSAD)
- Comorbidities – upper airways, mental health

- **Impact on treatment**

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