Division of Pulmonary, Critical Care
and Sleep Medicine

WTC respiratory disease findings in the WTC EHC "Survivor" population

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Funding

- WTC cooperative agreements
  - #200-2011-39413 Evaluation of Distal Airway Injury Following Exposure to World Trade Center Dust
  - U01 OH011317 (Small airway COPD in the Survivor population)
  - U01OH010404 (Uncontrolled Lower respiratory Symptoms in WTC Survivor population)
- Clinical Center: 1E11OH0030(2008 – 2011) 200-2011-39391C(previous), 200-2017-93427(current)
- Data Center: 200-2011-39379C(previous) 200-2017-93327 (current)

Goals

- What have we learned about lower respiratory symptoms in community members
  - Respiratory symptoms after 9/11and exposure
  - Location of lung injury
  - Mechanisms of LRS
- Implications for other exposures/illnesses
- What have we learned and what do we need next

Local workers/office workers,residents commuters, teachers, students

- Acute exposures
- Dust clouds

The cloud in Lower Manhattan, south of Chambers Street.

Chronic indoor and outdoor exposures from resuspended dust and fumes
Local workers returned to work September 17, 2001

Document respiratory symptoms in the community

WTC Residents Respiratory Health Study

- NYS DOH, local community, NYU
- Funded by CDC
- Cross-sectional study of “exposed” and “control” residential population
- Designed, implemented and completed 16 months after 9/11/01
- **One of few studies with a control population**

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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 $\geq$ 2 days per week in the past 4 weeks.

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

NYC HEALTH+ HOSPITALS

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

NYU Langone Health

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.

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

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Onset of LRS in community confirmed by NYC DOH WTC Health Registry

- NYC Department of Health WTC Registry
- 71,437 participants exposed individuals
- Survey initiated in 2003, repeated measures
- Adverse health effects in community
  - Brackbill et al. MMMWR Surveill Summ 2006;55:1-18
  - Farfel et al. J Urban Health 2008;85:880-909

WTC Environmental Health Center

- WTC EHC pilot program at Bellevue Hospital
- Philanthropic funds, City funds, Federal funds in 2008
- "WTC EHC Survivor program" 2011 James Zadroga 9/11 Health and Compensation Act
  - Highly regulated and monitored programs under the CDC/NIOSH
  - Provide treatment for "Certified Conditions" for symptomatic "Survivors" (community members)
  - Certified conditions include aerodigestive disorders, mental health diagnoses, cancers

Characteristics of patients in the WTC EHC differ from responders

Characteristics(n = 1898)	
Sex, N(%)	
Male	1005(53)
Female	893(47)
Age	48 ± 12
Race, N%	
White	867(46)
Black	318(17)
Asian	217(11)
Ethnicity, N%	
Hispanic	792(42)
Income	
< 30K	1178(62)
Exposure category, N%	
Local Worker	709(37)
Resident	378(20)
Clean-up worker	566(30)
Dust cloud, N%	
Yes	749(40)

Reibman et al. J Occup Environ Med. 2009

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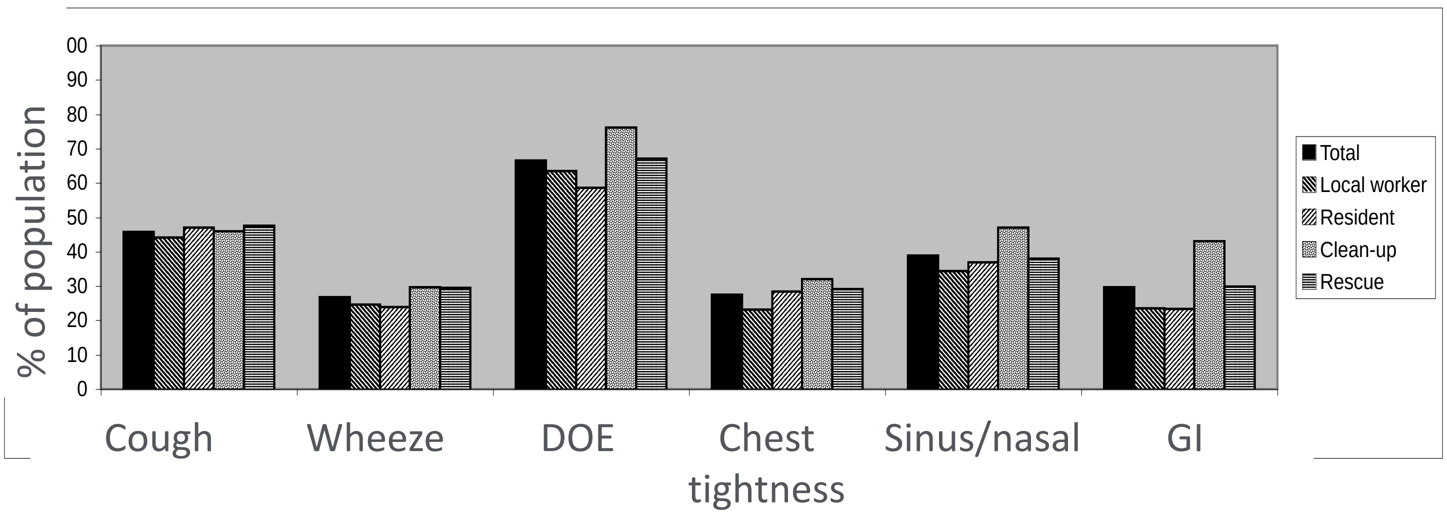
Aerodigestive symptoms in previously normal WTC EHC population are similar to those in responders

Lower respiratory symptoms

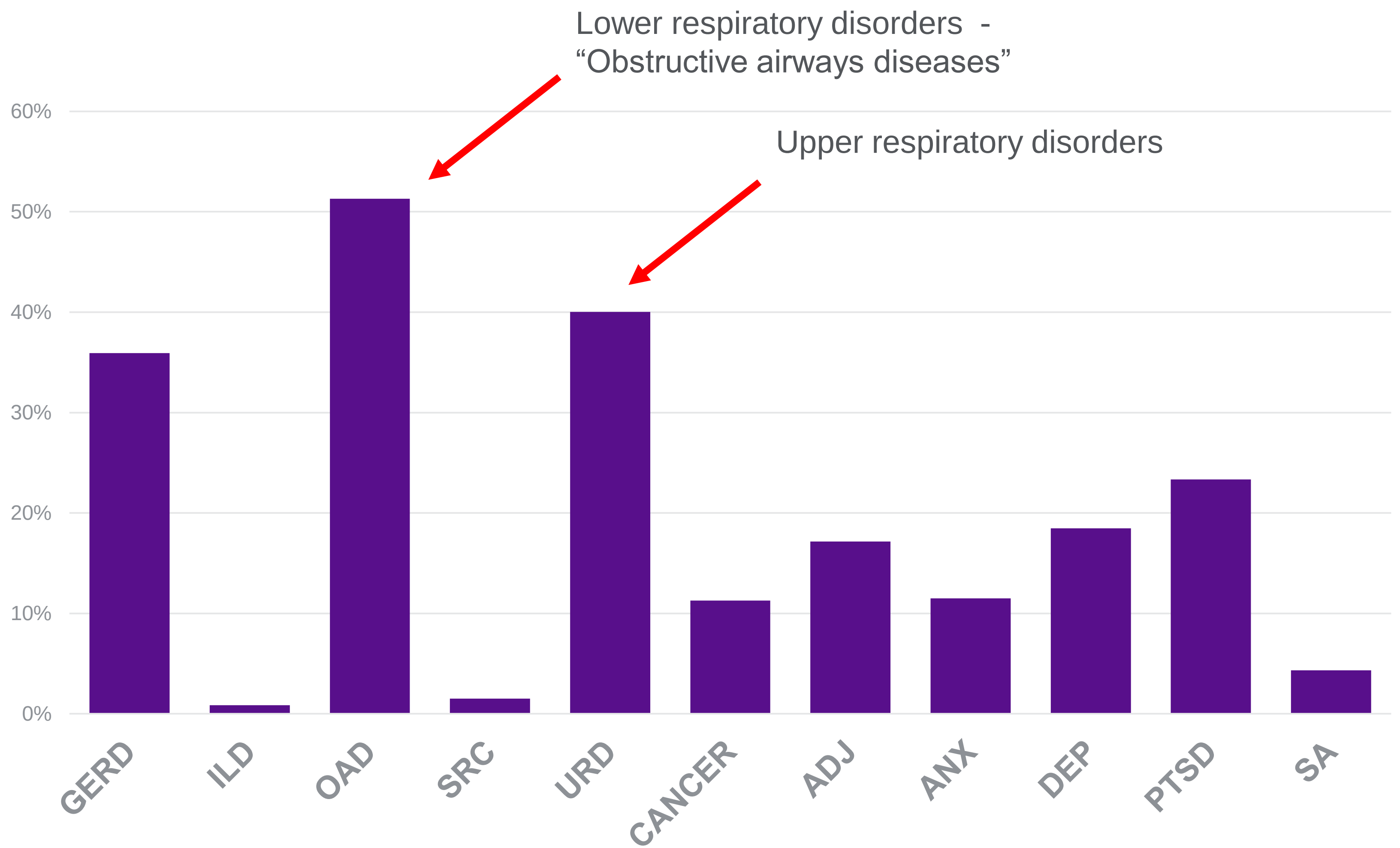
Upper respiratory symptoms

GERD



Reibman et al. J Occup Environ Med. 2009

Aerodigestive symptoms remain most common Certified WTC-related conditions in WTC EHC



(May 2016, n = 5677)

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

Composite Exposure Scale and Component Variables	All Participants (n = 785)			Residents[d] (n = 479)			Area Workers[d] (n = 422)		
	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

What have we learned about inhalation injury from WTC dust/fumes in Survivor population

- Location of injury

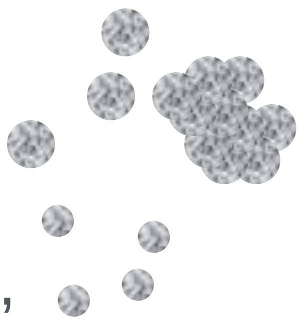
Particulate matter (PM) - Physical properties

- PM10 - aerodynamic diameter <10 μm
- PM2.5 – aerodynamic diameter ≤ 2.5 μm
- Ultrafine PM – aerodynamic diameter <0.1 μm

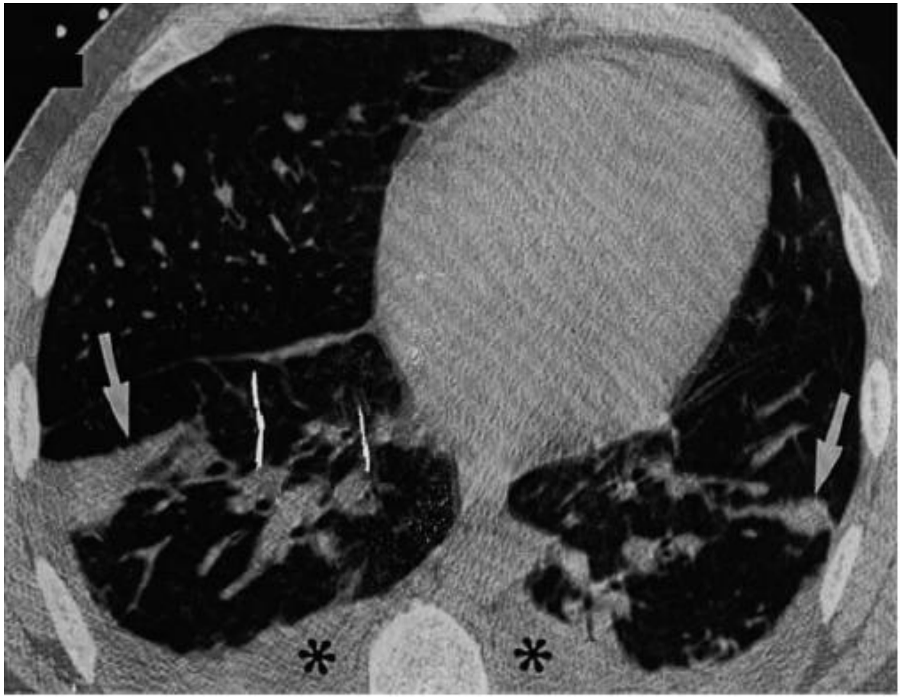
- Size influences site of damage in the airway
- Large particles expected to cause upper airway damage, smaller can traverse to lower airways

Physical properties of WTC dust

- 1.2 million tons of building materials
- 90% of settled particles >10 □m diameter
- 11,000 tons of particles < 2.5 □m diameter
- Acute exposures from massive dust from dust clouds
- Chronic exposures from resuspended dust, indoor resuspended dust
- Dust composed of large and small particles

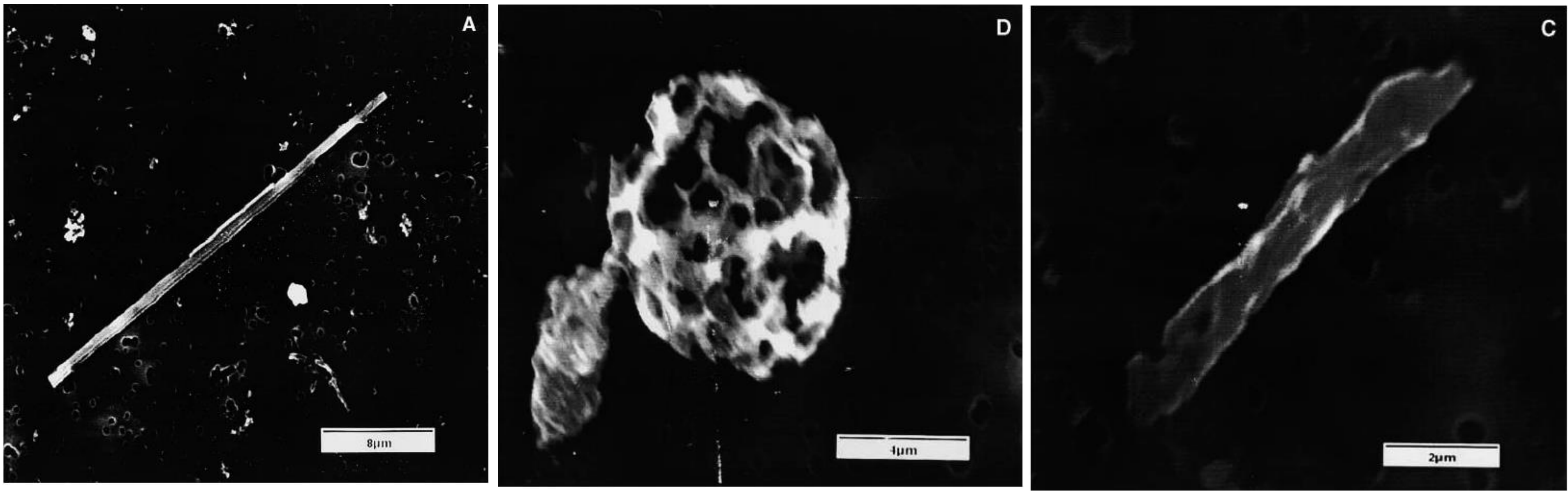


Acute pneumonia in a firefighter after WTC exposure



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.

- Environmental particles in the lung
- Large particles deep in the lung

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Rom et al. Am J Respir Crit Care Med 2002

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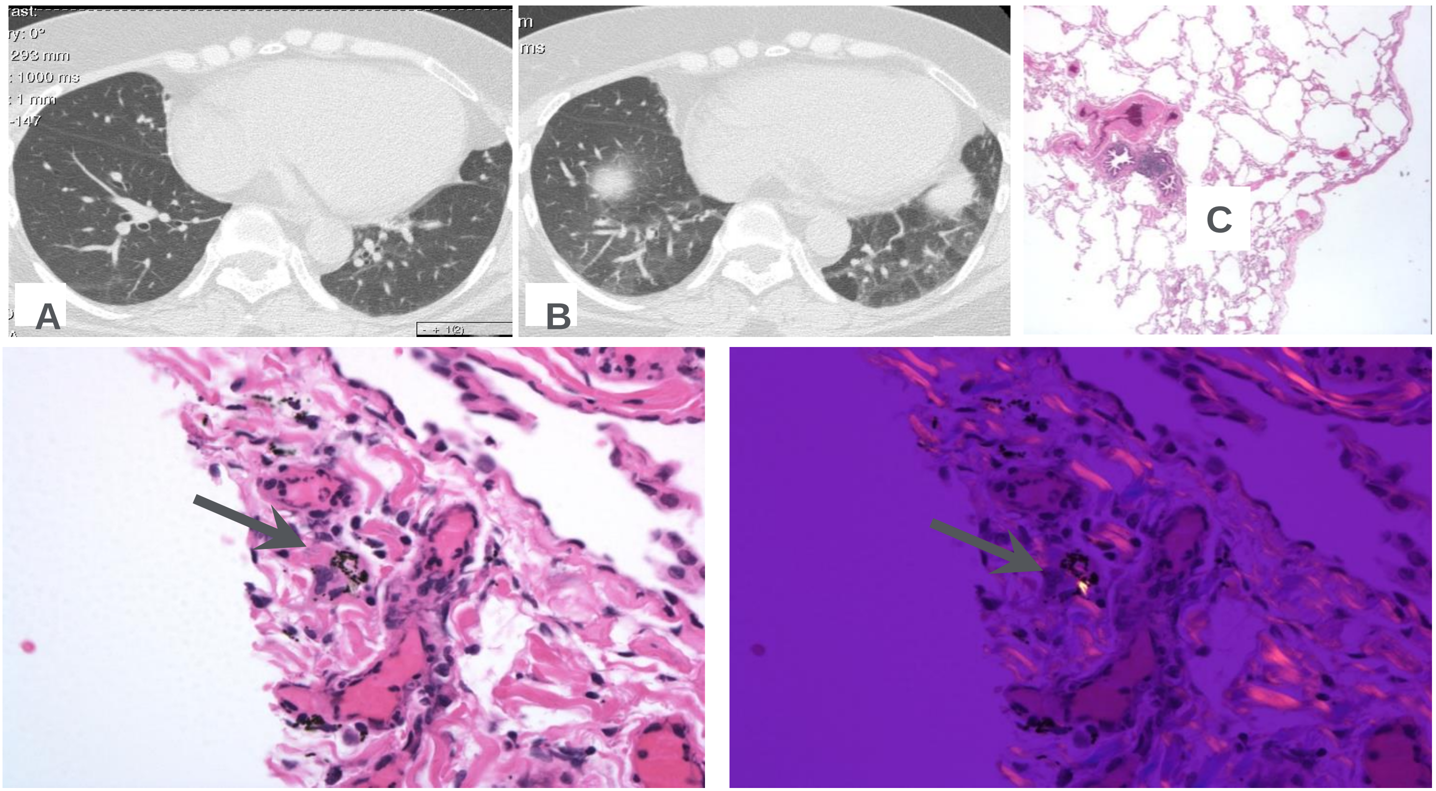
Pathologic findings in community member with WTC exposure – persistent particles in lung



D E

Scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM-EDS) revealed silica, AlSi, Ti, Talc, Metals (steel, copper, chromium)

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

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Location of injury

- In massive exposures, large particles able to access deep in lung
- Large and small particles persisted in the lung

Location of injury

- In massive exposures, large particles able to access deep in lung
- Large and small particles persisted in the lung
- Location of damage? Was there small airway/distal lung involvement associated with lower respiratory symptoms

Lung function studies used to detect airway injury

- Spirometry standard measure of lung function
- May not detect small airway abnormalities
- Forced oscillation techniques (impulse oscillometry) can detect subtle changes in airway function not identified by spirometry
- Did patients with lower respiratory symptoms have small airway abnormalities

Are LRS symptoms associated with small airway involvement not detected by spirometry?

- Routine measurements of forced oscillation in patients in the WTC EHC
- Most patients with normal spirometry had abnormal FOT measurements
- Couldn't interpret without a control population

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

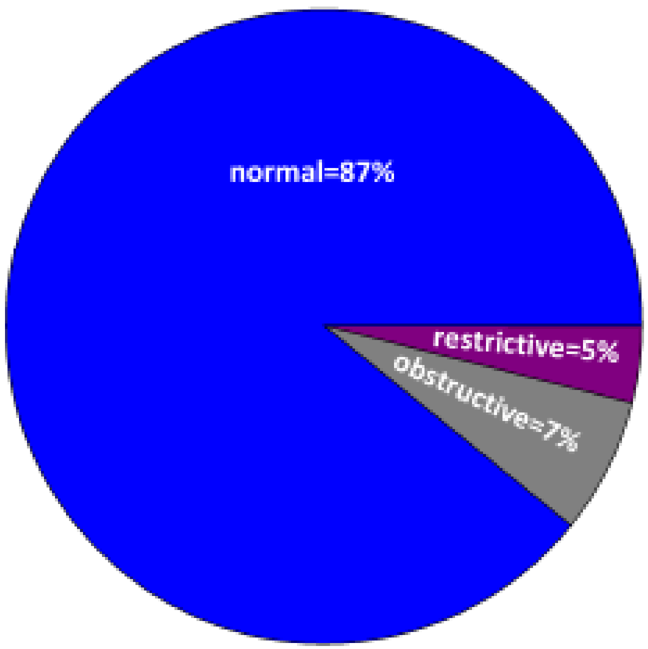
- DOH WTC Registry
- Field study of WTC Registry participants
- Symptomatic Cases – lower respiratory symptoms at repeated surveys
- Controls - no symptoms at any survey

- Compared lung function (spirometry and FOT) between Symptomatic Cases and Controls

Friedman et al. Amer J Resp Crit Care Med 2011

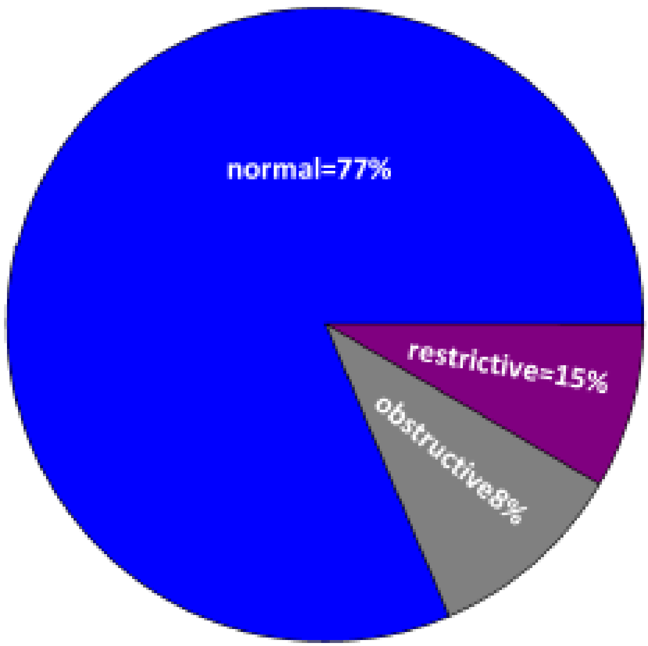
Most cases and controls had normal spirometry

Control
n = 473



Normal spirometry 87%

Symptomatic Cases
n = 180



Normal spirometry 77%

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Friedman et al. Amer J Resp Crit Care Med 2011

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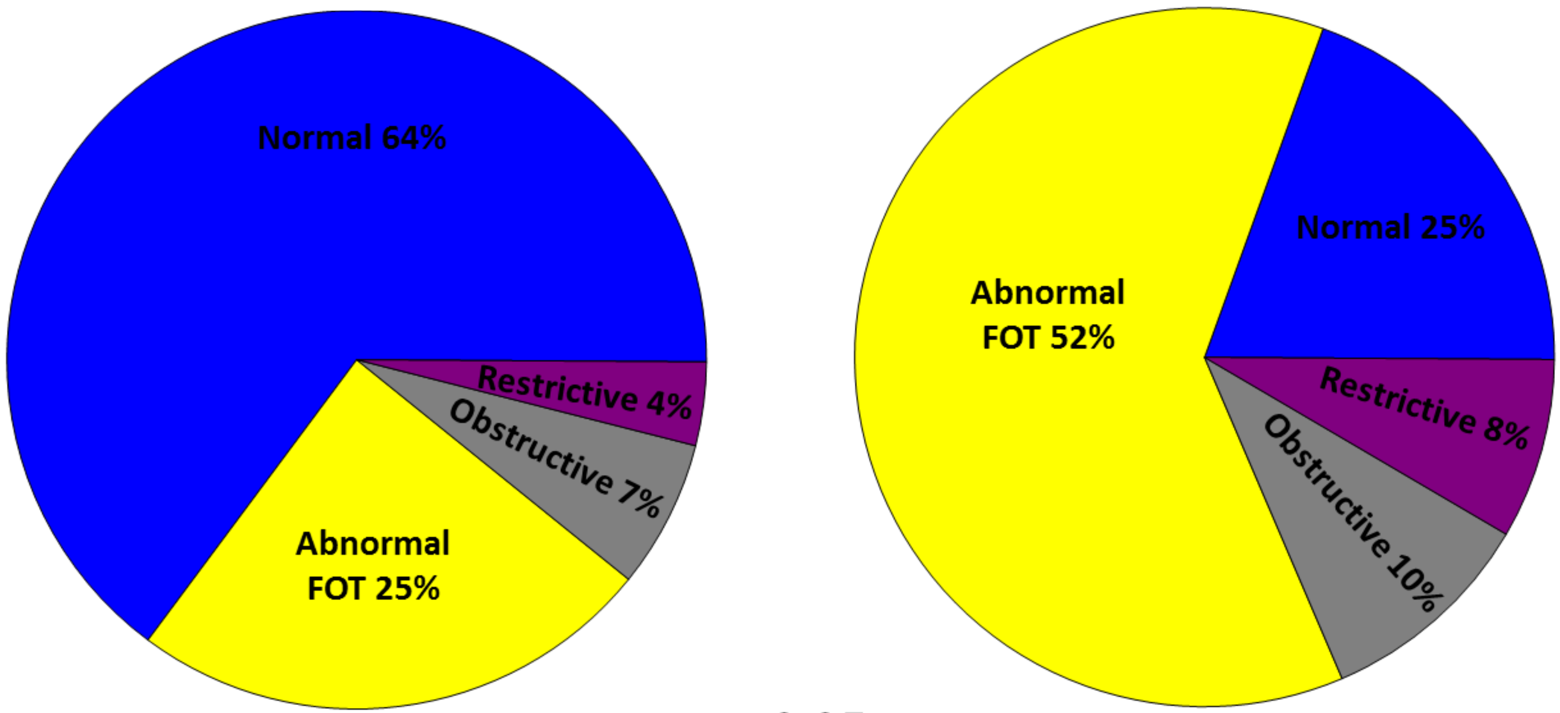
Symptomatic cases had abnormal small airway function (FOT)

Control
n = 473

Symptomatic Cases
n = 180



$p < 0.05$

Friedman et al. Amer J Resp Crit Care Med 2011

Abnormal small airway function associated with severity of LRS in patients with normal spirometry

	Total Resistance		Small Airway Function	
	R_5 ($cmH_2O/L/s$)		R_{5-20} ($cmH_2O/L/s$)	
	median	IQR	median	IQR
Wheeze Severity				
None (n = 384)	4.38	2.04	0.71	0.83
Mild (n = 97)	4.32	2.22	0.82	0.79
Moderate (n = 80)	4.66	2.36	0.80	0.90
Severe (n = 50)	5.06	1.95	0.99	1.03
p value*	NS		0.03	
Wheeze frequency (days/wk)				
0-1 (n = 400)	4.41	2.10	0.72	0.90
2-6 (n = 129)	4.46	2.20	0.79	0.70
7 (n = 70)	5.02	2.70	1.02	1.20
p value*	NS		0.05	

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

Small airway injury

- Small airway abnormalities detected in symptomatic WTC EHC patients even with normal screening spirometry
- Small airway abnormalities associated with exposure (data not shown)
- Small airway abnormalities associated with severity LRS

- **First use of FOT (IOS) to assess environmental injury in the lung**
- **Too for future use for environmental exposures**

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Mechanisms for WTC lower respiratory symptoms?

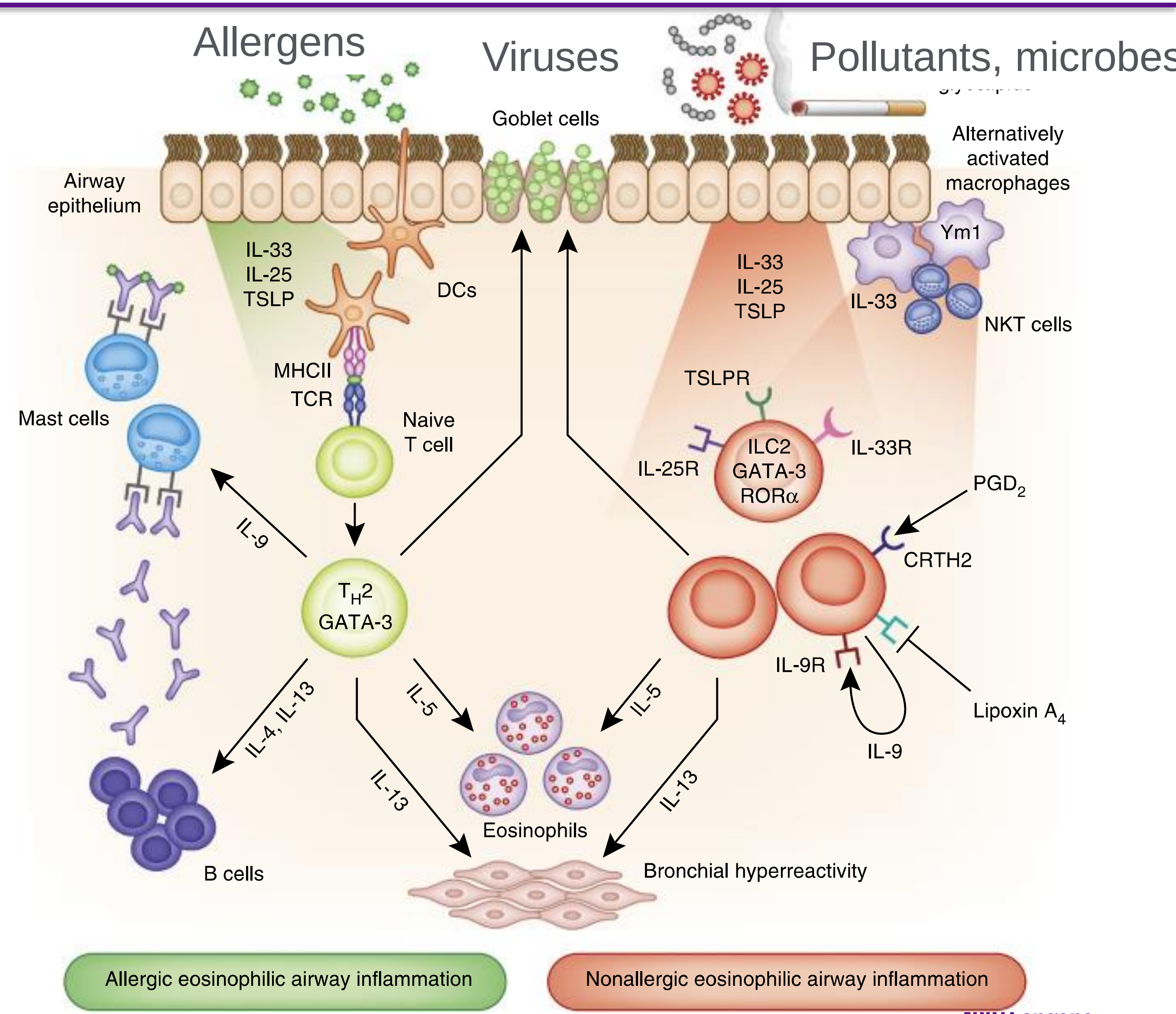
Mechanisms of asthma are complex

Many stimuli

Heterogeneous pathways

Redundant pathways

No all asthma is the same



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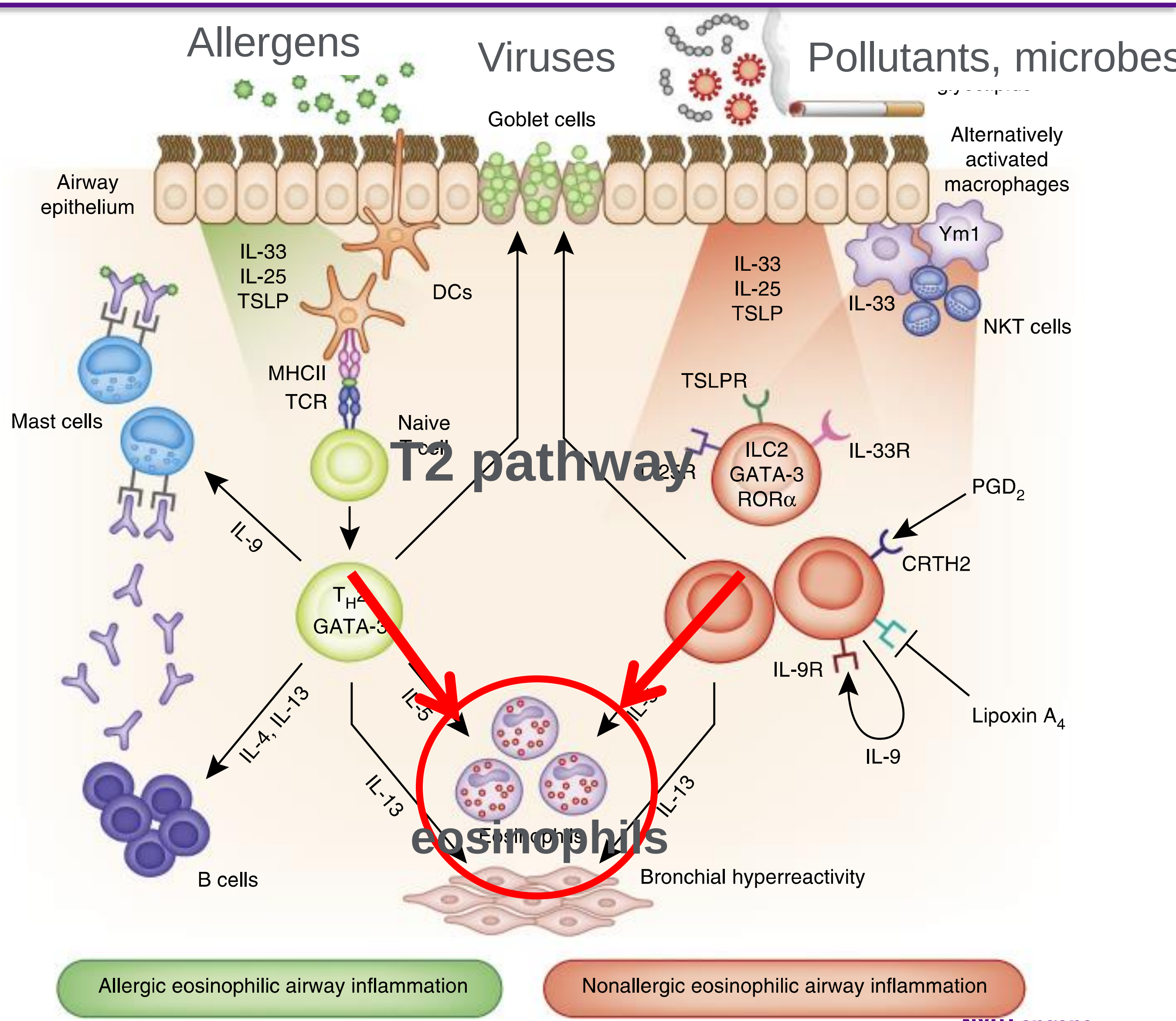
Type 2 inflammation in asthma



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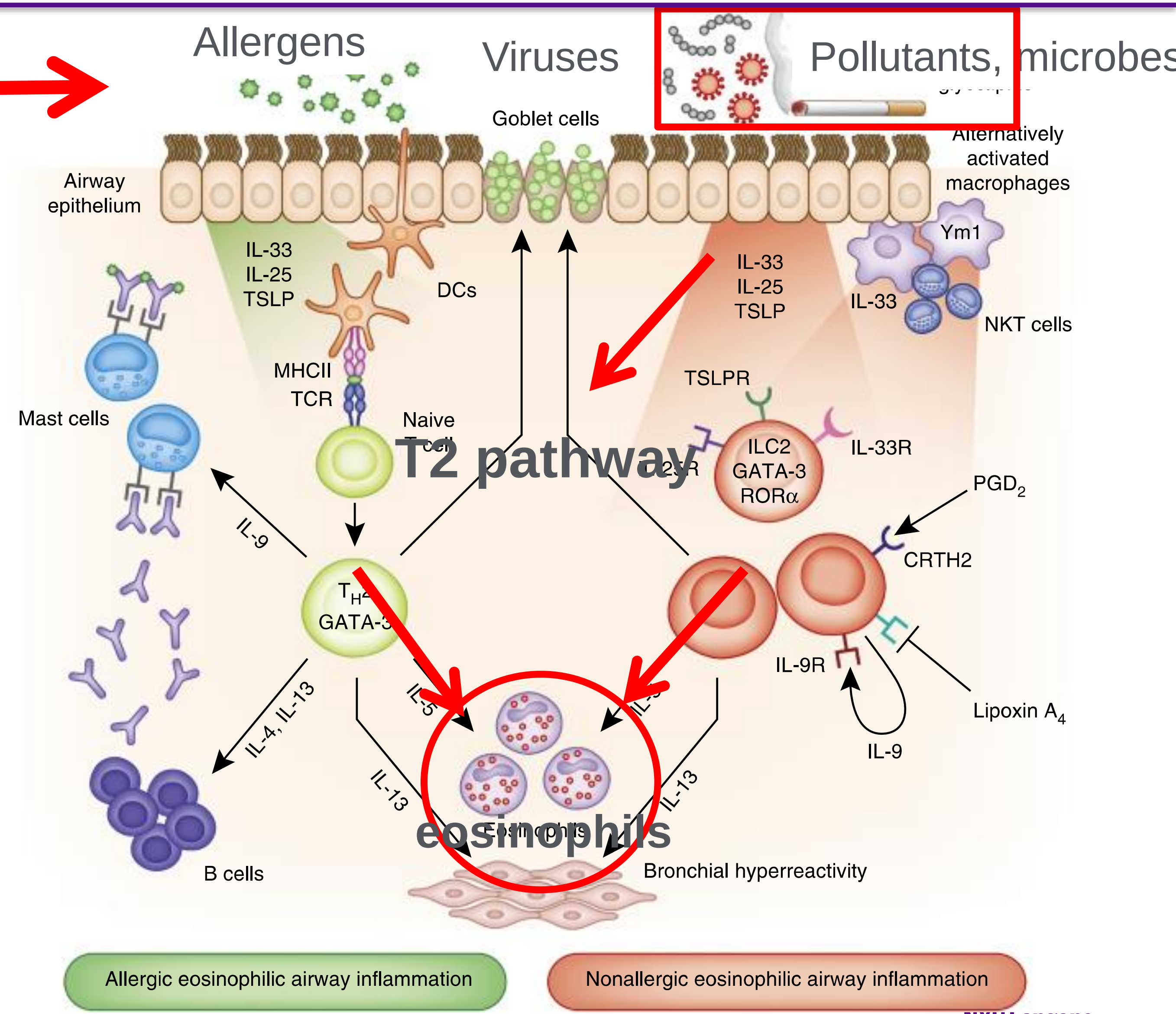
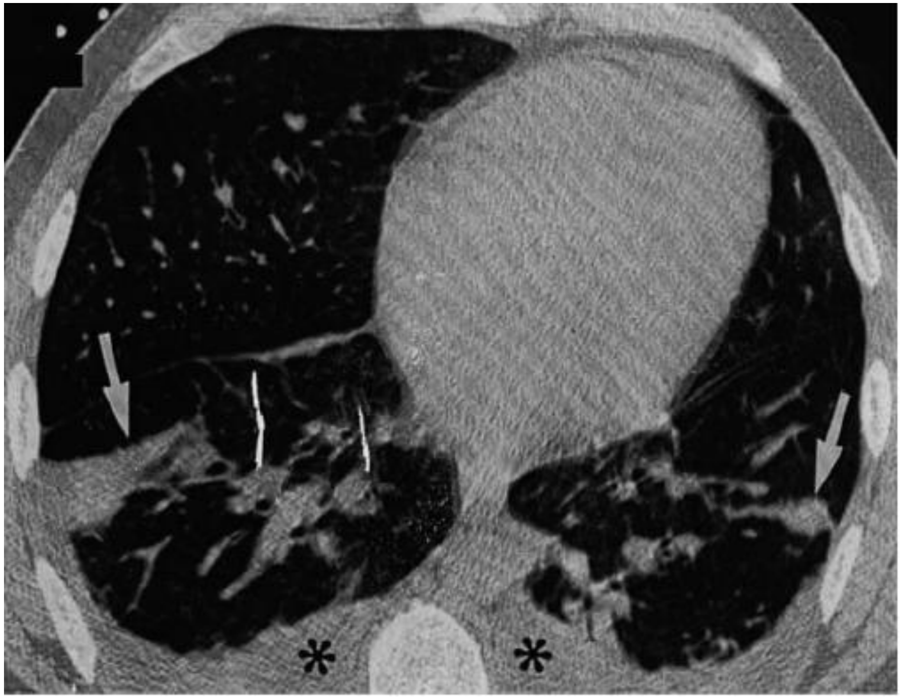
Inflammation in response to environmental stimuli

Damage

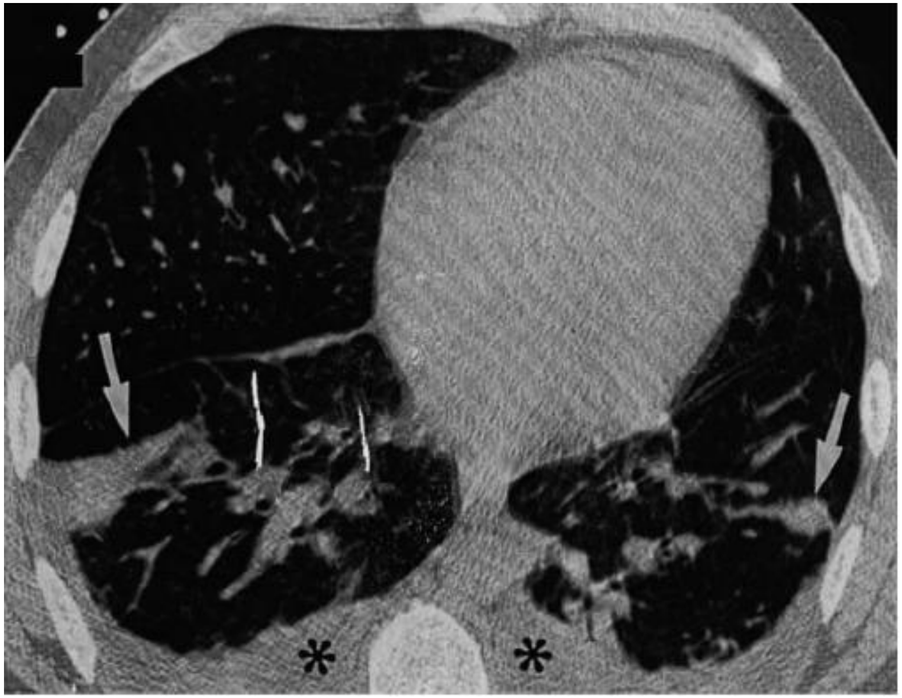


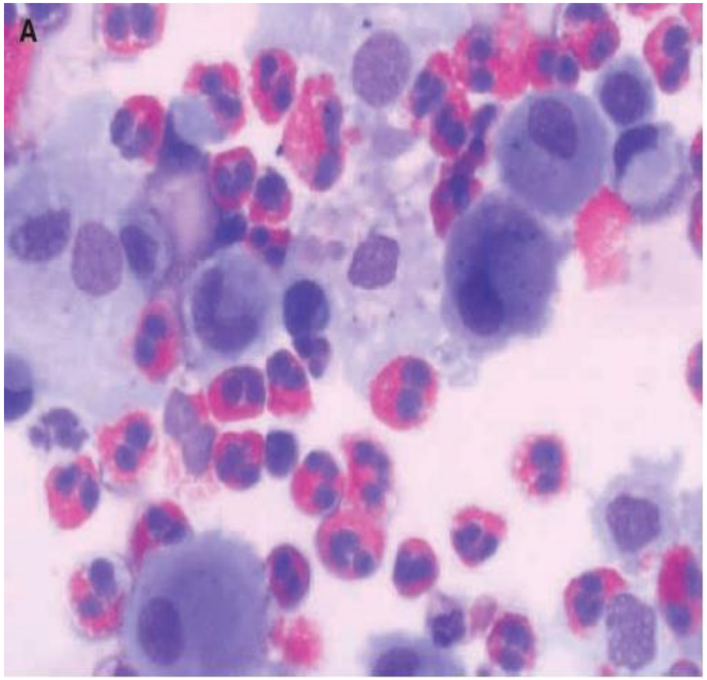
Acute pneumonia in a firefighter



Rom et al. Am J Respir Crit Care Med 2002

Acute eosinophilic pneumonia in a firefighter





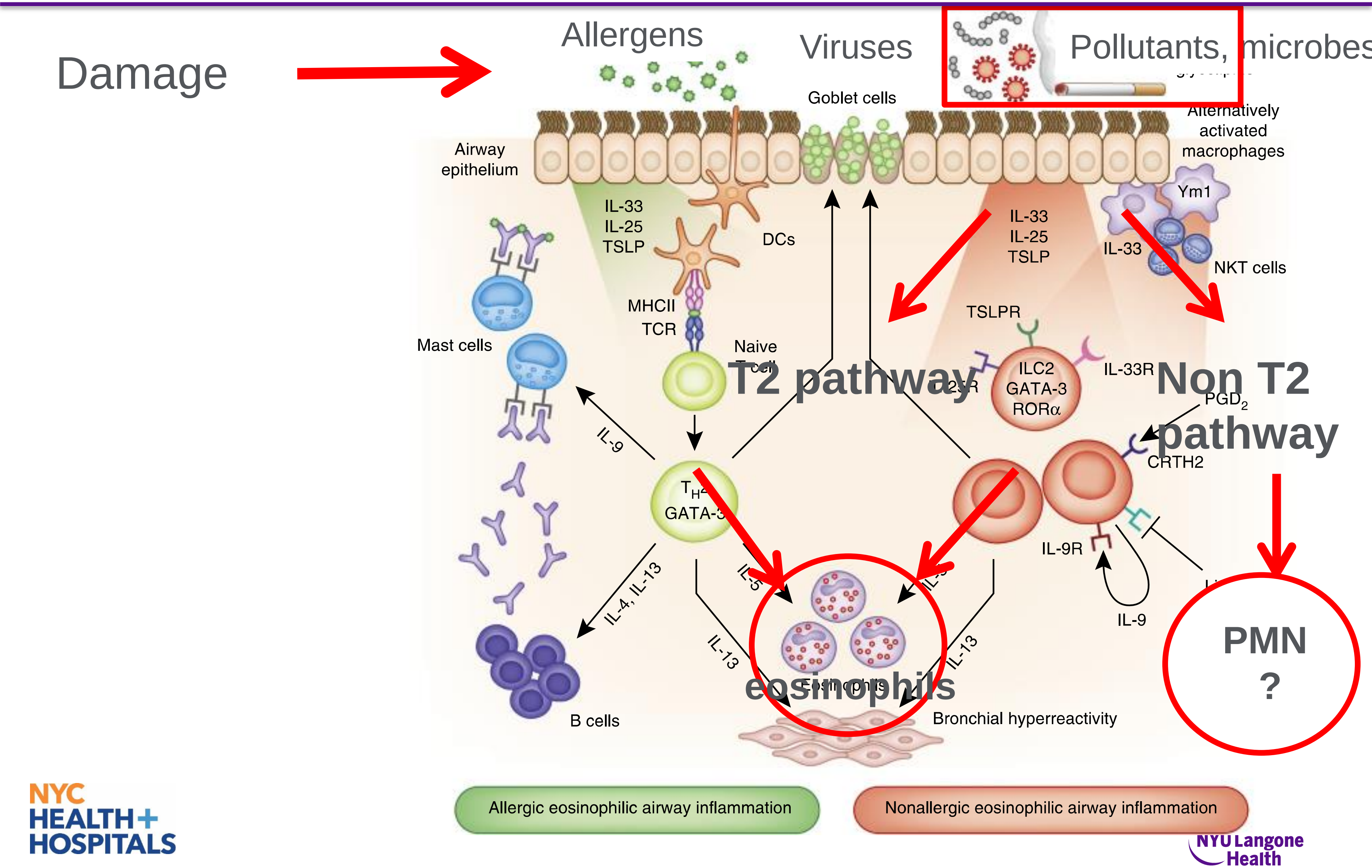
Rom et al. Am J Respir Crit Care Med 2002

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

Inflammation in response to environmental stimuli



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Lower respiratory symptoms associated with systemic inflammation C-reactive protein

- Symptomatic patients in WTC EHC (n = 754)

TABLE 3. Association of LRS With High CRP Level*

Symptom†	OR	*P* Value
Cough (n = 704)	1.83	0.001
Wheezing (n = 690)	1.73	0.008
Dyspnea at rest (n = 729)	1.67	0.008
Chest tightness (n = 698)	1.61	0.011

*Adjustment includes sex, Age, log (BMI), smoking status, caught in WTC dust cloud, and exposure category.
†The number varies for each symptom because of missing data.
OR, odds ratio.

Kazeros et al, J. Occ Environ Med 2013

Abnormal FVC and small airway measures associated with systemic inflammation - CRP

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 low FVC
- Elevated CRP associated with abnormal small airway measures (FOT) (data not shown)

Kazeros et al, J. Occ Environ Med 2013

C-reactive protein associated with +PTSD score

Table 3
Multiple linear regressions of PTSD, anxiety and depression scores; n = 641.

	PTSD		Anxiety		Depression[a]	
	β (SE)[b]	P value	β (SE)	P value	β (SE)	P value
log(CRP)	**1.12 (0.43)**	**0.01**	0.19 (0.18)	0.27	0.55 (0.29)	0.06
Demographics						
Gender - male	**−2.49 (1.25)**	**0.05**	−0.95 (0.51)	0.06	**−1.87 (0.84)**	**0.03**
Age at first visit	−0.07 (0.06)	0.26	−0.02 (0.02)	0.40	−0.07 (0.04)	0.06
Race/ethnicity Hispanic	**4.73 (1.53)**	**0.00**	**1.73 (0.62)**	**0.01**	**2.31 (1.03)**	**0.03**
Education ≤ High School	0.23 (1.5)	0.88	0.35 (0.61)	0.57	−0.08 (1.0)	0.93
Income ≤ $30k/year	**3.72 (1.36)**	**0.01**	**1.82 (0.55)**	**0.00**	**2.62 (0.91)**	**0.00**
log(BMI)	−3.57 (3.4)	0.29	−1.56 (1.38)	0.26	−2.28 (2.28)	0.32
Ever smoker	0.37 (1.54)	0.81	−0.62 (0.63)	0.33	0.06 (1.03)	0.95
Exposures						
WTC dust cloud exposure	**5.01 (1.3)**	**0.00**	**1.39 (0.53)**	**0.01**	**1.98 (0.87)**	**0.02**
Exposure classification						
Resident	−2.19 (1.72)	0.20	0.12 (0.70)	0.87	0.60 (1.15)	0.60
Clean-up worker	1.48 (2.16)	0.49	**2.41 (0.88)**	**0.01**	2.06 (1.44)	0.15
Other	−2.92 (2.0)	0.14	−0.49 (0.81)	0.55	−0.94 (1.34)	0.48
Lower respiratory symptoms						
Cough	0.47 (1.4)	0.74	0.52 (0.57)	0.37	0.87 (0.94)	0.35
Wheeze	0.71 (1.38)	0.61	0.38 (0.56)	0.50	0.41 (0.92)	0.66
Dyspnea at rest	**3.05 (1.37)**	**0.03**	**1.73 (0.56)**	**0.00**	**1.87 (0.92)**	**0.04**
Chest tightness	**4.70 (1.37)**	**0.00**	**2.61 (0.56)**	**0.00**	**2.79 (0.92)**	**0.00**

Significant P-values are bolded.
[a] 5 participants missing depression data: n = 636 for depression analysis.
[b] β, regression coefficient; (SE), standard error.

Rosen et al. J. Psychiatric Res 2017

C-reactive protein associated with PTSD clusters

Table 4
Multiple linear regressions of PTSD symptom cluster scores; n = 641.

	Re-experiencing		Avoidance		Negative cognitions/mood		Arousal	
	β (SE)[a]	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
log(CRP)	**0.08 (0.03)**	**0.002**	**0.08 (0.04)**	**0.02**	0.06 (0.03)	0.06	0.05 (0.03)	0.08
Demographics								
Gender - male	−0.13 (0.08)	0.09	**−0.35 (0.10)**	**0.001**	−0.07 (0.08)	0.42	−0.16 (0.09)	0.07
Age at first visit	0.00 (0.00)	0.78	0.00 (0.00)	0.41	−0.01 (0.00)	0.16	0.00 (0.00)	0.24
Race/ethnicity Hispanic	**0.25 (0.10)**	**0.008**	**0.30 (0.13)**	**0.02**	**0.21 (0.10)**	**0.04**	**0.36 (0.11)**	**0.001**
Education ≤ High school	0.04 (0.09)	0.67	−0.03 (0.13)	0.80	−0.04 (0.10)	0.68	0.06 (0.11)	0.58
Income≤ $30k/year	**0.29 (0.08)**	**0.001**	**0.34 (0.11)**	**0.003**	**0.19 (0.09)**	**0.04**	0.13 (0.10)	0.17
log(BMI)	−0.11 (0.21)	0.62	−0.52 (0.28)	0.07	−0.19 (0.23)	0.41	−0.21 (0.24)	0.39
Ever smoker	−0.08 (0.10)	0.40	−0.04 (0.13)	0.76	0.08 (0.10)	0.47	0.09 (0.11)	0.39
Exposures								
WTC dust cloud	**0.30 (0.08)**	**0.00**	**0.34 (0.11)**	**0.002**	**0.25 (0.09)**	**0.005**	**0.32 (0.09)**	**0.001**
Exposure classification								
Resident	−0.16 (0.11)	0.13	**−0.28 (0.14)**	**0.05**	−0.06 (0.12)	0.60	−0.11 (0.12)	0.39
Clean-up worker	0.02 (0.13)	0.89	0.06 (0.18)	0.74	0.17 (0.15)	0.23	0.08 (0.15)	0.61
Other	−0.17 (0.12)	0.16	−0.25 (0.17)	0.14	−0.19 (0.13)	0.17	−0.12 (0.14)	0.38
Lower respiratory symptoms								
Cough	0.01 (0.09)	0.88	−0.03 (0.12)	0.80	0.05 (0.09)	0.57	0.04 (0.10)	0.70
Wheeze	−0.01 (0.09)	0.89	0.08 (0.12)	0.50	0.04 (0.09)	0.66	0.08 (0.10)	0.42
Dyspnea at rest	**0.20 (0.08)**	**0.02**	0.21 (0.11)	0.07	0.17 (0.09)	0.06	0.15 (0.10)	0.13
Chest tightness	**0.30 (0.08)**	**0.00**	0.19 (0.11)	0.09	**0.24 (0.09)**	**0.01**	**0.33 (0.10)**	**0.001**

Significant P-values are bolded.
[a] β, regression coefficient; (SE), standard error.

Rosen et al. J. Psychiatric Res 2017

Mechanisms

- Multiple types of inflammation associated with LRS
  - Classic T2 inflammation (eosinophils)
  - Non eosinophilic inflammation
- Different types of inflammation associated with different patterns of lung function
- Systemic inflammatory marker (CRP) associated with both LRS and mental health symptoms

Longitudinal improvement in spirometry in WTC EHC

		FVC		FEV_1	
	No.	Estimate	95% CI	Estimate	95% CI
Exposure category[d]					
Local worker	438	28**	(13.0, 43.0)	24.6***	(12.3, 36.8)
Resident	172	59.5***	(31.3, 87.7)	44.5***	(25.4, 63.5)
Rescue/recovery	67	122.8***	(86.1, 159.6)	80.4***	(52.3, 108.5)
Clean-up worker	247	61.3***	(46.3, 76.3)	36.3***	(24.2, 48.4)

- Improvement in lung function
- Least improvement in local workers
- Patients with abnormal lung function at baseline, did not become normal

Linear mixed effects model, adjusted, * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$

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Liu et al. J Occup Environ Med 2012

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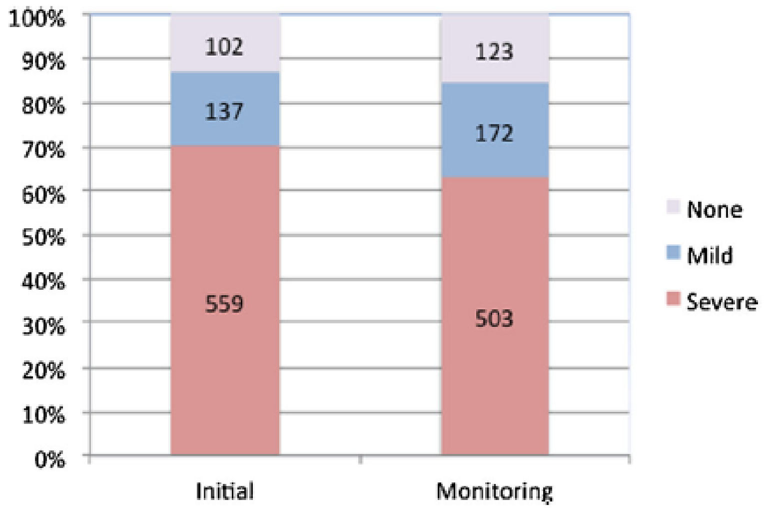
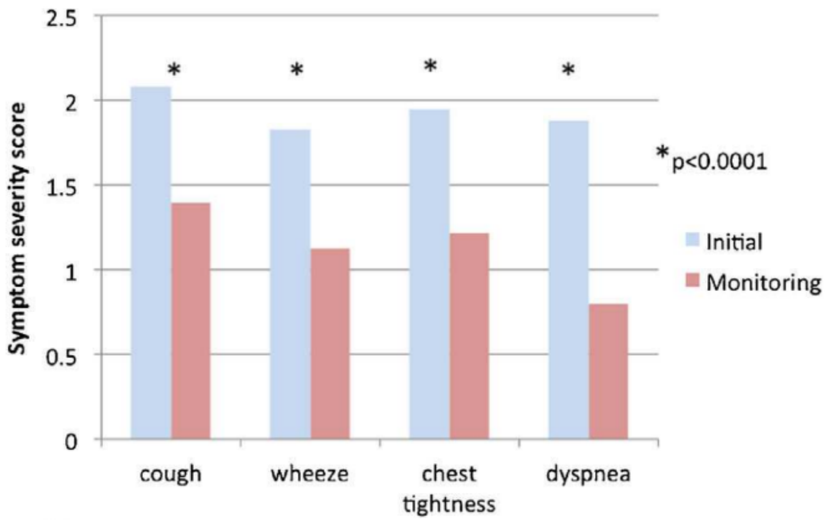
Many patients had persistence of lower respiratory symptoms at monitoring visits





Caplan-Shaw et al, AJIM 59; 777, 2016

Uncontrolled lower respiratory study

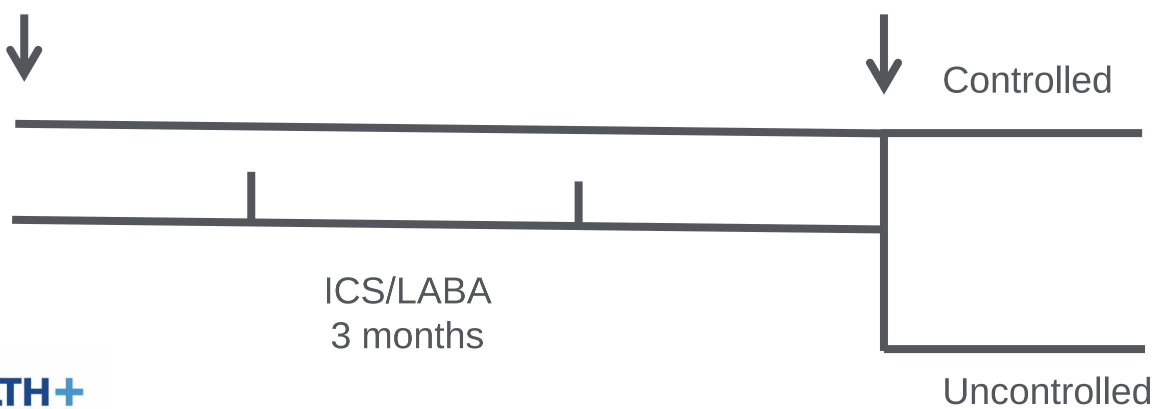
- Adherence to high dose inhaled corticosteroids and long acting β_2 agonist (therapy for severe asthma) would improve LRS (controlled LRS) and
- Patients with uncontrolled lower respiratory symptoms (ULRS) have higher rates of abnormal large and small airway function and hyperresponsiveness compared with those with controlled LRS
- CDC/NIOSH -funded study

Uncontrolled lower respiratory study

- Recruit patients with LRS at initial visit, normal spirometry and uncontrolled LRS at monitoring
- Run-in for 3 months to confirm adherence to ICS/LABA
- Compare those with controlled LRS vs uncontrolled LRS:
  - airway hyperresponsiveness (methacholine)
  - vocal cord hyperresponsiveness - paradoxical vocal cord movement (irritant exposure)

Adherence to ICS/LABA failed to improve LRS

- Few patients obtained controlled LRS
- Added patients with ULRS at initial visit, but controlled before enrollment into the study
-



Demographic and WTC exposure characteristics

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
Age	55.6	55.3	56.2	0.62
Sex				
Female, n (%)	51 (70)	36 (67)	15 (79)	0.39
Male, n (%)	22 (30)	18 (33)	4 (21)	
BMI (SD)	30.3(7)	30.2(5)	30.8(6)	0.95
Exposure				
Dust cloud, n (%)	37 (51)	29 (53.7)	8 (42.1)	0.43

Large and small airway lung function

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
FVC, % predicted	93 (0.89)	94.2 (13.3)	94.1 (13.8)	0.88
FEV_1, % predicted	90.9 (13.3)	90.1 (14.2)	93.6 (11)	0.13
FEV_1/FVC	76.5 (13.5)	75.5 (7.3)	79.4 (5.4)	0.08
R5	4.9 (1.6)	4.8 (1.5)	5.1 (2.1)	0.93
R5-20	1.13 (1.02)	1.11 (0.78)	1.2 (1.5)	0.48

Biomarkers of T2 inflammation not elevated

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
FeNO (median, IQR)	17 (9.25)	18 (9.5)	14 (7.5)	0.05
Eos > 300 cells/L, n (%)	12 (16.4)	11 (15.1)	1 (01.3)	0.2
Total IgE, kIU (median, IQR)	28.5 (63)	31 (74)	14 (7.5)	<0.0001

High rates of airway hyperresponsiveness (AHR)

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
AHR, n (%)*	32 (54)	21 (49)	11 (69)	0.24
PVCM, n (%)	34 (51)	23 (47)	11 (61)	0.43

*Completed by 59
** Completed by 67

High rates of paradoxical vocal cord movement (PVCM)

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
AHR (%)*	32 (54)	21 (49)	11 (69)	0.24
PVCM, n (%)	34 (51)	23 (47)	11 (61)	0.43

*Completed by 59
** Completed by 67

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High rates of either +AHR or +PVCM

	Total (n=73)	Uncontrolled (n = 54)	Controlled (n = 19)	p value
AHR(%)*	32 (54)	21 (49)	11 (69)	0.24
PVCM, n (%)	34 (51)	23 (47)	11 (61)	0.43
+AHR or +PVCM	48 (77)			

*Completed by 59
** Completed by 67

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Uncontrolled lower respiratory symptom study

- Most patients with persistent uncontrolled LRS had symptoms despite good adherence to high dose ICS/LABA
- High rates of AHR and PVCM despite therapy
- No difference in AHR or PVCM in those with controlled or uncontrolled LRS at time of study
- Few had evidence of type 2 inflammation (eosinophils, FeNO, IgE)

Future questions

- What are the underlying mechanisms for persistent LRS symptoms and hyperresponsiveness?
- Have pathways changed over time?
- Are inflammatory pathways involved in persistent LRS?
- Is there a role for persistent activation of irritant neural pathways?
- What is the role of systemic inflammation and interaction with comorbid conditions?

Future questions

- Need further studies to understand mechanisms for LRS
- Characterize heterogeneity among patients
- Biologic samples – blood samples
  - initial samples to predict disease (no longer possible)
  - current samples for persistent symptoms
- Need clinical trials to identify appropriate therapy
- Need to understand interaction with comorbidities
- Continue longitudinal studies to identify those that improve vs those with persistent symptoms

Importance

- Improved understanding of mechanisms can promote improved treatment of WTC population
  - Target location i.e small or large airways – target treatment
  - Target pathway of inflammation (precision medicine)
  - Target multiple co-morbid conditions or common pathways
- Study of WTC –related respiratory disease has/will provide information that can enhance our understanding of other environmental injury

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Thank You