



Differences in Inflammatory Responses to Exposures of Concentrated Ambient Particles in Susceptible Volunteers

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Objectives

- 1) Provide background for adverse respiratory health effects of air pollution
- 2) Review current concepts of pollutant inflammatory effects and individual susceptibility factors
- 3) Present study design and results from recent human exposure study using concentrated air particles in susceptible individuals
- 4) Discuss implications of study findings for future research

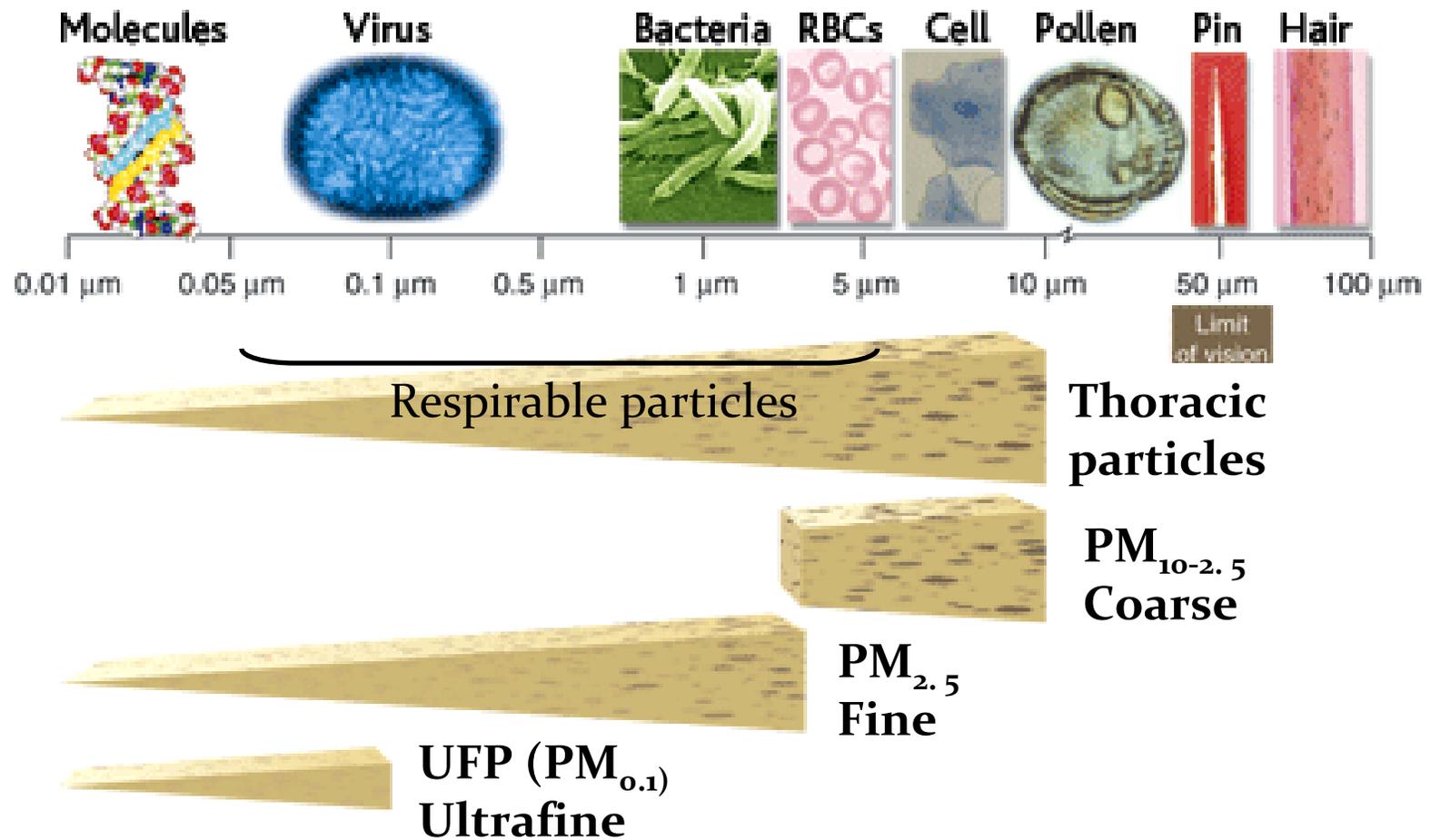
Air Pollutants

“pestilential vapors and soot” described by Roman Empire

- Particulates
- Nitrogen Dioxide
- Sulfur Dioxide
- Carbon Monoxide
- Ozone
- Environmental Tobacco Smoke (ETS)



Particulate matter size distribution



The Clinical Significance

- The Epidemiology
 - Observational studies convincingly link increased particulate air pollution levels with overall cardiorespiratory morbidity and mortality.
 - Numerous studies demonstrate association of increased particulate air pollution with:
 - asthma prevalence
 - asthma severity
 - asthma morbidity
 - asthma medication use
 - hospitalization for asthma
 - asthma mortality
 - allergic sensitization

Dose-response effect nearly linear; no threshold dose identified



Important questions on air pollution and respiratory diseases

Is there a link between air pollution and airway disease?

What are the mechanisms involved?

What confers susceptibility?

What can we do about it?

Effects of DEP in Human Controlled Exposure Studies

- Healthy subjects
 - ↑ Inflammatory cells in airways
 - ↑ Histamine levels in bronchial tissue
 - ↑ IL-6, IL-8
 - ↑ Expression of ICAM-1, VCAM-1
 - ↑ Airway resistance
- Subjects with mild asthma
 - ↑ Hyperresponsiveness to methacholine
 - ↑ Airway resistance
 - ↑ Sputum IL-6
 - No apparent increase in airway cellular inflammation
 - ↑ Epithelial IL-10 expression

Stenfors N et al. Eur Respir J 2004

- Activation of redox-sensitive transcription factors: NFκB, AP-1, JNK MAPK, p38 MAPK

Pourazar et al. Am J Physiol Lung Cell Mol Physiol 2005

Established Human Models Demonstrate DEP Pro-inflammatory and Pro-allergic Effects

1. Immediate phase response (minutes)

- Increased allergen-induced histamine release and symptoms

2. Short-term response (hours)

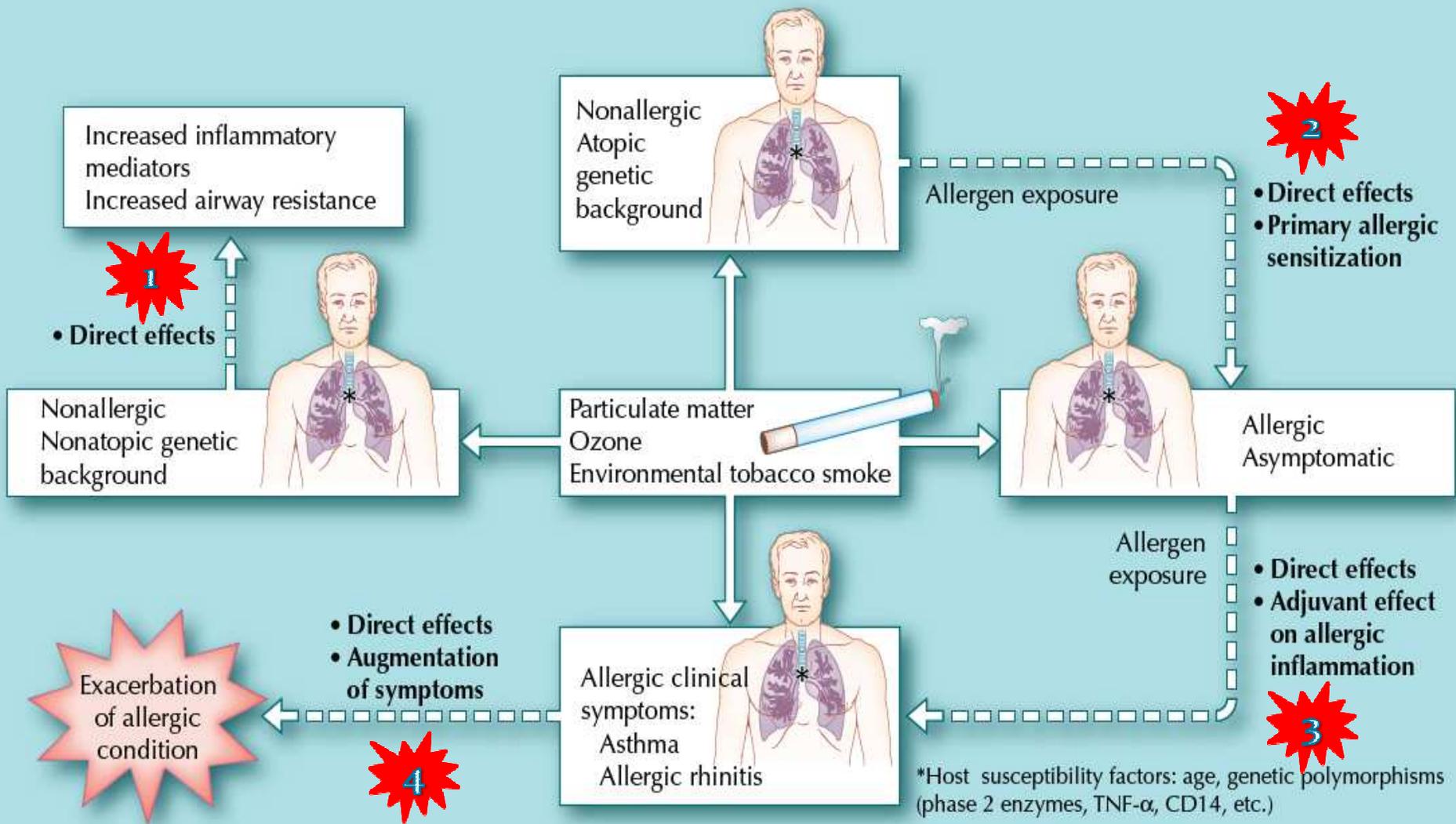
- Release of chemokines, cytokines and increased cellular inflammation

3. Intermediate-term response (days)

- Enhanced total and allergen-specific IgE response to allergens

4. Long term response (days to weeks)

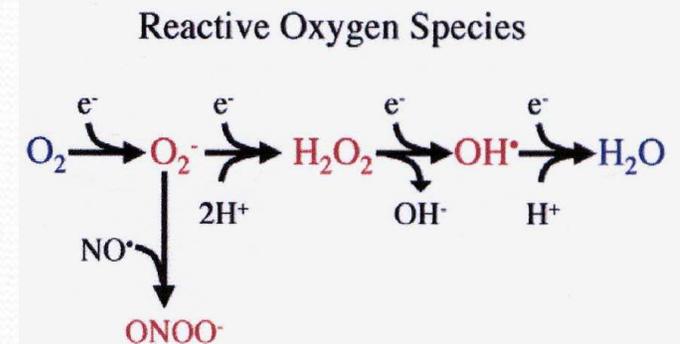
- Enhanced primary allergic sensitization



The Adverse Health effects of Particulate Pollutants in the Airways is Related to the Biology of Oxidative Stress

Oxidative Stress Approach

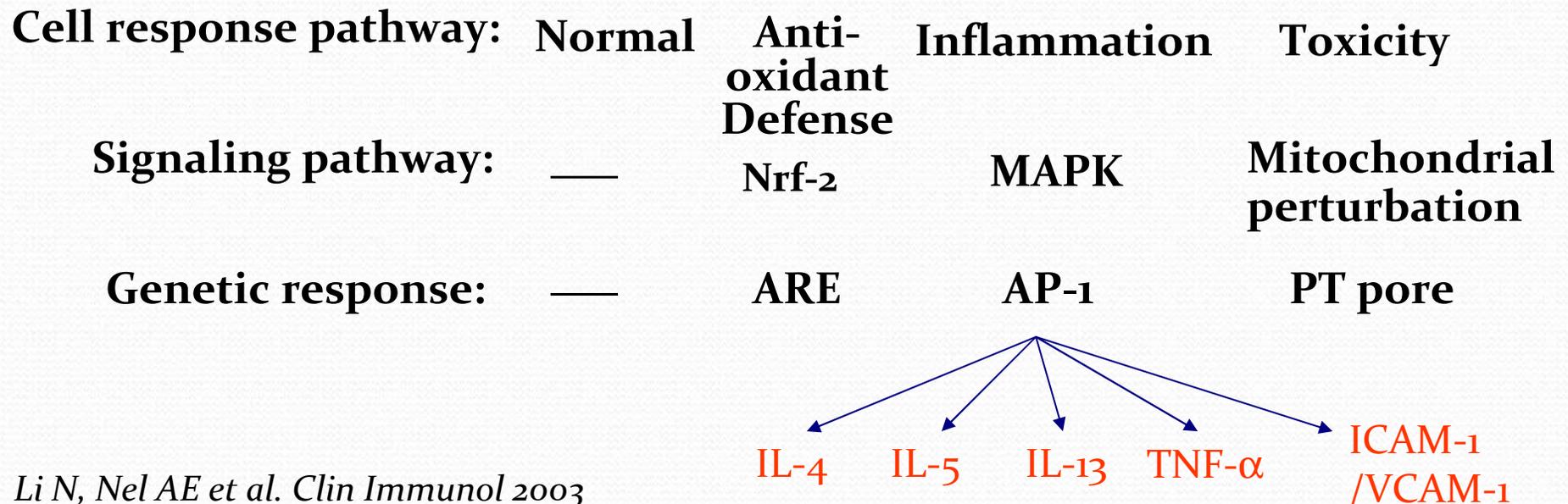
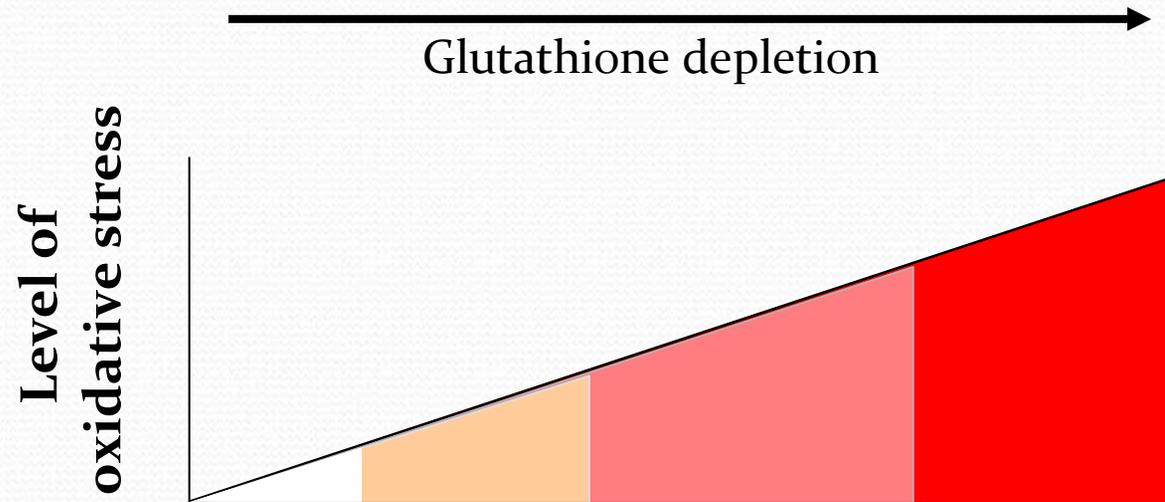
1. PM contains pro-oxidative chemicals
2. PM chemicals generate ROS → Oxidative stress
3. Oxidative stress → cytoprotective response
4. Increased Oxidative stress → pro-inflammatory effects



Bowler and Crapo JACI
2002

And what to do about it?

Hierarchical oxidative stress model of cellular response to DEP exposure





Important questions on air pollution and respiratory diseases

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What are the mechanisms involved?

What confers susceptibility?

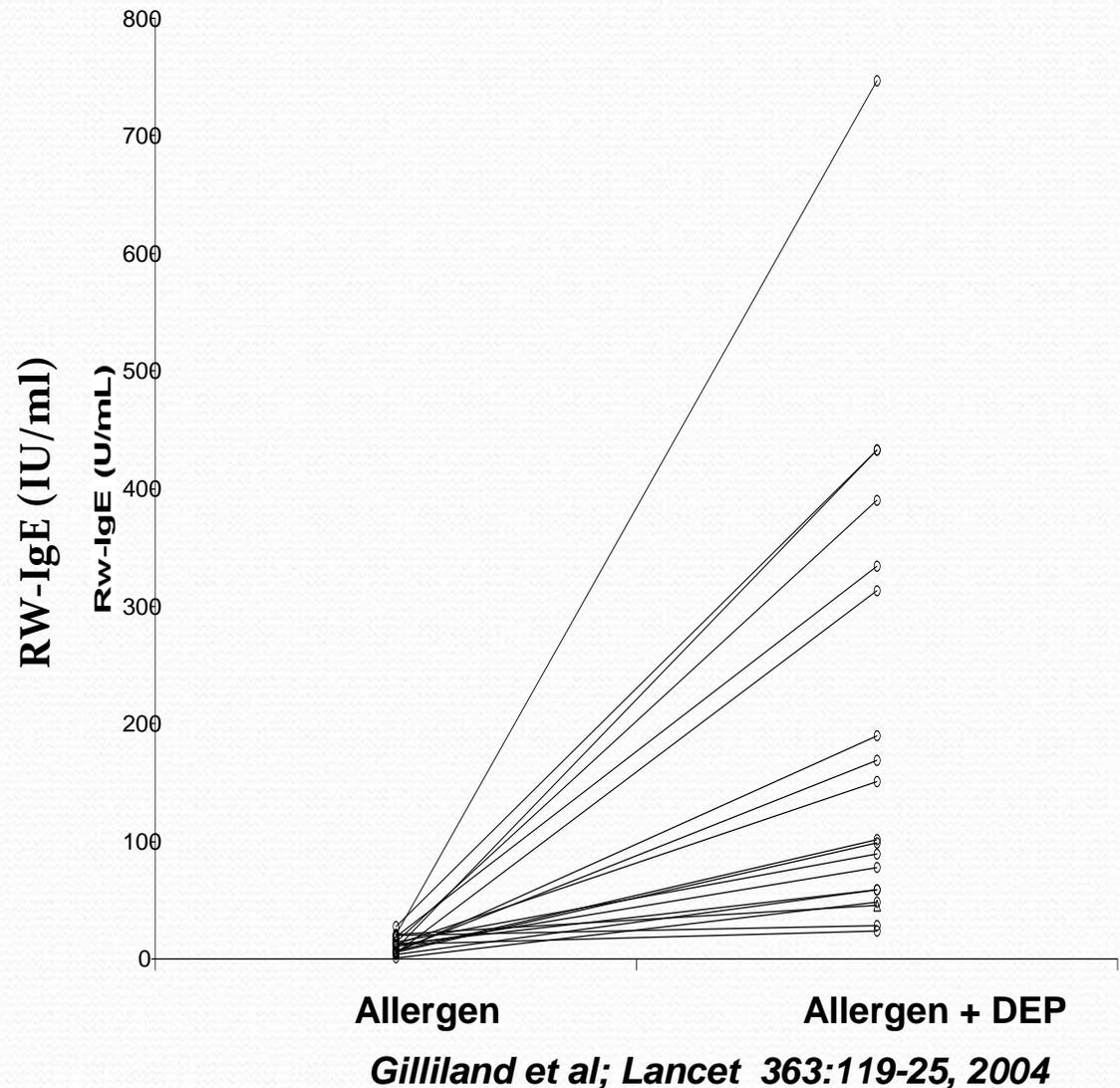
What can we do about it?

Identifying the Susceptible Individual

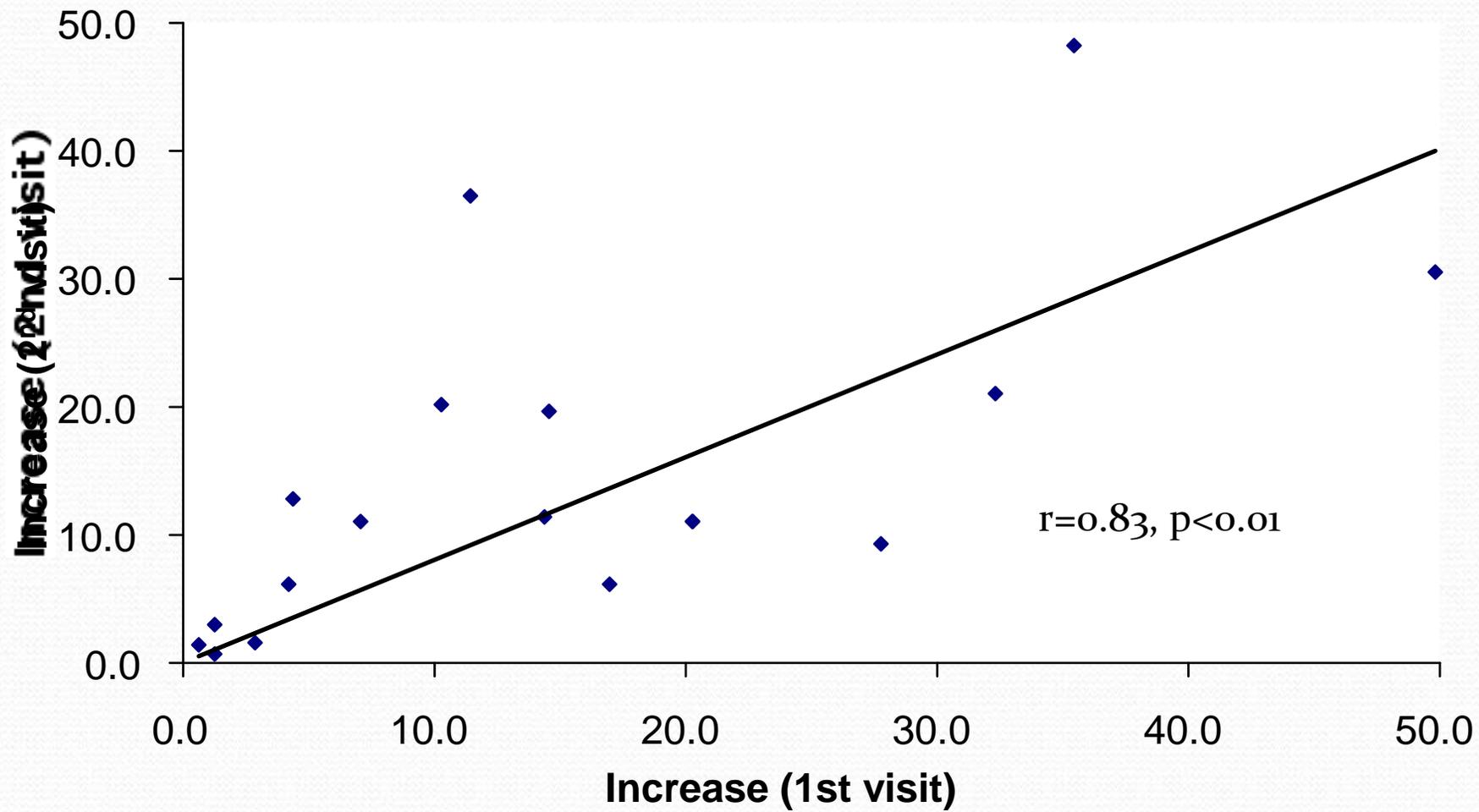
- Children, elderly, pre-existing respiratory conditions at risk
- Asthma severity may not be predictor for sensitivity to air pollution

Intermark T et al. Eur Respir J 1998

- Inter-individual variability in inflammatory response to DEP

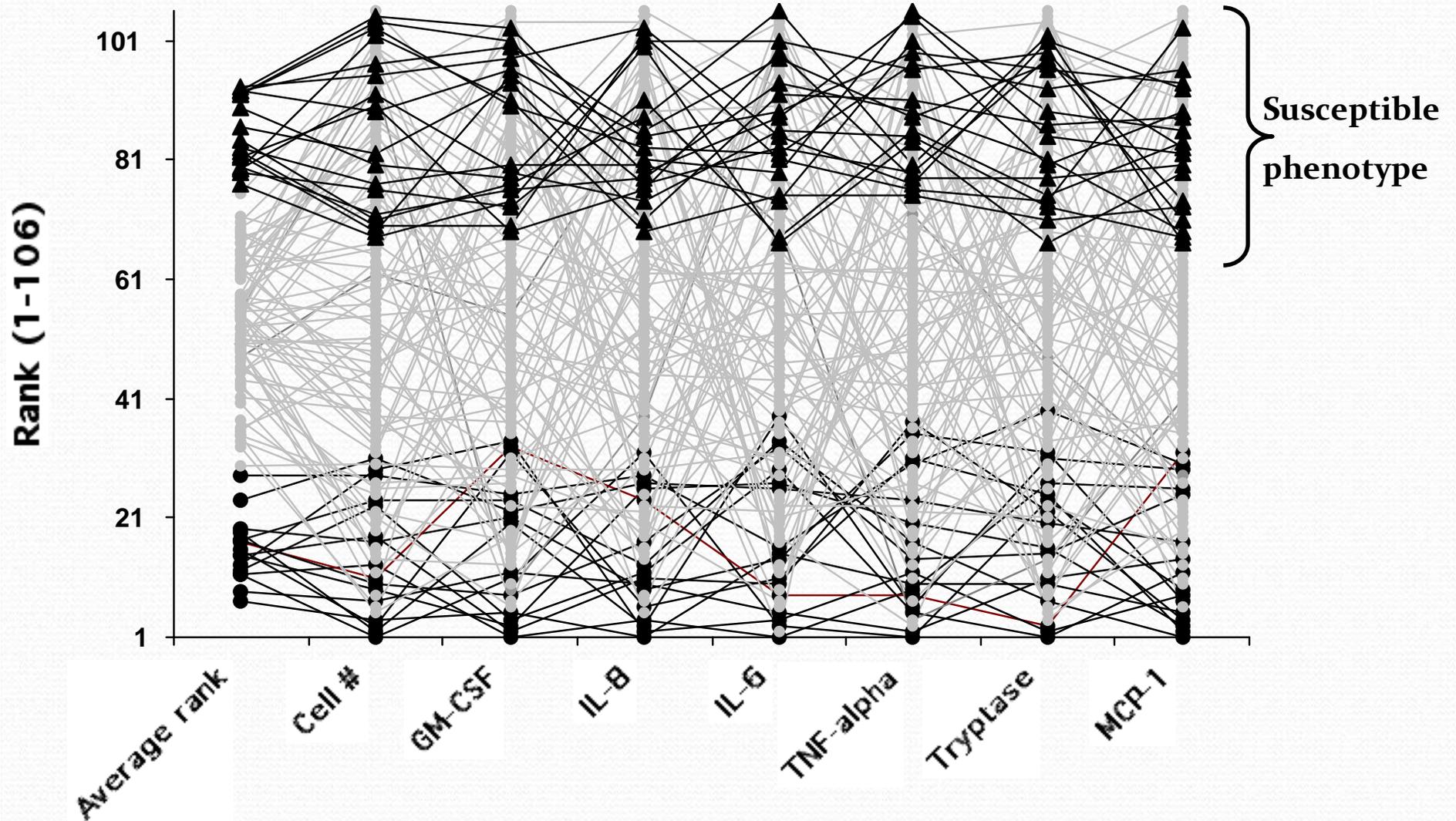


Augmentation of allergen-IgE production by DEP is reproducible and intrinsic



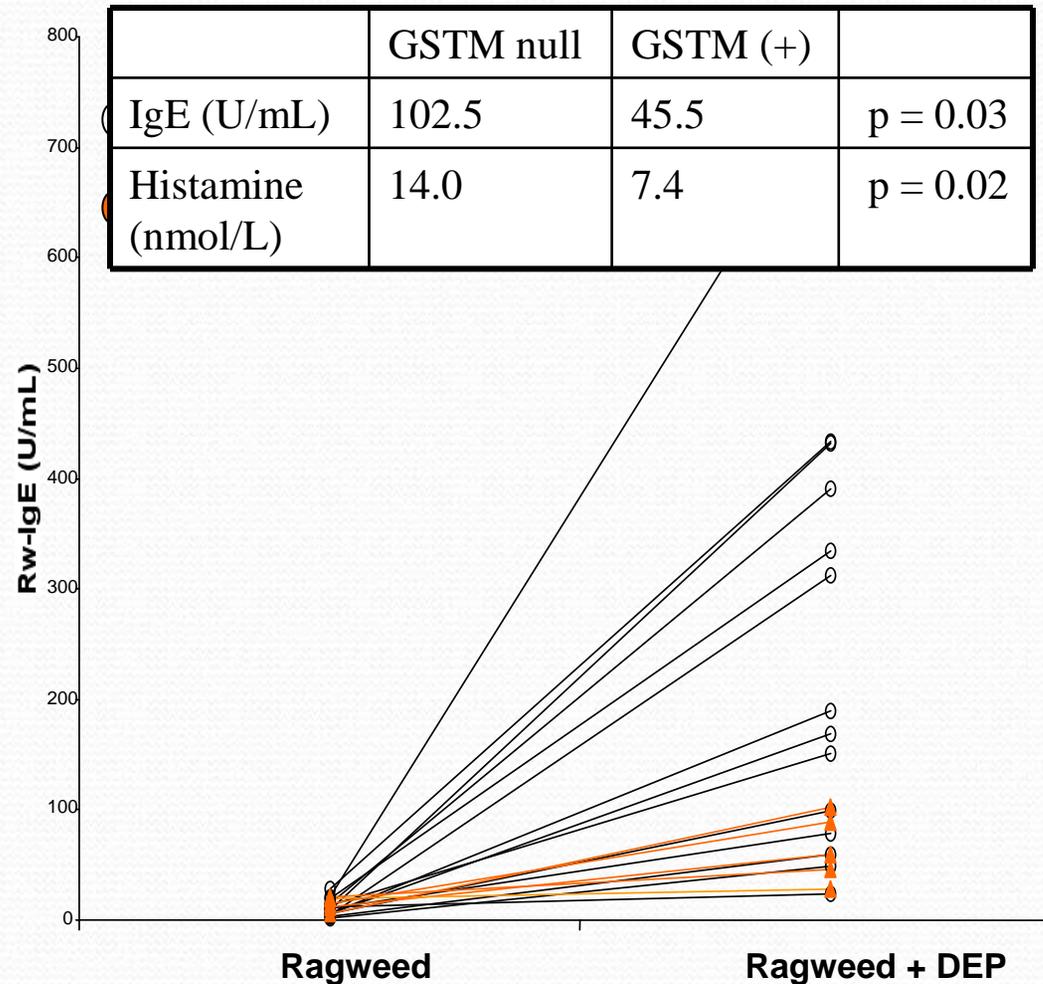
Bastain et al; *Clin. Immunol*, 109(2):130-6. 2003

Challenge with DEP defines high and low responder populations



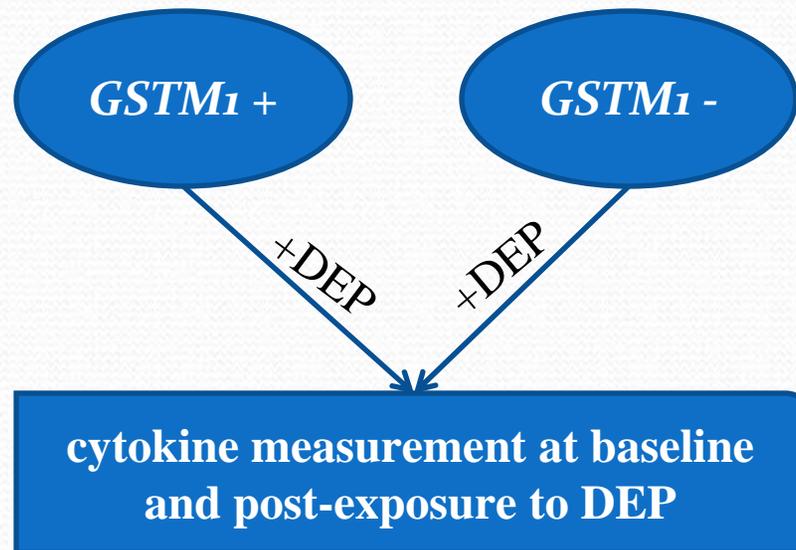
Enhanced susceptibility to DEP in GSTM1 null individuals

- Glutathione-S-transferases (GSTs)
 - Phase II metabolizing enzymes central to xenobiotic defense mechanisms
 - Protection against ROS generated oxidative stress
 - Detoxification of chemicals of particulate pollutants
 - Metabolism of reactive oxygen species

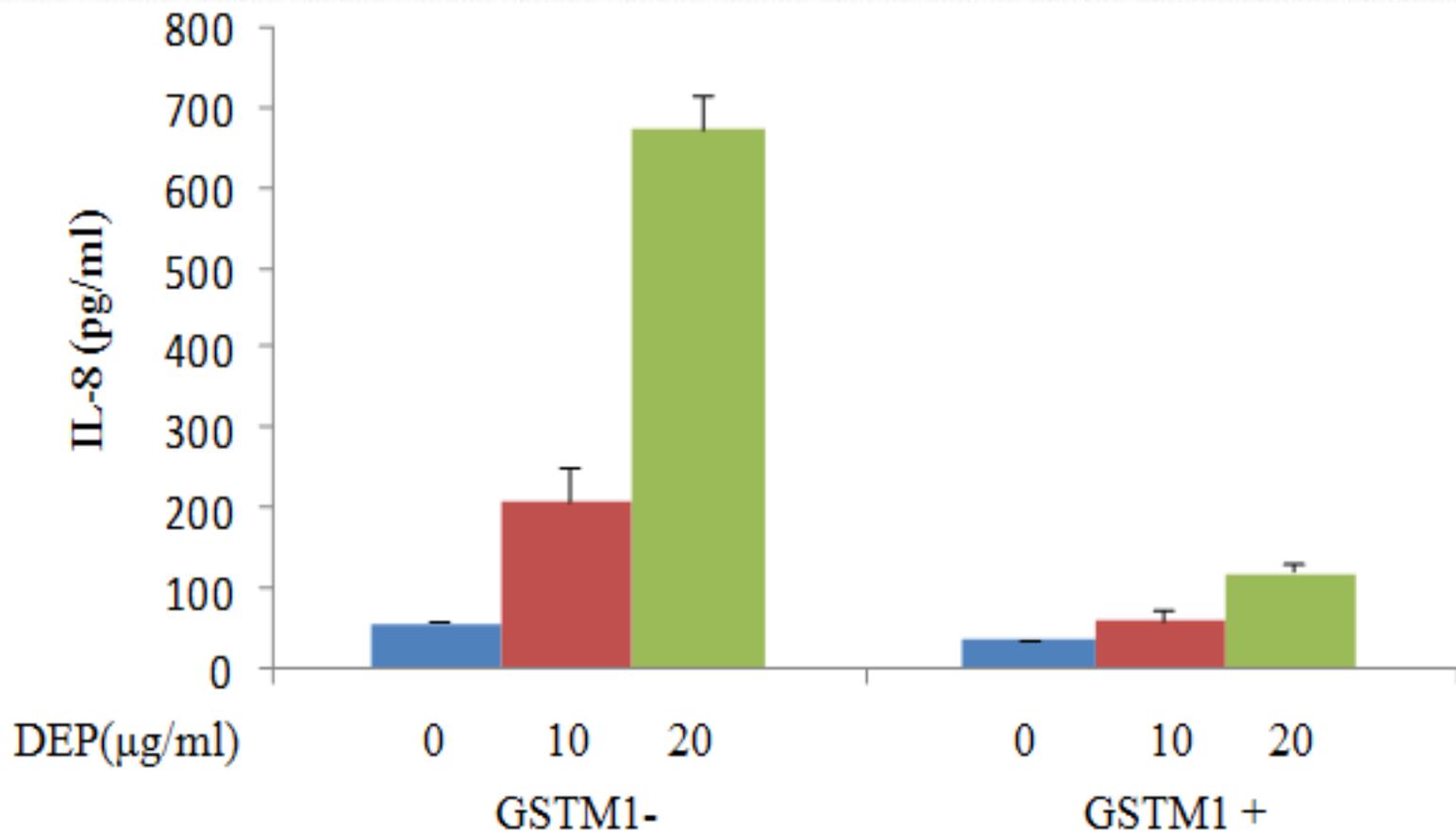


In Vitro Experimental Design

Human Bronchial Epithelial (HBE) cells

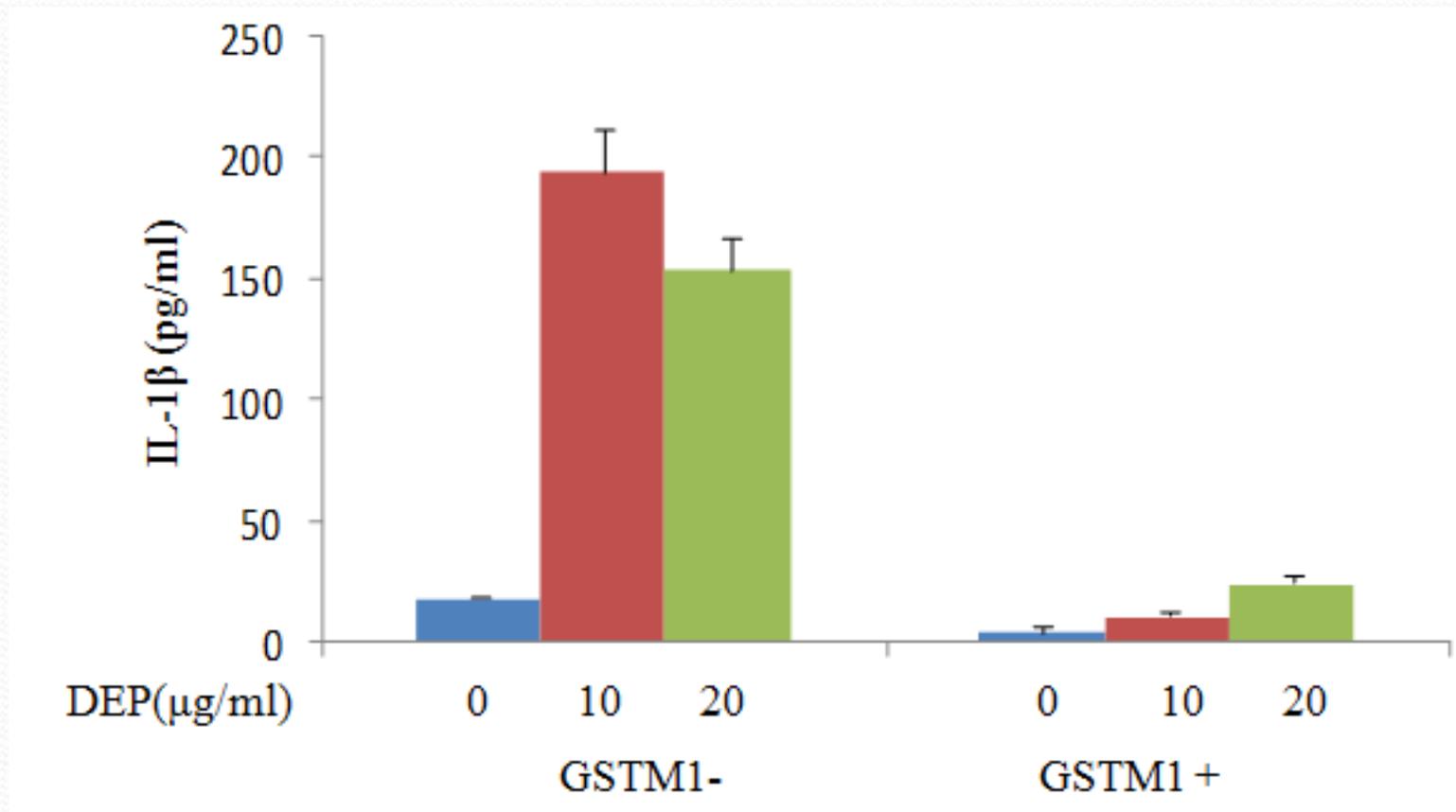


GSTM1 Function protective vs. DEP-induced inflammation



Wan et al. Unpublished data

GSTM1 Function protective vs. DEP-induced inflammation



Wan et al. Unpublished data

What are Concentrated Air Particles (CAPS)?

- “Real world” particles
- Chemically complex mixtures of soluble and insoluble components
- Components depend on geographic location and time
- Elements: carbon, sulfur, silicon, iron, calcium, zinc, nickel, copper, selenium, vanadium, etc.
- Reactive surface compounds: Sulfates, nitrates, acids, organics, polycyclic aromatic hydrocarbons (PAH)

Human Exposure Studies of CAP in Asthma

- Gong H Jr, Linn WS, Clark KW, Anderson KR, Sioutas C, Alexis NE, Cascio WE, Devlin RB. Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in Los Angeles. *Inhal Toxicol.* 2008;20:533-45.
- Gong H Jr, Linn WS, Terrell SL, Clark KW, Geller MD, Anderson KR, Cascio WE, Sioutas C. Altered heart-rate variability in asthmatic and healthy volunteers exposed to concentrated ambient coarse particles. *Inhal Toxicol.* 2004;16:335-43.
- Gong H Jr, Sioutas C, Linn WS. Controlled exposures of healthy and asthmatic volunteers to concentrated ambient particles in metropolitan Los Angeles. *Res Rep Health Eff Inst.* 2003;118:1-36.
- Gong H Jr, Linn WS, Sioutas C, Terrell SL, Clark KW, Anderson KR, Terrell LL. Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. *Inhal Toxicol.* 2003;15:305-25.



Differences in Inflammatory Responses to Exposures of Concentrated Ambient Particles in Susceptible Volunteers

Air Resources Board Contract #05-341

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Study Objective

- **To test hypothesis that individuals with certain ‘susceptibility factors’ will have heightened inflammatory and airway responses to exposure to concentrated ambient particles (CAPS)**
 - *GSTM1* null polymorphism
 - underlying asthma

Study Design

- Single-blind randomized crossover study of controlled exposure to filtered air (FA) and to concentrated ambient fine particles (CAPS)
 - 2 hours, submaximal exercise for 15 min of every half-hour
 - Target CAPS concentration: 200 $\mu\text{g}/\text{m}^3$
- Enrolled three distinct groups in exposure protocol:
 - 10 GSTM1-null asthmatics (mild-moderate)
 - 10 GSTM1-present asthmatics
 - 10 GSTM1-present healthy subjects.
- Comparison of resultant inflammatory and airway responses
- Cardiovascular measurements by 24-hour Holter monitor

Study Design

Schedule for exposures

Day 0 screening visit

Day 14 exposure to 200 ug/m³ CAPS*

Day 15 follow-up visit

Day 28 exposure to filtered air*

Day 29 follow-up visit

* Order of exposure to CAPS and FA randomized for each subject

Study Design

Pre-Exposure

- Symptom score sheet completed
- Initiation of Holter monitoring, ECG telemetry and pulse oximeter
- Vital signs
- 12-lead ECG at rest
- Venous blood drawing (20 cc)
- Nitric oxide measurement
- Nasal lavage
- Pre-exposure spirometry
- Urine collection

Post-Exposure

- Nasal Lavage
- Vital signs
- Spirometry
- Symptom score sheets
- Methacholine bronchoprovocation with spirometry
- Subject leaves laboratory with diary and Holter monitor

DAY 2

- Diary collected.
- Symptom score sheet
- Vital signs
- Venous blood drawing (20 cc)
- Urine collection
- Spirometry
- 12-lead ECG at rest
- Nitric oxide measurement
- Nasal Lavage
- Sputum induction
- Spirometry.
- Holter monitoring ends

Biologic Endpoints

- Vital Signs: Pulse, BP, O₂ saturation
- Bronchial reactivity
- Spirometry
- Exhaled NO, CO
- CV Holter: Indices of HRV, S-T voltage, repolarization
- Sputum: Differential cell counts, IgG, IgG₄, IgA, IgM, IgE; IL-4, IL-5, IL-8; GM-CSF; IFN- γ , TNF- α
- Nasal Lavage: Differential cell counts, IgG, IgG₄, IgA, IgM, IgE; IL-4, IL-5, IL-8; IFN- γ , TNF- α
- Blood: C-reactive protein, Factor VII, von Willebrand factor, fibrinogen, IL-8, IgG, IgG₄, IgA, IgM, IgE
- Urine: 8-isoprostane
- Symptom score sheet

CAPS Exposure Methods

- Whole-body chamber: CAPS (PM_{2.5})
 - concentration of 200 µg/m³ monitored real time by nephelometer
 - controlled by diluting output of the ambient fine particle concentrator with varying amounts of filtered air
 - Concentrator resembles that used by EPA
 - Outdoor ambient air drawn from above the roof of the laboratory about 4 m above grade
 - Ambient particles are concentrated up to 9 times

CAPS Exposure Methods

- Important contributors to ambient PM at laboratory location include southern Los Angeles County background pollution, locally heavy surface-street traffic, diesel-truck-heavy I-710 freeway one mile west, port complex about 10 miles south
- Previous work has characterized neighborhood's pollution and fine CAPS exposure atmospheres
- Nitrate, organic carbon, sulfate, and elemental carbon are major constituents of the fine CAPS
- Particle size distribution measurements performed with a micro-orifice uniform-deposit impactor (MOUDI) to determine contribution of ultrafine particles to CAPS

Geller MD, et al. J Air Waste Manag Assoc 2004; 54:1029-39.

Zhu Y, et al. Aerosol Sci Tech 2004; 38:5-13.

Gong H, et al. Inhal Toxicol 2005; 17:123-32.

Gong H, et al. Inhal Toxicol 2004; 16:731-44.

Filtered Air Exposures

- Filtered air (FA) exposure was used as control arm
- All FA exposures performed in the same chamber with same protocol except that ambient air was filtered by HEPA particle filtration
- Carbon monoxide, nitrogen oxides, sulfur dioxide, and ozone levels were monitored in incoming ambient air upstream of the particle concentrator during FA and CAPS exposures
- Prior testing has shown little difference between ambient and in-chamber measurements of gases

Study Subjects Enrolled

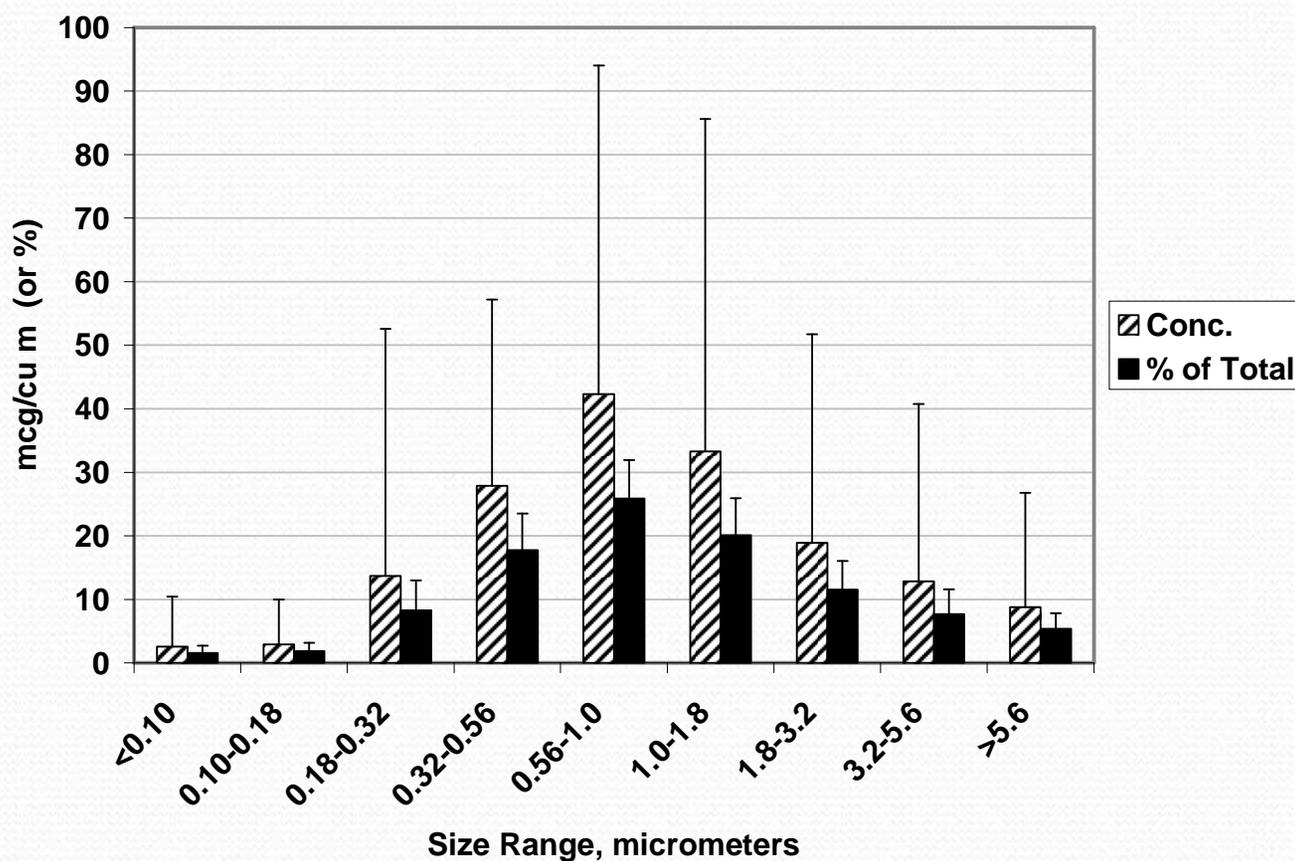
Group	Age (Mean, range)	Gender (F/M)	Ethnicity (A/B/H/W)*
Asthma/GSTM (-)	30.4 (21-43)	9/1	1/0/6/3
Asthma/GSTM (+)	41.9 (20-55)	6/4	0/3/5/2
Healthy/GSTM (+)	32.0 (18-53)	7/3	0/1/8/1

*A Asian, B African-American, H Hispanic, W white non-Hispanic

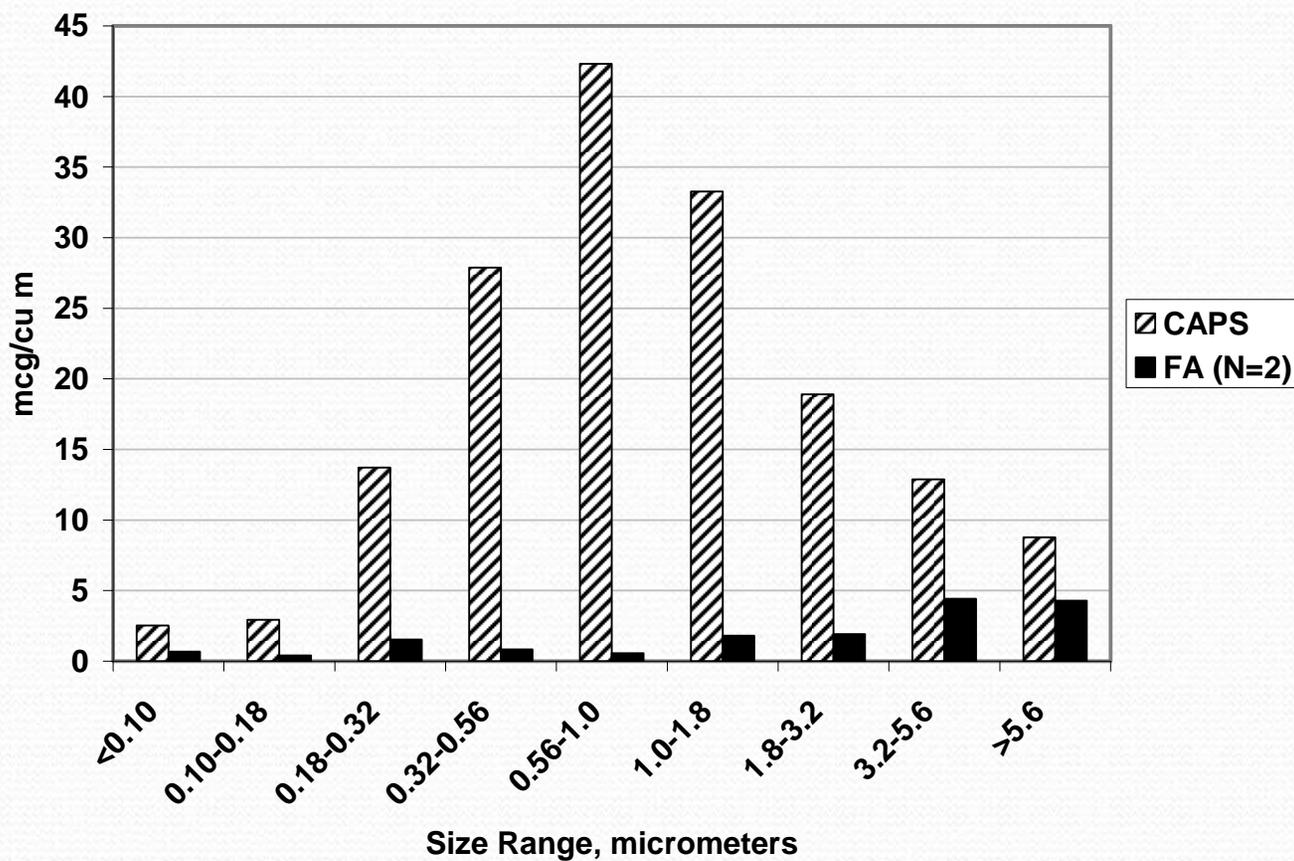
Environmental Measurements (Mean ± SD) in Filtered Air Control Studies vs. Concentrated Fine Particle Exposures

Measure	Filtered Air Controls	CAPS Exposures
Mass concentration, total filter ($\mu\text{g}/\text{m}^3$)	35 ± 16	187 ± 42
Mass concentration, DataRAM ($\mu\text{g}/\text{m}^3$)	13 ± 7	288 ± 55
Mass concentration, MOUDI ($\mu\text{g}/\text{m}^3$)	16 ± 3 ^[b]	164 ± 39
O ₃ (ppb)	23 ± 11	20 ± 11
NO ₂ (ppb)	24 ± 14	34 ± 21
SO ₂ (ppb)	1.8 ± 1.3	1.6 ± 0.8
CO (ppm)	1.6 ± 1.2	1.6 ± 1.1
Chamber temperature (°F)	71 ± 2	72 ± 2
Chamber relative humidity (%)	69 ± 11	70 ± 11
Outdoor temperature (°F)	76 ± 7	78 ± 7
Outdoor relative humidity (%)	44 ± 13	41 ± 7

Average Particle Mass vs. Size Range as Determined by MOUDI Sampling in CAPS Exposures



Average Particle Mass vs. Size Range as Determined by MOUDI Sampling in FA Exposures vs. CAPS Exposures



Summary Statistics for Chemical Analyses of Particulate Samples from Exposures

Species	Units	CAPs		FA	
		Mean	SD	Mean	SD
(total mass)	µg/m ³	186	43	34	17
EC	µg/m ³	2.7	1.9	0.1	0.2
OC	µg/m ³	32.4	8.0	21.1	5.3
Al	ng/l extract	30.1	16.7	13.5	5.7
K	ng/l extract	21.4	13.2	7.1	5.8
Ca	ng/l extract	34.7	20.2	18.8	5.1
Ti	ng/l extract	1.03	1.07	-0.23	0.47
V	ng/l extract	0.46	0.31	-0.06	0.07
Cr	ng/l extract	0.52	0.28	0.31	0.10
Fe	ng/l extract	36.3	19.1	7.2	3.7
Cu	ng/l extract	2.7	2.2	0.5	0.2
Zn	ng/l extract	8.0	3.5	3.0	0.7
Ba	ng/l extract	3.0	2.2	1.8	1.1
P	ng/l extract	3.6	7.0	1.7	6.0
S	ng/l extract	158	90	9	35

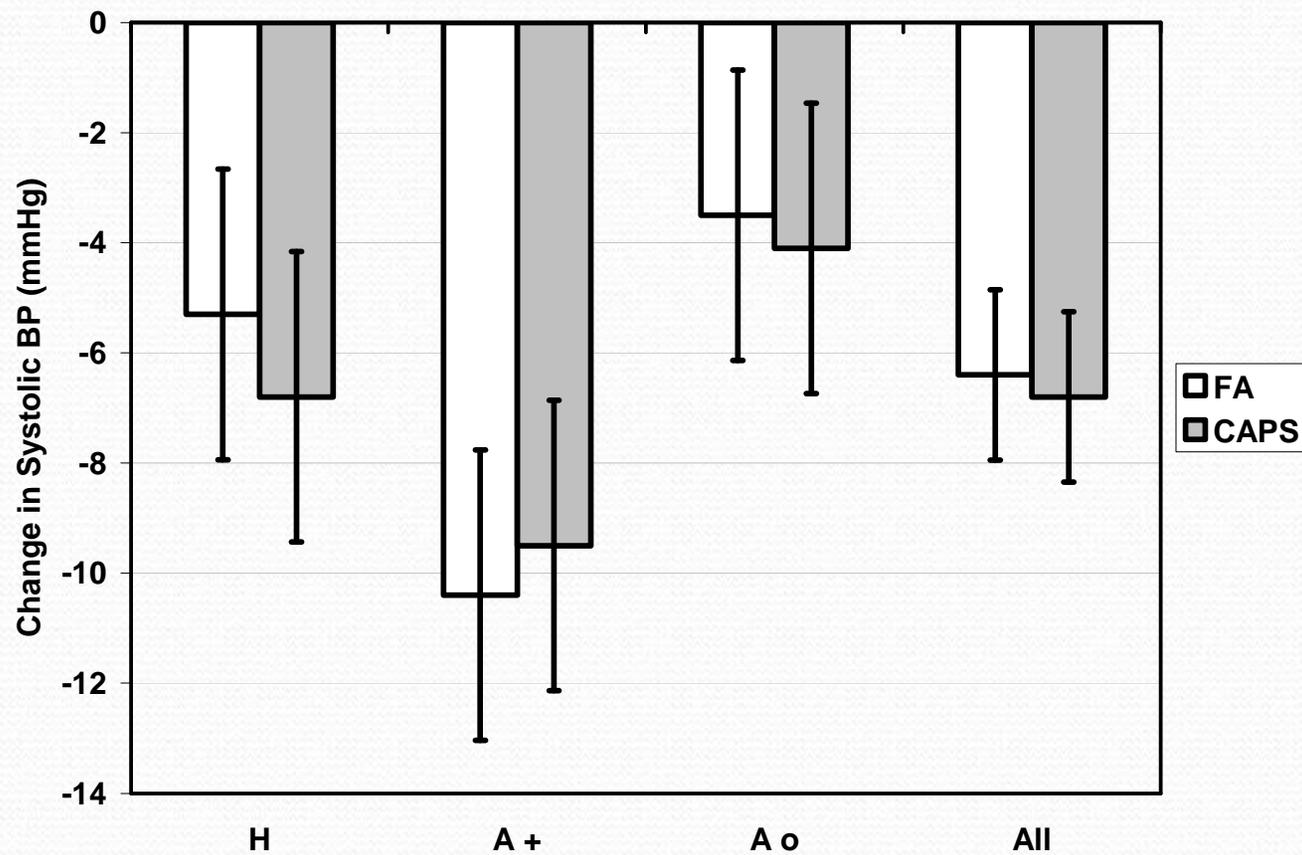
Pre Exposure Physiologic and Symptom Measurements: Mean and (Standard Deviation) by Group

	Healthy	Asthma GSTM1 +	Asthma GSTM1 null
Symptom Score	1.1 (2.0)	2.7 (3.3)	1.6 (2.4)
FVC (ml)	4038 (850)	3786 (550)	4044 (796)
FEV ₁ (ml)	3298 (686)	3002 (481)	3050 (622)
FEV ₁ /FVC (%)	81.9 (4.4)	79.5 (7.9)	75.6 (6.4)
BP systolic (mmHg)	115 (12)	109 (10)	111 (12)
BP diastolic (mmHg)	74 (11)	74 (9)	73 (12)
SaO ₂ (%)	98.5 (0.9)	98.2 (2.0)	98.4 (1.3)
FeNO (ppb)	26 (13)	50 (53)	42 (30)
FeCO (ppm)	1.3 (0.9)	1.3 (1.2)	1.0 (0.8)

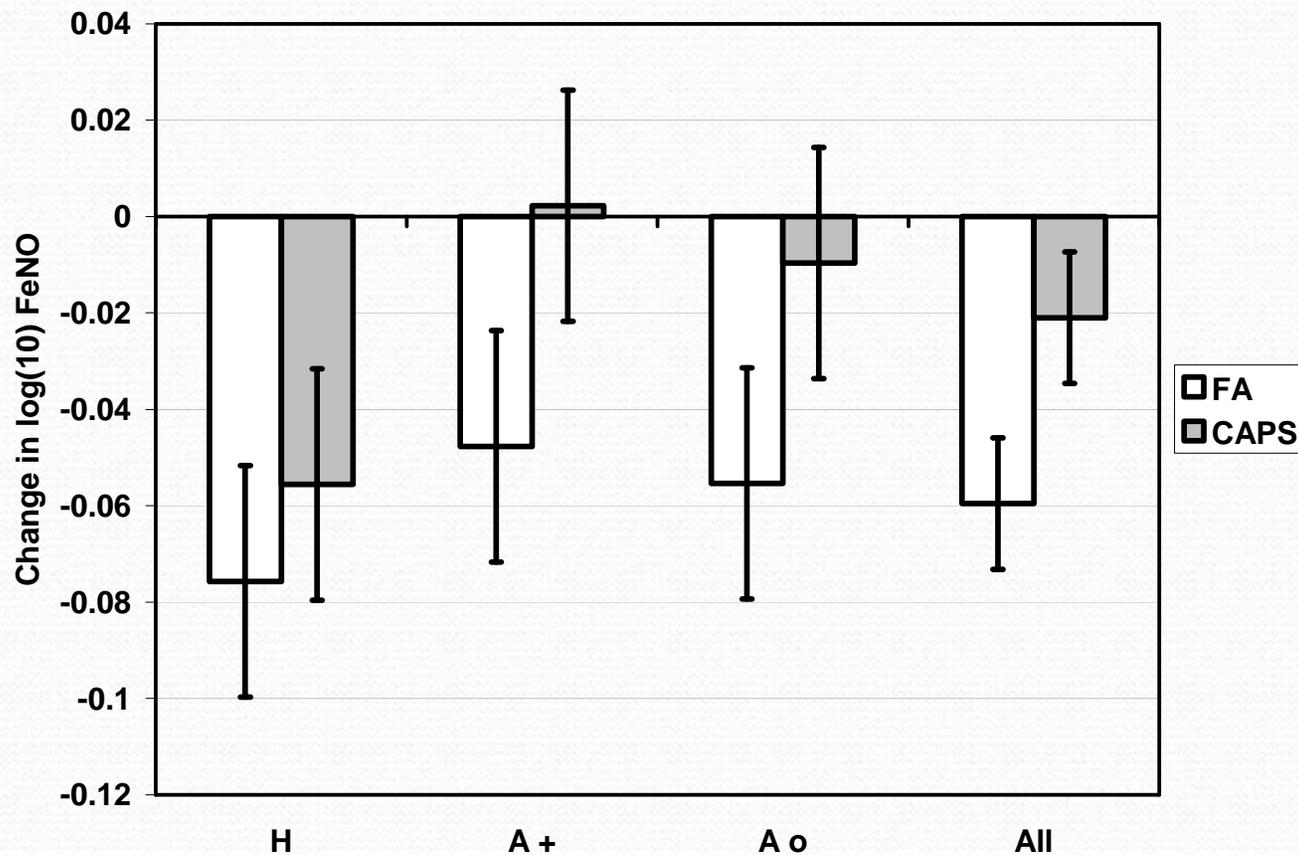
Summary of Mixed-Model Analyses of Physiology and Symptom Data

Measure of Response	Significant (P < 0.05) Results
Symptom score during exp.	increase from pre-exposure, larger in GSTM1-null
Symptom score after exp.	increase from pre-exposure in GSTM1-null only
Δ FVC post - pre or day 2 - pre	(none)
Δ FEV ₁ post - pre or day 2 - pre	(none)
Δ BP systolic post - pre (mmHg)	decrease from pre-exposure, less in GSTM1-null
Δ BP systolic day 2 - pre (mmHg)	(none)
Δ BP diastolic post-pre or d2-pre	(none)
Δ SaO ₂ post - pre (%)	(none)
Δ FeNO post - pre (ppb)	increase after CAPS relative to FA
Δ FeNO day 2 - pre (ppb)	(none)
Δ FeCO post-pre or day 2 - pre	(none)

Mean Change in SBP pre- to post-exposure, FA vs. CAPS, for Each Group and for All Subjects Pooled



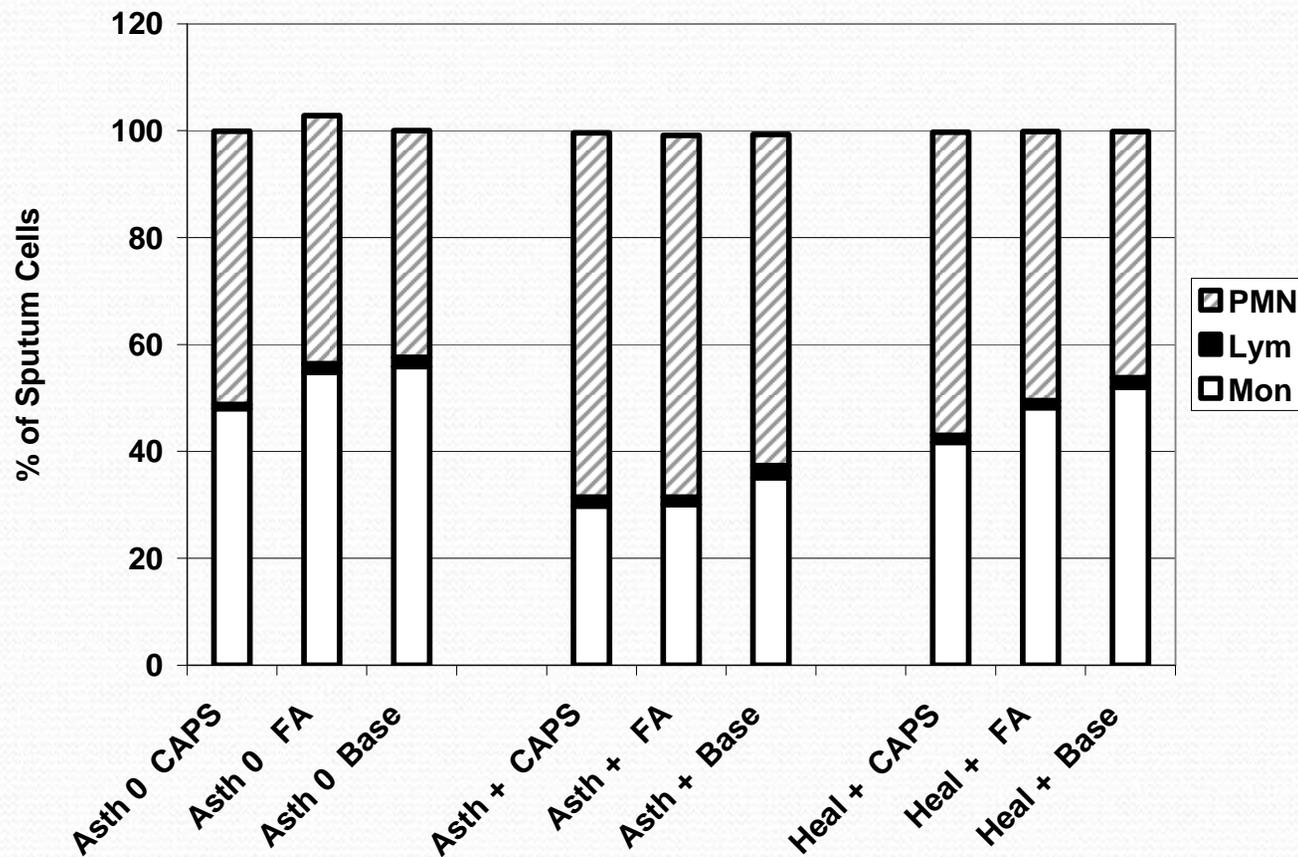
Mean change in log-transformed FeNO pre- to post-exposure, FA vs. CAPS, for Each Group and for All Subjects Pooled



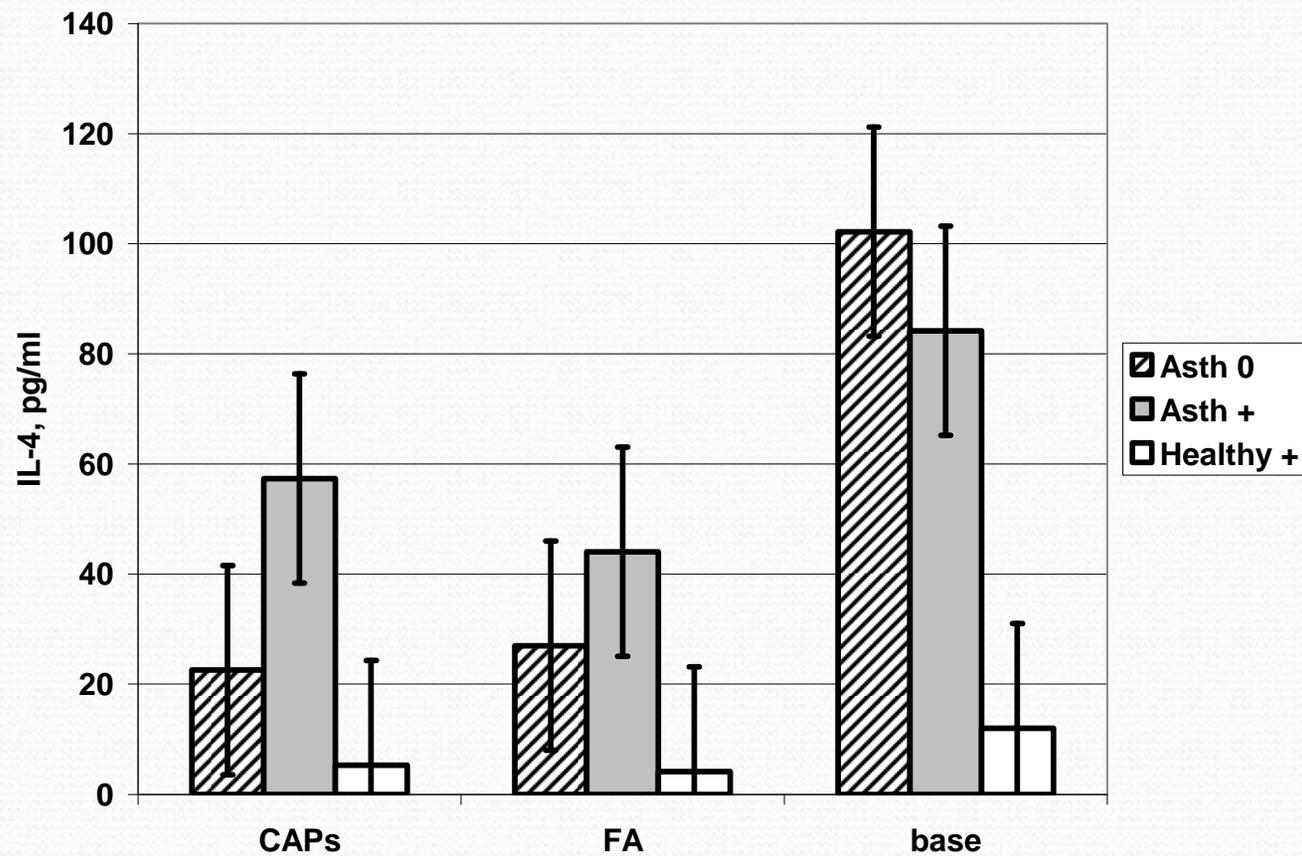
Correlations of Response Measures with Exposure Measures

	FVC	FEV ₁	BP systolic	BP diastolic	SaO ₂	Symptom Score	FeNO
Concentration (filter sample)	-0.01	+0.04	-0.28	+0.19	+0.25	-0.20	-0.15
Concentration (DataRAM)	+0.07	+0.19	-0.11	-0.06	-0.00	-0.29	+0.11
NO ₂	+0.15	+0.34	-0.04	-0.29	+0.33	-0.63 (P < .001)	-0.12
Chamber Temperature	-0.02	-0.17	-0.02	+0.14	+0.05	+0.13	+0.14

Mean Percentage of Monocytes, Lymphocytes, and Neutrophils in Induced Sputum, by Susceptibility Group and Induction Condition



Mean Concentration of IL-4 in Induced Sputum, by Susceptibility Group and Induction Condition

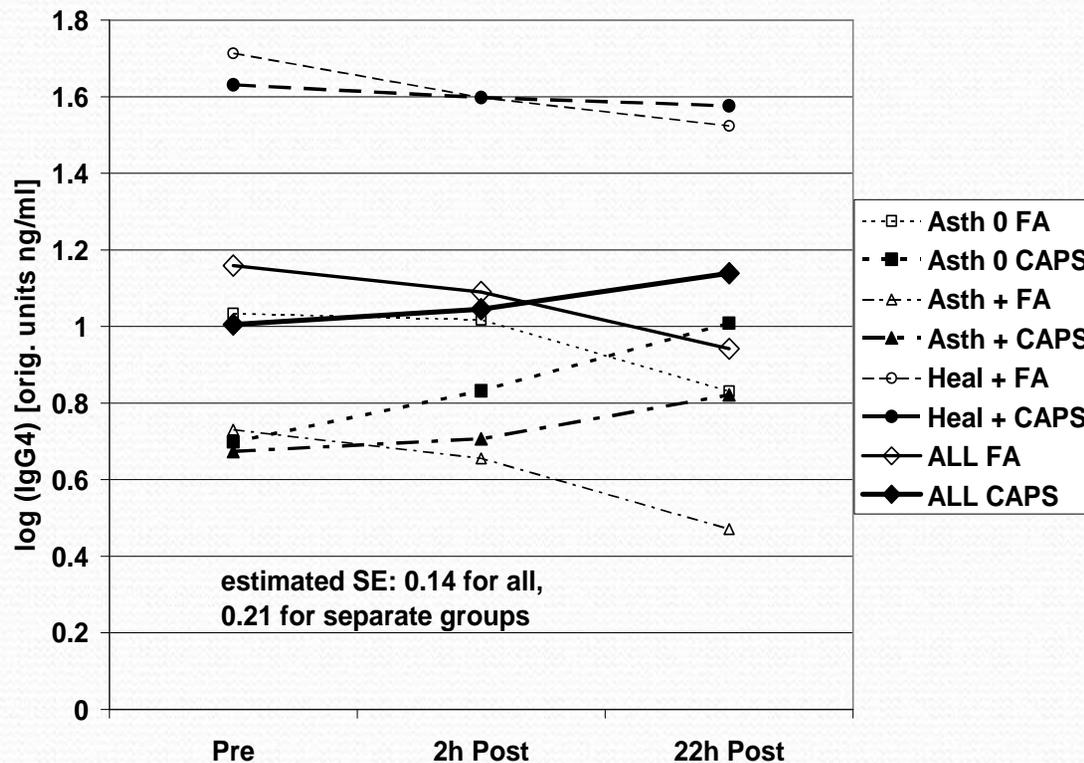


Percentage of Subjects with Detectable Concentrations of Usually Nondetectable Biomarkers in Sputum: Comparison between Filtered Air and CAPS

	% after FA	% after CAPS	P
Eosinophils	27	17	0.16
Immunoglobulin E	7	3	0.38
Interferon-gamma	7	17	0.16
GMCSF	10	17	0.23
TNF-alpha	13	27	0.11

Estimated Mean IgG4 in Nasal Lavage Fluid, as a Function of Time, by Group and Exposure Atmosphere

Variable	Effect P-value				Comment
	Group	CAPs	Time	Interaction	
IgG4	.002			C*T .009	healthy > asthma(0) > asthma(+) down after FA, up after CAPS



Pairwise Rank Correlations between Exposure and Sputum Response Variables

	Mass	Fe	Cu	Cr	Zr	Ba	% Lym	IL5	IgA
Fe	+0.32								
Cu	+0.24	+0.47**							
Cr	+0.64***	+0.60**	+0.31						
Zr	+0.36	+0.44*	+0.15	+0.35					
Ba	+0.32	+0.87***	+0.39*	+0.62***	+0.54**				
% Lym	-0.20	-0.36	-0.43*	-0.28	-0.11	-0.32			
IL5	+0.17	-0.37*	-0.02	-0.12	-0.30	-0.40*	+0.07		
IgA	+0.41*	-0.14	+0.01	+0.37*	-0.13	-0.14	+0.07	+0.19	
IgG4	+0.43*	-0.10	-0.05	+0.40*	-0.06	+0.02	+0.04	+0.02	+0.68***

*P < 0.05, **P < 0.01, ***P < 0.001

Heart Rate Variability

Variable

Mean RR interval

Calculated HR

log (pNN50)

log (normalized high-frequency power)

Median ST voltage V5

Mean lead II QTcB

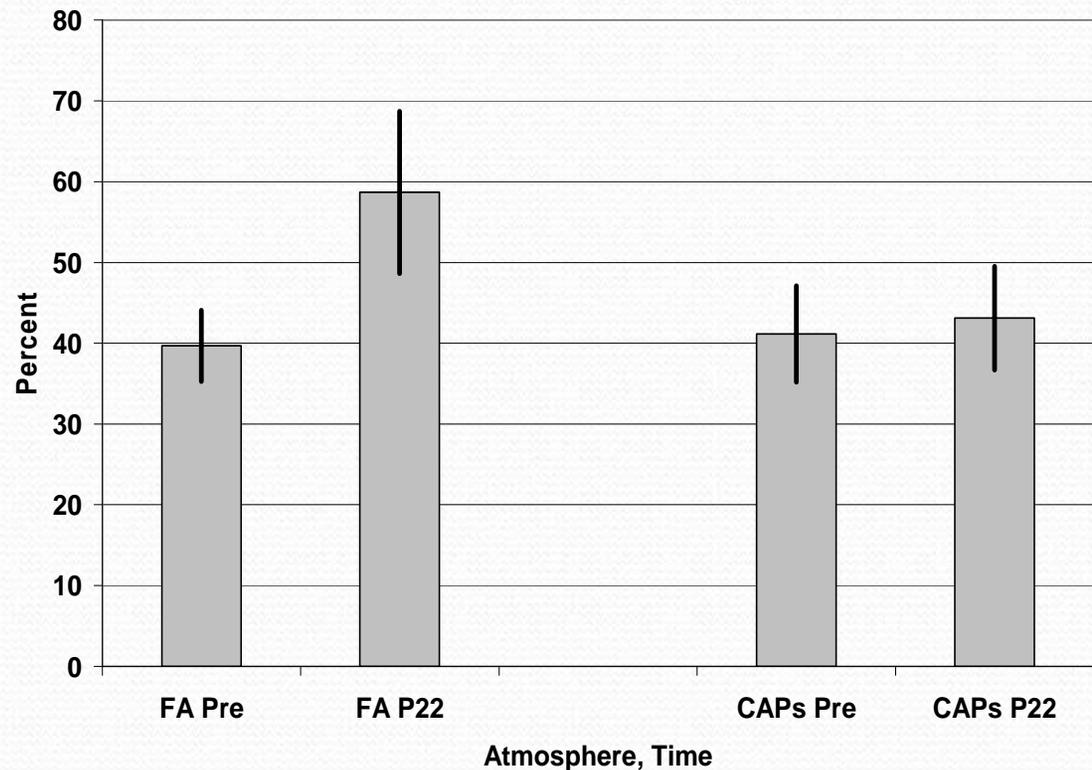
T amplitude

log (SD QTcB)

log (TD/II norm variance)

TD/II variability index

T-wave Complexity



Overall Conclusions

- No demonstrated clear robust differences between exposure responses of normal vs. susceptible subjects
- With exception of increase in FeNO for all groups, CAPS exposure as performed in this study does not appear to produce a robust inflammatory respiratory or systemic response in human subjects
- Study did not find that subjects with asthma and/or GSTM1 null genotype were more susceptible to the inflammatory effects of CAPS exposure

Summary of Findings for Biologic Endpoints

- Significant baseline differences in FeNO for asthmatic vs. healthy subjects
- Trend but nonsignificant difference in FEV₁/FVC for asthmatics vs. healthy subjects: mild asthma in study population
- Few differences in responses attributable to exposure conditions (FA vs. CAPS) or between susceptibility groups

Changes in FeNO

- Increases in CAPS exposure vs. FA
- Did not vary significantly based on GSTM or asthma status, though mean increase greater in asthma vs. healthy groups
- Previously reported in observational studies
- No previous controlled fine CAPS study for comparison
- Coarse CAPS, UF CAPS, DEP exposures have not shown consistent increases in FeNO

Sputum Biomarkers

- GSTM1-positive asthmatics had significantly higher levels of sputum PMN counts, sputum IgA, and lower levels of sputum monocytes compared to other groups
- Explanation for finding in GSTM1-positive vs. GSTM1-null asthmatics not clear
- Not significantly affected by exposure conditions

Sputum IgA

- Significant group differences for sputum IgA with CAPS vs. FA
- Healthy subjects showed a significant increase while GSTM1-positive asthmatics showed little change and GSTM-null asthmatics showed a mild decrease with CAPS exposure
- Overall group variation with CAPS exposure approached statistical significance ($p=0.06$)

Sputum IgA

- Recently recognized anti-inflammatory role of mucosal and systemic IgA
- Speculative link between IgA and the anti-oxidant role of GSTM₁ that could potentially explain association
- Requires additional study to investigate the association and/or mechanism

Sputum IL-4

- Asthmatic groups had higher mean sputum IL-4 levels compared to the healthy controls
- All groups showed decreases in mean IL-4 levels after either exposure (CAPS or FA) relative to baseline
- Contrasts with previous data from DEP studies suggesting that particulate air pollutants induce increased IL-4 production from T-cells

Blood and Urine Biomarkers

- Blood and urine biomarkers did not show exposure differences attributable to CAPS
- Previous human studies of CAPS exposure effects on various serologic biomarkers have yielded variable results from no significant change to mild increases in fibrinogen, D-dimer, and IL-8 (latter two effects observed with concentrated ultrafine particles)

Harder SD et al. Environ Health Perspect. 2001;109:599-604.

Ghio AJ, et al. Am J Respir Crit Care Med. 2000;162:981-8.

Samet JM, et al. Am J Respir Crit Care Med. 2009;179:1034-42.

Heart Rate Variability

- HRV recognized as an important cardiovascular outcome
- Reduced HRV considered a prognostic marker for the development of cardiac arrhythmia
- HRV changes in our study that appeared attributable to CAPS exposure across all groups included a mild decrease in HR and decreased T-wave complexity and variability

Heart Rate Variability

- Our results inconsistent with previous reports of increases in both HR and T-wave complexity/variability after particle exposure
- Differences with regard to particle size (ultrafine) and study population (ischemic heart disease)

Gong H, et al. *Inhal Toxicol* 2004; 16:335-43

Zareba W, et al. *Inhal Toxicol*. 2009;21:223-33

Henneberger A, et al. *Environ Health Perspect*. 2005;113:440-6.

Exposure Analysis

- Exposures Adequate?
- Employed well-established protocols and equipment which have been used successfully for a number of previous exposure studies
- Air monitoring results showed experimental exposures to fine CAPS close to target concentration of $200 \mu\text{g}/\text{m}^3$

Particle Characteristics

- EC/OC results consistent with previous CAPS exposures
- PAH levels detected in particles appear relatively low with many filter samples below limit of detection for a number PAHs
- Reduced PAH content may be a contributing factor to findings if particle redox activity strongly correlated to PAH
- Detectable but lower than expected levels of a number of transition metals and elements believed to be important in the generation of ROS and inflammation
- No reason to believe collected air particles in region have changed substantially compared to previous studies at our site
- Qualitatively, chemical composition of CAPS used in our study may differ from those in other CAPS exposure studies

Study Limitations

- Individuals in asthma groups were clinically mild-moderate
 - Subjects not taking inhaled or systemic corticosteroids and required to have baseline FEV₁ >70%
- Strength of conclusion limited by study power
 - Designed to detect a 3% exposure-related reduction in FEV₁ (smallest clinically meaningful FEV₁ change) with power of 0.8 using a one-tail test with alpha = 0.05 and N = 10
 - More subtle changes in biomarkers could have gone undetected

Study Limitations

- Many response variables measured in relatively few subjects with biologic variability due to personal environmental stresses outside the confines of the experiment
- Possible that spurious statistically significant differences will be found
 - Due to uncontrolled and unmeasured intercurrent interferences
 - Due to a few "significant" differences found by chance in any large collection of statistical test results

Study Limitations

- Biologic heterogeneity between human individuals with considerable inter- and intra-subject variability over time
- Variations due to age, diet, genetic background, activity level, ambient exposures, and disease history
 - Obesity as emerging factor with potential impact on individual response to particulate matter, not included in original hypotheses
 - Susceptibility groups had similar numbers of overweight or obese subjects (7 asthmatic GSTM1 null, 7 asthmatic GSTM1 present, 8 healthy GSTM1 present)

Schwartz J, et al. Am J Respir Crit Care Med. 2005;172:1529-33.

Baja ES, et al. Environ Health Perspect. 2010

Study Limitations

- Important co-factors, genetic or otherwise, may modulate the response to particle exposure or oxidative stress in the absence of GSTM₁
 - other Phase II antioxidant enzymes
 - cytoprotective mechanisms may play a role in reducing cellular oxidative stress

Considerations for Future Studies

- Larger-scale experiments with increased power
- Alternatives to spirometric changes as primary endpoints
- Increased CAPS exposure (higher concentration and/or greater duration)
- Ethical inclusion of more clinically severe asthmatics
- Consideration of additional genetic and host co-factors (i.e. dietary) that may modulate inflammatory response to oxidative stress
- Inclusion of FeNO measurement in future fine CAPS exposures to determine changes, significance

**Greetings from
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