



The Role of Air Pollution Particles as a Potent Adjuvant that Causes Allergic Disease and Asthma

*David Diaz-Sanchez
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Allergy*

Important questions on air pollution & respiratory diseases

Is there a link between air pollution and airway disease?

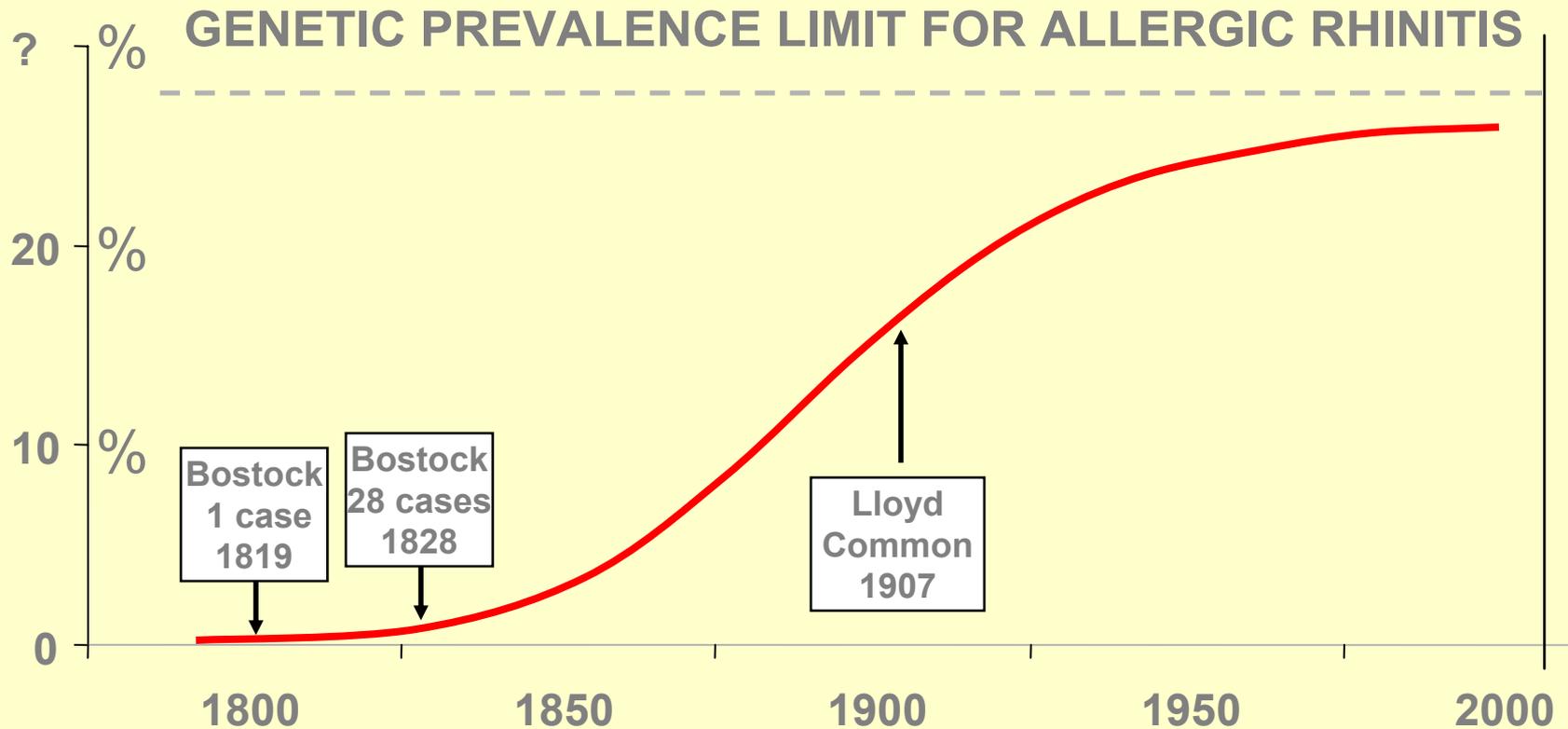
What components are involved?

What are the mechanisms involved?

What confers susceptibility?

What can we do about it?

PREVALENCE OF ALLERGIC RHINITIS SINCE THE INDUSTRIAL REVOLUTION



EXPERIMENTAL RESEARCHERS

OF THE

CAUSES AND NATURE

OF

CATARRHUS AESTIVUS

(HAY-FEVER OR HAY-ASTHMA)

BY

CHARLES H. BLACKLEY, M.R.C.S.ENG

LONDON

DAWSON'S OF PALL MALL

1873

ON THE GREATER PREVALANCE OF HAY-FEVER AND ON THE INCREASE OF ITS PREDISPOSING AND EXCITING CAUSES

162

Experimental Researchers on Hay-Fever

and I have shown that large numbers of the people have been transferred from the country to the workshops and mills of the towns, and have thus been placed in circumstances where the predisposition to hay-fever would be most rapidly developed in those who rise to a place amongst the educated class. And lately, I have shown that the production of the exciting cause has of late years been largely increased.

Taking all these circumstances into account it is a highly probable that hay-fever was at one time altogether unknown, and it is tolerably certain that it has not only been much more frequent of late, but that, as population increases and as civilization and education advance, the disorder will become more common than it is at the present time.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 9, 2004

VOL. 351 NO. 11

The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age

W. James Gauderman, Ph.D., Edward Avol, M.S., Frank Gilliland, M.D., Ph.D., Hita Vora, M.S.,
Duncan Thomas, Ph.D., Kiros Berhane, Ph.D., Rob McConnell, M.D., Nino Kuenzli, M.D., Fred Lurmann, M.S.,
Edward Rappaport, M.S., Helene Margolis, Ph.D., David Bates, M.D., and John Peters, M.D.

1759 kids

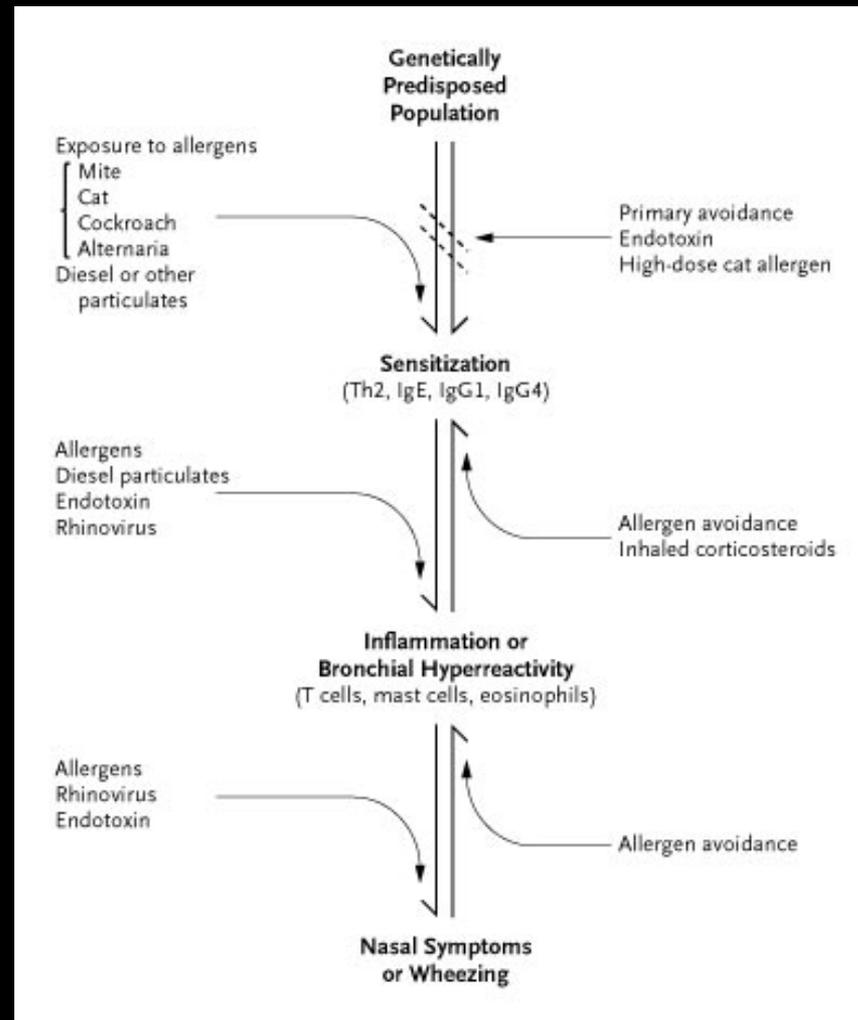
1993-2001

12 communities

FEV1, FVC, MMEF



Allergen Avoidance as a Treatment for Perennial Rhinitis and Asthma.



Platts-Mills, T. A.E. N Engl J Med 2003;349:207-208



Components of Air Pollution

A. Primary-secondary pollutants

- (i) Primary: pollutants emitted directly into the atmosphere (eg, SO₂, some NO_x species, CO, PM)
- (ii) Secondary: pollutants that form in the air as a result of chemical reactions with other pollutants and gases (eg, ozone, NO_x, and some particulates)

B. Indoor-outdoor pollutants

(i) Indoor pollutants

- (a) Sources: cooking and combustion, particle resuspension, building materials, air conditioning, consumer products, smoking, heating, biologic agents
- (b) Products: Combustion products (eg, tobacco and wood smoke), CO, CO₂, SVOC (eg, aldehydes, alcohols, alkanes, and ketones), microbial agents and organic dusts, radon, manmade vitreous fibers

(ii) Outdoor pollutants

- (a) Sources: industrial, commercial, mobile, urban, regional, agricultural, natural
- (b) Products: SO₂, ozone, NO_x, CO, PM, SVOC

C. Gaseous-particulate pollutants

- (i) Gaseous: SO₂, NO_x, ozone, CO, SVOC (eg, PAH, dioxins, benzene, aldehydes, 1,3-butadiene)
- (ii) Particulate: coarse PM (2.5-10 μm; regulatory standard = PM₁₀), fine PM (0.1-2.5 μm; regulatory standard = PM_{2.5}); ultrafine PM (<0.1 μm; not regulated)

NO_x, Nitrogen oxides; SVOC, specific volatile organic compounds.

Health effects of air pollution

Editor: Jonathan A. Bernstein, MD^a

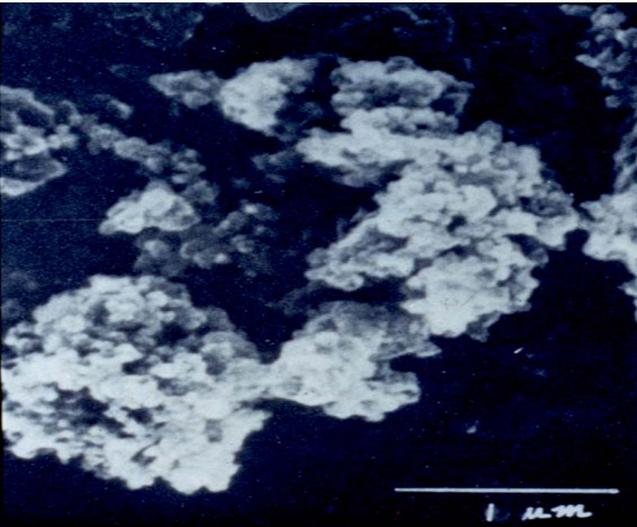
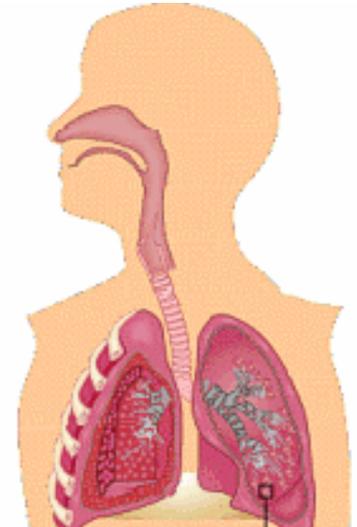
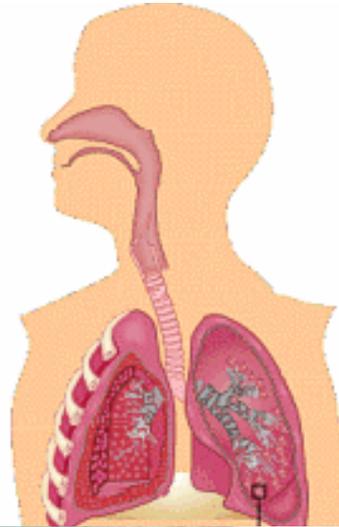
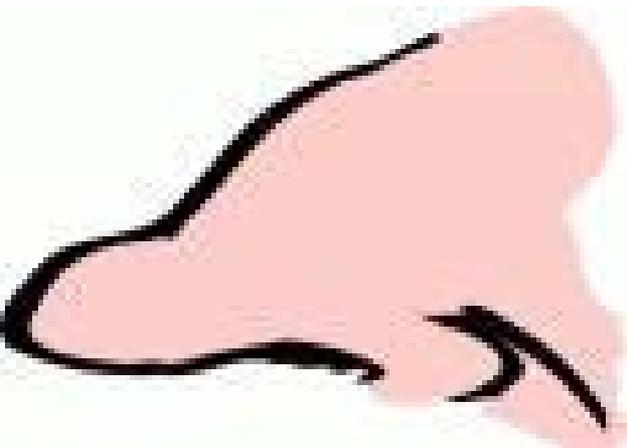
Contributors: Neil Alexis, PhD,^b Charles Barnes, PhD,^c I. Leonard Bernstein, MD,^a Jonathan A. Bernstein, MD, Andre Nel, MD, PhD,^d David Peden, MD,^b David Diaz-Sanchez, PhD,^d Susan M. Tarlo, MB, BS,^e and P. Brock Williams, PhD^c

J Allergy Clin Immunol 2004;114:1116-23

Nasal DEP

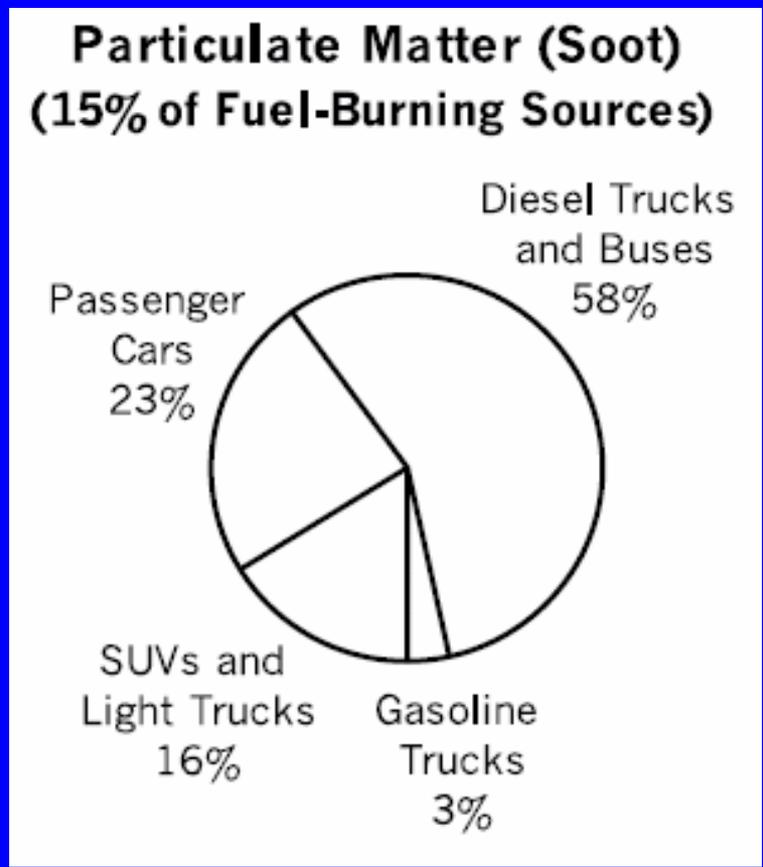
Inhaled Diesel

Inhaled ETS



Diesel- a model combustion particulate pollutant

Figure 2. Highway Sources of Pollution



- Respirable median dia 0.2 microns
- Carbon core surrounded by chemicals
 - PAH
 - Metals
- Major source of particulates especially in Europe and Japan

Diesel Exhaust Particles Affect Four Phases of Allergic Airway Disease

Immediate phase response

- Increased mediator release and symptoms

- Short term response

- Release of chemokines, cytokines and increased cellular inflammation

- Intermediate term response

- Enhanced IgE antibody response to allergens

- Long term response

- Primary allergic sensitization

**Nasal lavage as a tool in
assessing acute inflammation
in response to inhaled
pollutants.**

Koren HS, Hatch GE, Graham DE.

**Clinical Research Branch, U.S. Environmental
Protection Agency**

Toxicology 1990 Jan-Feb;60(1-2):15-25

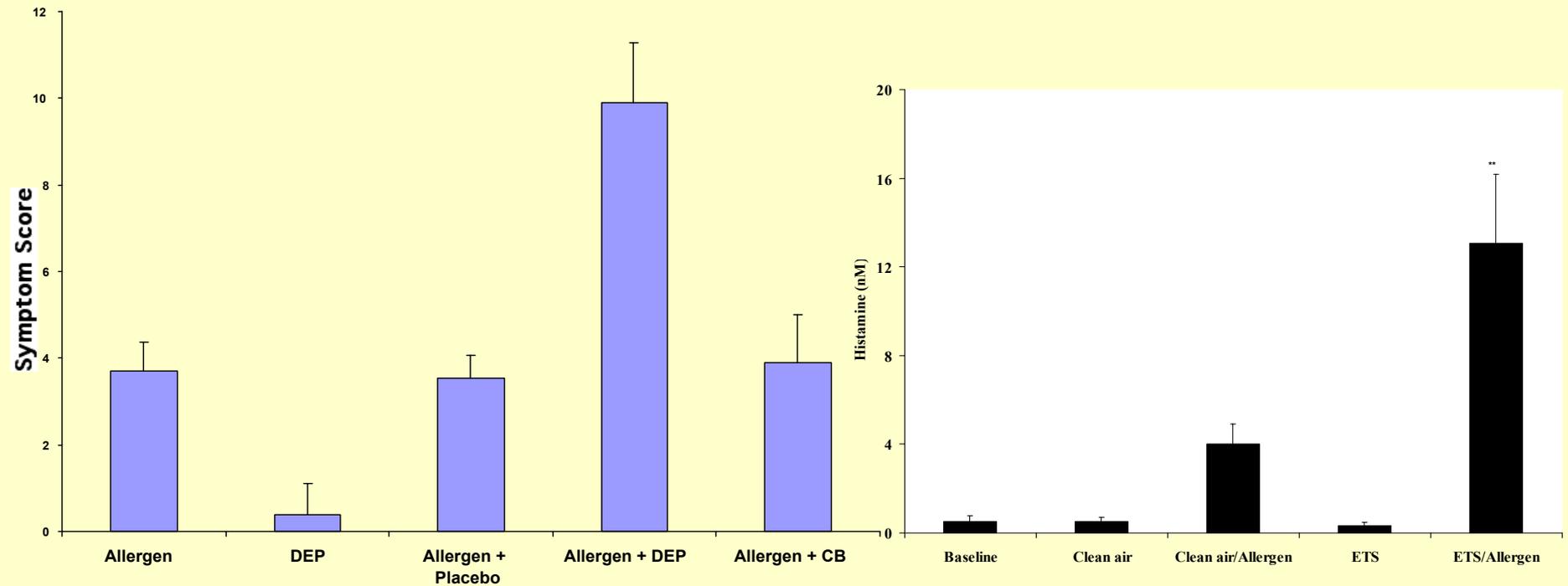


Nasal Lavage/challenge Model Of Allergic Inflammation (Fishing In The Nose)



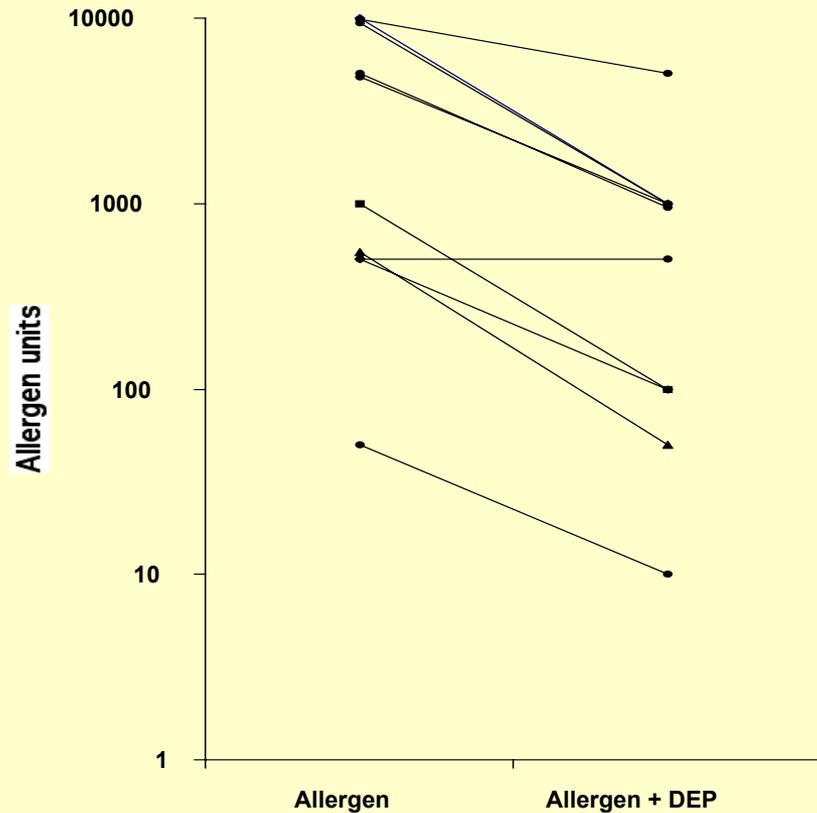
- Day 0, Nasal Lavage
 - Baseline levels
- Nasal challenge with:
 - Allergen
 - DEP (300 μg)
- Measure response in min, hrs, days

Diesel Particles Enhances Allergy Symptoms and Histamine release

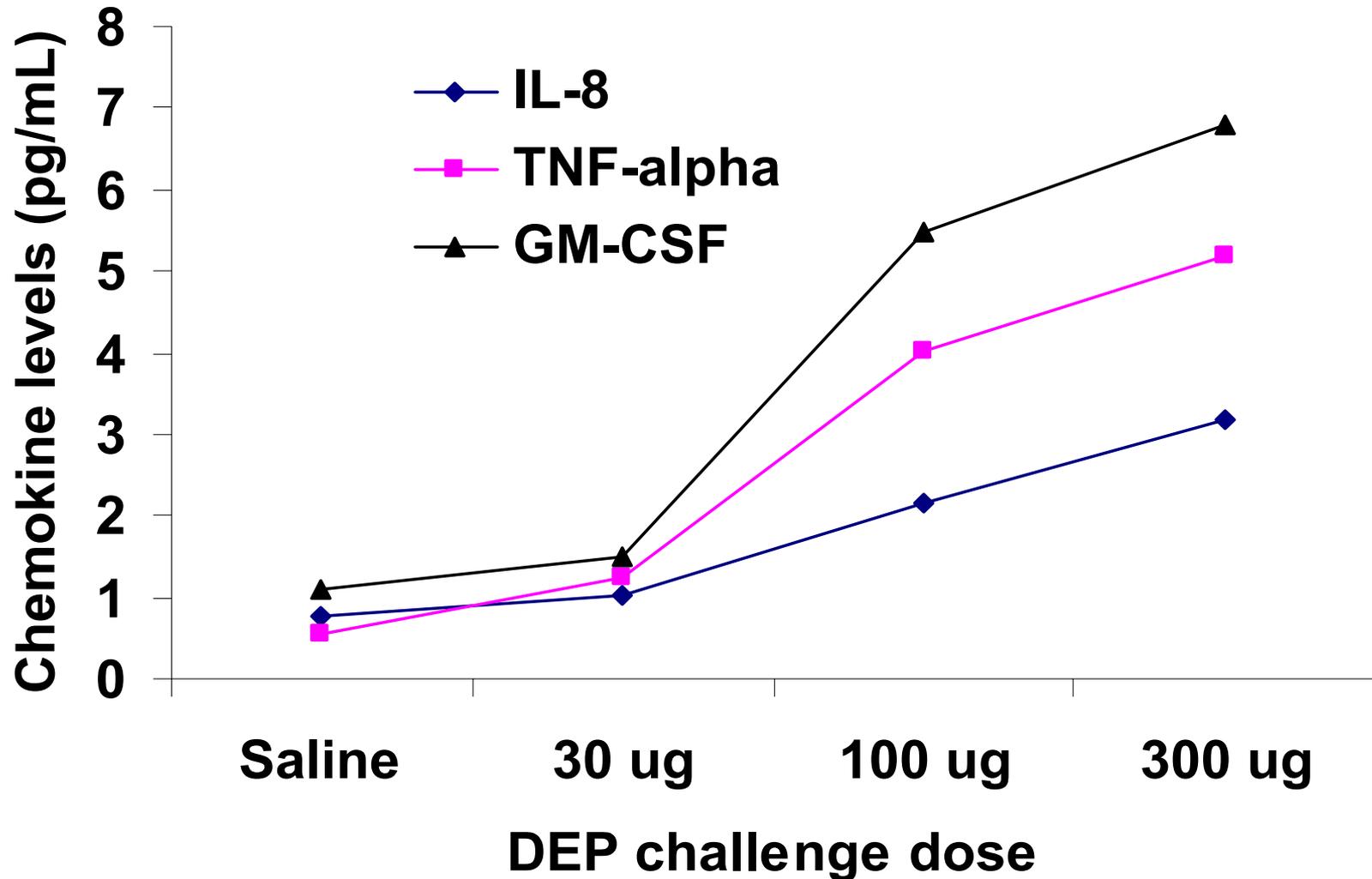


Diesel Particles Reduce Allergen Threshold

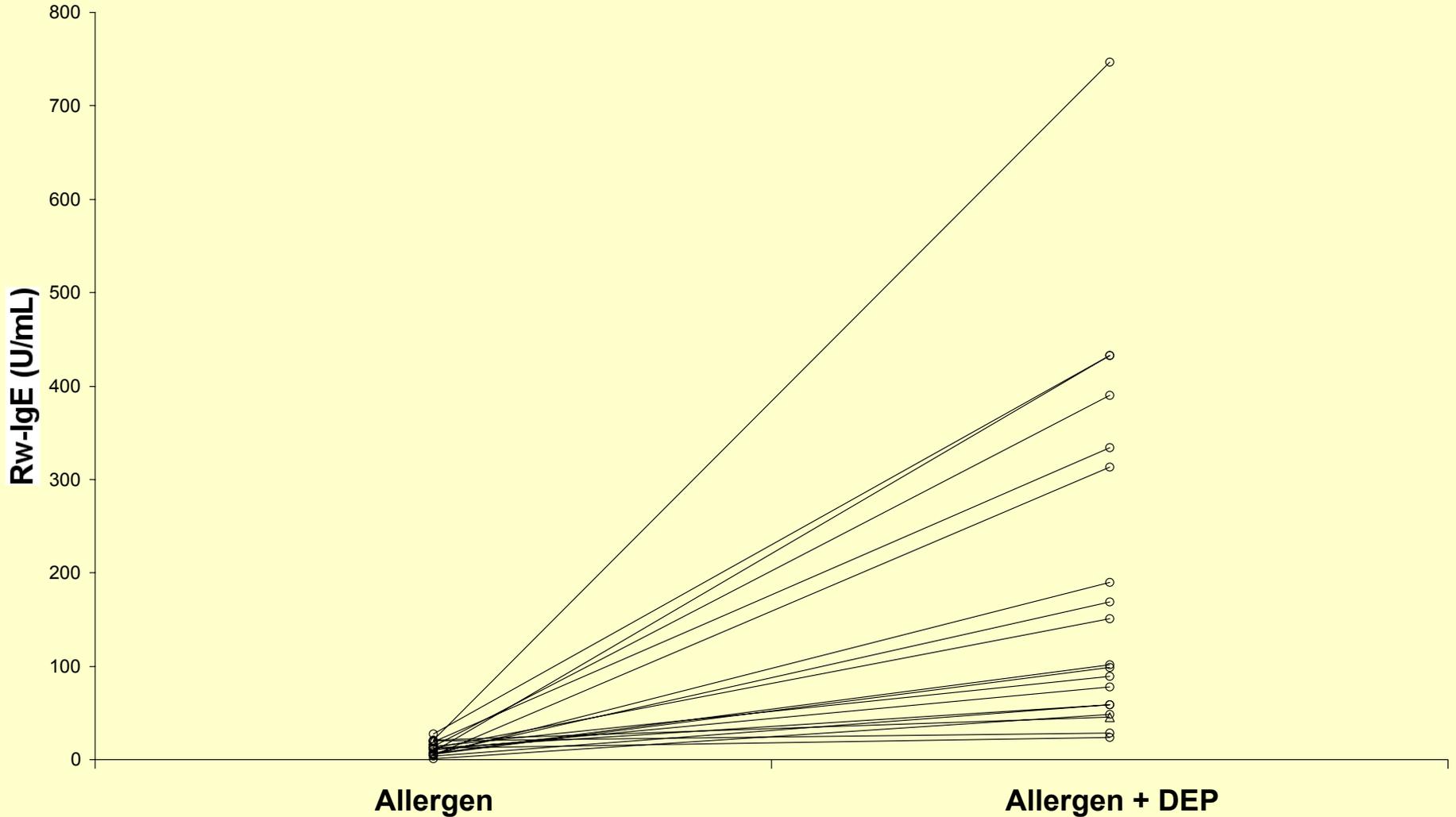
Only 1/5th of the normal amount of allergen is needed to get allergic symptoms when diesel particles are present.



DEP enhances the inflammatory response



DEP enhances allergen-IgE responses



Diaz-Sanchez, et al. *J Clin Invest* 1994

Sensitization

- Cause an allergy to a substance which was previously “harmless”
- Can Pollution make subjects allergic to a “neo-allergen”?
- Keyhole Limpet Haemocyanin (KLH)



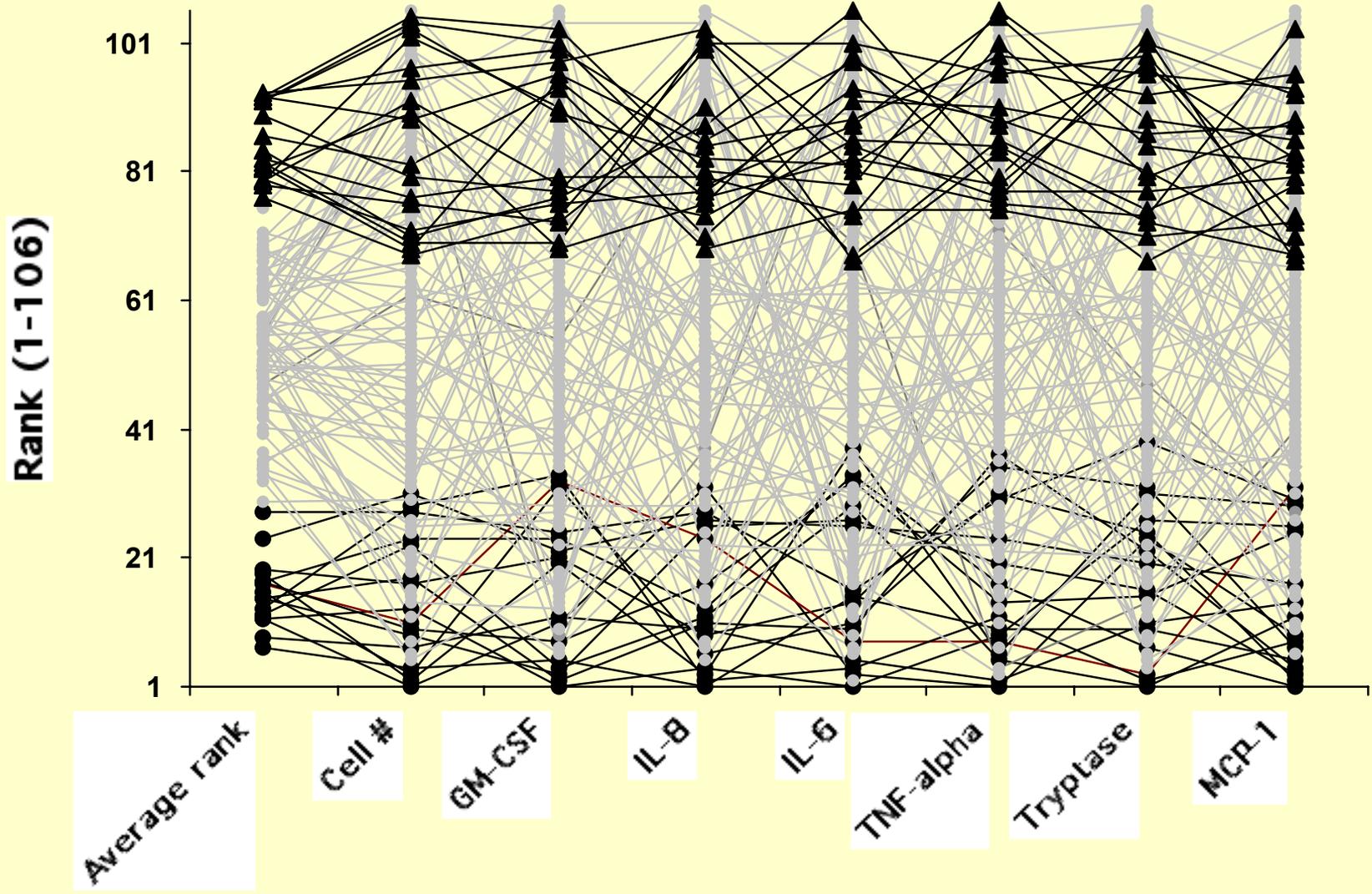
Sensitization

- KLH alone -> NO IgE
 IgG, IgA

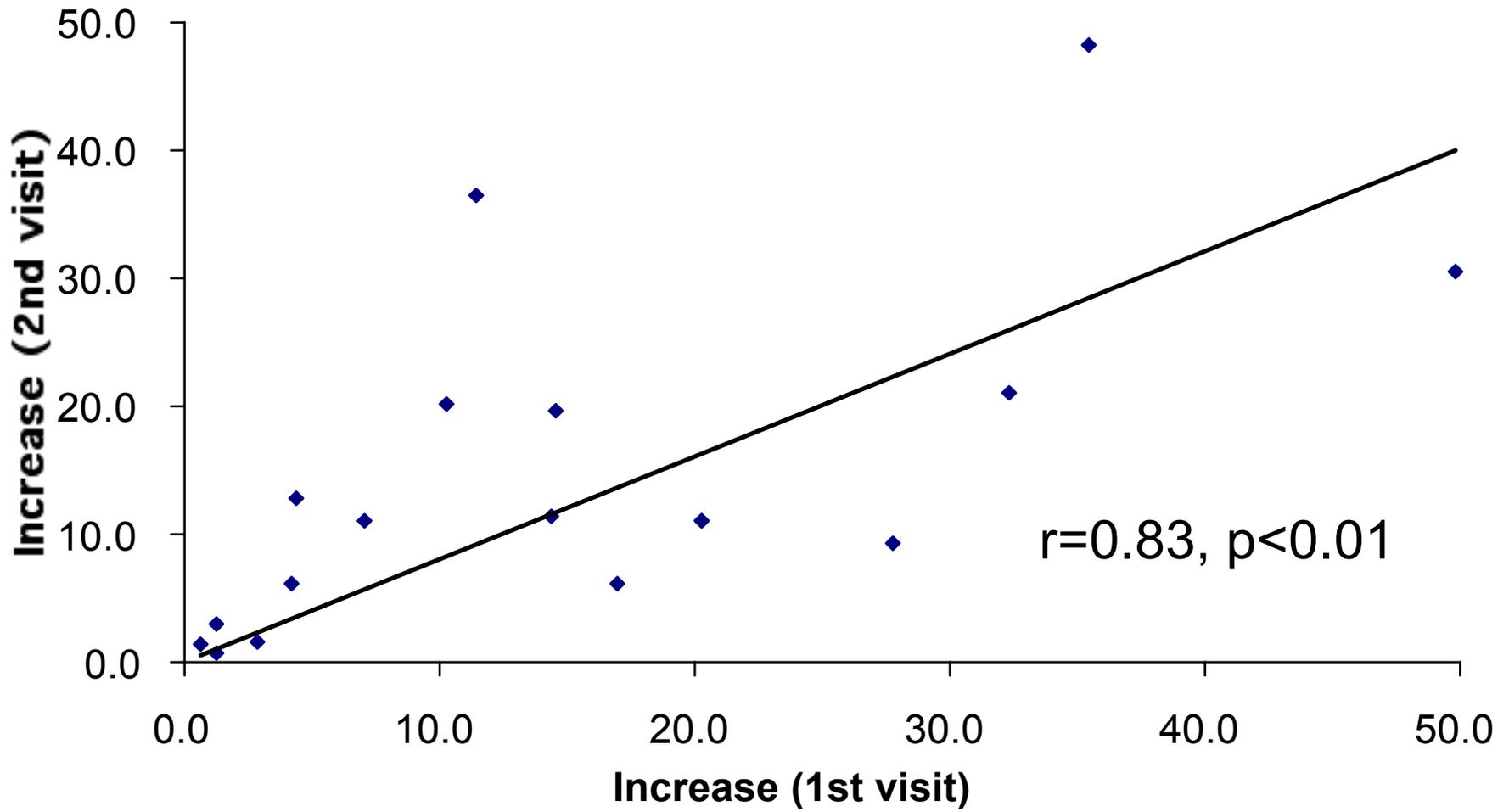
- KLH + DEP -> 60-90% subjects sensitized
 KLH-IgE apparent at Day 32
 (3rd exposure)
 allergic symptoms upon
 rechallenge

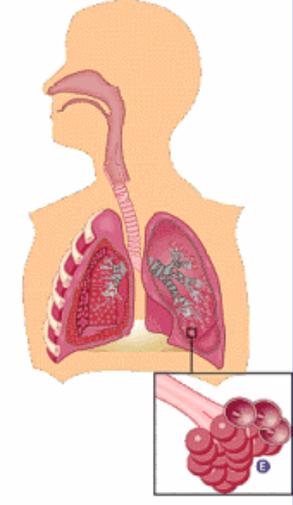
(Diaz-Sanchez et al., J. Allergy Clin Immunol 1999; **104**:1183-8)

Challenge with DEP can define high and low responder populations



Increase of allergen-IgE by DEP is reproducible and intrinsic





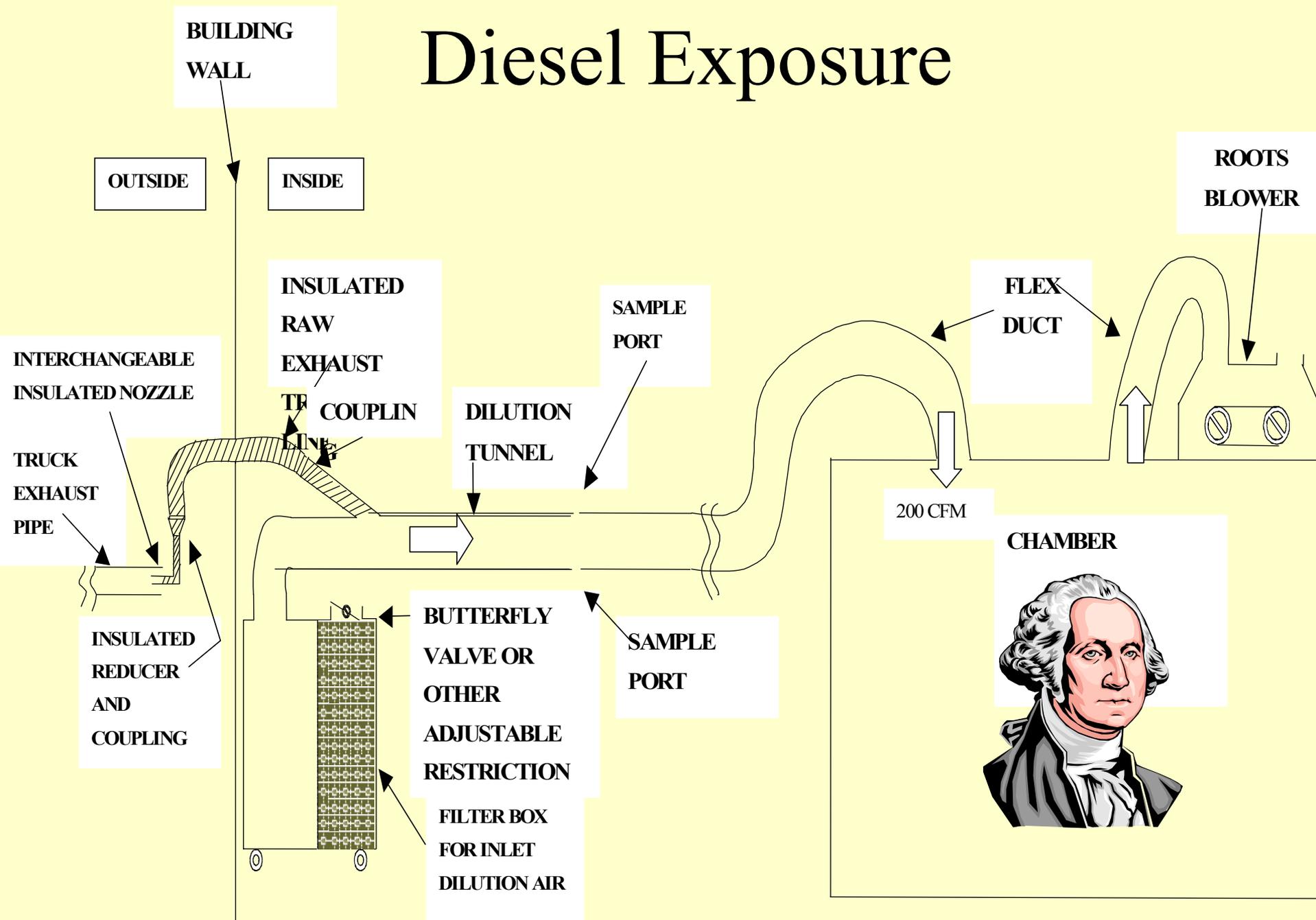
Effect of diesel exhaust on healthy human lower airways

- Sandström and co-workers
- Increased number of inflammatory cells in the airways
- Increase in histamine levels
- Increased levels of inflammatory mediators and molecules
- Decreased macrophage function

Diesel exhaust enhances airway responsiveness in asthmatic subjects

- 14 nonsmoking, atopic asthmatics
- 300 $\mu\text{g}/\text{m}^3$ DE or air for 1 h
- Increase in:
 - hyperresponsiveness to methacholine
 - airway resistance
 - sputum levels IL-6
- Nordenhall et al., Eur Respir J 2001 17:909-15

Diesel Exposure



STUDY DESIGN

A double-blind randomized cross-over controlled exposure to filtered air, diesel exhaust (100 ug/m³) and nitrogen dioxide for 2hours.

Chamber

350-ft³ plexiglass chamber, 74-81°F; relative humidity 35-50%, air exchange rate of 17 changes/hour

Subjects

18-45 years of age

Ten mild asthmatic subjects with skin test sensitivity to at least one allergen

Four non-allergic, non-asthmatic subjects.

Endpoints

Lung function

FEV1, Airway hyperresponsiveness, Airway Resistance

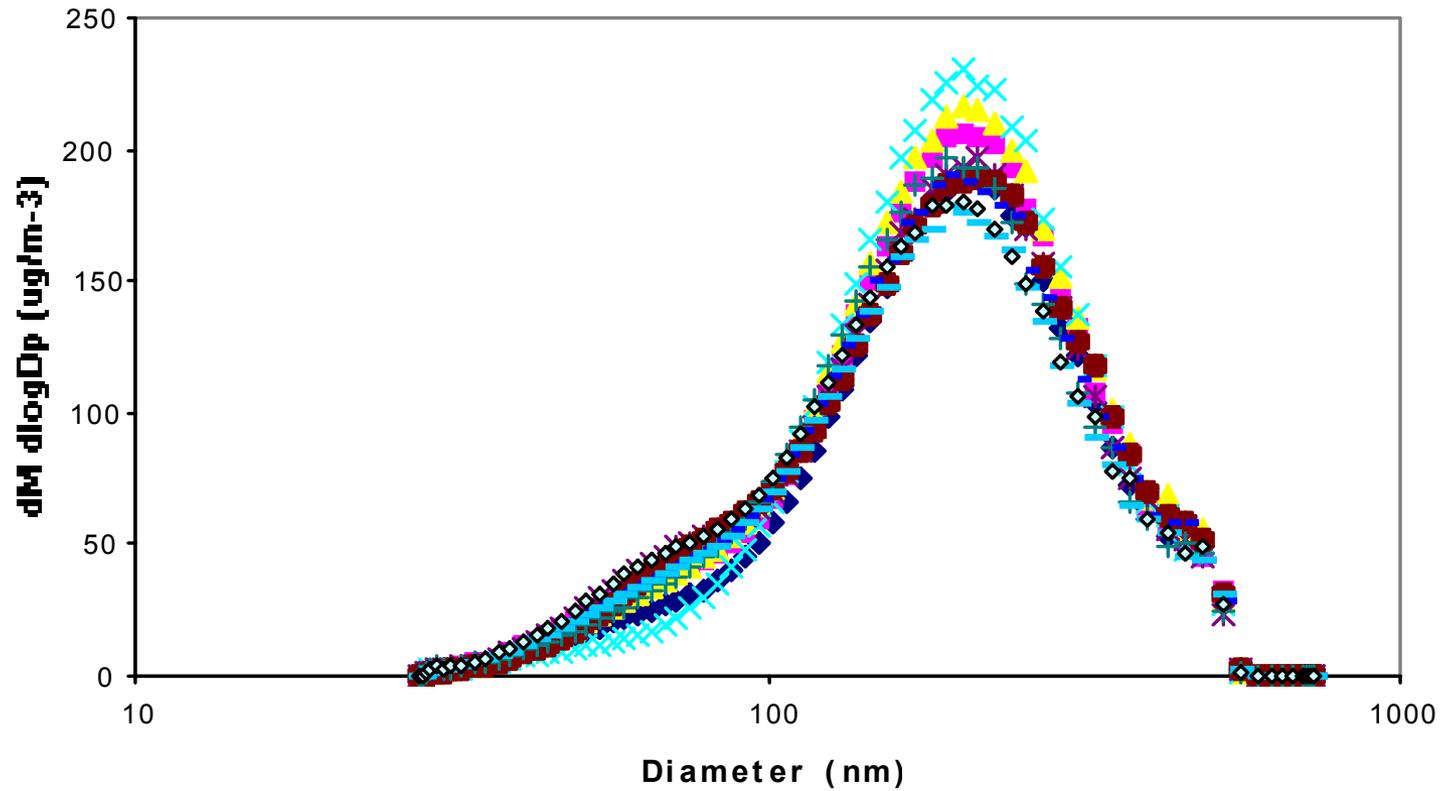
Immune function

Cell influx, allergic antibody, cytokine, chemokine and mediator production in sputum

Symptoms

Continual health questionnaire, EKG monitoring, pulse oximetry

Comparison of mass distributions between different diesel exposures



The PM mass loadings for individual human exposures ($\mu\text{g}/\text{m}^{-3}$)

Filter ID	SMPS Set		OC ($\mu\text{g m}^{-3}$)	EC ($\mu\text{g m}^{-3}$)
	Point ($\mu\text{g m}^{-3}$)	Point ($\mu\text{g m}^{-3}$)		
0003	no data		77.4	32.9
0004	no data		66.4	30.6
0009	96.2		51.3	32.7
0010	96.2		49.4	28.8
0005	107.6		69.4	30.2
0006	107.6		67.2	34.0
0008	112.1		61.4	36.2
0011	112.1		68.1	31.1
0012	110.2		67.7	34.3
0013	110.2		65.6	32.5
0014	104.9		53.6	33.6
0015	104.9		56.3	35.6
40910	no data		57.9	31.3
xx	no data		59.1	30.8
0032	104.2		65.1	29.9
0033	104.2		62.6	30.2
0157	103.8	no data	no data	no data
0158	103.8	no data	no data	no data
0155	96.8		64.4	24.0
0156	96.8		62.0	27.6
0137	101.5		61.9	31.5
0159	101.5		61.4	32.1

Note SMPS set point.
Values are within 6% of target ($100 \mu\text{g}/\text{m}^{-3}$ diesel particles)

FEV₁ Change Pre- to Post-Exposure, in ml: Mean, (SD)

	Healthy	Asthmatic	All
Filtered Air	+38 (71)	-24 (302)	-2 (239)
NO ₂	-20 (43)	+59 (136)	+30 (115)
Diesel Exhaust	+30 (107)	+17 (186)	+22 (155)

Bronchial reactivity to methacholine

Rank 1 indicated highest bronchial reactivity.

Filtered Air 2.2

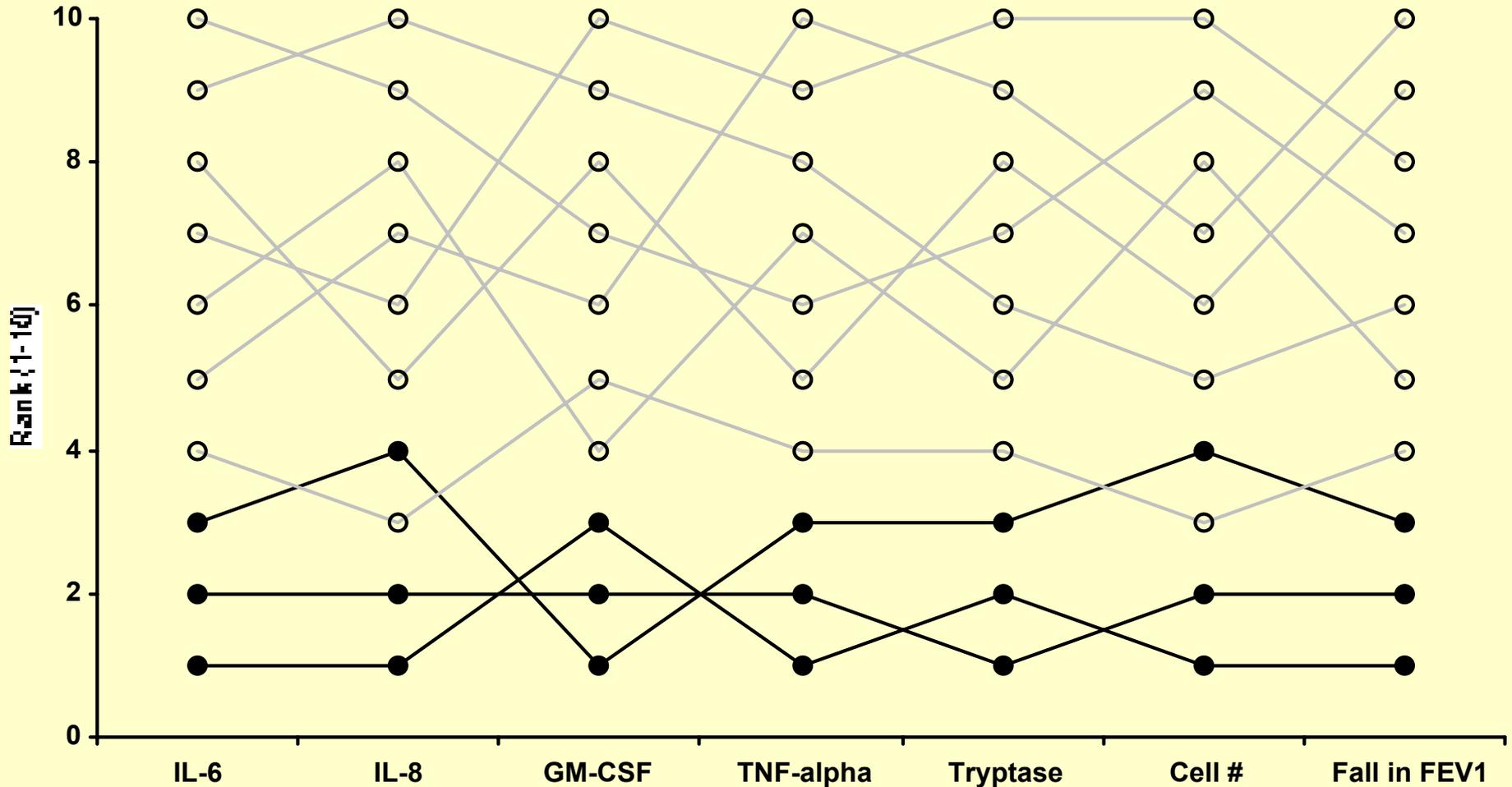
NO₂ 2.2

Diesel Exhaust 1.7

p>0.05

The rank order of key endpoints of airway inflammation following diesel exhaust exposure

$P = 4.87 \times 10^{-7}$



ETS exposure protocol

-2h NL

0h 2hr Clean air/ETS exposure

2h NL

Allergen challenge

24h NL

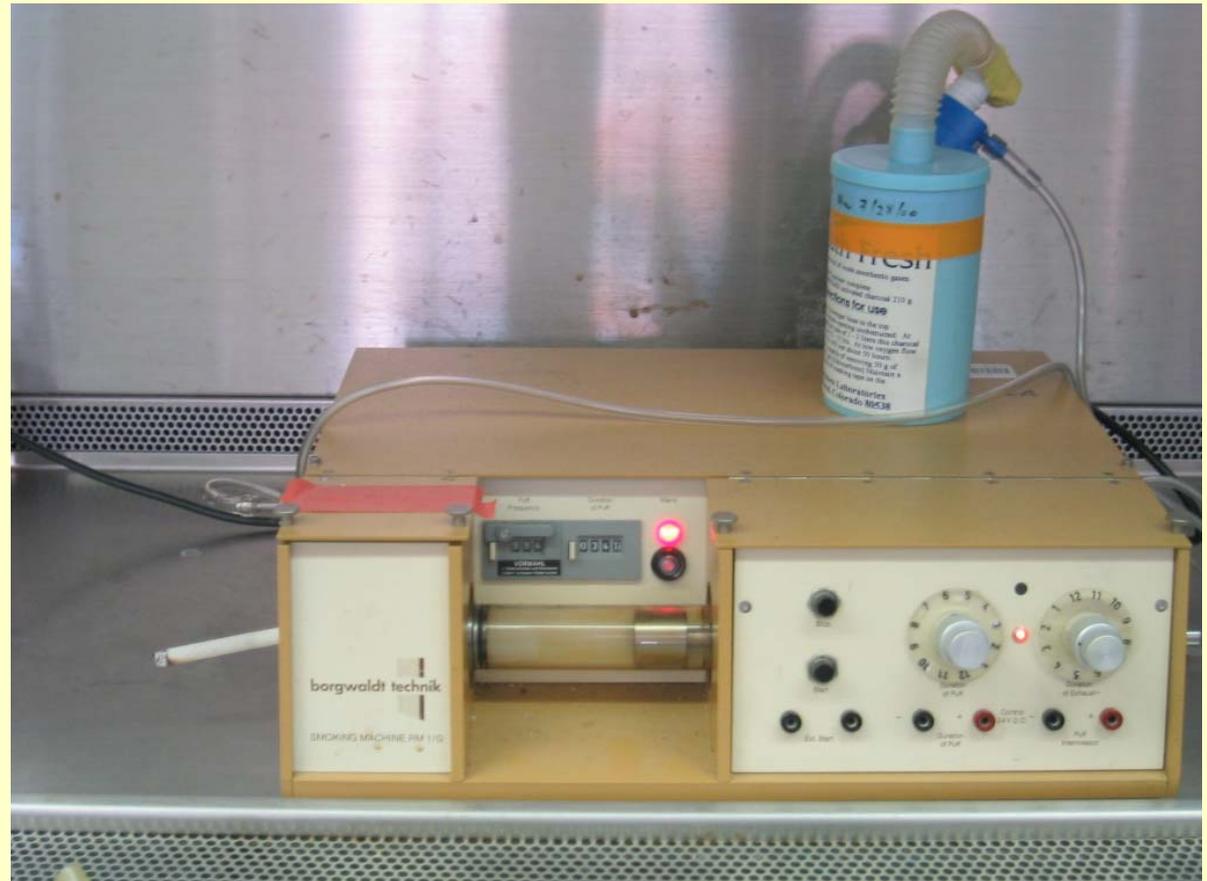
96 h NL

Generation of ETS

FTC guidelines

RM G1
Borgwaldt
Smoking
machine

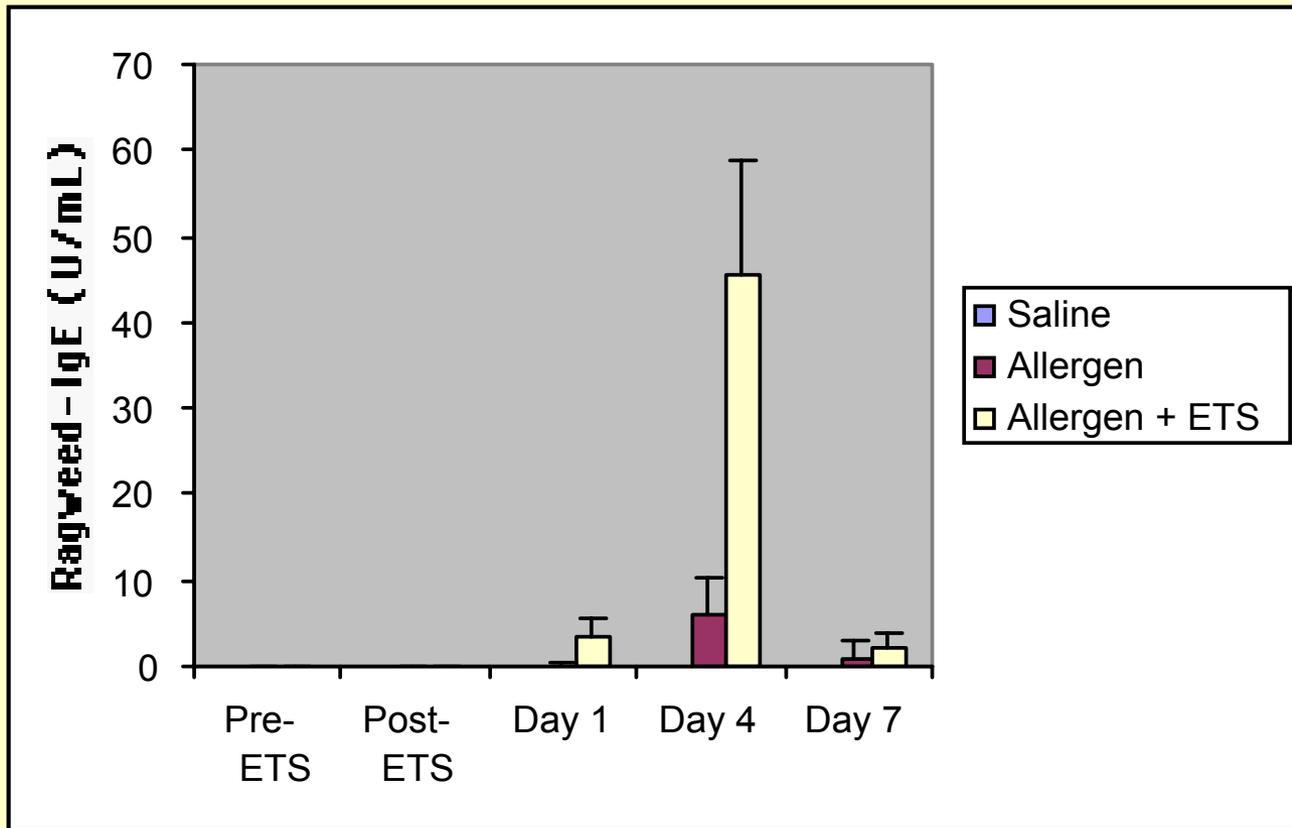
1R4F
reference
cigarettes
9.2 mg Tar
0.8 mg
nicotine



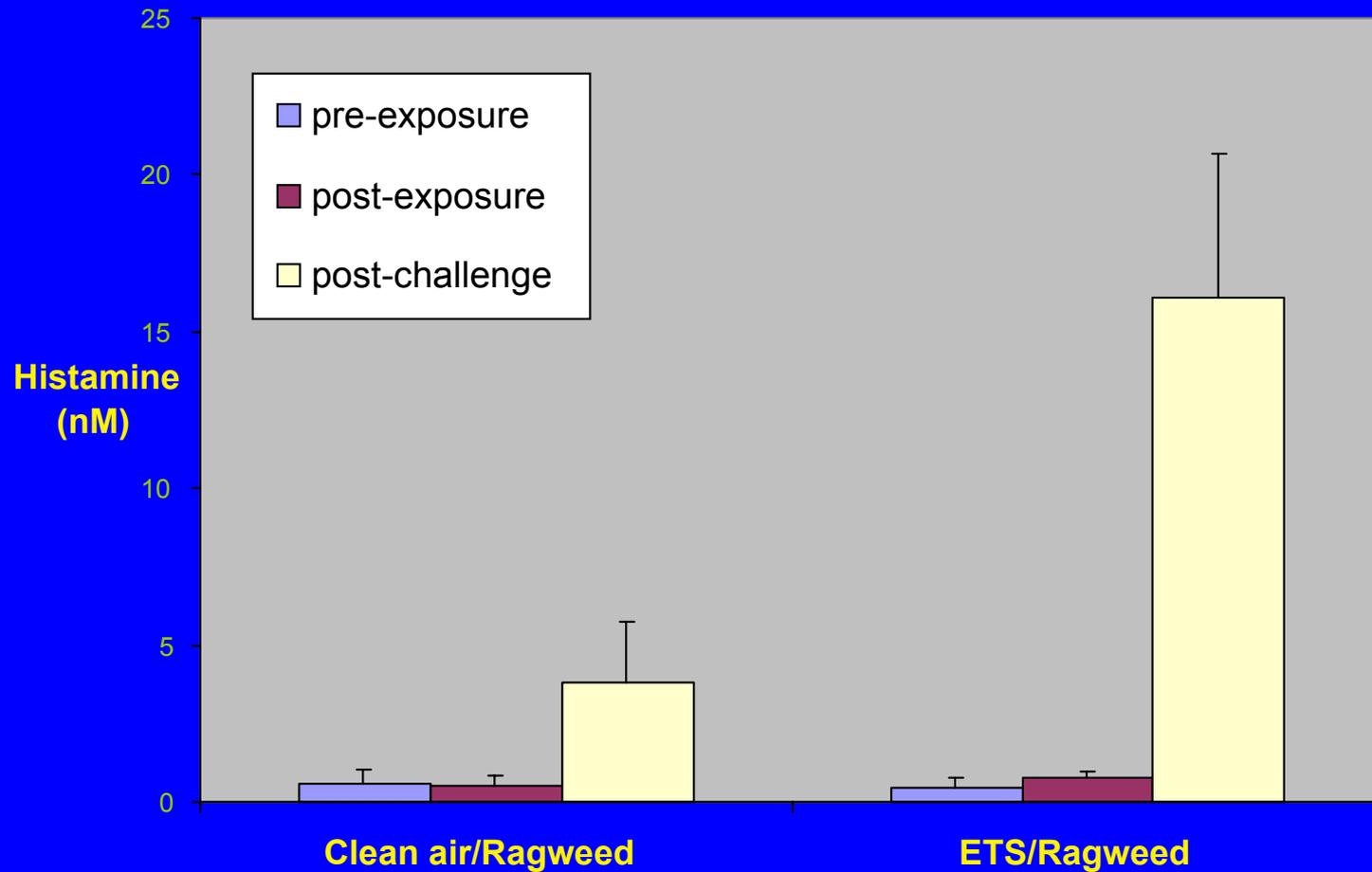
ETS exposure

- Five cigarettes
- Two hour period
- Carbon monoxide < 5 ppm
- PM level $\approx 400 \mu\text{g}/\text{m}^3$

Secondhand smoke exposure exacerbates IgE responses



ETS enhances allergen-induced histamine release



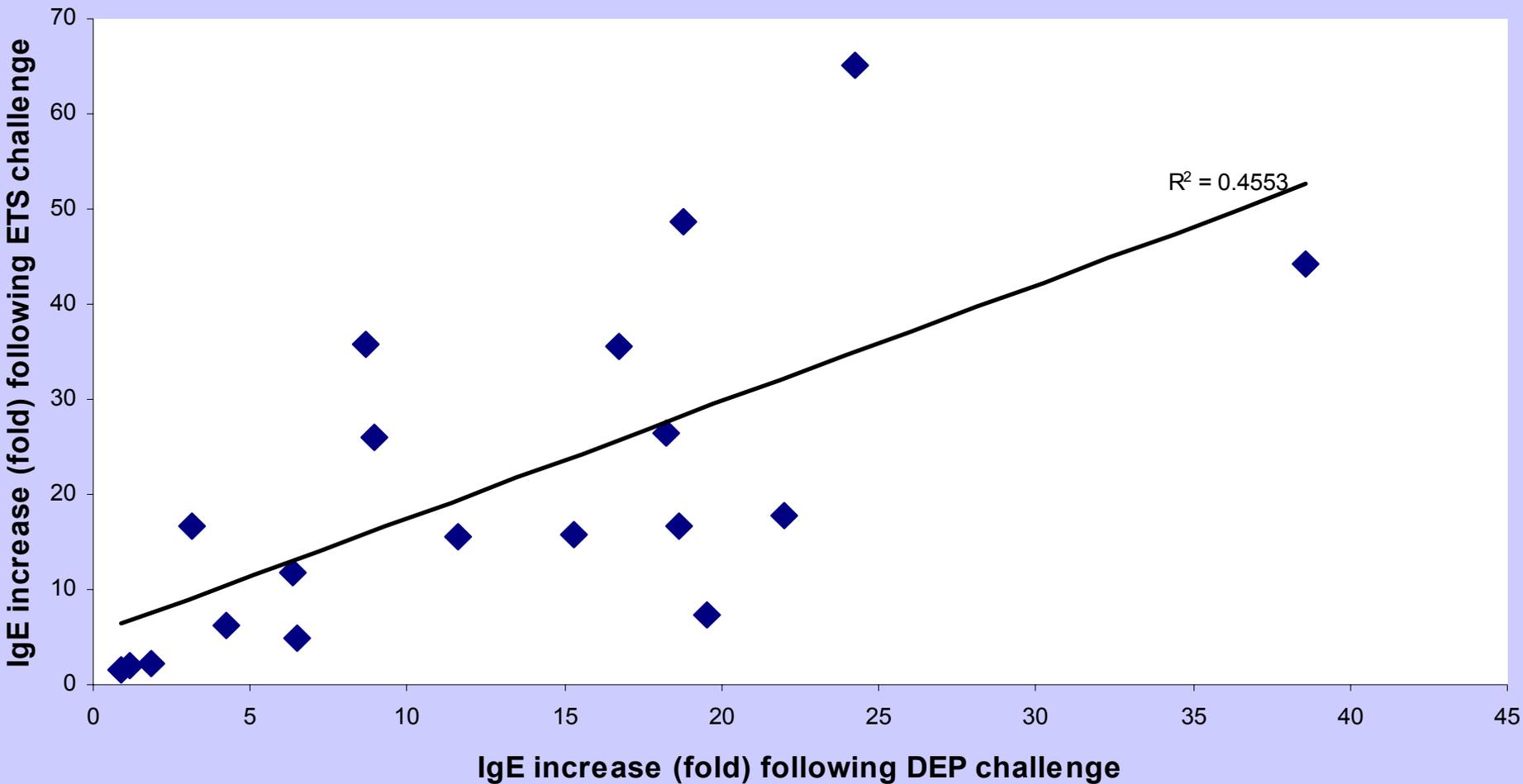
In mouse model ETS

- Induces sensitization in low responder strain
 - OVA-IgE formation
 - Eosinophilia
 - Th2 cytokines in BAL
- Enhances secondary allergic response in high responder strain

DEP and/or ETS Affect Four Phases of Allergic Airway Disease

- Immediate phase response
 - Increased mediator release and symptoms
- Short term response
 - Release of chemokines, cytokines and increased cellular inflammation
- Intermediate term response
 - Enhanced IgE antibody response to allergens
- Long term response
 - Primary allergic sensitization

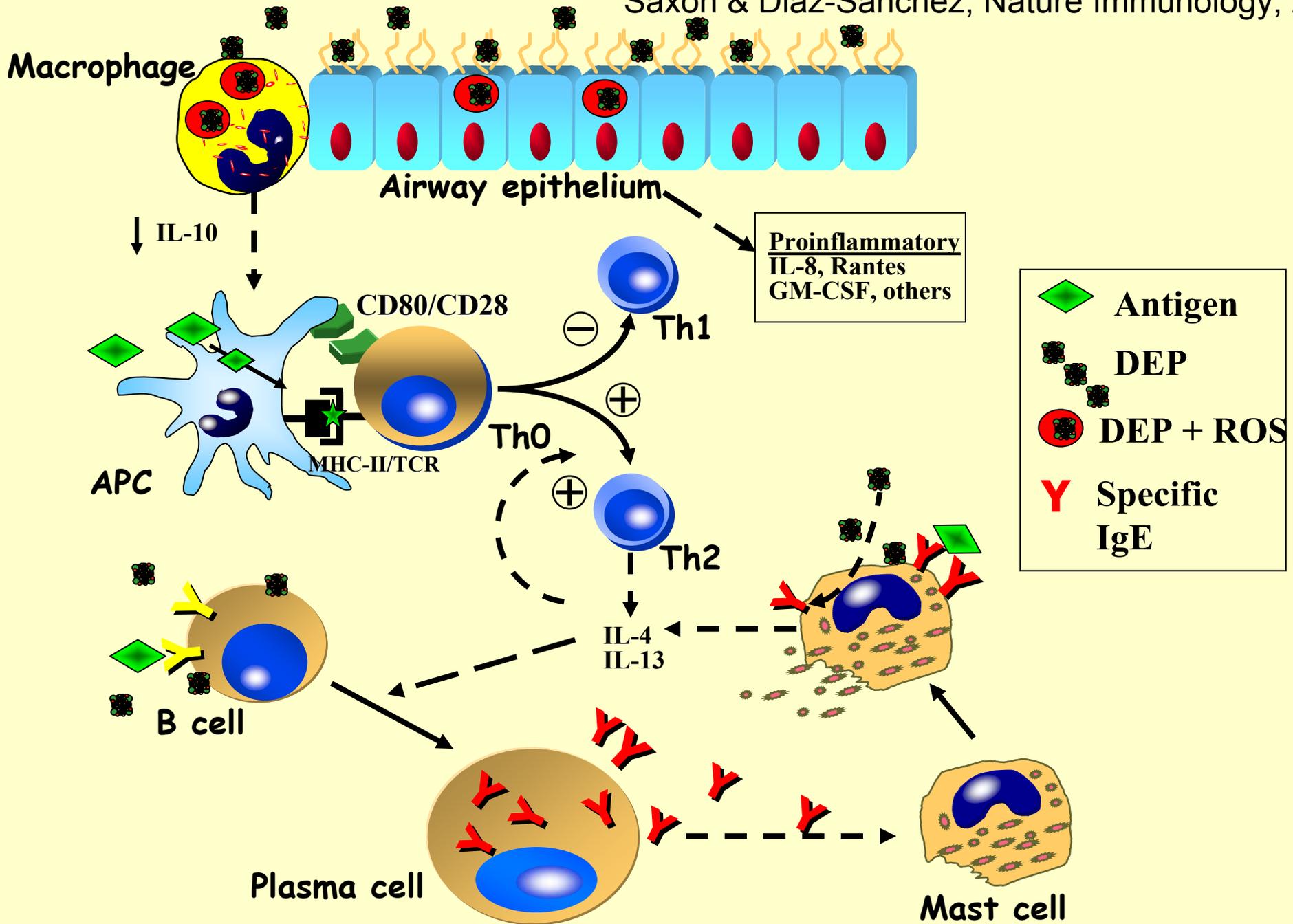
Individuals Respond the Same to DEP and ETS





Susceptibility

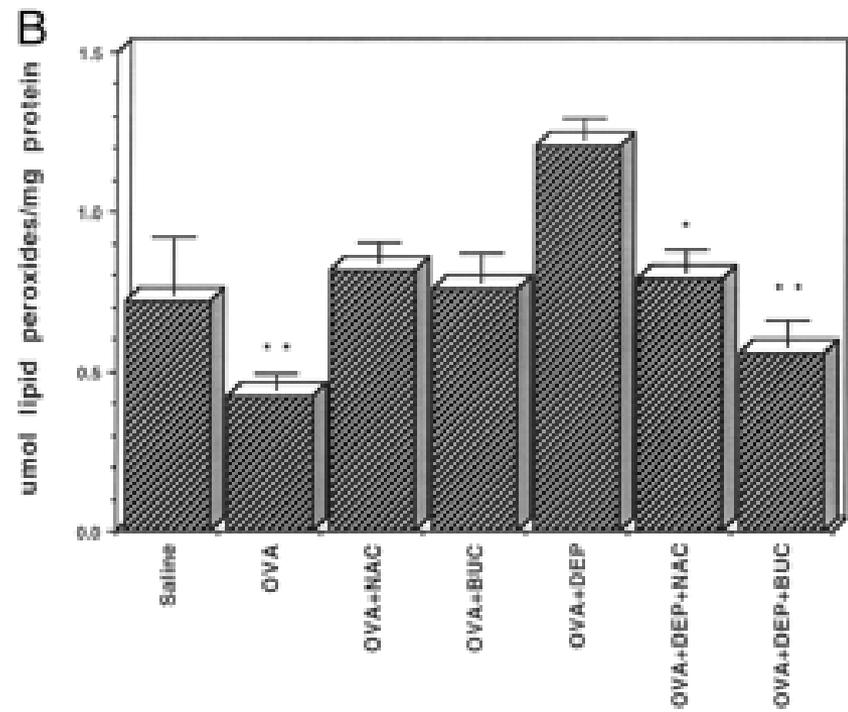
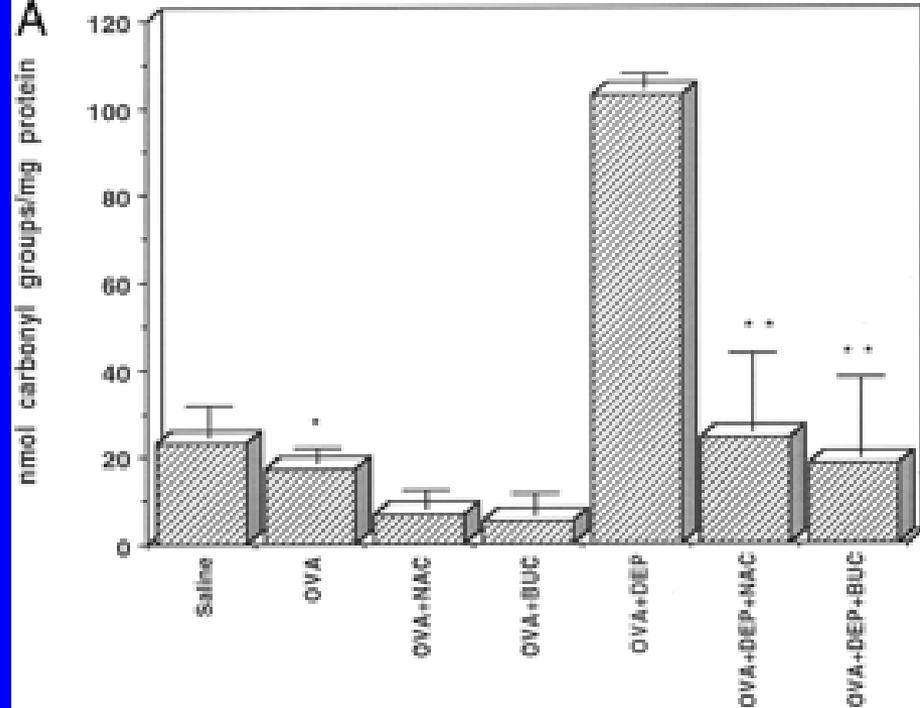
What makes some people sensitive to the pro-inflammatory/pro-allergenic effects of ETS/DEP and others not?



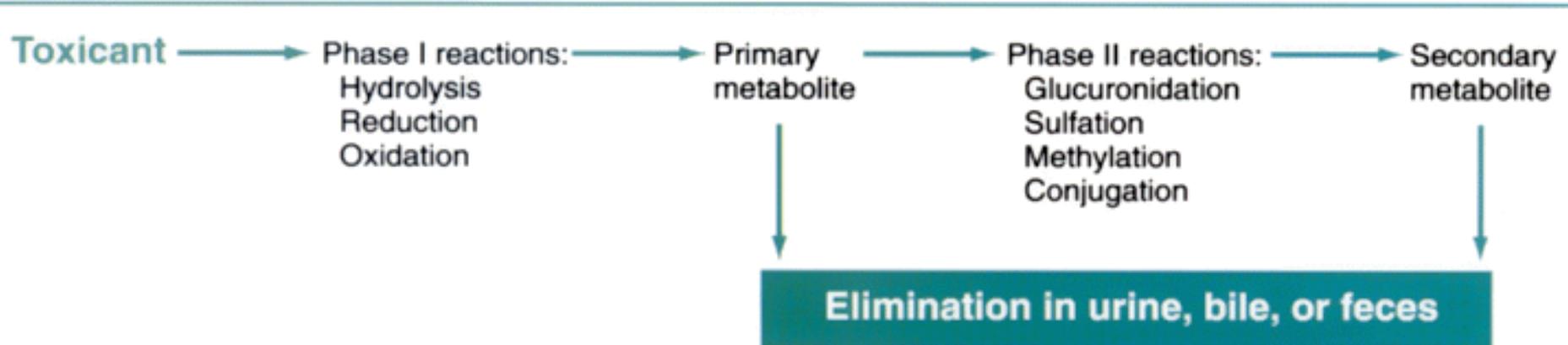
Inhaled DEP-induces Oxidative Stress in Murine Lungs

BALB/c mice exposed to saline, OVA, or OVA plus DEP by aerosolized inhalation daily for 10 days

Assays for carbonyl protein content (*A*) and lipid hydroperoxides (*B*) in the lung homogenates



Metabolic Pathway for Detoxification of DEP chemicals



Phase II enzymes can metabolize reactive oxygen species (ROS) by conjugating them into small hydrophilic moieties, thereby rendering them soluble and excretable.

**ETS or DEP effects on allergic inflammation
mediated by oxidative stress are modulated by
Phase II enzymes**

**Quinones, oxy-PAH-----> redox cycling ----
> Phase II enzymes**

**Phase II enzymes (e.g NQO1, GSTM1)
Quinones -----> hydroquinones**

Is the enhancement of allergic/immune responses caused by DEP dependent on genotype?

Allergic subjects

Cross-over study

Challenge with:

allergen/saline

allergen/DEP

GSTM1

Member of the Glutathione S-transferases family

Involved in oxy-PAH detoxification

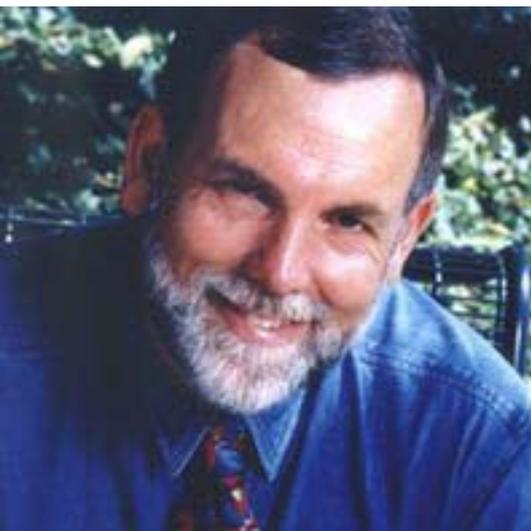
Identified in lung and nasal tissue

Homozygous GSTM1*0/GSTM1*0 (i.e. null genotype) completely lack activity

Null Frequency is 20-50%

Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study

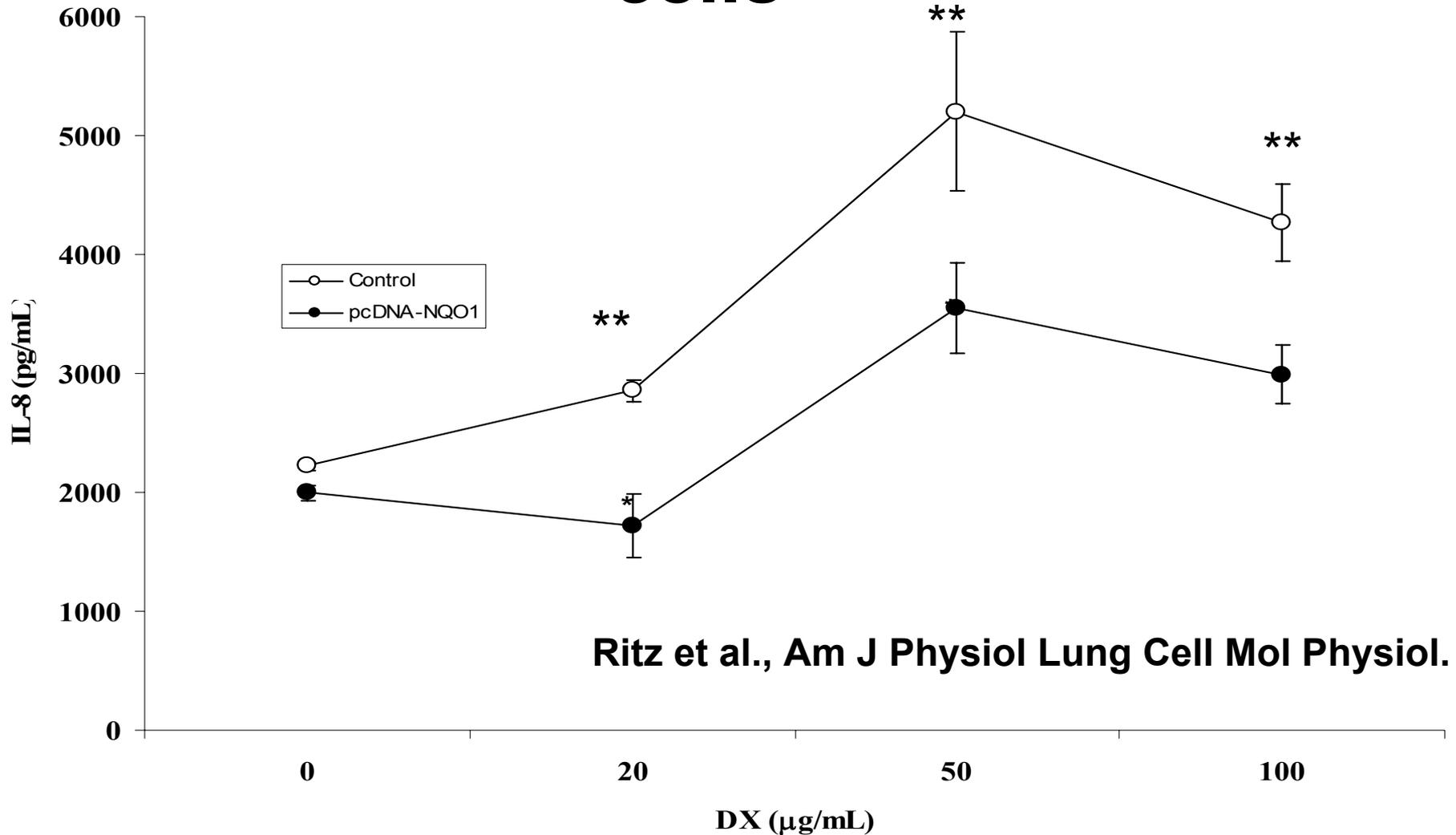
Frank D Gilliland, Yu-Fen Li, Andrew Saxon, David Diaz-Sanchez



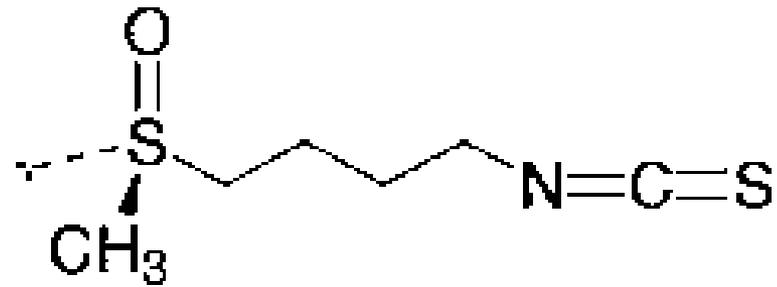
	GSTM1		p
	Null (n=14)	Present (n=5)	
IgE			
Clean air and allergen	6.9 (2.6–24.3)	8.9 (4.3–18.8)	0.40
DEP and allergen	106.6 (8.8–534.8)	49.8 (14.2–79.4)	0.15
Difference	102.5 (1.0–510.5)	45.5 (–1.5–60.6)	0.03
Histamine			
Clean air and allergen	2.9 (1.3–5.9)	2.8 (1.9–6.7)	0.96
DEP and allergen	16.9 (2.9–27.6)	9.8 (3.1–19.0)	0.08
Difference	14.0 (–0.2–24.7)	7.4 (1.2–12.3)	0.02

Lancet 2004;
363: 119–25

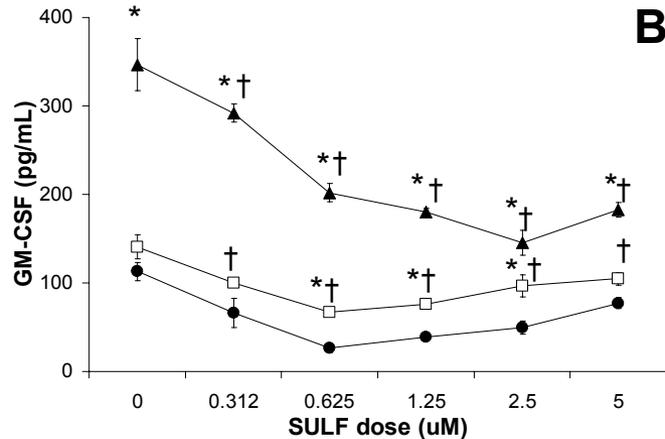
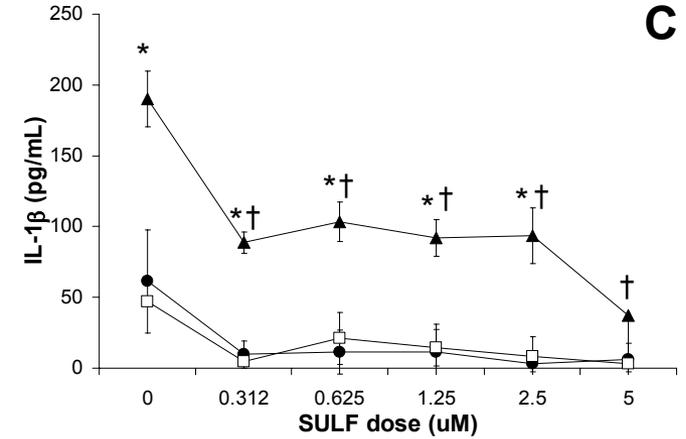
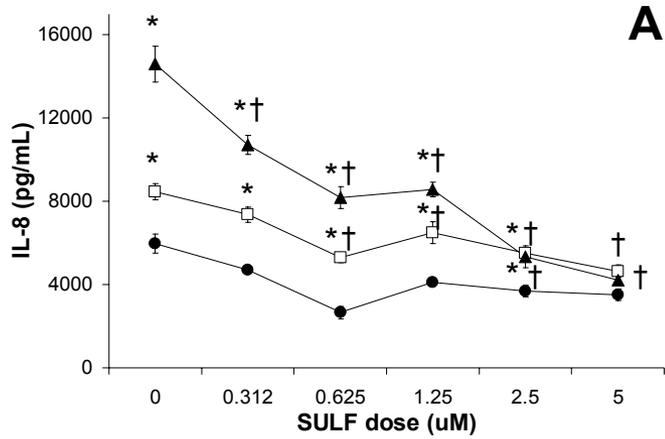
NQO1 over-expression decreases IL-8 production in DX-stimulated BEAS-2B cells



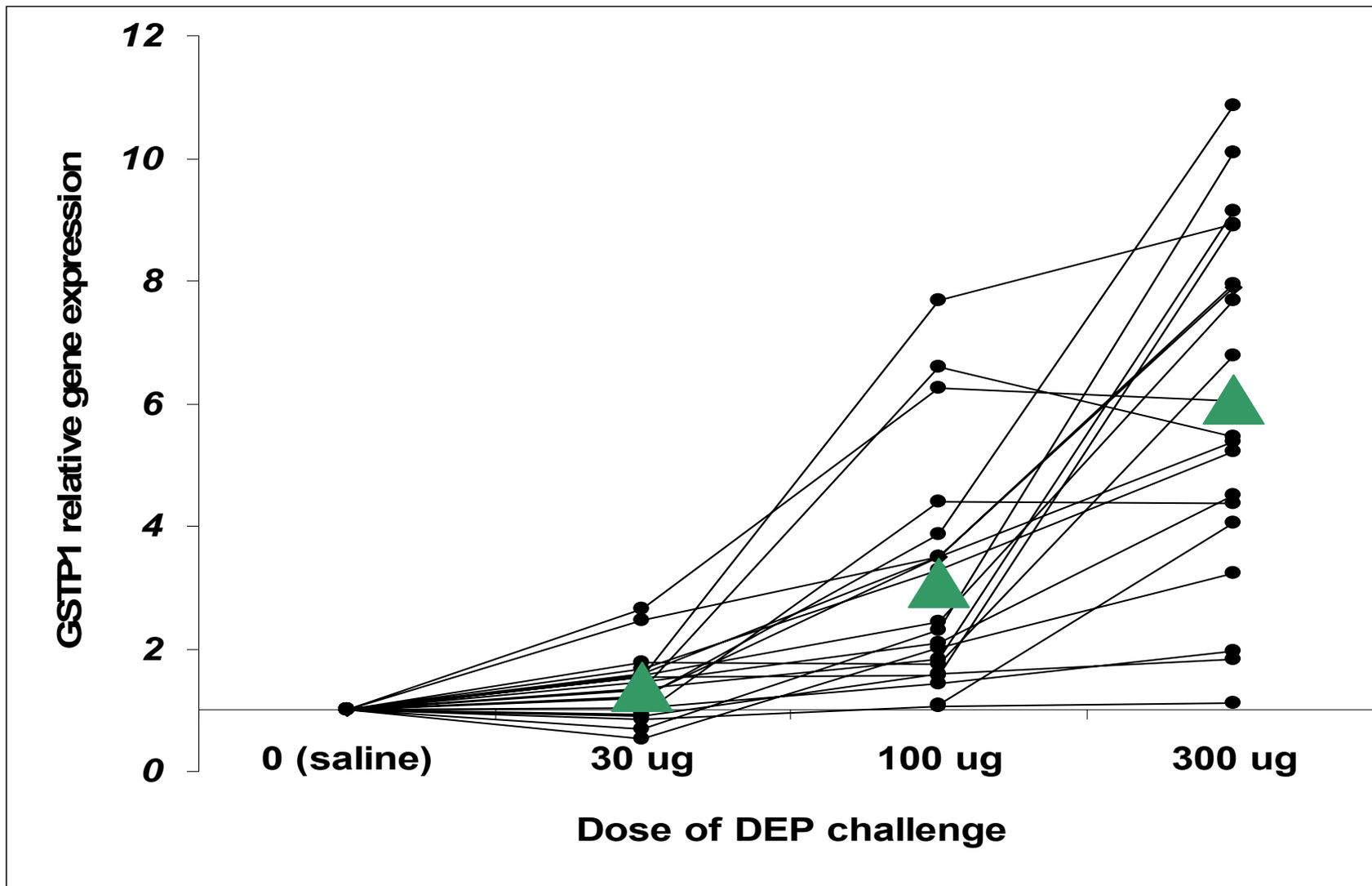
Sulforaphane



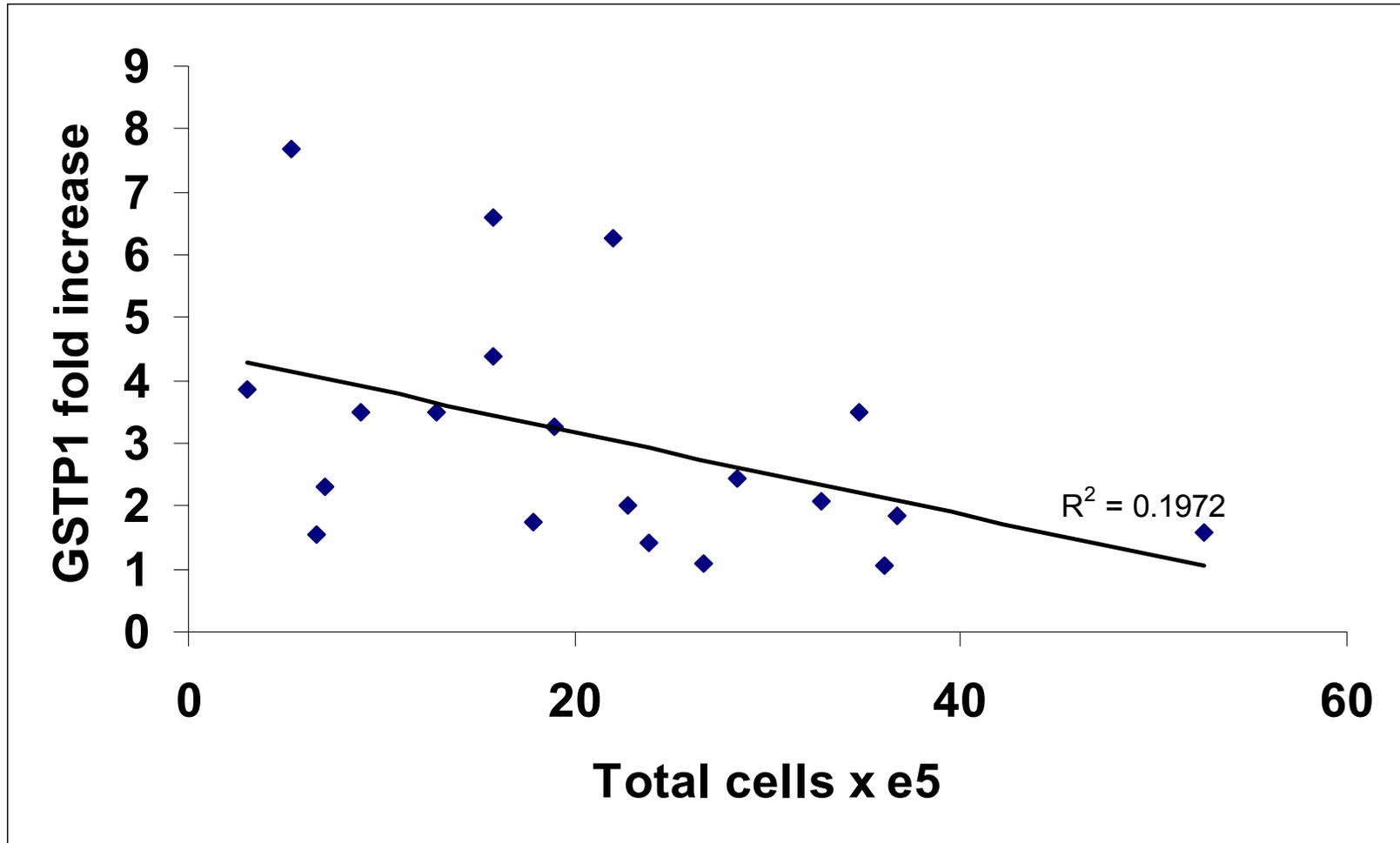
Sulforaphane inhibits DEP increased cytokine expression by NHBECs



GSTP1 Gene Expression and DEP Challenge Dose



GSTP1 Gene Expression and Total Cell Count after DEP challenge



Dietary Sulforaphane - brocco shakes!

Step-up dose-ranging randomised placebo-controlled study

Oral dosing begins at 200 μmol = 25 grams (1/2 cup) BroccoSprouts®/daily for 4 days

Follow-up visits:

400 μmol (50 grams)

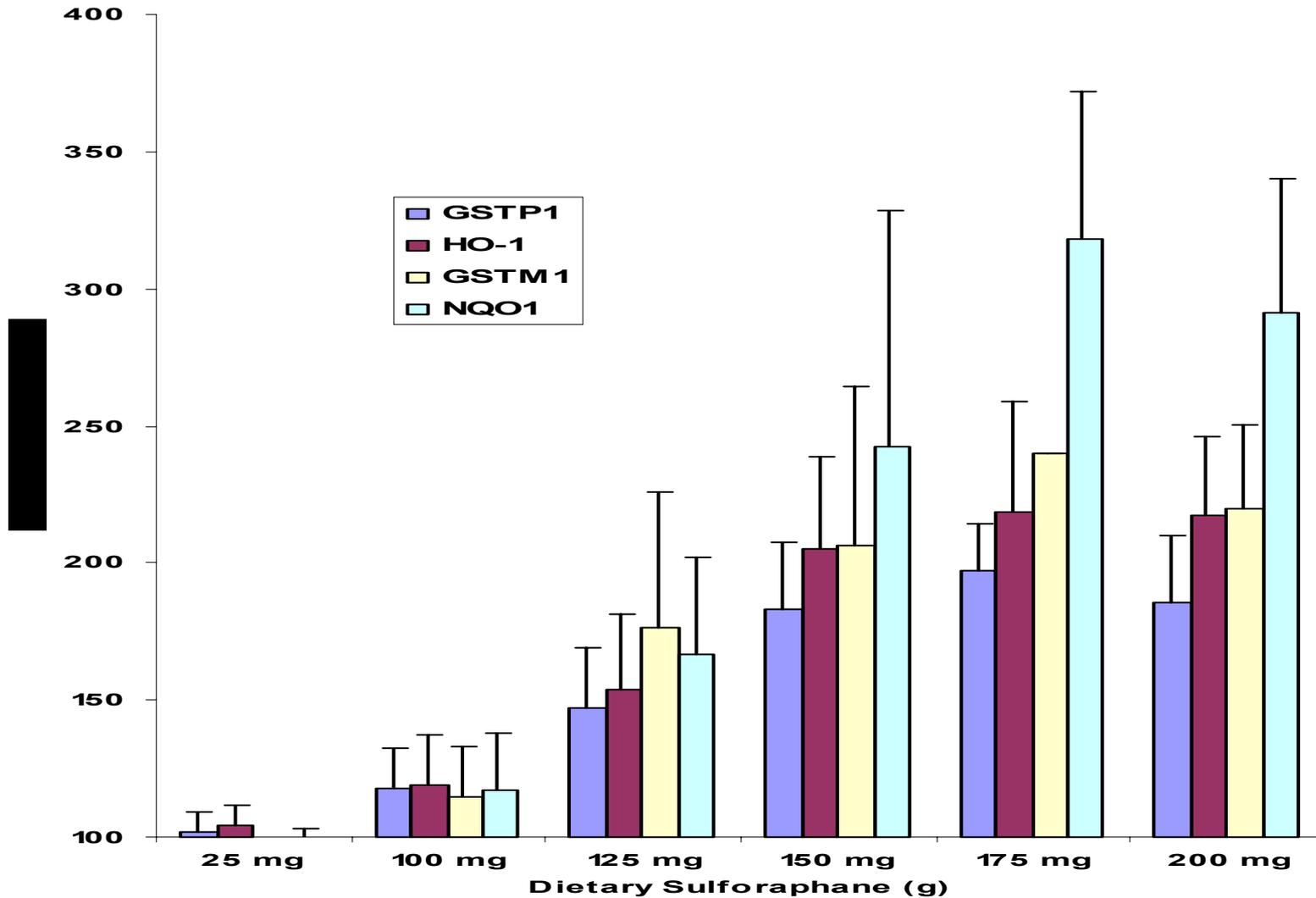
600 μmol (75 grams)

800 μmol (100 grams)

1000 μmol (125 grams) daily



Dietary Sulforaphane increases phase II expression in nasal cells



Individuals Respond the Same to DEP and ETS

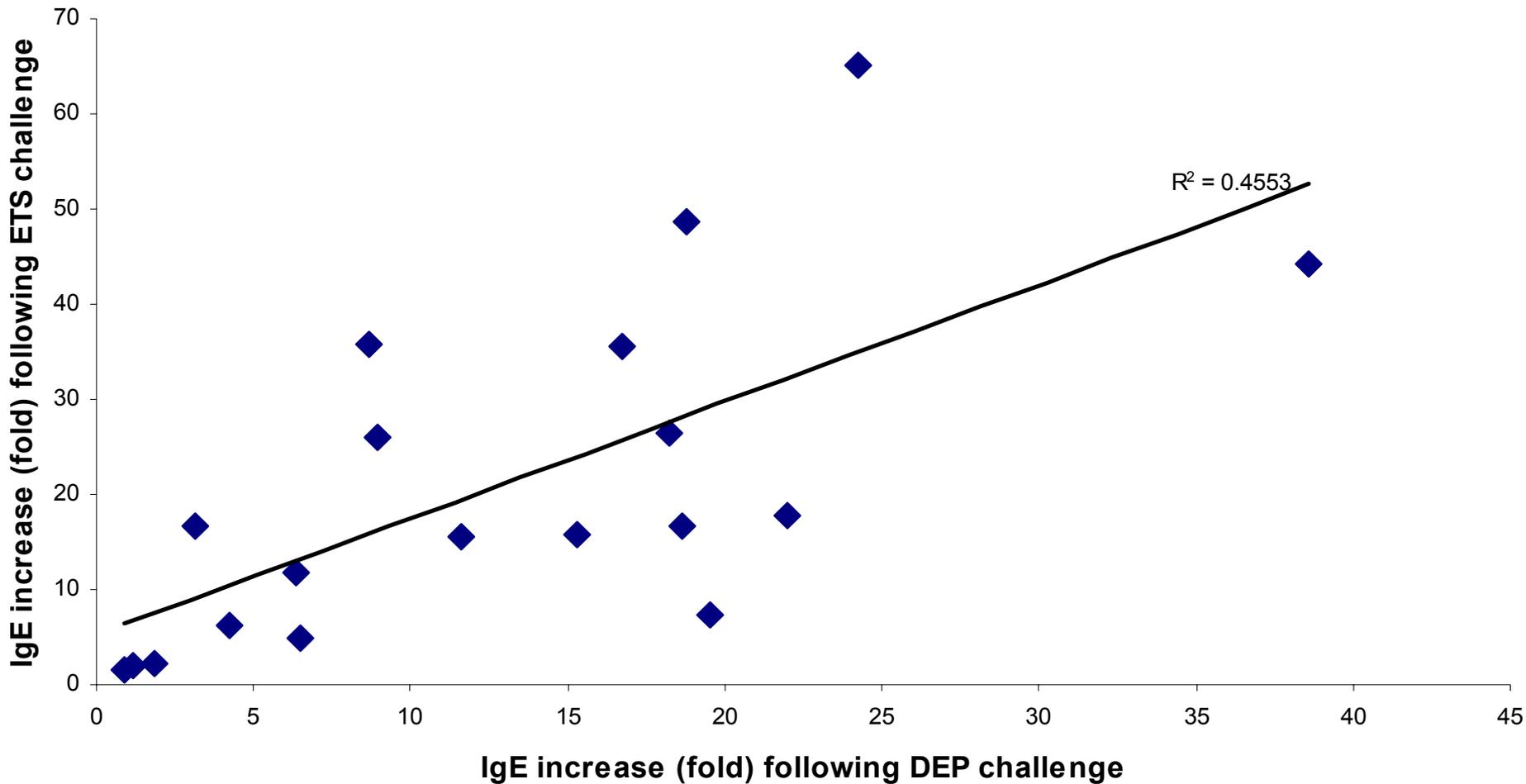
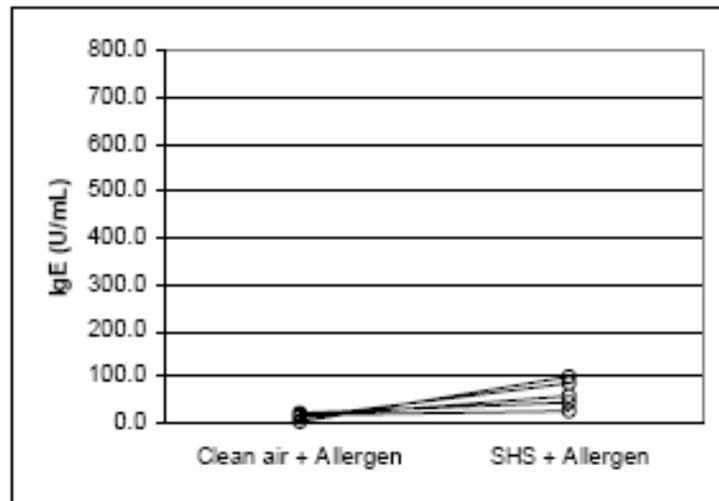
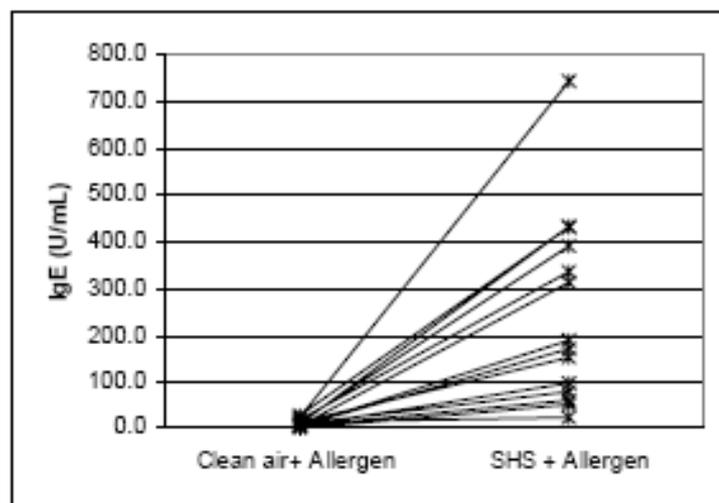


Figure 1.



Legend: * *GSTM1* null o *GSTM1* present

AJRCCM Articles in Press. Published on October 5, 2006 as doi:10.1164/rccm.200509-1424OC

Glutathione-S-Transferase M1 and P1 Prevent Aggravation of Allergic Responses by Secondhand Smoke

Frank D. Gilliland, M.D., Ph.D.¹, Yu-Fen Li, Ph.D.^{1,2}, Henry Gong, Jr., M.D.¹,

David Diaz-Sanchez, Ph.D.³

ASTHMA

Glutathione S transferase deficiency and passive smoking increase childhood asthma

M Kabesch, C Hoefler, D Carr, W Leupold, S K Weiland, E von Mutius

Thorax 2004;**59**:569–573. doi: 10.1136/thx.2003.016667

See end of article for
authors' affiliations

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Received 7 October 2003
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Background: It has been suggested that the genetically determined deficiency of glutathione S transferase (GST) enzymes involved in the detoxification of environmental tobacco smoke (ETS) components may contribute to the development of asthma.

Methods: A large population of German schoolchildren (n = 3054) was genotyped for deficiencies of the GST isoforms M1 and T1. The association between GSTM1 and GSTT1 genotypes and asthma as well as atopy was investigated with respect to current and in utero ETS exposure.

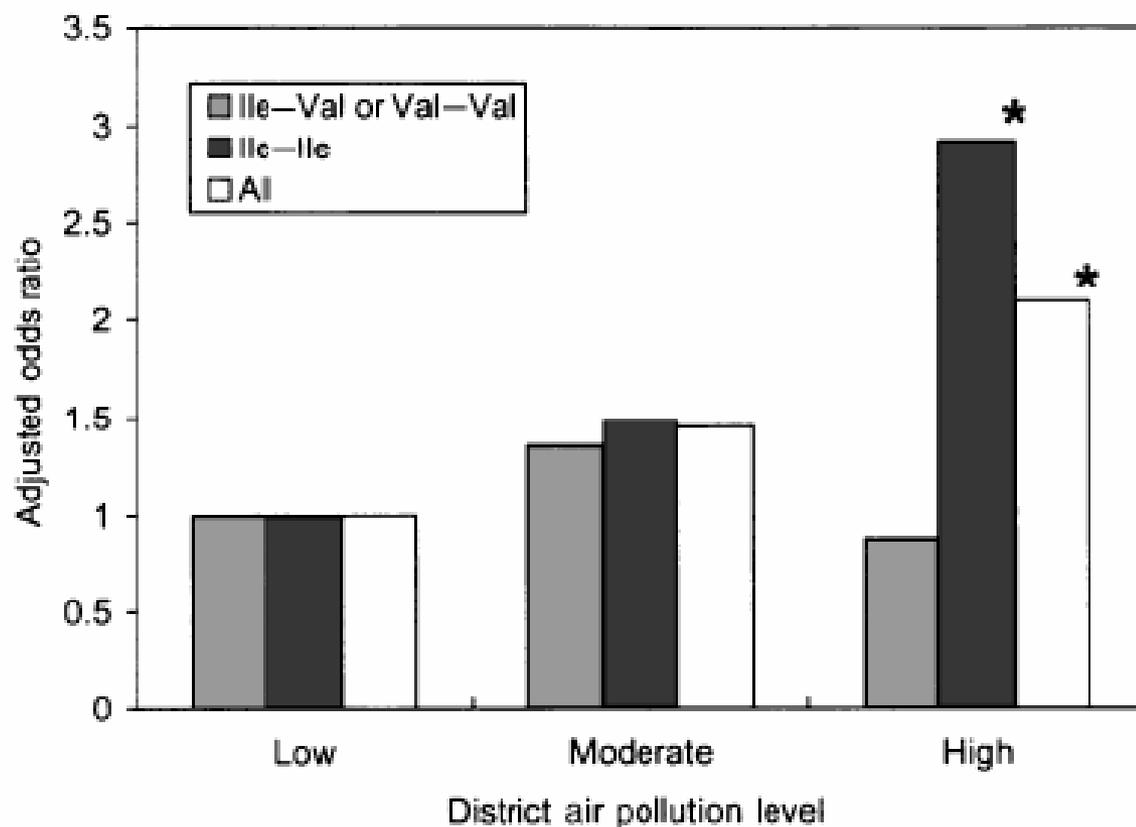
Results: In children lacking the GSTM1 allele who were exposed to current ETS the risk for current asthma (OR 5.5, 95% CI 1.6 to 18.6) and asthma symptoms such as wheeze ever (OR 2.8, 95% CI 1.3 to 6.0), current wheezing (OR 4.7, 95% CI 1.8 to 12.6) and shortness of breath (OR 8.9, 95% CI 2.1 to 38.4) was higher than in GSTM1 positive individuals without ETS exposure. Hints of an interaction between ETS exposure and GSTM1 deficiency were identified. In utero smoke exposure in GSTT1 deficient children was associated with significant decrements in lung function compared with GSTT1 positive children not exposed to ETS.

Conclusions: GSTM1 and GSTT1 deficiency may increase the adverse health effects of in utero and current smoke exposure.

Glutathione S-transferase P1 gene polymorphism and air pollution as interactive risk factors for childhood asthma

Y.-L. Lee*†‡, Y.-C. Lin*§, Y.-C. Lee*, J.-Y. Wang¶, T.-R. Hsiue‡ and Y. L. Guo*‡

Nox
SO₂



Genetic polymorphism of *GSTM1* and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City

I Romieu, J J Sienna-Monge, M Ramírez-Aguilar, H Moreno-Macías, N I Reyes-Ruiz, B Estela del Río-Navarro, M Hernández-Avila, S J London

Thorax 2004;**59**:8–10

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Received 31 March 2003
Accepted 13 August 2003

Background: We recently reported that antioxidant supplementation with vitamins C and E mitigated ozone related decline in forced expiratory flow (FEF₂₅₋₇₅) in 158 asthmatic children in an area with high ozone exposure in Mexico City.

Methods: A study was undertaken to determine whether deletion of glutathione S-transferase M1 (*GSTM1* null genotype), a gene involved in response to oxidative stress, influences ozone related decline in FEF₂₅₋₇₅ and the benefit of antioxidant supplementation.

Results: *GSTM1* null children receiving placebo had significant ozone related decrements in FEF₂₅₋₇₅ (percentage change per 50 ppb of ozone 2.9 (95% CI -5.2 to -0.6), $p=0.01$); *GSTM1* positive children did not. Conversely, the effect of antioxidants was stronger in children with the *GSTM1* null genotype.

Conclusions: Asthmatic children with a genetic deficiency of *GSTM1* may be more susceptible to the deleterious effects of ozone on the small airways and might derive greater benefit from antioxidant supplementation.

Gene x Gene x Environment

<i>GSTM1</i>	<i>GSTP1</i>	n	IgE difference	Histamine difference
Present	I/I	2	26.1 (6.7–45.5)	7.73 (3.13–12.32)
Present	I/V	3	48.9 (–1.5–60.6)	7.44 (1.22–7.48)
Null	I/I	11*	137.0 (29.9–510.5)	14.33 (8.14–24.67)
Null	I/V	3	9.1 (1.0–46.2)	2.98 (–0.22–19.59)

Values are median (range). *p=0.0034 for IgE and p=0.0073 for histamine calculated by the Wilcoxon test comparing *GSTM1* null/*GSTP1* I/I with the other three genotype groups combined.

Table 4: IgE (U/mL) and histamine (nmol/L) differences by joint *GSTM1* and *GSTP1* genotype

Joint effects of genotypes on median nasal allergic endpoints when exposed to allergen plus clean air or allergen plus second hand smoke (SHS) exposure.

Genotypes			Second hand smoke exposure response			
			IgE (U/mL)	IL-4 (U/mL)	IFN- γ (ng/L)	Histamine (nM/L)
<i>GSTM1</i>	<i>GSTP1 Ile105Val</i>	n	Median (min~max)	Median (min~max)	Median (min~max)	Median (min~max)
+	Ile/Ile	2	59.8 (24.6~95.0)	2.7 (0.0~5.4)	-0.5 (-0.9~-0.1)	9.3 (8.4~10.2)
+	Ile/Val	3	46.7 (8.9~74.7)	3.2 (0.0~3.3)	-0.2 (-1.0~-0.2)	3.2 (-0.9~10.1)
-	Ile/Ile	11	184.4 (47.6~725.5) *	2.9 (0.4~13.1)	-0.2 (-0.8~0.1)	10.3 (2.3~20.6) **
-	Ile/Val	3	55.2 (11.3~423.6)	11.3 (-0.4~12.2)	-0.9 (-1.5~-0.1)	6.0 (-0.9~6.3)

Gililand et al., Am J Respir Crit Care Med, 2006

Cell number changes following DEP challenge

Genotypes			Change from saline
<i>GSTM1</i>	<i>GSTP1 Ile105Val</i>	n	Median (min~max)
+	Ile/Ile	8	6.3 (-3.2~18.1)
+	Ile/Val	12	-1.0 (-1.5~-0.7)
-	Ile/Ile	31	19.5 (1.8~50.2)
-	Ile/Val	9	26.3 (-4.2~38.7)
<i>GSTM1</i>	<i>TNFα G-308A</i>	n	Median (min~max)
+	GG	13	-0.9 (-1.3~15.2)
+	GA	5	-2.5 (-2.5~-2.5)
-	GG	36	14.8 (-4.0~40.1)
-	GA	6	26.3 (10.5~37.2)
<i>GSTM1</i>	<i>NQO1Pro187Ser</i>	n	Median (min~max)
+	Pro/Pro	6	5.8 (-2.5~14.1)
+	Pro/Ser or Ser/Ser	10	3.6 (-1.2~-10.6)
-	Pro/Pro	22	39.3 (3.0~49.4)
-	Pro/Ser or Ser/Ser	22	7.2 (2.4~40.1)

***GSTM1* and *GSTP1* and respiratory health in asthmatic children exposed to ozone**

Isabelle Romieu¹, Matiana Ramirez-Aguilar¹, Juan José Sienra-Monge², Hortensia Moreno-Macías¹, Blanca Estela del Rio-Navarro², Gloria David³, Jacqui Marzec³, Mauricio Hernández-Avila¹, Stephanie London³,

ERJ 2006

Table 4. Effect of ozone* (20 ppb) on the risk of reporting difficulty breathing on a given day according to combined *GSTM1* and *GSTP1* genotypes among 151 asthmatic children in Mexico City.

	<i>GSTM1</i> null and <i>GSTP1</i> Val/Val n=22 OR ⁺ 95% CI	<i>GSTM1</i> positive and <i>GSTP1</i> Ile/Ile and Ile/Val n=61 OR 95% CI
Ozone 1-day lag	1.08 (1.00-1.17)	1.00 (0.94-1.05) ⁺
Ozone 2-day average	1.12 (1.02-1.23)	1.00 (0.94-1.05) ⁺
Ozone-6-day average	1.22 (1.07-1.40)	1.04 (0.96-1.12) ⁺

* Odds ratio and 95% CI calculated using GEE for logistic regression separately for each genotype cross-classification adjusting for previous day temperature and chronological time

⁺ p≤0.05. p-value obtained comparings ORs within ozone exposure categories between combined genotype groups (*GSTM1* null and *GSTP1* Val/Val versus *GSTM1* positive and *GSTP1* Ile/Ile, Ile/Val).

**Greetings from
Los Angeles**



Inhale Warm Medical Smoke

It Goes Where Heavy Forms of Internal
Medication Cannot Reach

Blosser's Cigarettes

(No Tobacco)

For the relief of the symptoms of Asthma and Bronchitis, Blosser's Cigarettes are the most effective and safe remedy known. They are specially prepared with a warm medicinal smoke that reaches the lungs directly. Blosser's Cigarettes are the only cigarettes of their kind in the world. They are made by The Blosser Company and are guaranteed to be of the highest quality.

They are made of a special mixture of warm medicinal smoke and a special paper that allows the smoke to pass through the paper and into the lungs. They are the only cigarettes of their kind in the world. They are made by The Blosser Company and are guaranteed to be of the highest quality.

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A warm medicinal smoke is that produced by a special mixture of warm medicinal smoke and a special paper that allows the smoke to pass through the paper and into the lungs. They are the only cigarettes of their kind in the world. They are made by The Blosser Company and are guaranteed to be of the highest quality.

The Chambers of Asthma Physicians
Guaranteeing the Smokers' Health



What Can We Do About It?



Nasal Glucocorticoids are NOT effective at blocking the effects of DEP challenge

Fifteen ragweed- rhinitic, nonsmoking volunteers, age 18 to 50 years old

Treatment with fluticasone propionate at recommended dose- two sprays (50 ug each) per nostril once daily

7 days prior to & including the day of challenge

Challenge with 300 ug DEP

No effect on DEP-induced nasal IgE, IgE-secreting cells and Th2 cytokines

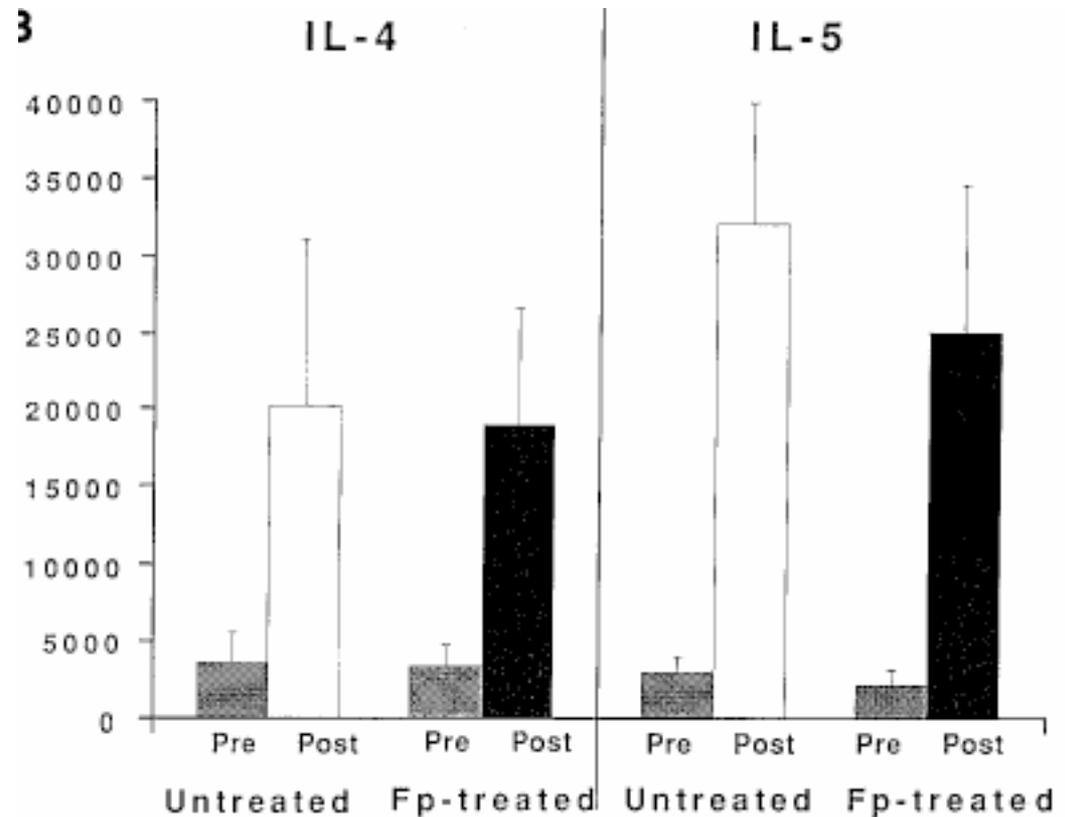


TABLE III. Interventions reported to decrease the effect of pollutants*

Intervention	Ozone	DEP	LPS	PM
Decreased exposure to motor vehicle exhaust	Decreased ED hospital use by asthmatic subjects	Unknown	Unknown	Decreased ED hospital use by asthmatic subjects
Decreased point source emissions	Unclear	Unclear	Unclear	Decreased ED hospital use by asthmatic subjects, decreased death rates
Inhaled corticosteroids	Decreased response to ozone by allergic asthmatic subjects, no protection in healthy volunteers	Ineffective in one study	Decreased response to LPS by allergic asthmatic subjects, mild protection in healthy volunteers	Unknown
Vitamins C and E	Reports of protection from asthma exacerbation	Unknown	Unknown	Unknown
Non-steroidal anti-inflammatory agents	Protection from immediate decrease in lung function caused by ozone in both asthmatic and healthy volunteers, not a clear effect on allergic inflammation	Unknown	Unknown	Unknown

DEP, Diesel exhaust particle.

*Many items listed as unknown are currently under study, and existing current studies are inconclusive.



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Environmental Research 100 (2006) 431–440

**Environmental
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www.elsevier.com/locate/envres

The avoidable health effects of air pollution in three Latin American cities: Santiago, São Paulo, and Mexico City

Michelle L. Bell^{a,*}, Devra L. Davis^b, Nelson Gouveia^c, Víctor H. Borja-Aburto^d,
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Comparative study of two systems:

Actual vs. Control

Control:

Existing technologies

Transport, Residencial and Industrial

Reduction of 10% in PM10 y O3 in 20 years

Benefit of a control strategy in Mexico City 2000 to 2020

Health endpoint	Mexico City
<i>Mortality</i>	
Adult	33,084
Infant (<1 year)	2648
<i>Medical visits</i>	
Children's medical visits (3 to 15 years)	113,623
Hospital admissions (cardiovascular)	2919
Hospital admissions (respiratory)	46,275
Children's hospital admissions (<13 years for PM ₁₀ , <5 years for O ₃)	4836
Emergency room visits (respiratory)	537,826
<i>Bronchitis and asthma</i>	
Asthma attacks	2,988,077
Acute bronchitis	78,528
Chronic bronchitis	28,371
<i>Activity effects</i>	
Restricted activity days (18 to 65 years)	12,722,033
Work loss days	4,412,424



Table 2 Summary of pooled percentage difference (95% confidence intervals) for effect of parental smoking on lung function

	<i>No. of studies</i>	<i>% difference (95% CI) fixed effect</i>	<i>% difference (95% CI) random effect</i>
FVC	19	-0.2 (-0.4 to +0.1)	-0.4 (-0.8 to +0.0)
FEV ₁	21	-0.9 (-1.2 to -0.7)	-1.4 (-1.9 to -1.0)
MEF	19	-4.8 (-5.4 to -4.3)	-5.0 (-6.6 to -3.3)
EEF	9	-4.3 (-5.3 to -3.3)	-4.3 (-5.5 to -3.1)

FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; MEF = mid expiratory flow rate; EEF = end expiratory flow rate.



Cook and Strachan *Thorax* 1999;**54**:357–366

“ETS exposure clearly confers an increased risk of acute lower respiratory disease in young children”

California EPA review

Effects of Glutathione S-Transferase M1, Maternal Smoking during Pregnancy, and Environmental Tobacco Smoke on Asthma and Wheezing in Children

Am J Respir Crit Care Med Vol 166. pp 457–463, 2002

Frank D. Gilliland, Yu-Fen Li, Louis Dubeau, Kiros Berhane, Edward Avol, Rob McConnell, W. James Gauderman, and John M. Peters

TABLE 4. ADJUSTED* ODDS RATIOS AND 95% CI FOR THE JOINT EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND GSTM1 GENOTYPE ON ASTHMA AND WHEEZE, ODDS RATIO AND 95% CONFIDENCE INTERVAL

Outcomes	No <i>in utero</i> GSTM1 (+)	No <i>in utero</i> GSTM1 (–)		<i>In utero</i> GSTM1 (+)		<i>In utero</i> GSTM1 (–)	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Asthma							
Ever asthma	Reference group	1.0	(0.8, 1.2)	0.9	(0.6, 1.4)	1.4	(0.9, 2.1)
Active asthma [†]	Reference group	0.8	(0.6, 1.1)	0.8	(0.5, 1.3)	1.7	(1.1, 2.8)
Medication for asthma [†]	Reference group	0.9	(0.7, 1.2)	0.7	(0.4, 1.2)	1.8	(1.1, 2.8)
Early onset asthma [†]	Reference group	0.9	(0.7, 1.2)	0.9	(0.7, 1.4)	1.6	(1.0, 2.5)
Persistent asthma [†]	Reference group	1.0	(0.8, 1.2)	0.9	(0.6, 1.4)	1.6	(1.1, 2.4)
Wheezing							
Ever wheezing	Reference group	1.0	(0.8, 1.2)	1.3	(1.0, 1.8)	1.8	(1.3, 2.5)
Wheeze with cold [†]	Reference group	1.0	(0.8, 1.2)	1.1	(0.8, 1.7)	1.8	(1.2, 2.7)
Wheeze without cold [†]	Reference group	1.0	(0.8, 1.3)	1.1	(0.7, 1.8)	2.3	(1.4, 3.5)
Persistent wheeze	Reference group	0.8	(0.6, 1.2)	1.6	(0.9, 2.8)	2.2	(1.3, 4.0)
Attacks of wheezing							
Shortness of breath	Reference group	1.0	(0.7, 1.3)	1.4	(0.9, 2.3)	2.3	(1.4, 3.8)
Awakened at night	Reference group	0.9	(0.7, 1.3)	1.1	(0.6, 1.9)	1.8	(1.0, 3.1)
Wheeze with exercise [†]	Reference group	0.9	(0.7, 1.2)	1.0	(0.6, 1.6)	2.1	(1.3, 3.3)
Treatments for wheezing							
Medication for wheeze [†]	Reference group	1.0	(0.7, 1.2)	1.0	(0.6, 1.5)	2.2	(1.4, 3.4)
Emergency room for wheeze [†]	Reference group	0.9	(0.5, 1.5)	1.0	(0.4, 2.4)	3.7	(1.9, 7.3)

How many smokers keep smoking when pregnant?

75%

Ebrahim, et al Trends in pregnancy-related smoking rates in the United States, 1987–1996.
JAMA 2000;283,361-366

Ebrahim, et al

Large population-based survey from 33 states

8803 pregnant women

Prevalence of smoking among pregnant women = 16.3% in 1987
11.8% in 1996

Quitting rate = 26.3% in 1987
25.2% in 1996

Early Asthma Risk Factor Study [EARS]

691 pregnant women 1975 and 1986

Prevalence of smoking among pregnant women

First trimester 19%

second trimester 13%

third trimester 12%

cessation rate 15%

Early Asthma Risk Factor Study

Table 3—Multivariable Analysis of the Joint Associations of In Utero Exposure to Maternal Smoking and Family History of Asthma With Childhood Asthma, OR, and 95% CI*

<i>In Utero</i> Exposure	Family History	No.†	OR	95% CI
Unexposed	No	88/90	1.0	
	Yes	165/26	2.6	1.4–3.8
Exposed	No	56/116	1.3	0.7–2.3
	Yes	97/43	3.6	2.2–6.3

*Models are adjusted for race/ethnicity, gestational age, and SHS exposure.

†Number of countermatched control subjects/case patients.

Children's Health Study
Southern California.

338 children with asthma
diagnosed in first 5 years
of life,

570 control subjects were
countermatched on *in utero*
exposure to
maternal smoking within
grade, sex, and
community of residence.

“Grandma's Behavior While Pregnant Affects Her Grandkids' Health”



Table 4—Multivariable Analysis of the Joint Associations of Maternal and Child's In Utero Exposure to Maternal Smoking With Child's Asthma Risk, OR, and 95% CI*

In Utero Exposure to Maternal Smoking		No.†	OR	95% CI
Mother	Child			
Unexposed	Unexposed	118/151	1.0	
	Exposed	27/58	1.3	0.8–2.1
Exposed	Unexposed	165/34	1.8	1.0–3.3
	Exposed	102/36	2.6	1.6–4.5

*Models are adjusted for race/ethnicity, gestational age, and SHS exposure.

†Number of countermatched control subjects/case patients.

Testing the Grandmother effect

Pregnant mice receive either 1 h ETS or saline daily for duration of pregnancy

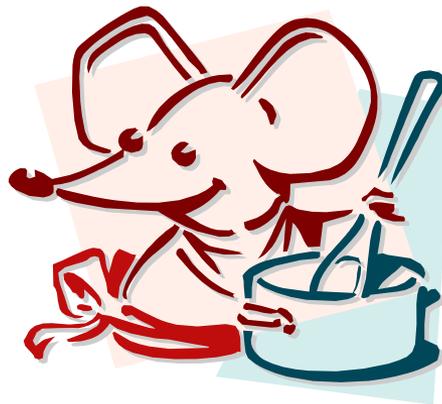
Fathers receive either 1 h ETS or saline for 10 consecutive days before mating

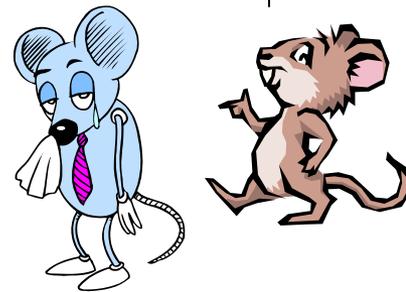
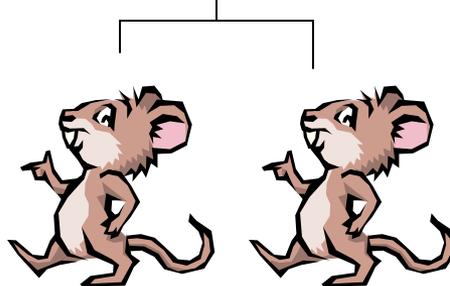
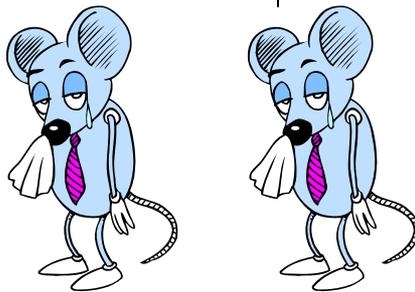
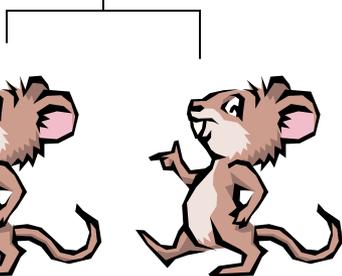
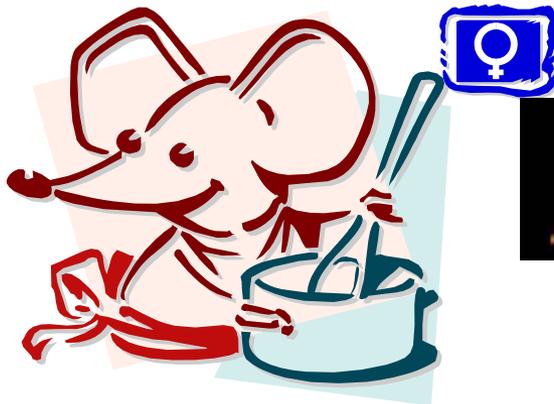
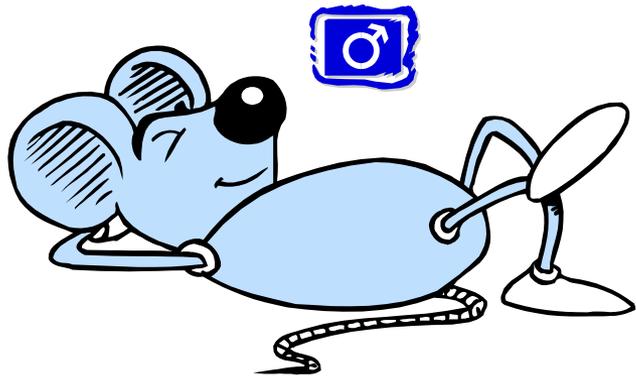
Offspring bred

F2 at 6 weeks receive:

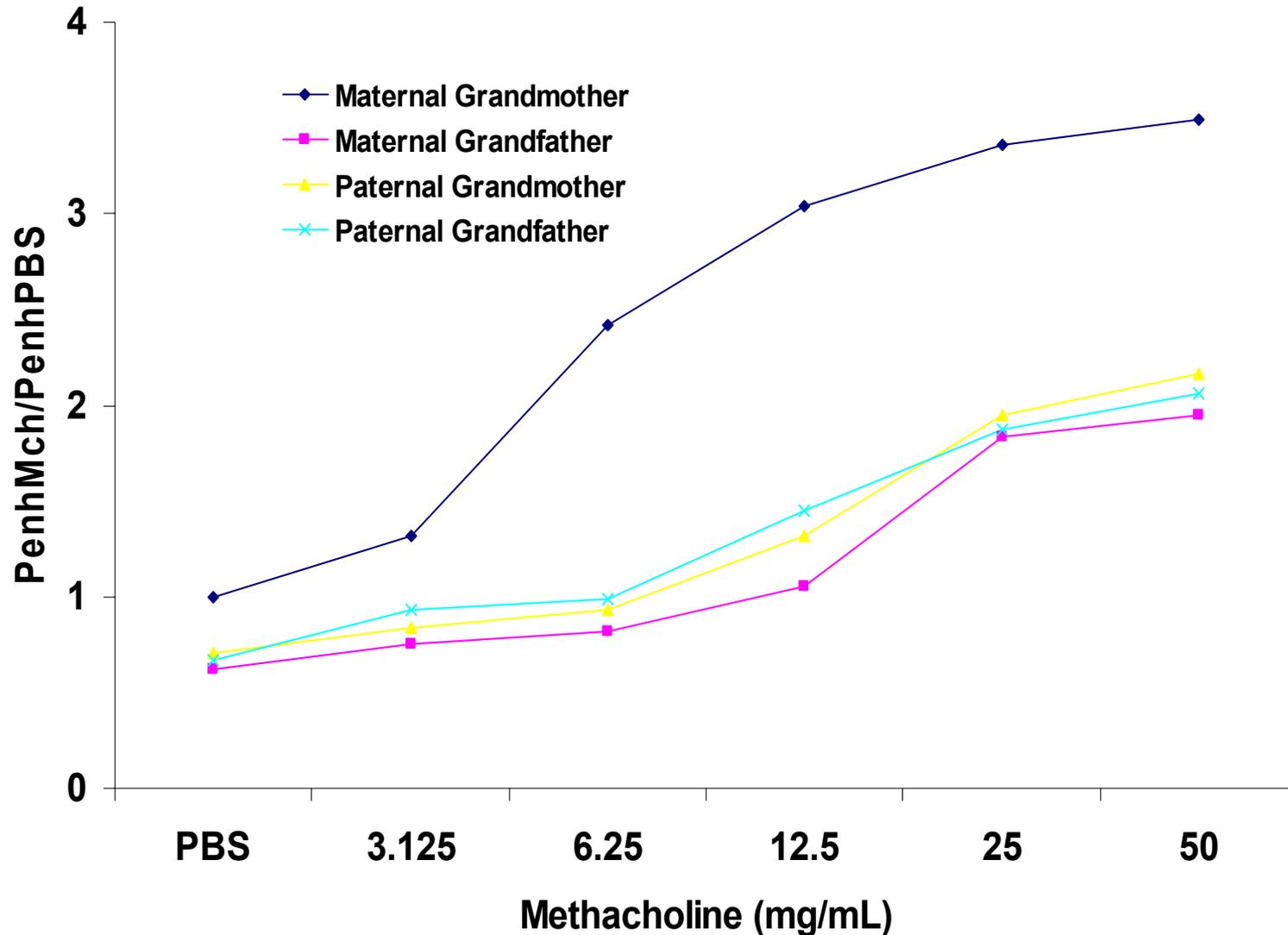
1% OVA for 20 min for 10 days

OVA i.t and methacholine challenge 48h later





Exposure of maternal Grandmother to ETS increases airway responsiveness



Are Children at Increased Risk?



Children vs. Adults

Children spend more time outdoors

They are more active outside

Their total inhaled volume/mass is greater

They breathe through their mouth more

More difficult to avoid smoke

Health effects can last a life time

Their immune system is different

Allergic Endpoints Are Greater After ETS/OA Exposure in Younger Mice



	Day	Young mice (2-3 weeks)	Mature mice (8-12 weeks)
Serum OA-IgE (U/mL)	12	1032	528
Serum OA-IgG1 (ng/mL)	12	216	48
IL-5 (pg/mL)	31	104	69
IL-2 (pg/mL)	31	142	73
IFN- γ (pg/mL)	31	N.D.	5
GM-CSF (pg/mL)	31	439	198
Total cells in BAL (% increase over OA alone)	31	492%	226%

Effects of DEP challenge on Adults vs. Children

DESIGN

A single-blind randomized exposure design

4 different DEP doses – 0 (control), 30, 100, 300 μg

nasal lavage immediately before and 24 hours after DEP challenge

four week wash-out period between each DEP exposure

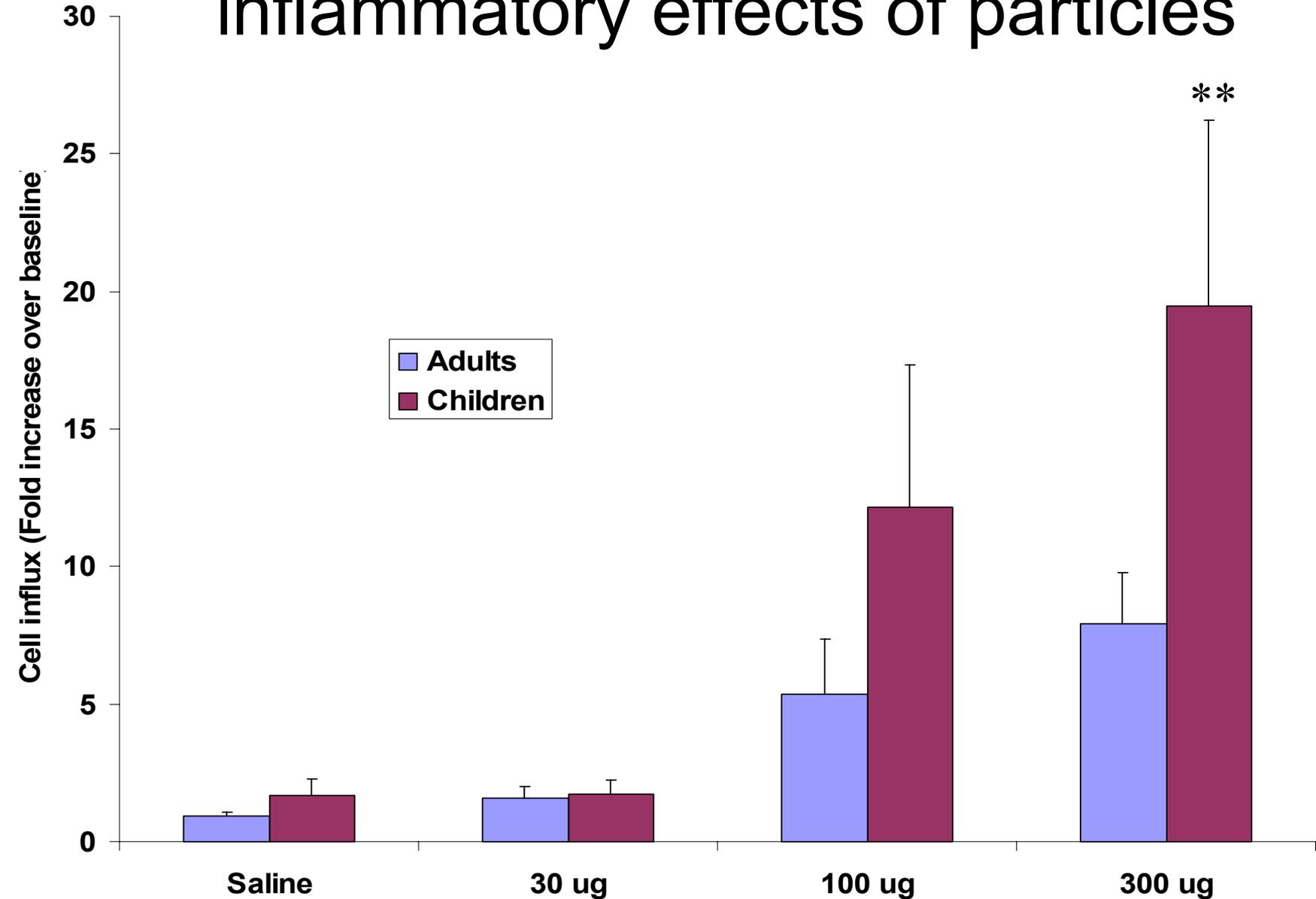
Study Population

Twenty adults (25-55 years of age)

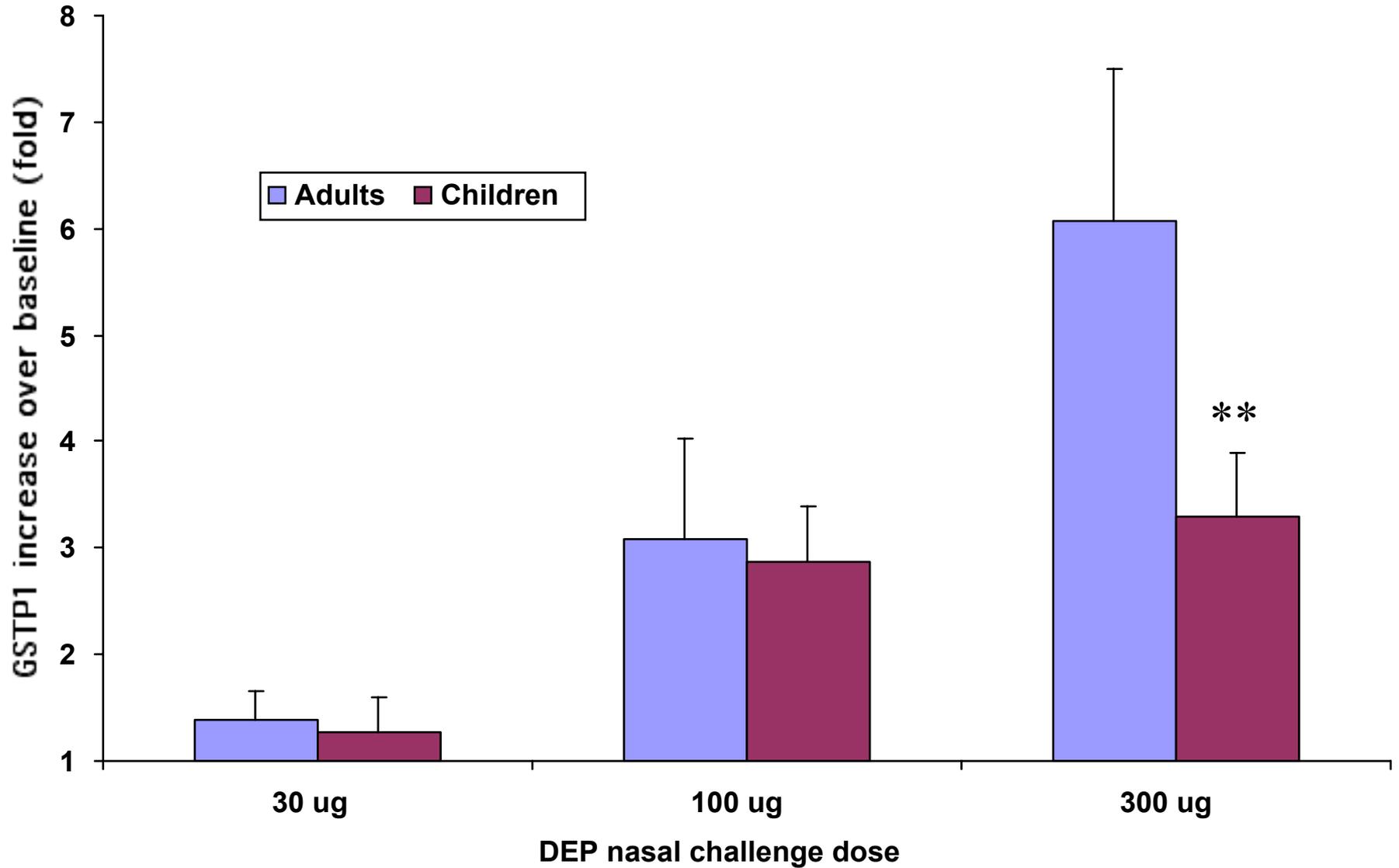
Fifteen children (10-15 years of age)

Matched for sex/ethnicity

Children are more susceptible to the pro-inflammatory effects of particles



Children have reduced antioxidant defense to pollutants





! Kids are not mini-adults !

UCLA

Andrew Saxon

André Nel

Oliver Hankinson

Marc Riedl

Stacey Ritz

Rancho Los Amigos

Henry Gong

USC

Frank Gilliland

Tracy Bastain

Rob McConnell

University of Osaka

Hiroshi Takenaka

Fukui University

Shigeharu Fujeida

Johns Hopkins

Paul Talalay

Jed Fahey

NIH

Dean Metcalfe

U. Cincinnati

Fred Finkelman

Aomori University

Masaru Sagai

