

# Air Pollution and Health

## *The Latest Science*

Dan Greenbaum, President  
Health Effects Institute

Centre for Science and Environment  
Conference on Health and Environment  
Habitat Centre  
New Delhi  
March 24, 2006

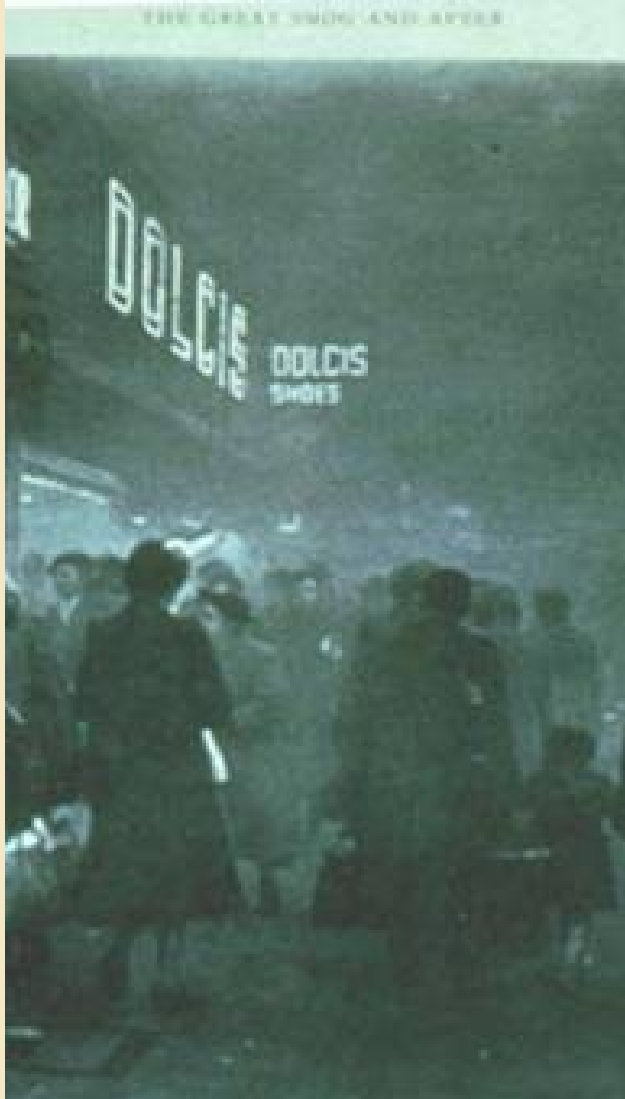


# *The Latest Science on Air Pollution and Health*

- Fifty years of Science
  - London 1952 and onwards
- Particulate Matter Air Pollution (PM)
  - Recent Results
- The Other Major Pollutants
  - Sulfur Dioxide (SO<sub>2</sub>),
  - Ozone,
  - Nitrogen Dioxide (NO<sub>2</sub>)



# London, December 1952



## Public Health

### MORTALITY IN THE LONDON FOG INCIDENT, 1952

W. P. D. LOGAN  
M.D. Glasg., Ph.D. Lond.

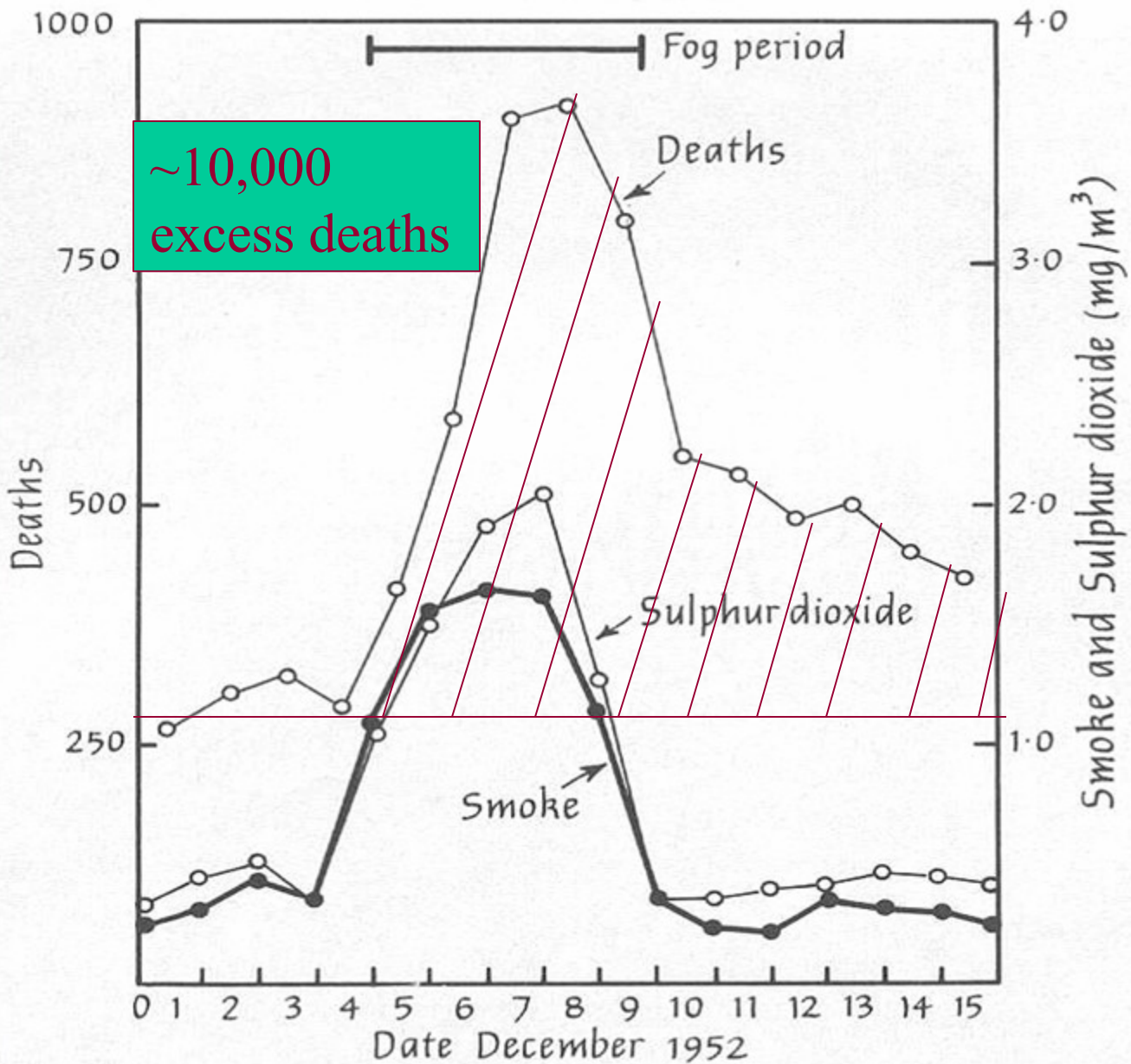
CHIEF MEDICAL STATISTICIAN, GENERAL REGISTER OFFICE

THE Meuse Valley fog episode in 1930 caused 64 deaths, and the Donora (Pennsylvania) episode in 1948 caused 20 deaths. In December, 1952, a four-day fog in London caused about 4000 deaths. This paper gives a short account of when and where these deaths occurred, the age-distribution, and the reported medical causes. No attempt is made here to present detailed meteorological data or to discuss clinical aspects; these and other features of the incident, including additional details about mortality, will no doubt be discussed in a report which, it is understood, will be made to the Minister of Health when investigations have been completed. Two papers have already been published concerning the

TABLE I—DEATHS REGISTERED IN GREATER LONDON FROM  
WEEK ENDED NOV. 15, 1952, TO JAN. 10, 1953, COMPARED

*Source: Lancet 1953*

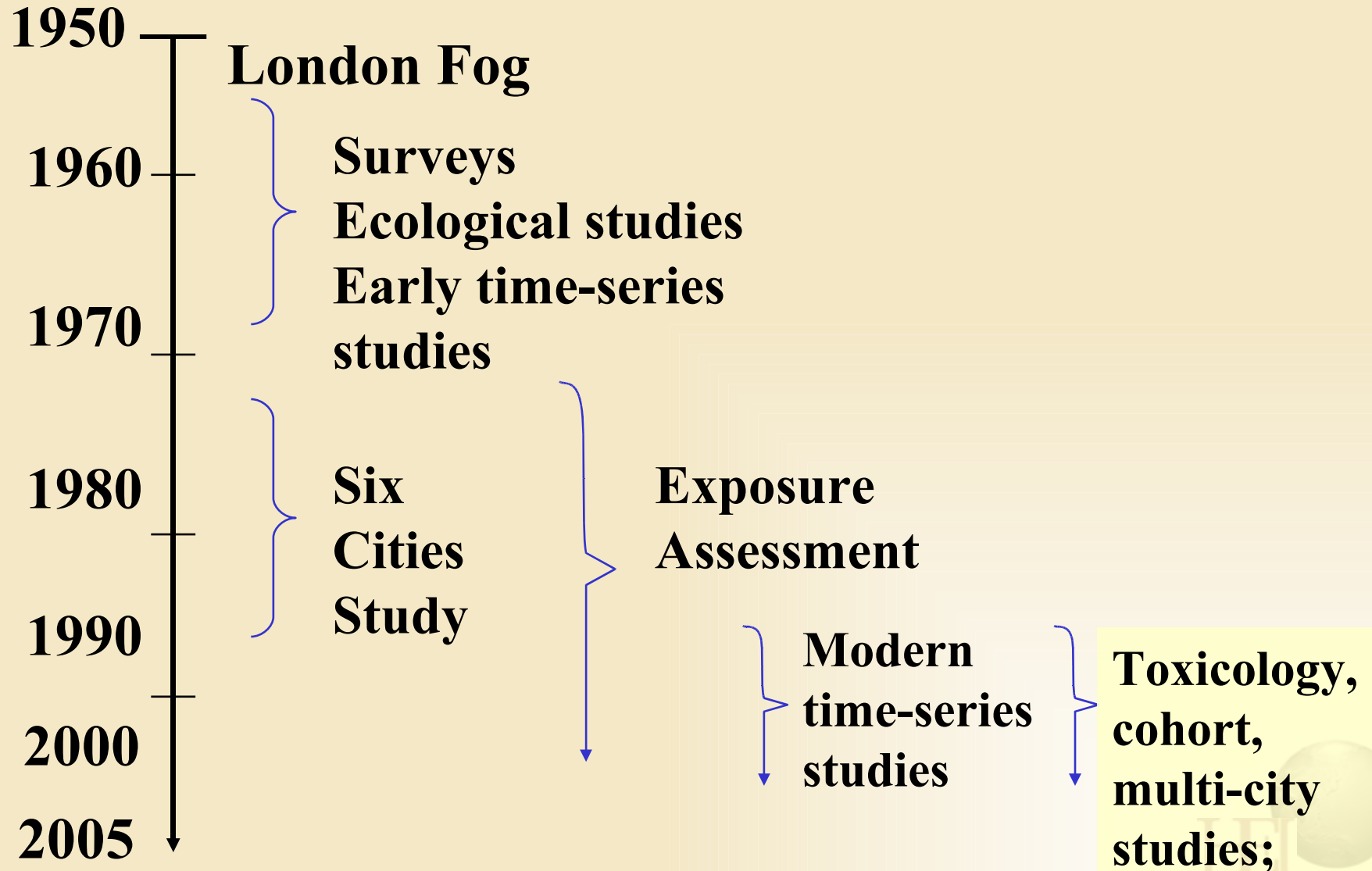




Source: Bell and Davis, 1971



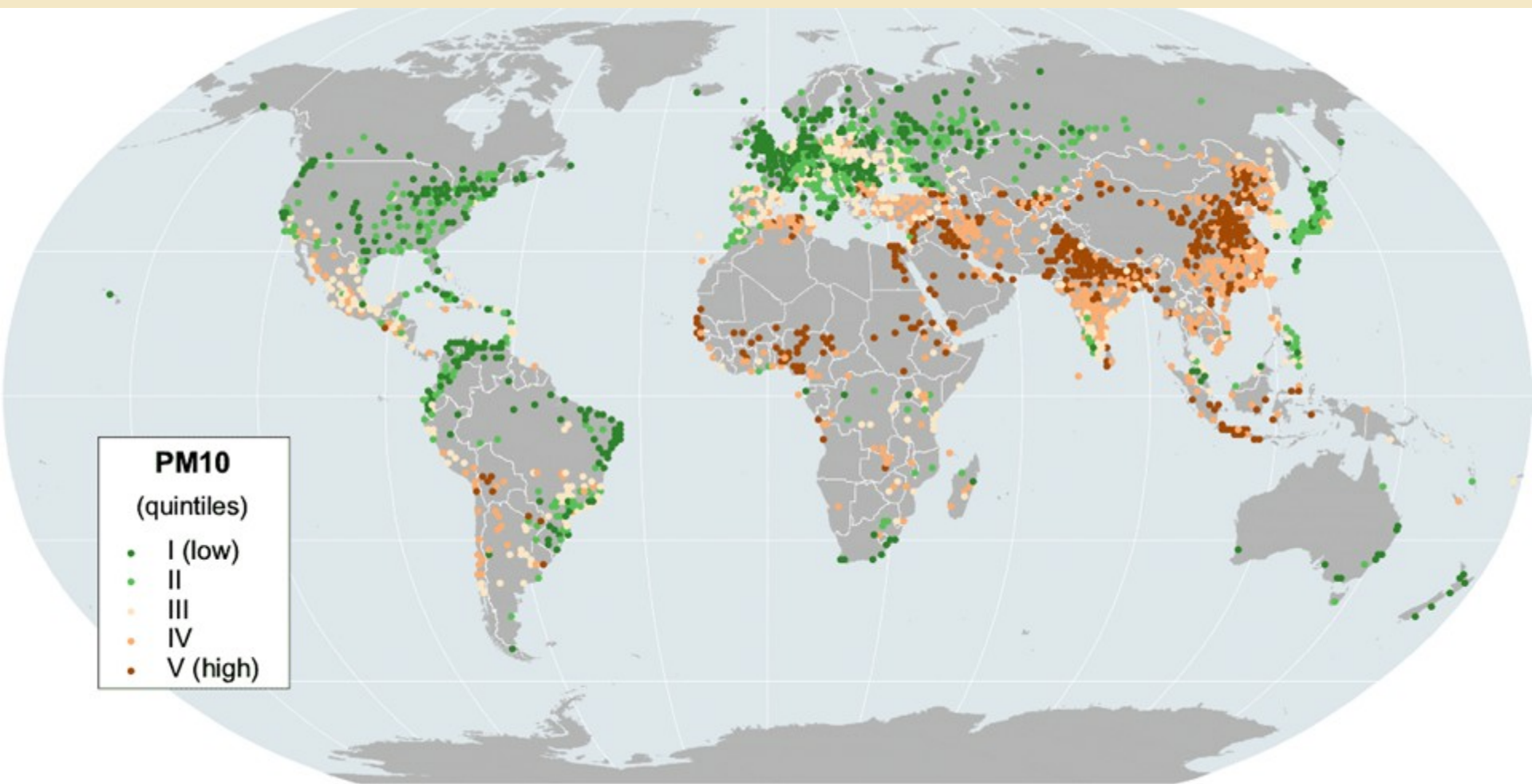
# *50+ Years of Air Pollution Research*



# *Particulate Matter a Worldwide Issue*

*Estimated PM10 Concentration in World Cities (pop=100,000+)*

*(World Bank Econometric Model)*



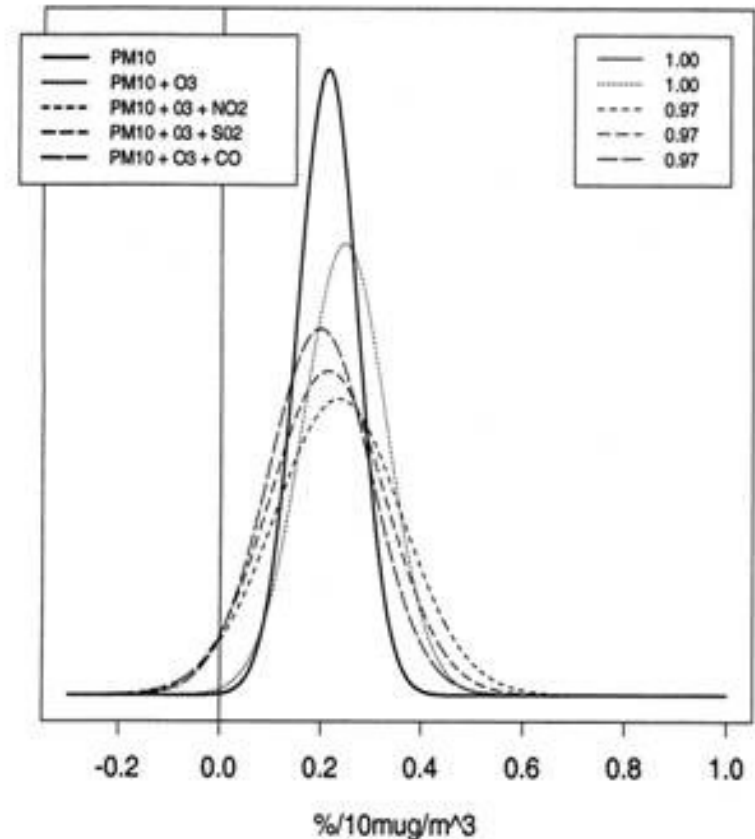


# *Key PM Data: Short-Term Effects*

## *The National Morbidity, Mortality and Air Pollution Study*

*(NMMAPS)*

- Daily changes in PM, mortality, weather: 90 largest US cities
- Relatively consistent increase in Mortality:
  - 0.2% per 10 : /m<sup>3</sup> of PM<sub>10</sub>
- Smaller results than previous U.S. analyses
- Apparently not sensitive to inclusion of other pollutants
- Some continuing questions
  - Especially different results in different regions



# *New, Larger Analyses in 130+ Cities: Air Pollution and Health: European and North American Approach (APHENA) Funded by HEI and the EU*



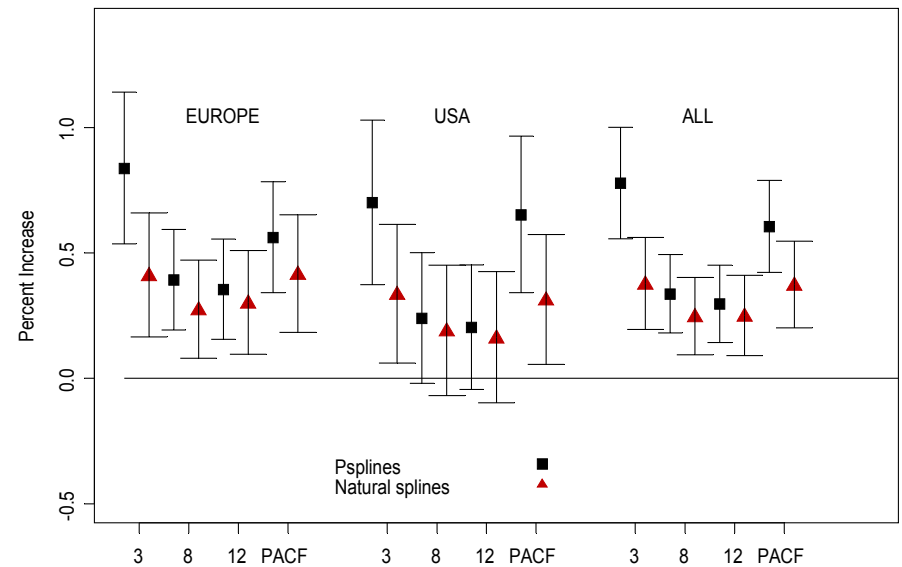
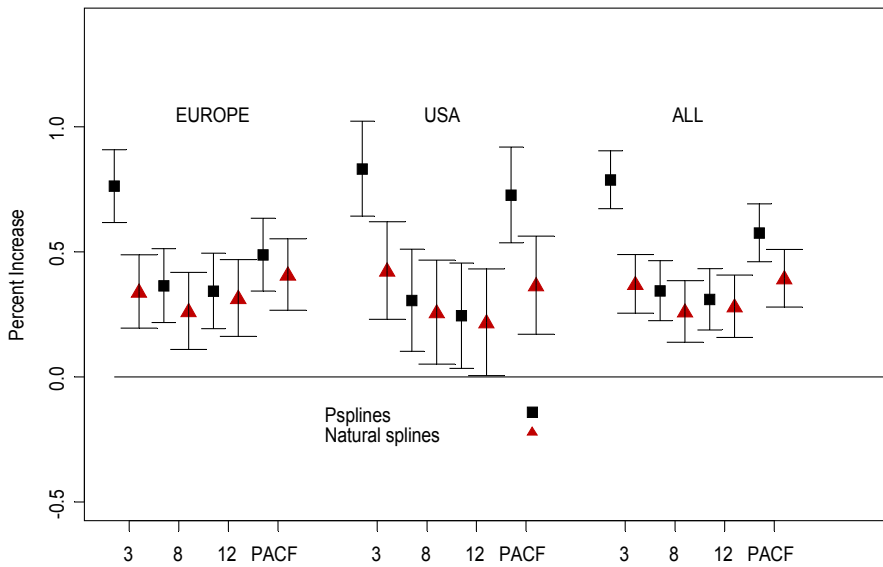


# Preliminary APHENA Results

Bringing NMMAPS and APHEA investigators together for joint, rigorous analyses using latest statistics

Fixed effects

Random effects



df/year  
PACF: No of df based on the minimization of the partial autocorrelation function

**Preliminary PM Results: Percent increase in the daily deaths among those >75 yrs associated with 10  $\mu\text{g}/\text{m}^3$  increase in PM10 (lags 0 and 1)**



# Key PM Data: Long Term Effects

## HEI Reanalysis (Krewski, et al, 2000)

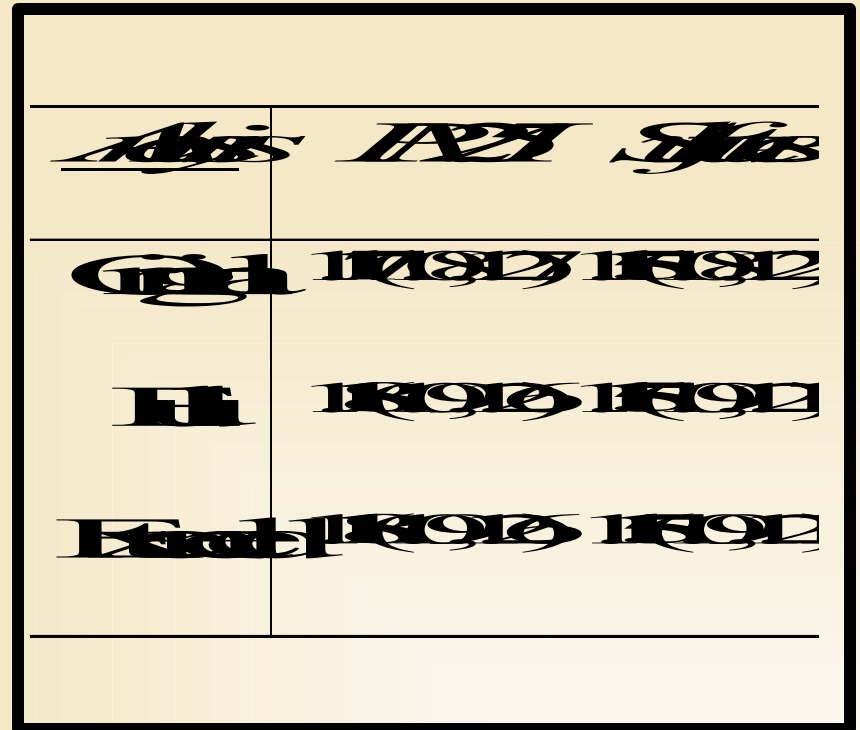
### Two Cohort Studies

- *American Cancer Society*: 550,000 individuals; 150 cities
- *Harvard Six Cities*: 8,000 individuals
- Detailed health, socioeconomic info on each subject
- *HEI reanalysis*: Identified robust associations of mortality with PM2.5, SO2, Sulfate

### Recent similar results in

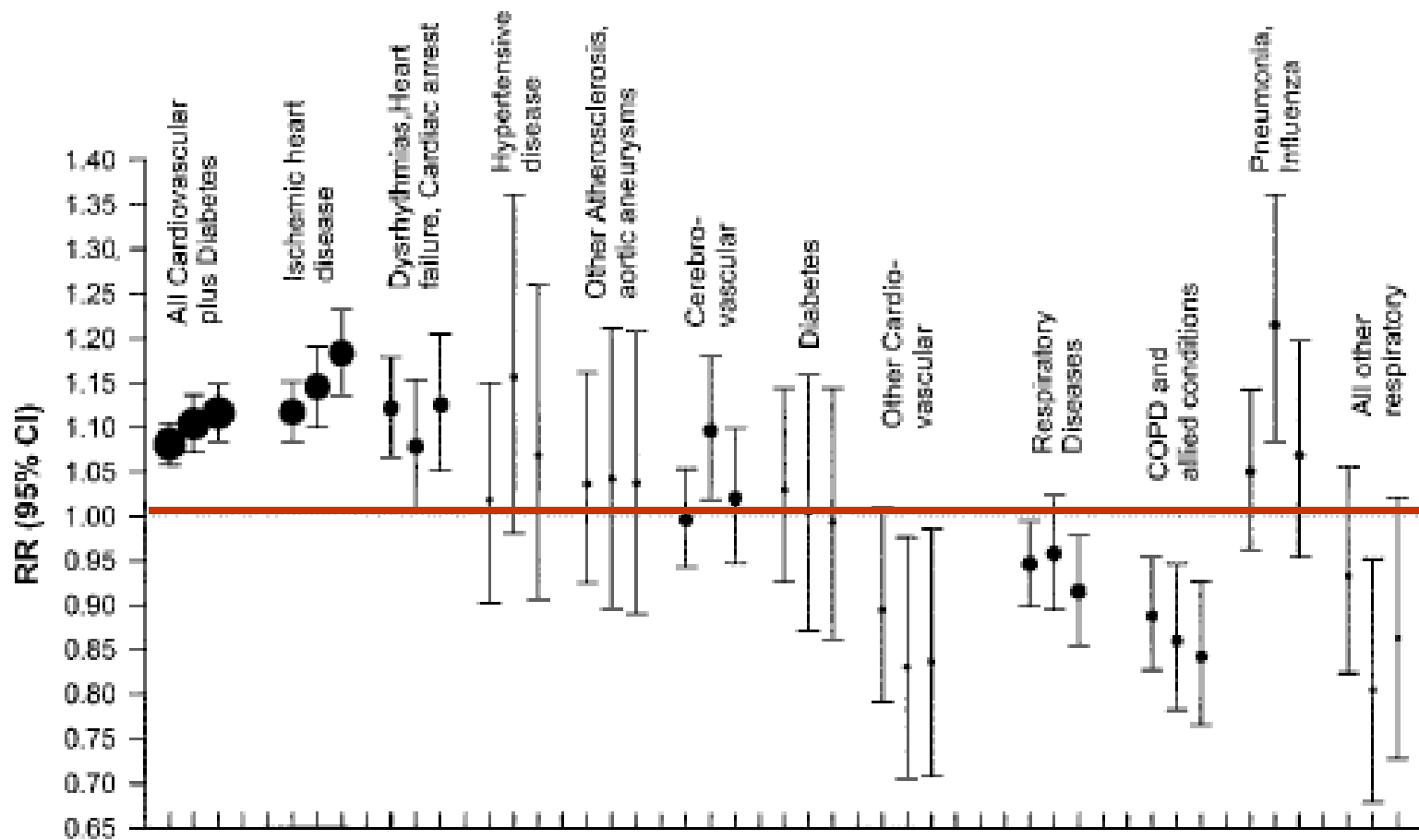
- *Extended ACS Cohort* (Pope, et al 2002, 2004) found cancer, heart effects
- *Extended Harvard Six Cities*

### Results from ACS Study Reanalysis



# Extended Follow-up of ACS Study

Adjusted relative risk of cause-specific mortality per 10 unit increase in PM<sub>2.5</sub> for 1979-1983, 1999-2000 and overall



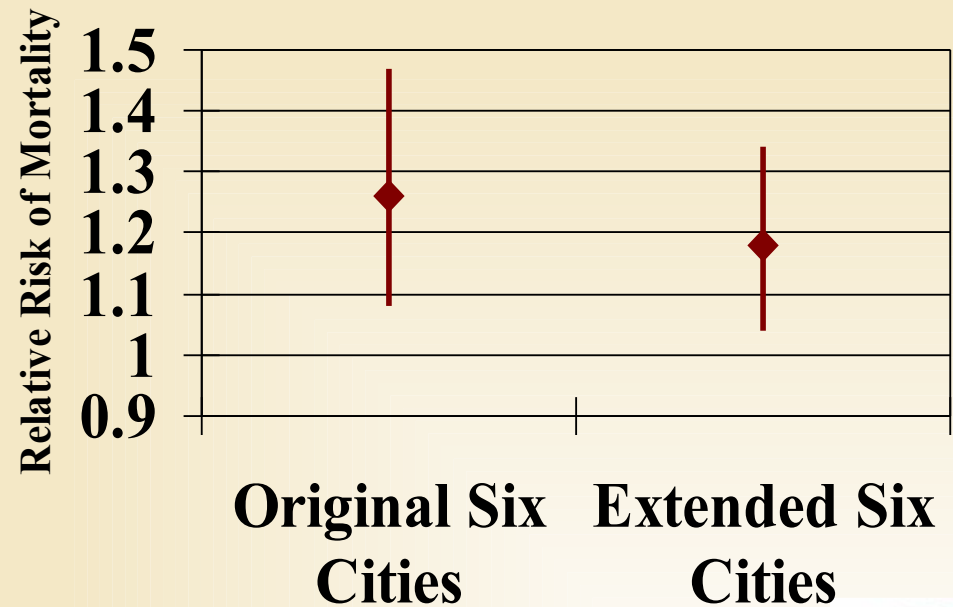
Pope et al Circulation 2004



# *Extended Follow-up of Harvard Six Cities Study (Laden, et al 2006)*

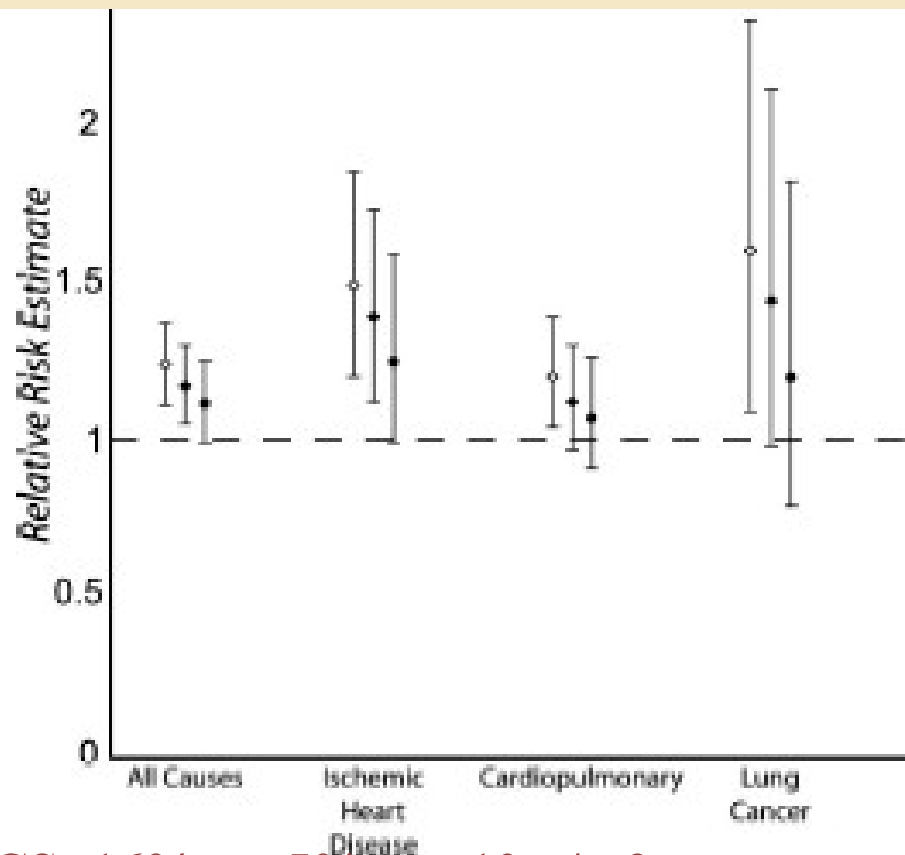
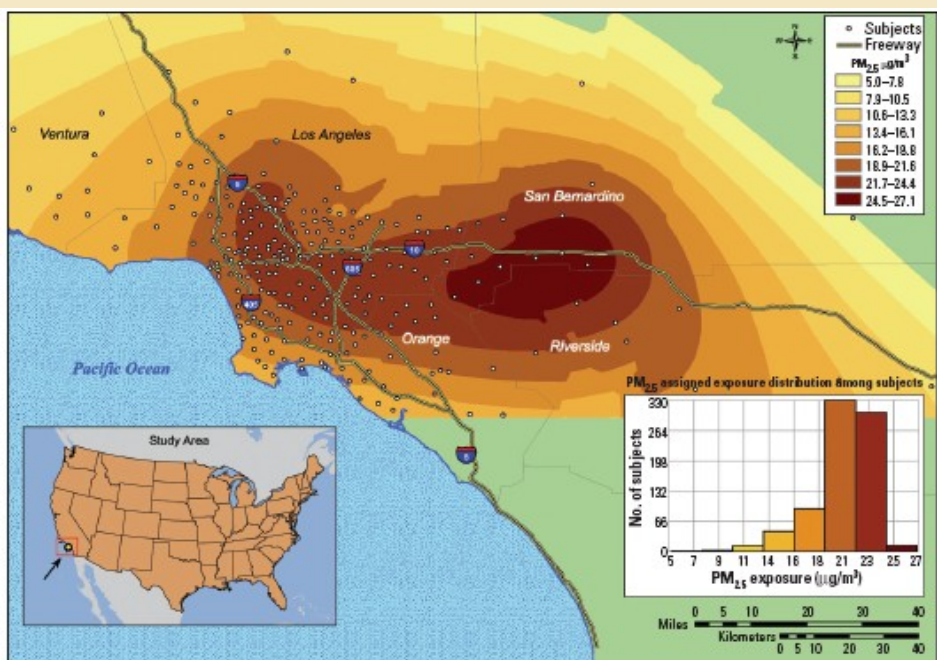
- Additional air pollution and mortality data
  - 1988 – 1998
- Continued to find increased risk of premature mortality despite reduced PM
  - Though lower risk overall
- Measured reduced mortality with improvement in air pollution

## **Analysis of Most-to-Least-Polluted City**



# *New Study In Los Angeles finds Larger Long-Term Effects on Mortality*

*(Jerrett, et al 2005)*



Used 23,000 cases from ACS Cohort in LA.

Found mortality risk 3 times higher than ACS: 16% vs. 5% per 10 µ/m<sup>3</sup>  
(Despite including many other personal characteristics)

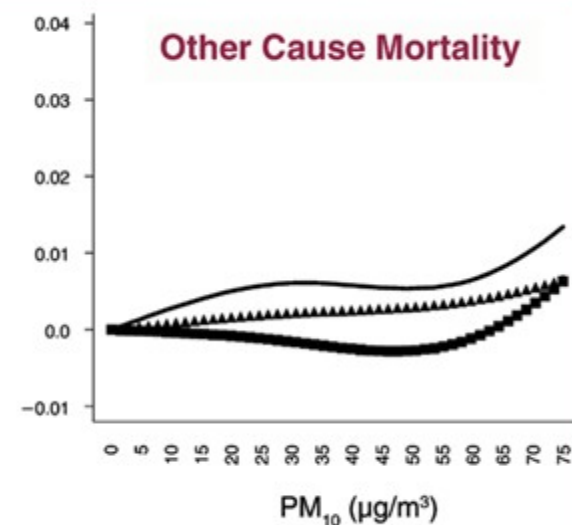
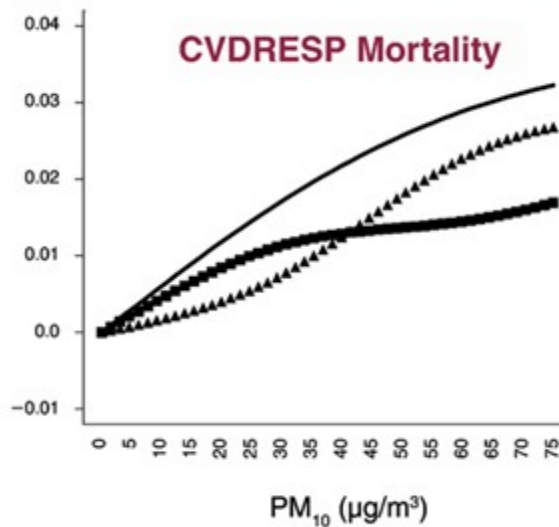
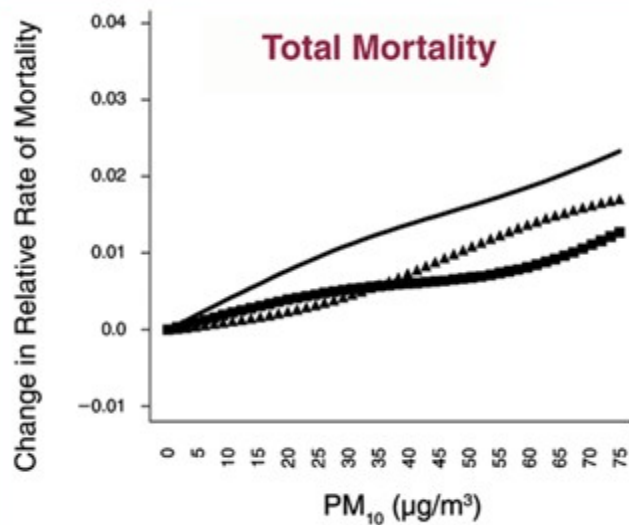
Funded by HEI, entering full review





# Key data for setting standards: “Concentration-Response”

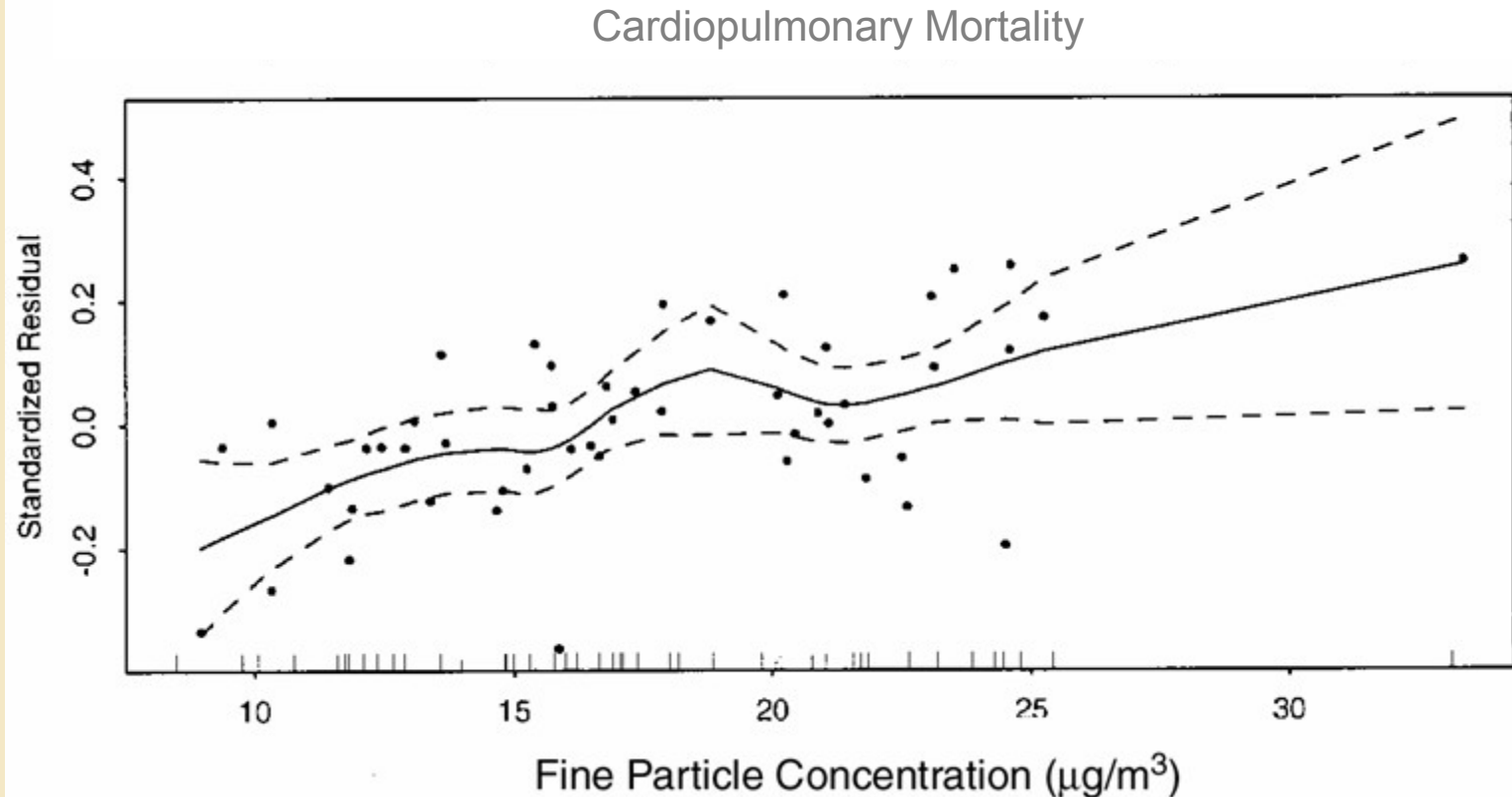
Short Term (Daily) Analysis of Concentration - Response  
for the 20 Largest US Cities: NMMAPS  
(Daniels et al HEI 2004)



# *American Cancer Society*

## *Long-term analysis of “Concentration-Response”*

HEI Reanalysis Results (Krewski, et al 2000)



# *Key Challenge for Science: HOW can PM have these effects?*

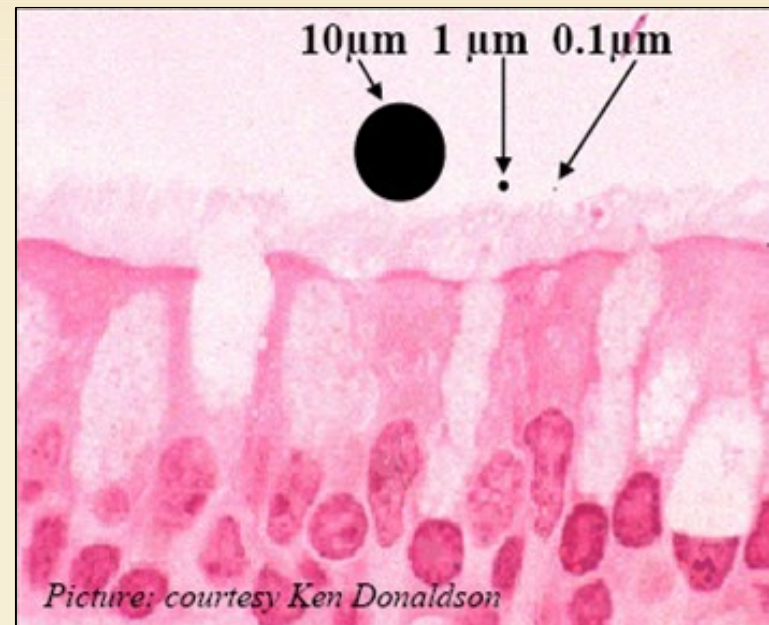
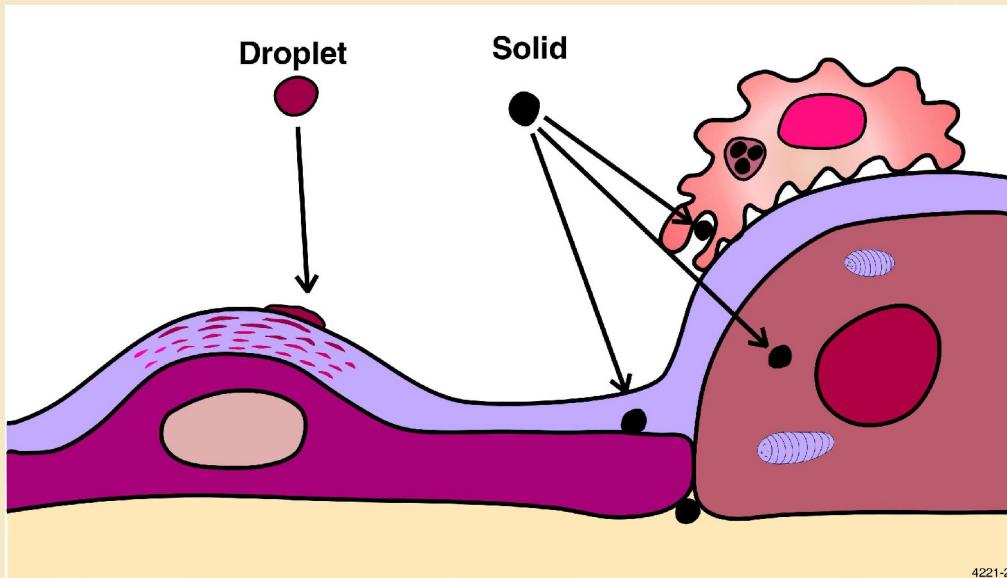
- Toxicology (laboratory) research for, mechanisms, “biological plausibility”

Focused initially on respiratory system

Expanded to cardiovascular system

Now excludes few organs

- Deposition of PM on respiratory surfaces



# RESPIRATORY EFFECTS

- **Injure or stimulate cells**

  - Stimulate production of reactive oxidant species

  - Form DNA adducts

  - Injure mitochondria

- **Cause inflammation**

  - Induce pro-inflammatory cytokines

  - Stimulate neural pathways

- **Enhance airway constrictive responses**

  - Increase epithelial permeability to stimulants

  - Increase reactivity of smooth muscle

- **Increase response to antigens (asthma, allergic rhinitis)**

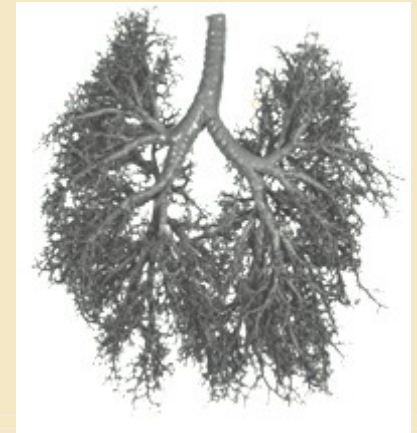
  - Enhance development of allergic state

  - Enhance allergic responses to antigen challenges

- **Impair pulmonary defenses**

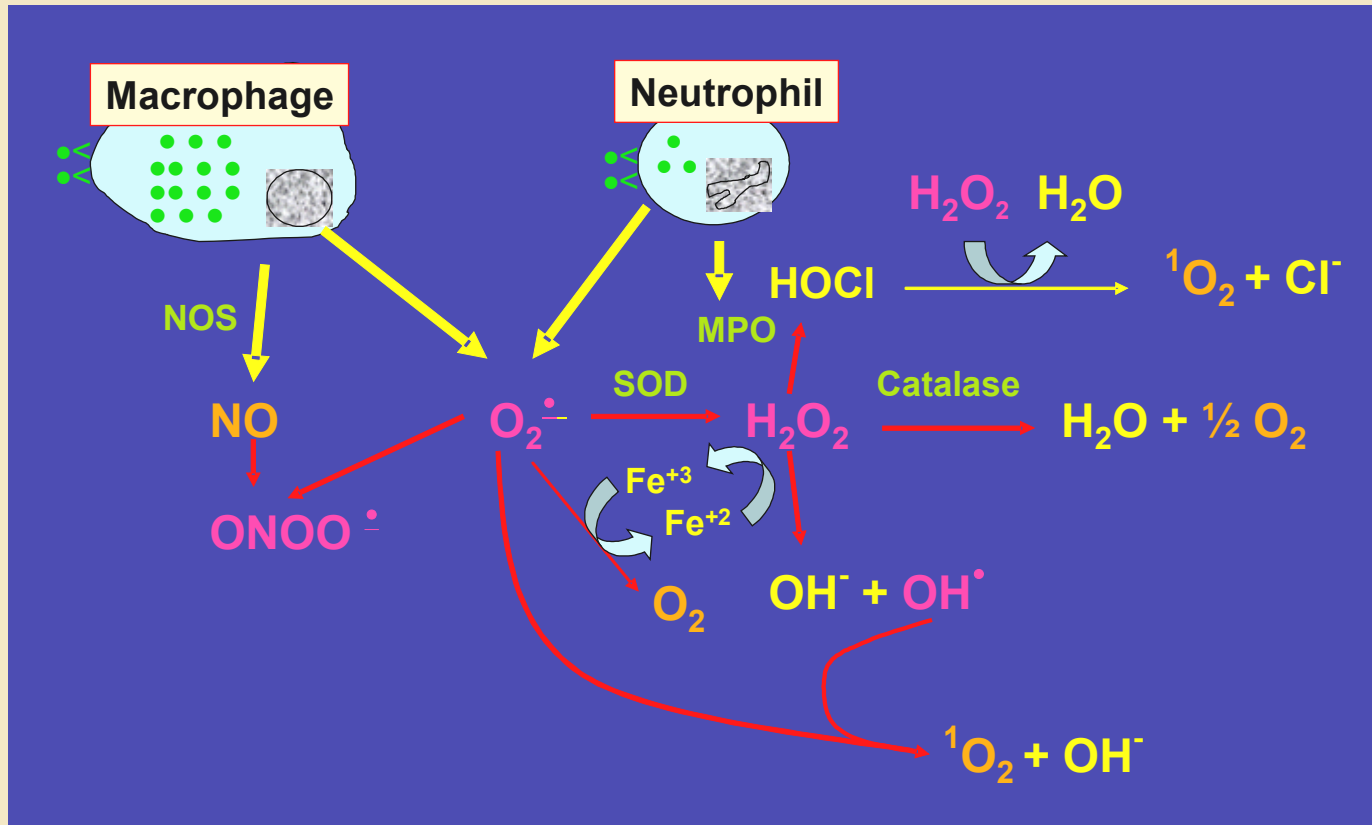
  - Deplete antioxidants, increase permeability of epithelium

  - Retard killing & clearance of pathogens



# OXIDATIVE STRESS and INJURY

- PM components (especially transition metals) participate in chemical reactions that produce reactive oxygen species
- PM causes lung defense cells to promote an oxidative cascade





*An Example:  
Geneva Steel Mill: Utah Valley*



# HEALTH IMPACTS (Pope, et al)

## Monthly Bronchitis and Asthma Admissions in Utah Valley: All Ages



# Study of Utah Valley PM in Human Volunteers

*Ghio and Devlin 2001*

- Volunteers exposed to aqueous extracts of PM
- Extracts from PM collected before and after reopening of a steel mill
- provoked a greater inflammatory response relative to extracts from PM collected during plant shutdown
  - Possible role of metals?

TABLE 1. NEUTROPHILS, PROTEIN, AND IL-8 IN LAVAGE FLUID AFTER INSTILLATION OF LOWER MASS (100  $\mu$ g) OF EXTRACT

	1986	1987	1988
Neutrophils, %	37.0 $\pm$ 6.6	15.7 $\pm$ 2.7	31.5 $\pm$ 6.2
Protein, $\mu$ g/ml	175 $\pm$ 29	76 $\pm$ 14	153 $\pm$ 32
IL-8, pg/ml	56.5 $\pm$ 17.4	18.8 $\pm$ 10.1	61.0 $\pm$ 10.5

TABLE 2. METAL CONCENTRATIONS IN THE THREE PM EXTRACTS FROM UTAH VALLEY (NG METAL/MG EXTRACT)

	1986	1987	1988
Iron	82.2	14.8	257.5
Copper	402.8	29.1	471.8
Zinc	1276.5	20.2	690.2
Lead	186.6	5.7	286.7
Nickel	17.6	3.8	11.0
Vanadium	6.0	7.4	37.7



# CARDIOVASCULAR EFFECTS

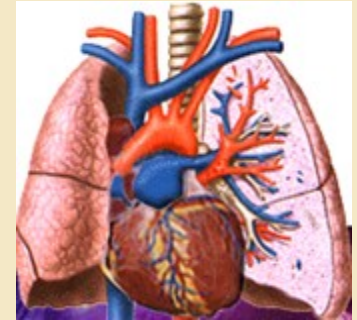
- **Alter cardiac electrophysiology**

  - Alter heart rate

  - Decrease heart rate variability

  - Alter conductivity

  - Alter re-polarization rate or pattern (local)



- **Cause inflammation**

  - Induce pro-inflammatory cytokines (local, or from lung)

  - Increase blood cell adhesion

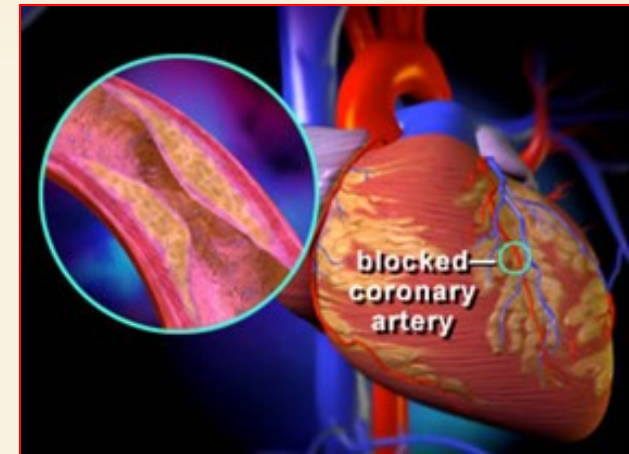
- **Reduce vascular blood flow**

  - Alter vasodilator-vasoconstrictor balance

  - Increase reactivity of smooth muscle

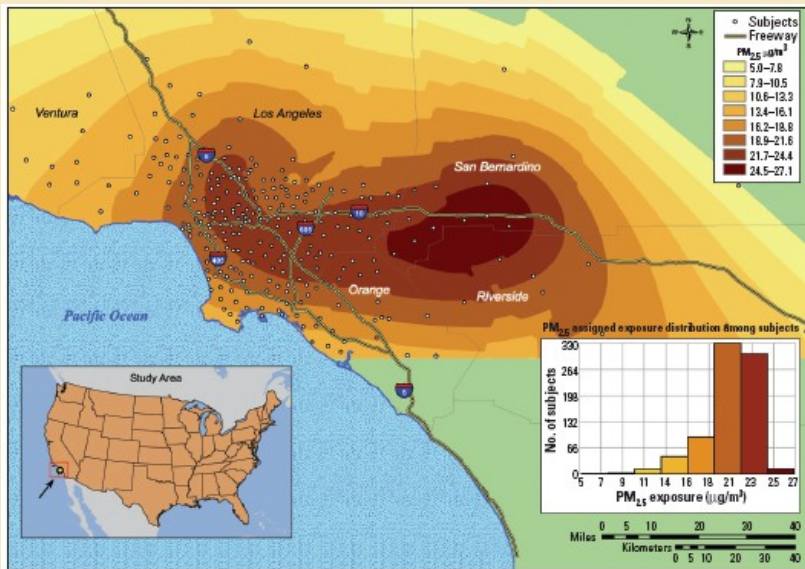
  - Enhance atherosclerotic plaque formation

  - Promote clotting

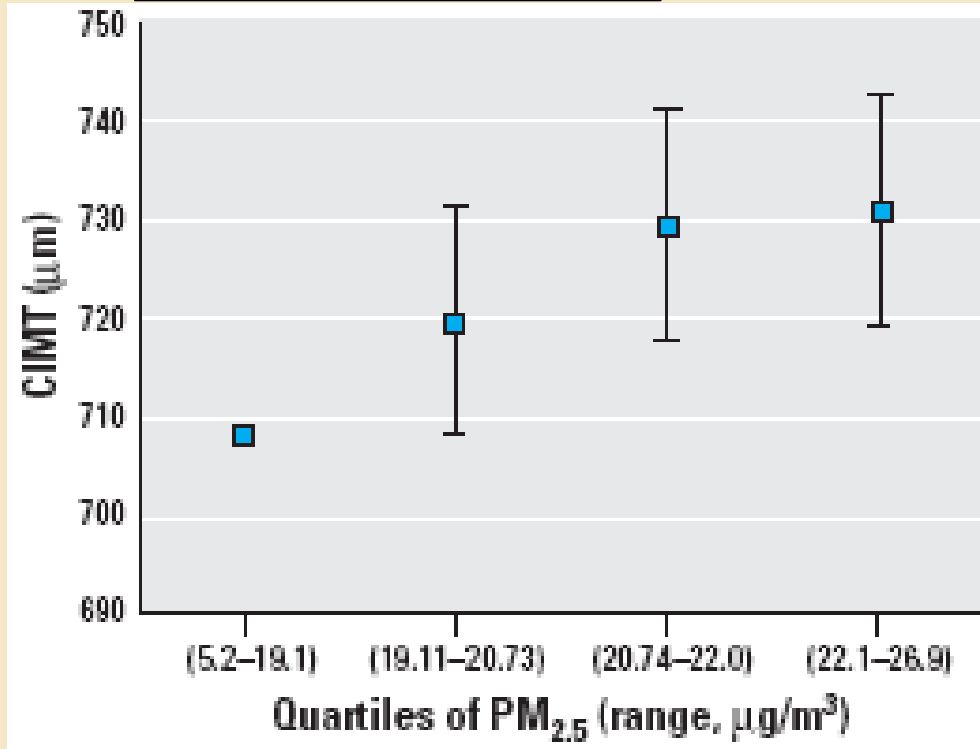


# *PM<sub>2.5</sub> vs. CAROTID ARTERY WALL THICKNESS*

Thickness (an indicator of arteriosclerosis) measured by imaging in people living in areas of different PM levels



Mean thickness  $\pm$  SE



Künzli et al. 2005





# *A Second Key Challenge:*

## *Are all PM Components and Sources equally toxic?*

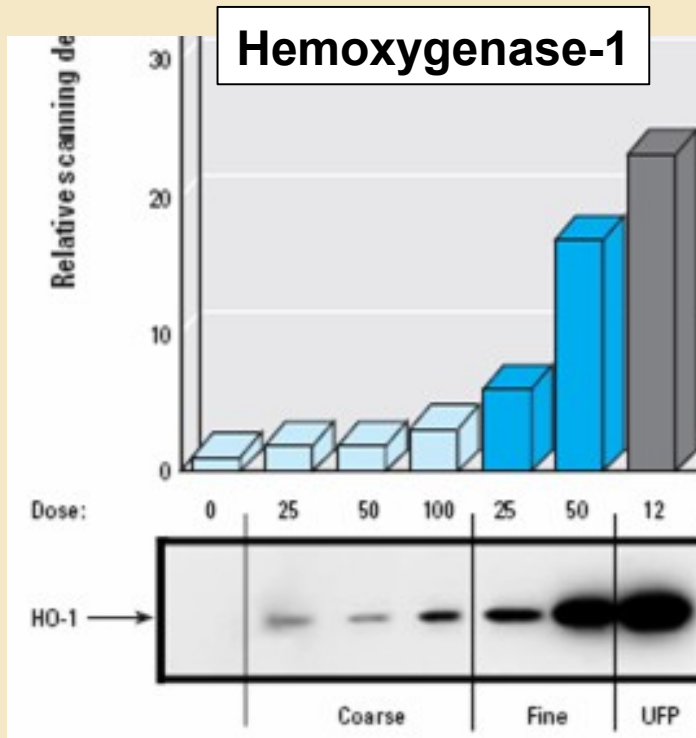
- PM is a complex mixture from many sources
- Not all components and sources likely to be equally toxic
- Three examples:
  - Metals (Utah Valley)
  - Ultrafines
  - Exposure to Traffic
- Much work still to be done
  - HEI currently seeking systematic, comprehensive studies



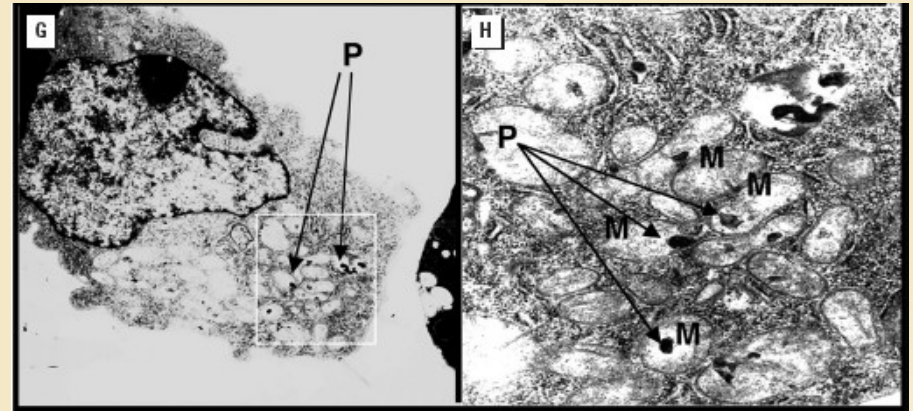
# PM SIZE AFFECTS NATURE AND LOCATION OF TOXICITY

- Exposed rat macrophage cell line *in vitro* to ambient L.A. PM  
3 sizes:  $PM_{10-2.5}$  (coarse)  $PM_{<2.5}$  (fine)  $PM_{<0.15}$  (ultrafine)

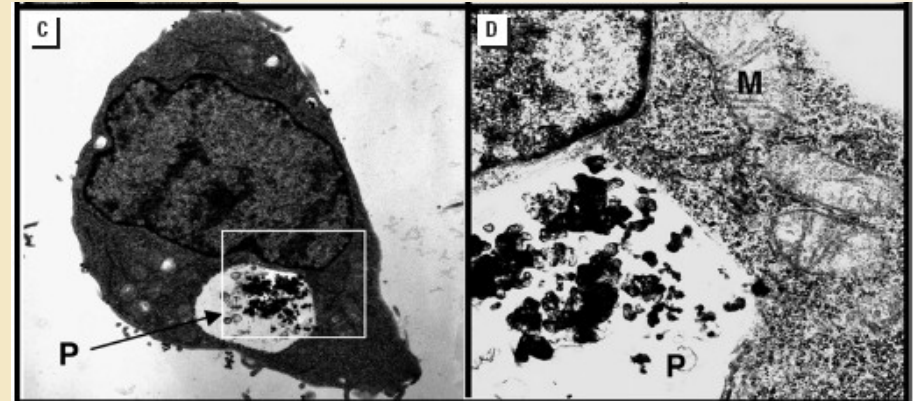
**Ultrafine PM caused greatest oxidative stress**



**Ultrafines found in damaged mitochondria**

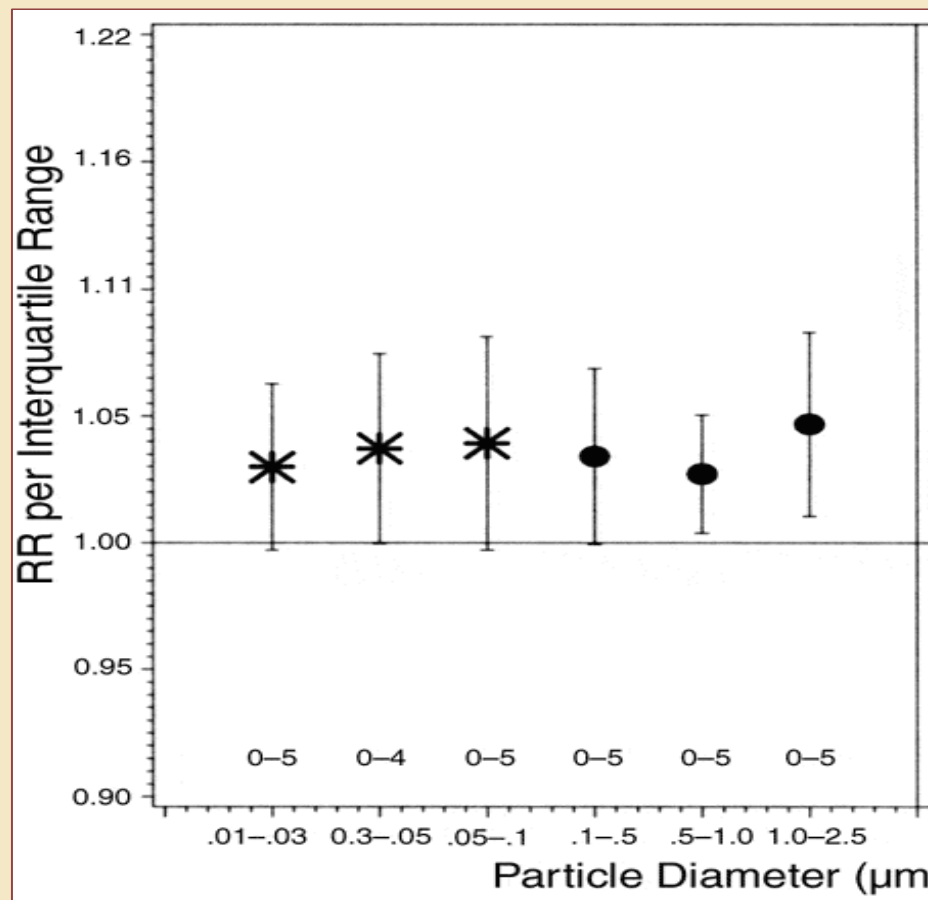


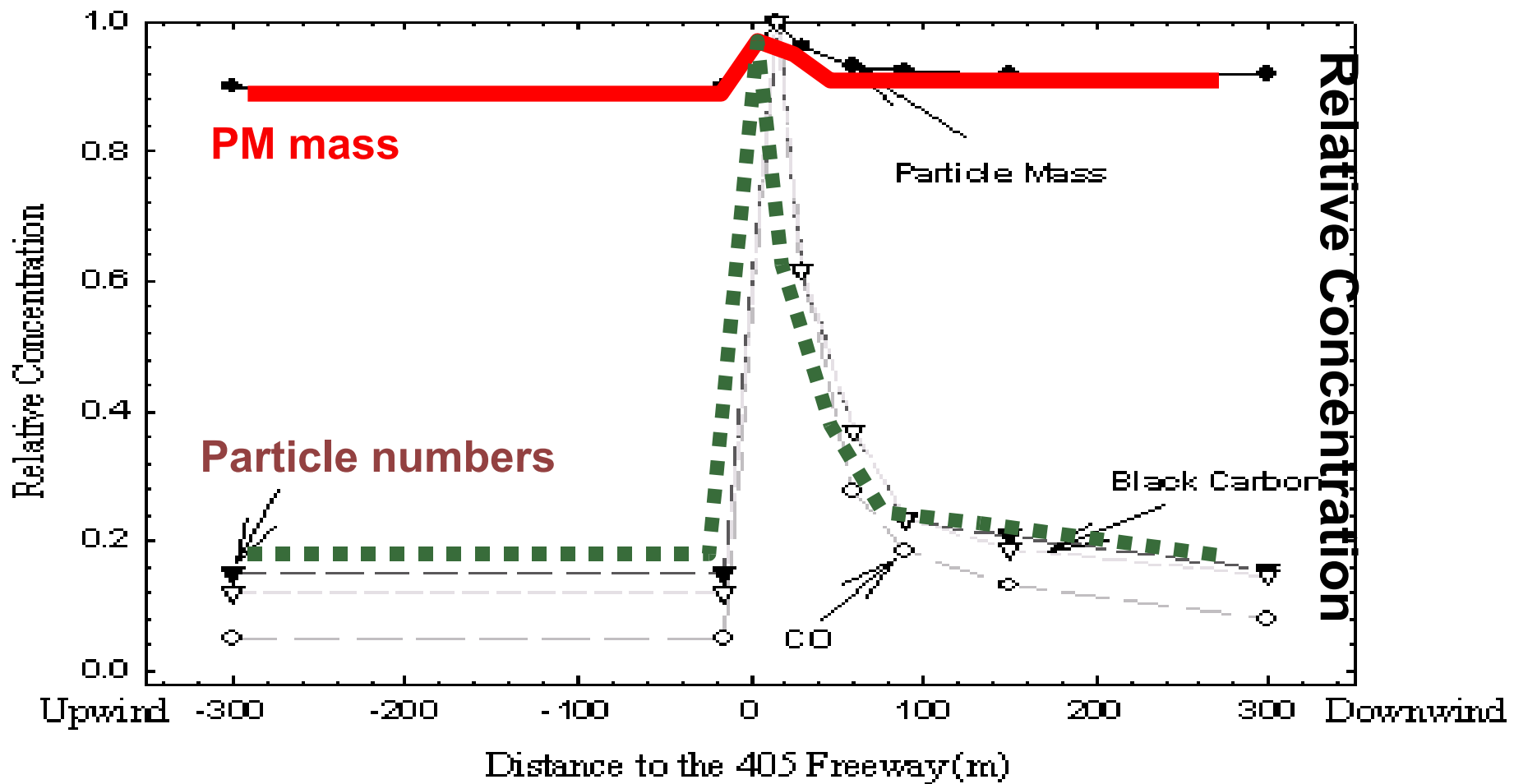
**Coarse PM found in large vacuoles (not in mitochondria)**



# *However, in epidemiology, similar effects of ultrafine and fine particles on daily mortality*

*HEI Research Report # 98 (Wichmann et al, 2000) Erfurt, Germany*





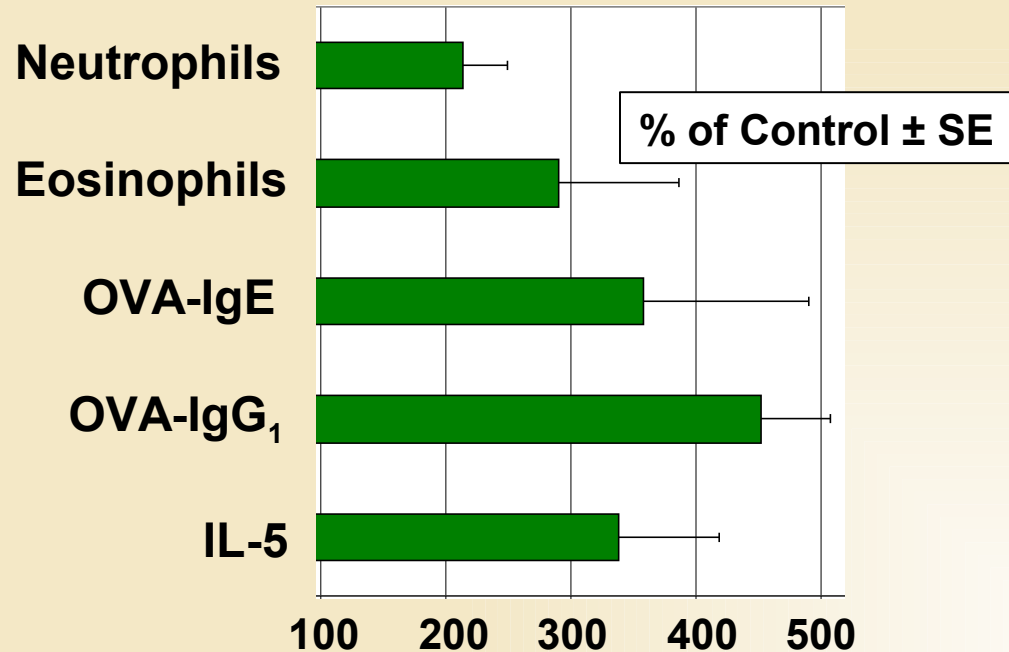
*A Third Challenge: Are some sources more toxic?*  
 One example: *Exposure to Traffic*

**PM<sub>2.5</sub> varies little; Ultrafines, Black Carbon, CO: peak near roads**

Source: Zhu et al. 2002:

# *INHALATION OF PM NEAR FREEWAY AMPLIFIES LUNG ALLERGIC RESPONSE*

- Exposed BALB/c mice to PM<sub>2.5</sub> CAPs
  - 50 m downwind from L.A. freeway
  - 4 hr/day x 10 days at 361 µg/m<sup>3</sup>
- Simultaneously sensitized to antigen (ovalbumin)
- Challenged with inhaled antigen after exposure





# *Netherlands Cohort Study (NLCS)*

- NLCS Cohort
  - 120,852 subjects
  - 55-69 yrs
  - enrolled in 1986
- Investigate mortality related to traffic-related air pollution

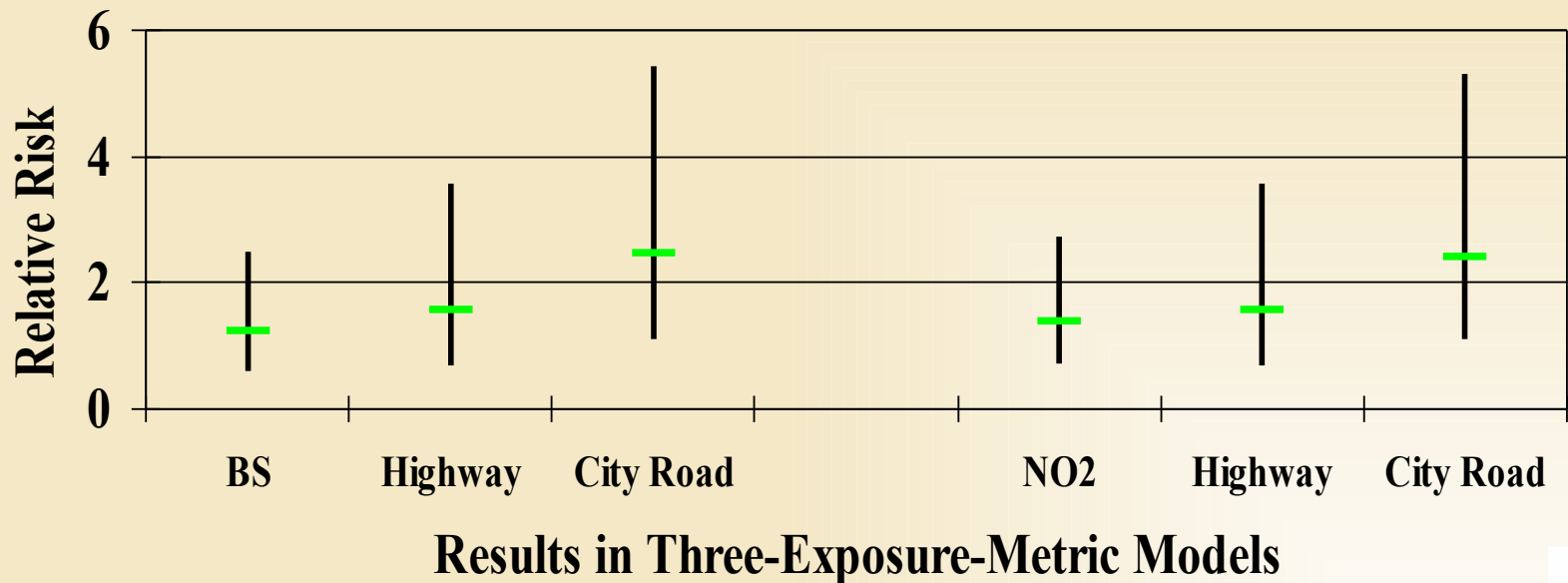


Figure 1: **Distribution of the municipalities of the NLCS study population over the Netherlands**

Area of the Netherlands is 41 562 km<sup>2</sup>. Shaded regions are included communities.

# *Long Term Effects of Traffic* (Hoek et al 2002)

**Association with Cardiopulmonary Mortality in  
Dutch Cohort**  
(Pilot Study results; Full HEI Study underway)



# Traffic “Exposure” and Heart Attack HEI Study (Peters et al 2005)

The NEW ENGLAND  
JOURNAL of MEDICINE

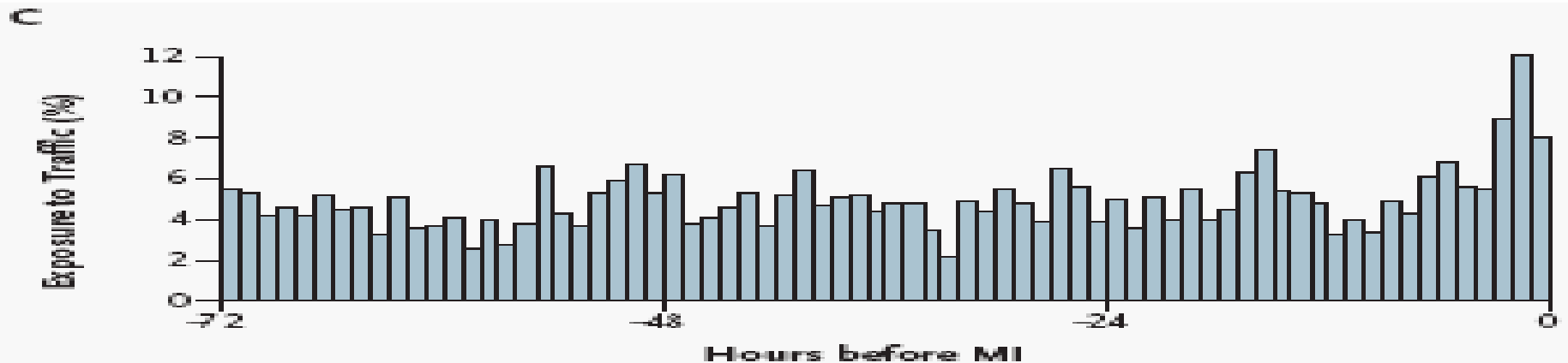
ESTABLISHED IN 1812

OCTOBER 21, 2004

VOL. 351 NO. 17

## Exposure to Traffic and the Onset of Myocardial Infarction

Annette Peters, Ph.D., Stephanie von Klot, M.P.H., Margit Heier, M.D.,  
Ines Trentinaglia, B.S., Allmut Hörmann, M.S., H. Erich Wichmann, M.D., Ph.D., and Hannelore Löwel, M.D.,  
for the Cooperative Health Research in the Region of Augsburg Study Group

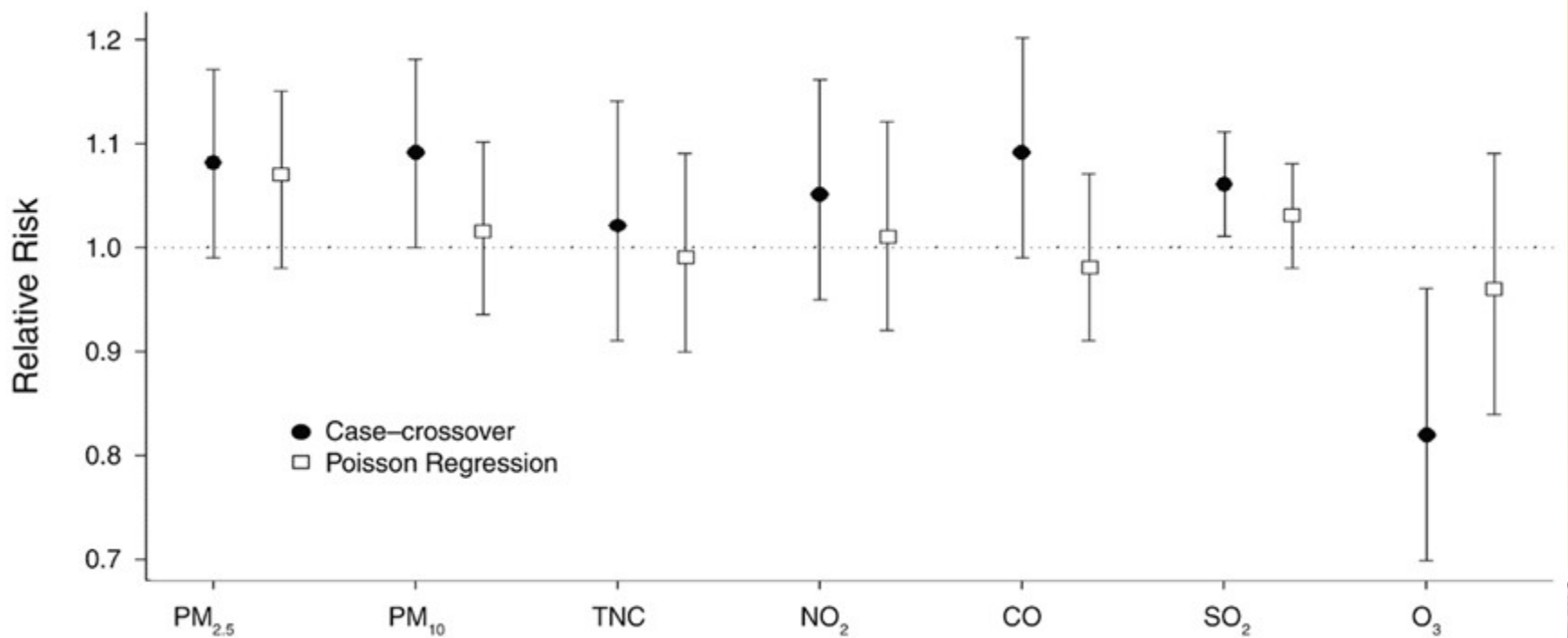


**Figure 1.** The Onset of 691 Nonfatal Myocardial Infarctions (MI) in Relation to Exposure to Traffic, According to the Amount of Time Spent in Traffic, February 1999 to July 2001, in the Region of Augsburg, Germany.

# *May be other factors in traffic in addition to air pollution (e.g. stress, noise)*

**Did not find association with air pollution two hours before heart attack (had found association in previous Boston study)**

**Found some associations with SO<sub>2</sub> and PM<sub>10</sub>, not ultrafine particles**



# *Answering Key Questions about Traffic and Health:* An HEI Special Literature Review

- Questions of:
  - What is the best *exposure metric*?
  - What other things in traffic can affect health? (*stress, noise*)
  - Which *air pollutants* may be most relevant
- HEI is launching expert review of current and emerging research



# *The “Other” Pollutants*

## **Recent Findings**

- Sulfur Dioxide (SO<sub>2</sub>)
- Ozone
- Nitrogen Dioxide (NO<sub>2</sub>)



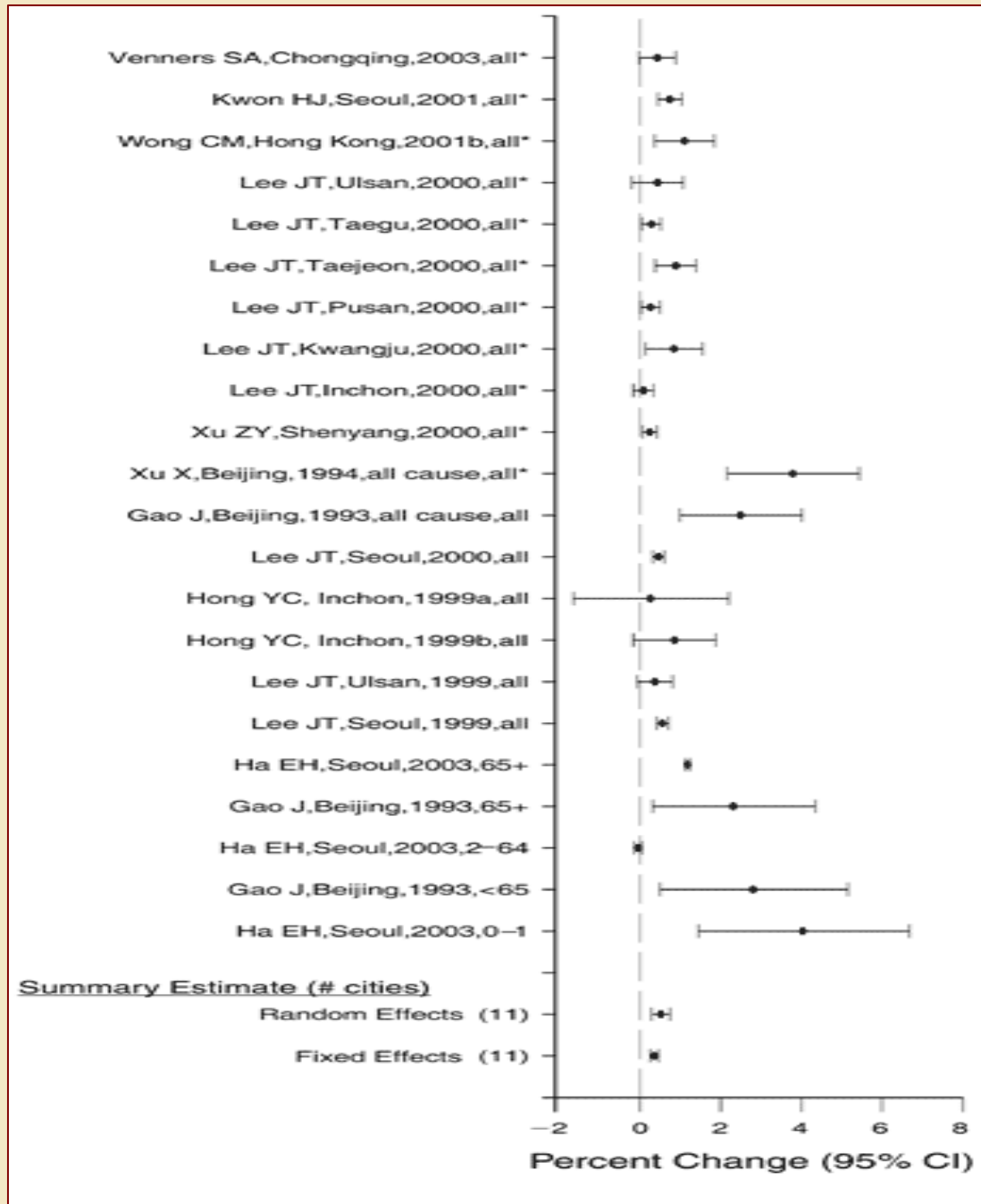


# *Sulfur Dioxide*

- Emitted from fossil fuel combustion
- Impairs breathing in asthmatic children and adults
- Has been associated, along with PM, with premature mortality (ACS Study 2000, 2002)
- Recent study in Hong Kong (Lancet 2002) has found benefits of reduction

<b>ACS Extended Analysis (Pope 2002)</b>			
<b>Type of Mortality</b>	<b>Statistically Significant Effect?</b>		
	PM <sub>2.5</sub>	SO <sub>2</sub>	Sulfate
<b>All Cause</b>	++	++	++
<b>Cardio-pulmonary</b>	++	++	++
<b>Lung Cancer</b>	++	+	+
<b>Other Cause</b>	-	++	++

*Acute  
Evidence  
from Asia:  
SO<sub>2</sub> and  
All Cause  
Mortality*



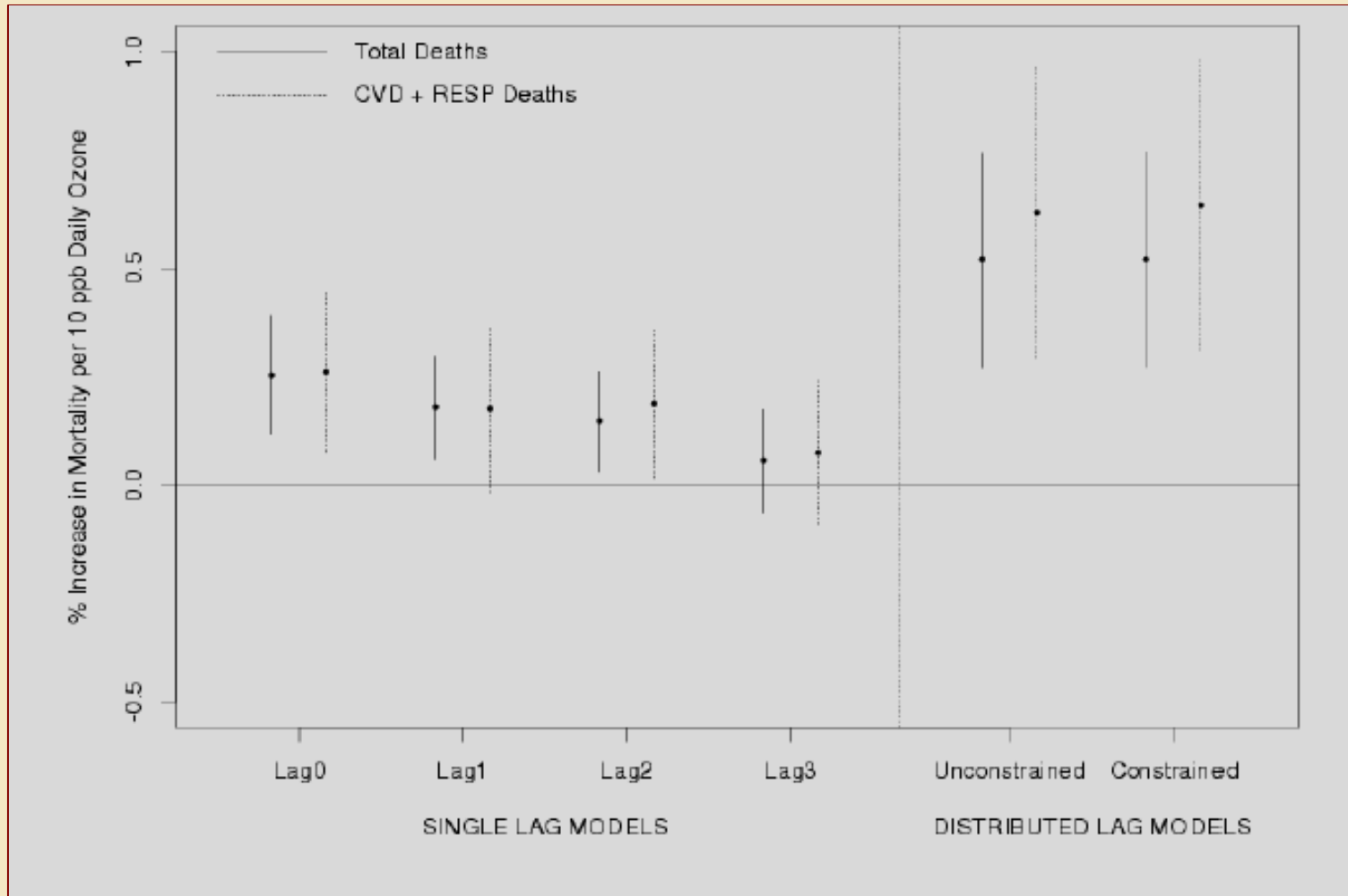
# *Ozone Health Effects*

- Known to cause inflammation in respiratory tract
- Reduces ability to breathe (lung function) for some people
- Increases hospitalization for asthma, other lung diseases
- Recent systematic evidence of effects on premature mortality
- Effects have been demonstrated for short term exposure, long term effects are less certain

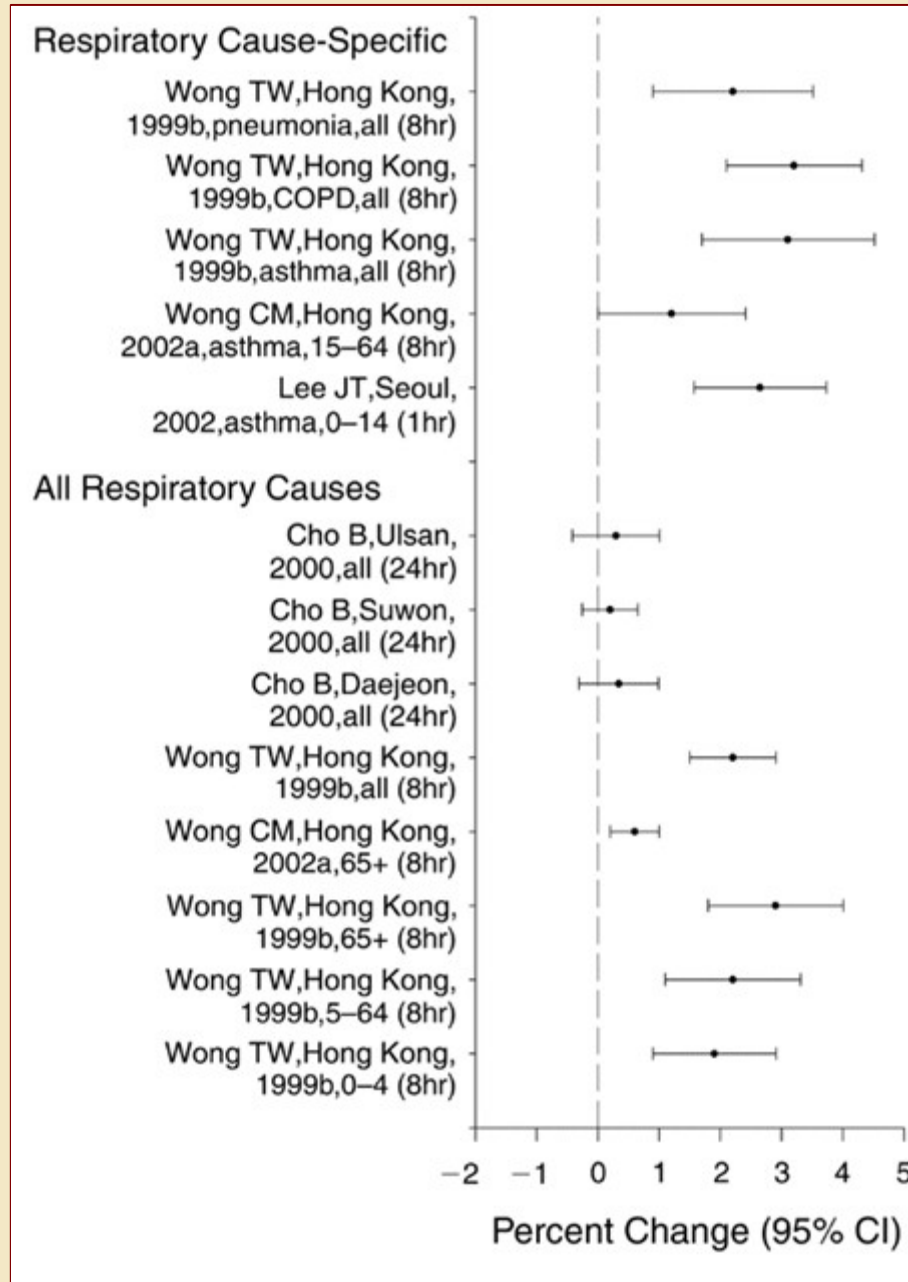


# *Ozone Effects on Mortality 95 US Cities*

Approximately 0.5% increase in mortality /10ppb  
(Bell et al 2004)



***Evidence  
from Asia:  
Ozone and  
Respiratory  
Hospital  
Admissions  
(PAPA, 2004)***



# *Nitrogen Dioxide (NO<sub>2</sub>)*

- Known, like many “oxidants” to cause inflammation
- May cause serious problems at lower levels and short, high doses
- Also may be a “marker” for other pollutants (e.g. fine PM)



# The NEW ENGLAND JOURNAL of MEDICINE

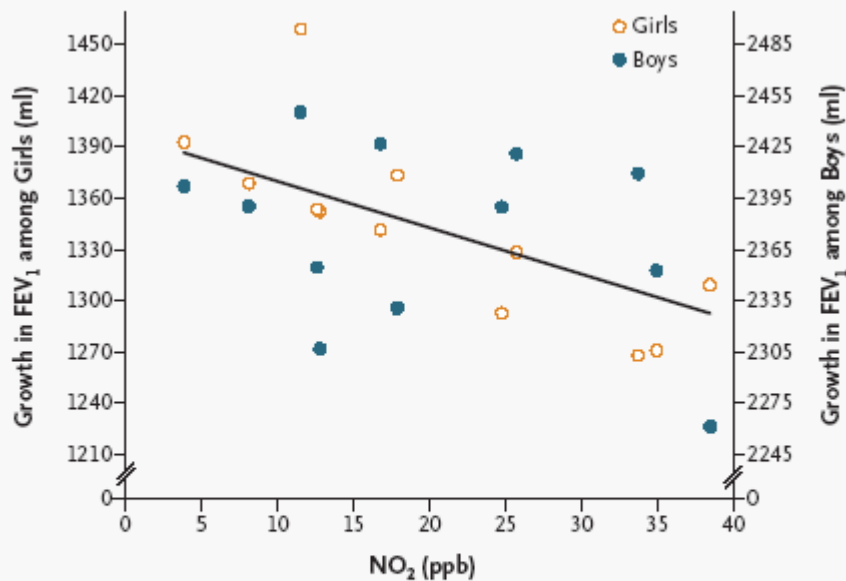
ESTABLISHED IN 1812

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 Kuerzli, M.D., Fred Lurmann, M.S.,  
Edward Rappaport, M.S., Helene Margolis, Ph.D., David Bates, M.D., and John Peters, M.D.

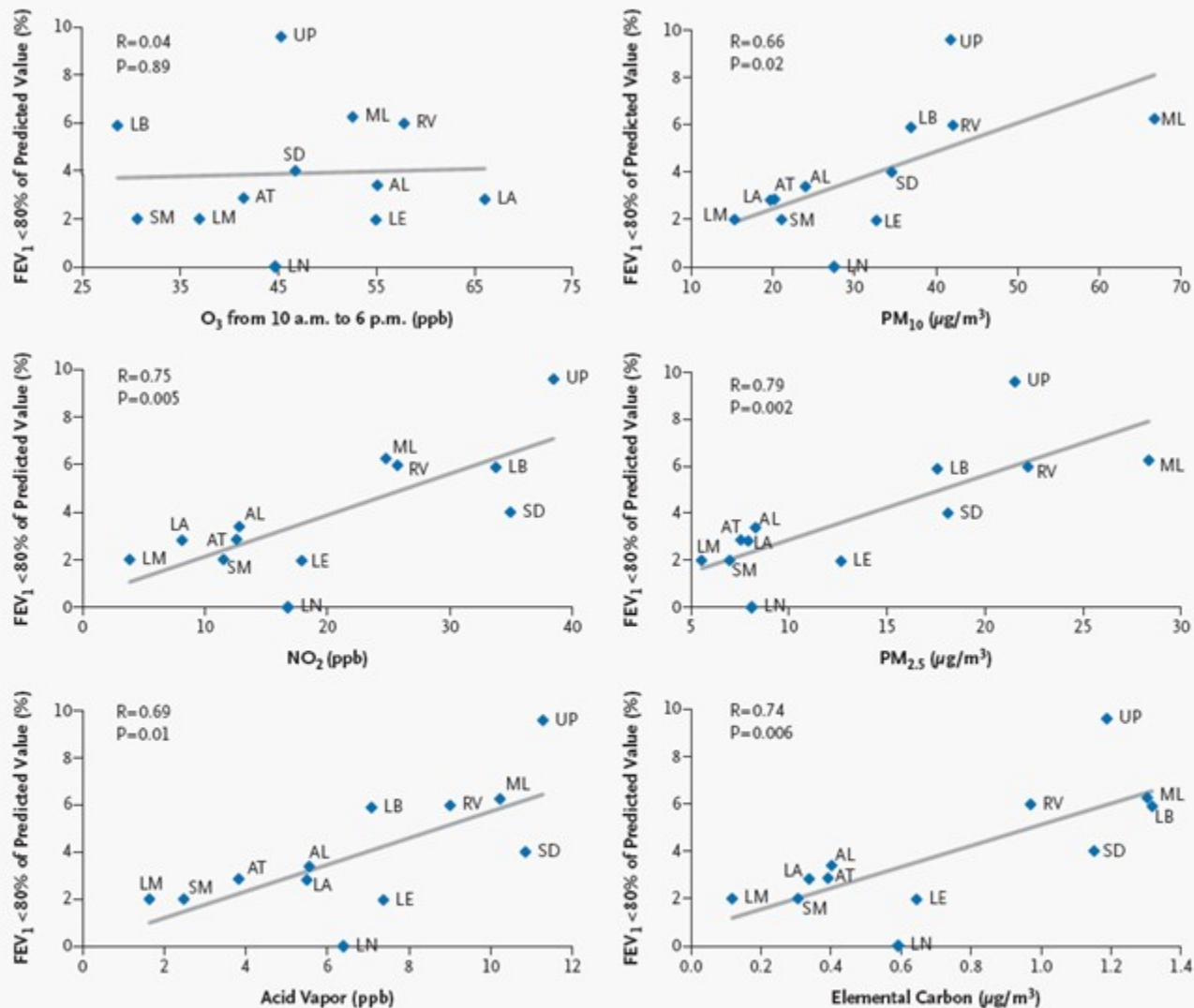


**Figure 2.** Community-Specific Average Growth in FEV<sub>1</sub> among Girls and Boys During the Eight-Year Period from 1993 to 2001 Plotted against Average Nitrogen Dioxide (NO<sub>2</sub>) Levels from 1994 through 2000.

**Childhood lung function  
development reduced in those  
exposed to higher NO<sub>2</sub>**

**Community-specific average growth in  
FEV<sub>1</sub> among Girls and Boys for the  
period 1993 to 2001 plotted against  
average nitrogen dioxide (NO<sub>2</sub>) levels  
from 1994 to 2000 (Gauderman 2004)**





**Figure 3.** Community-Specific Proportion of 18-Year-Olds with a FEV<sub>1</sub> below 80 Percent of the Predicted Value Plotted against the Average Levels of Pollutants from 1994 through 2000.

The correlation coefficient (R) and P value are shown for each comparison. AL denotes Alpine, AT Atascadero, LE Lake Elsinore, LA Lake Arrowhead, LN Lancaster, LM Lompoc, LB Long Beach, ML Mira Loma, RV Riverside, SD San Dimas, SM Santa Maria, and UP Upland. O<sub>3</sub> denotes ozone, NO<sub>2</sub> nitrogen dioxide, and PM<sub>10</sub> and PM<sub>2.5</sub> particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.

However, long-term effects from several pollutants on children's lung function

NO<sub>2</sub>, PM, Acid (Gauderman et al 2004)



# *Conclusions*

- We know much more about air pollution effects than we did 50 years ago
  - Knowledge has accelerated in the last 10 years
  - Including better understanding of the “concentration-response” relationship (little evidence of a *threshold*)
- The epidemiology of short and long term effects has strengthened
  - For the first time we have toxicology that suggests why this may happen to the lungs *and the heart*
- Of course, still more to learn
  - Especially about whether some particle components and sources are more toxic than others



*Thank You*

[dgreenbaum@healtheffects.org](mailto:dgreenbaum@healtheffects.org)

