Health Effects of Particulate Matter Air Pollution

C. Arden Pope III

Mary Lou Fulton Professor of Economics

Presented at

EPA Wood Smoke Health Effects Webinar

July 28, 2011

What we breath impacts our health

- Pure Air--nitrogen (78%),Oxygen (21%), Argon, CO_2. . .

+

- Various gaseous pollutants including:
  - SO_2, NO_2, CO, **O_3** . . .

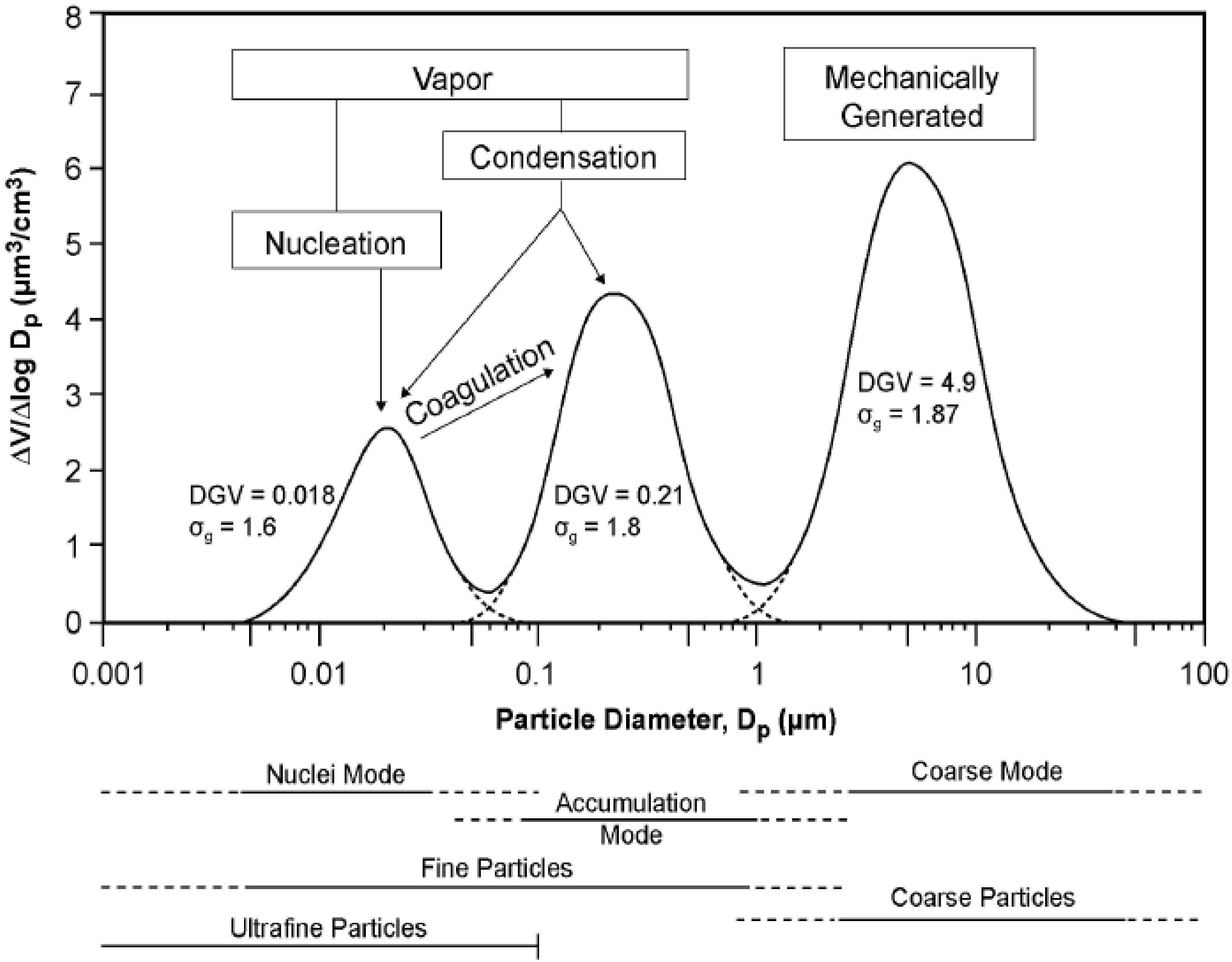
+

- **Particulate matter:**
  - Course particles (> 2.5 μm in diameter)
  - **Fine particles** (< 2.5 μm in diameter)

+

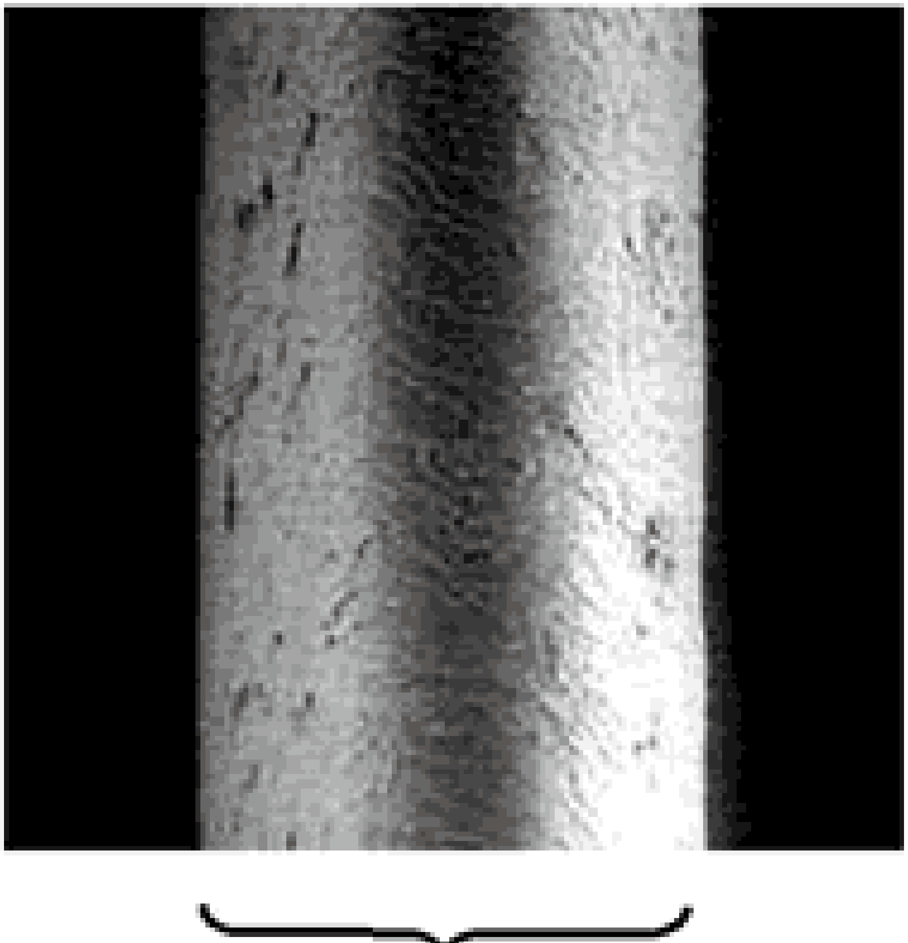
- Other air toxics

Wood Smoke

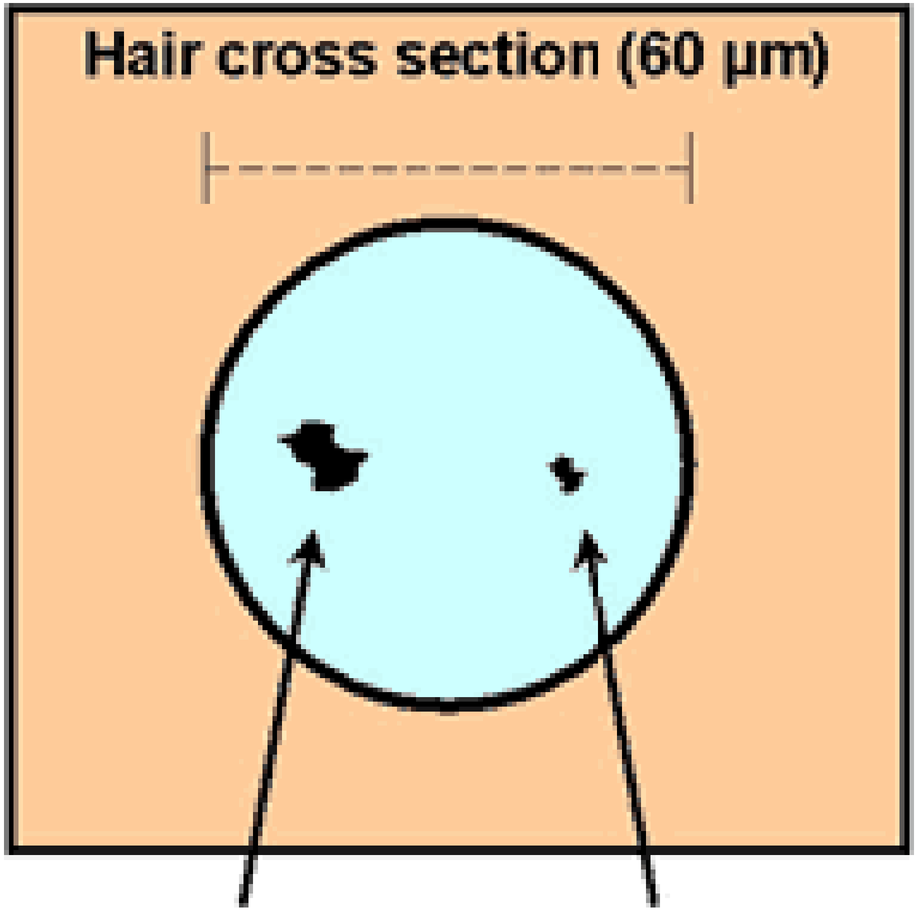


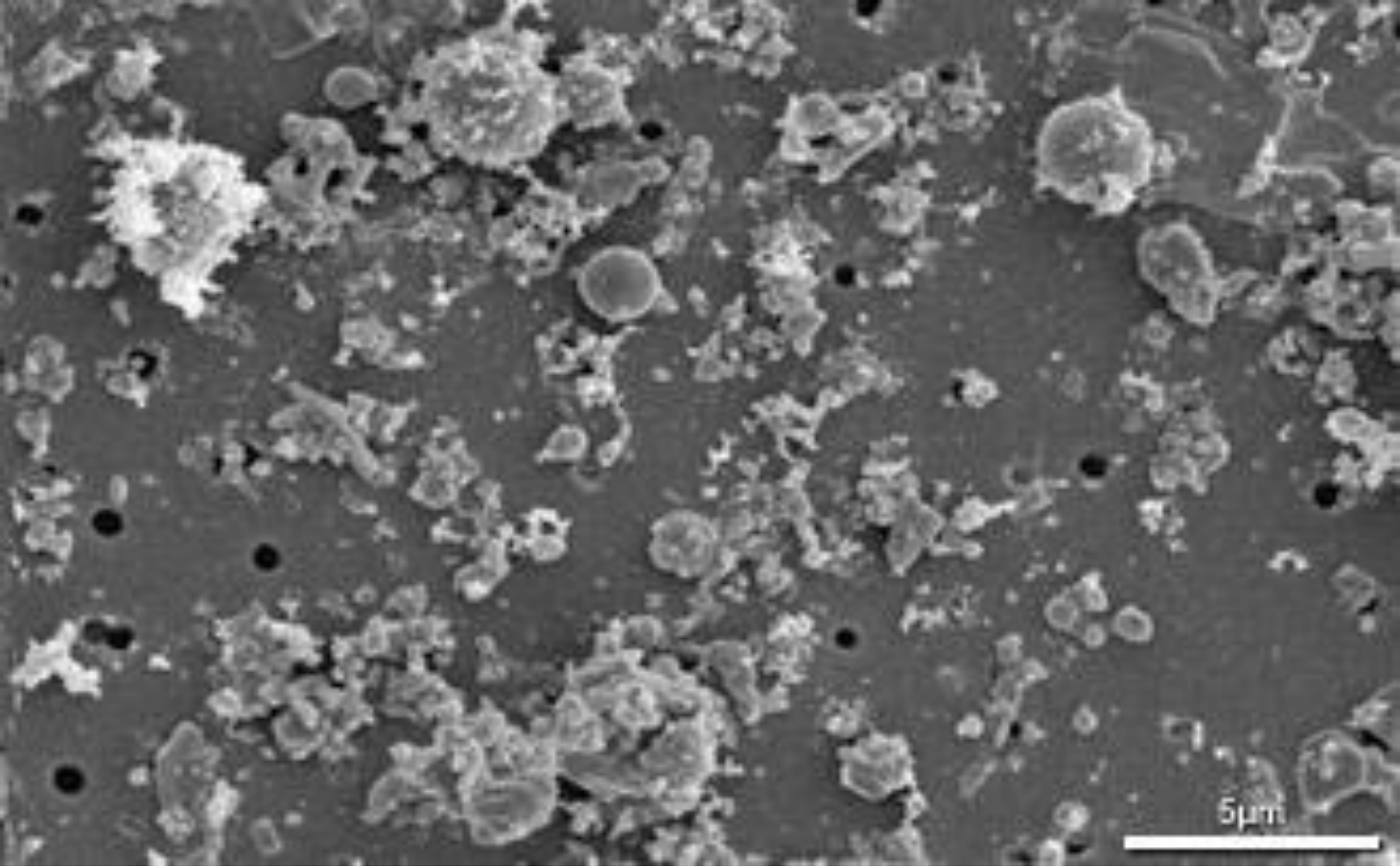
EPA PM Criteria Document, 2004

How small are fine particles?



Human Hair
(60 μm diameter)





Magnified ambient particles (www.nasa.gov/vision/earth/environment)

This presentation not organized chronologically, but methodologically

Studies of short-term exposure (hours-days)

- Episode
- Population-based daily time-series
- Panel-based acute exposure
- Case-crossover

Studies of long-term exposure (years-decades)

- Population-based cross-sectional
- Cohort-based mortality
- Cohort- and panel-based morbidity
- Case-control studies

Intervention/natural experiment (months-years)

Controlled experimental human and animal

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Q & A

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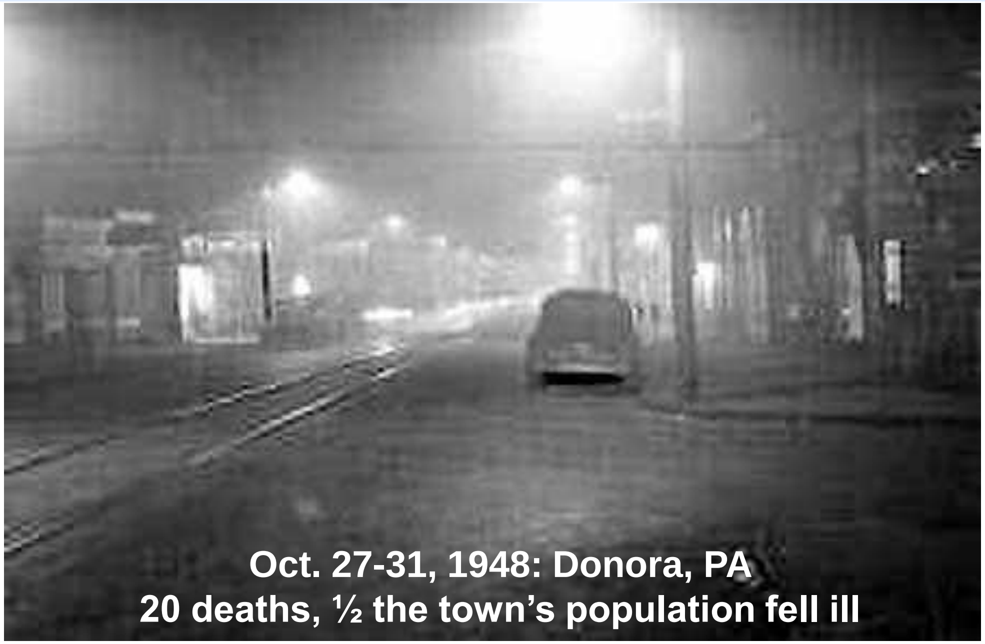
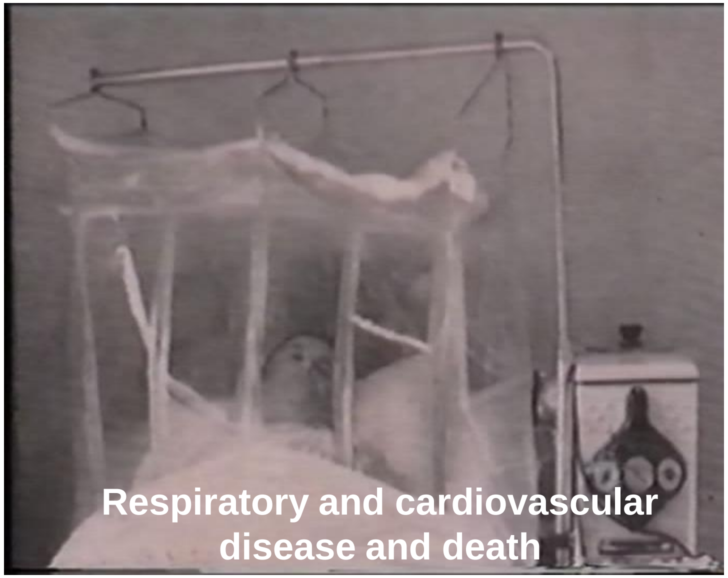
Early **"Killer smog"** episodes demonstrated that air pollution at extreme levels can contribute to respiratory and cardiovascular disease and death

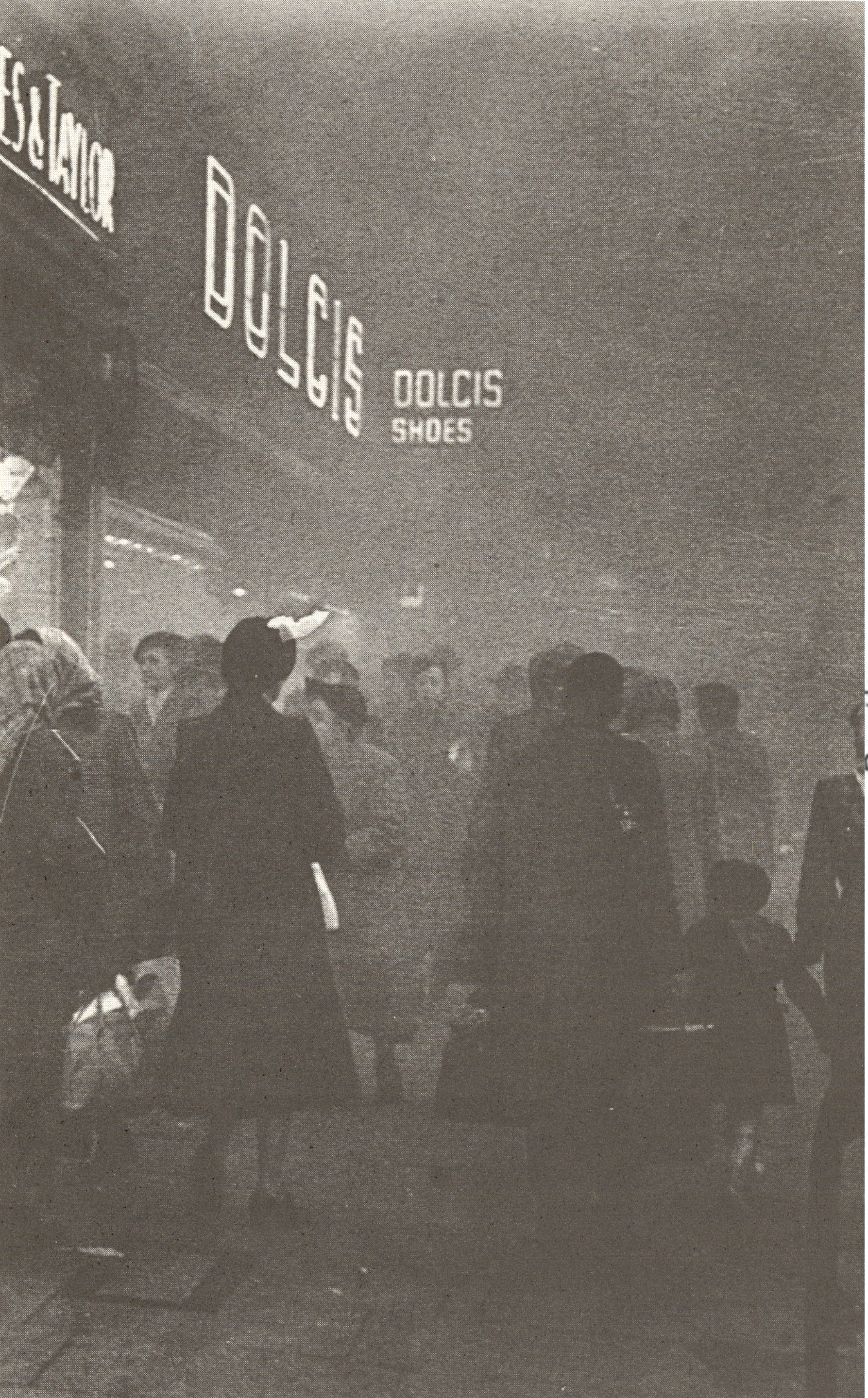

Dec. 1-5, 1930: Meuse Valley, *Belgium*
60 deaths (10x expected)

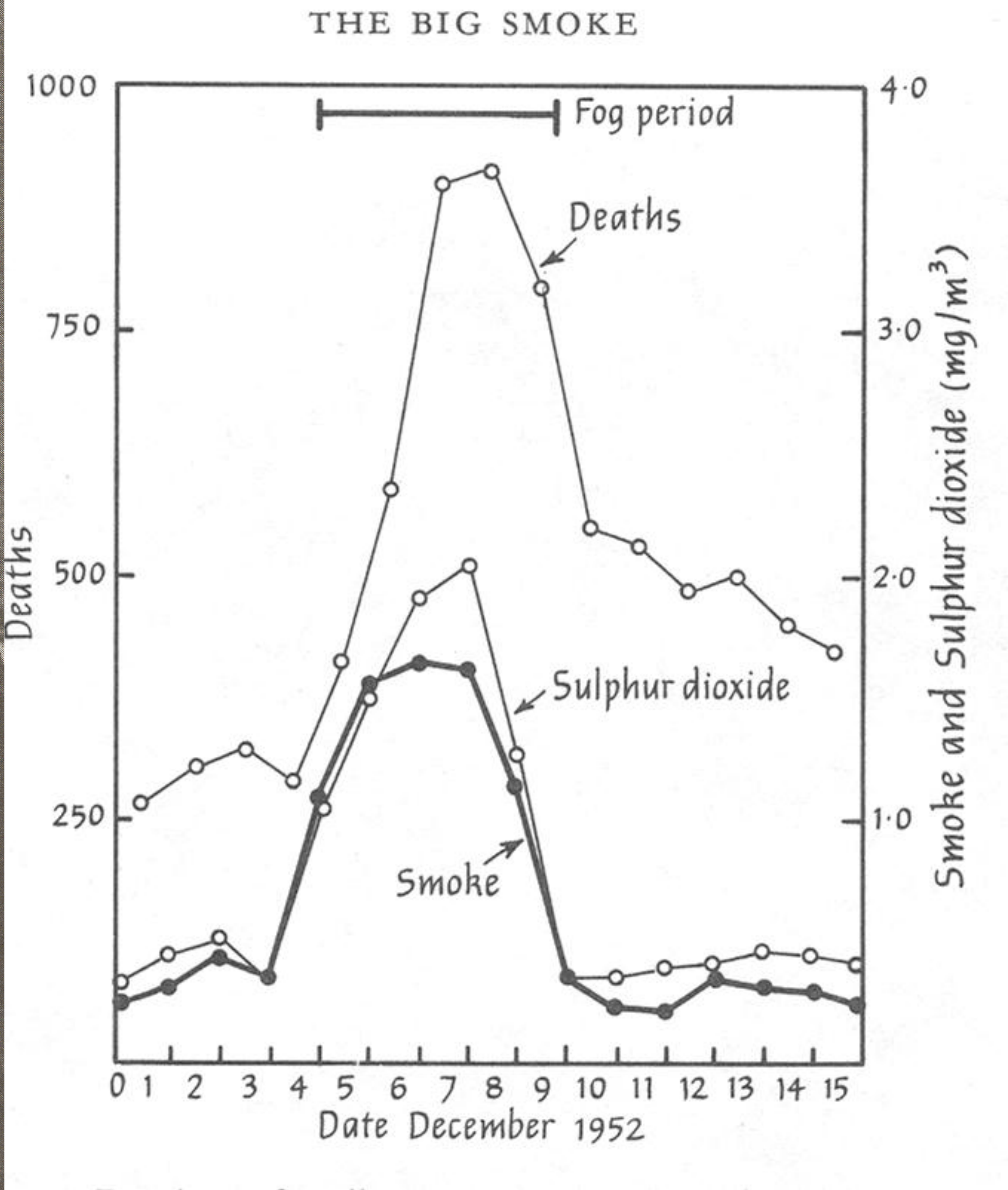

Oct. 27-31, 1948: Donora, PA
20 deaths, ½ the town's population fell ill


Dec. 5-9, 1952: London--1000's of excess deaths


Respiratory and cardiovascular disease and death

London Fog Episode, Dec. 1952



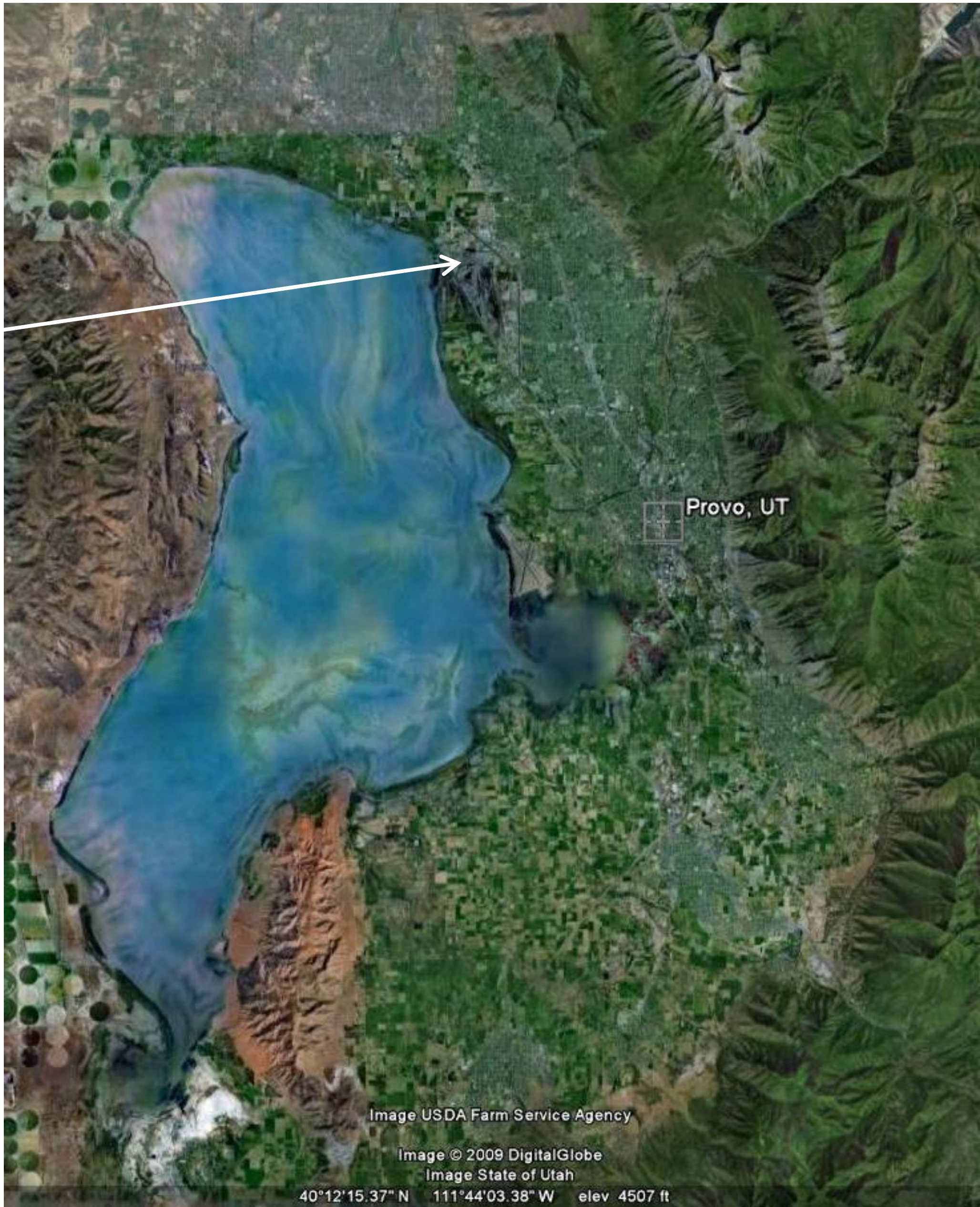


From: Brimblecombe P. The Big Smoke, Methu

Utah Valley, 1980s

- Winter inversions trap local pollution
- Natural test chamber

- Local Steel mill contributed ~50% $PM_{2.5}$
- Shut down July 1986-August 1987
- Natural Experiment

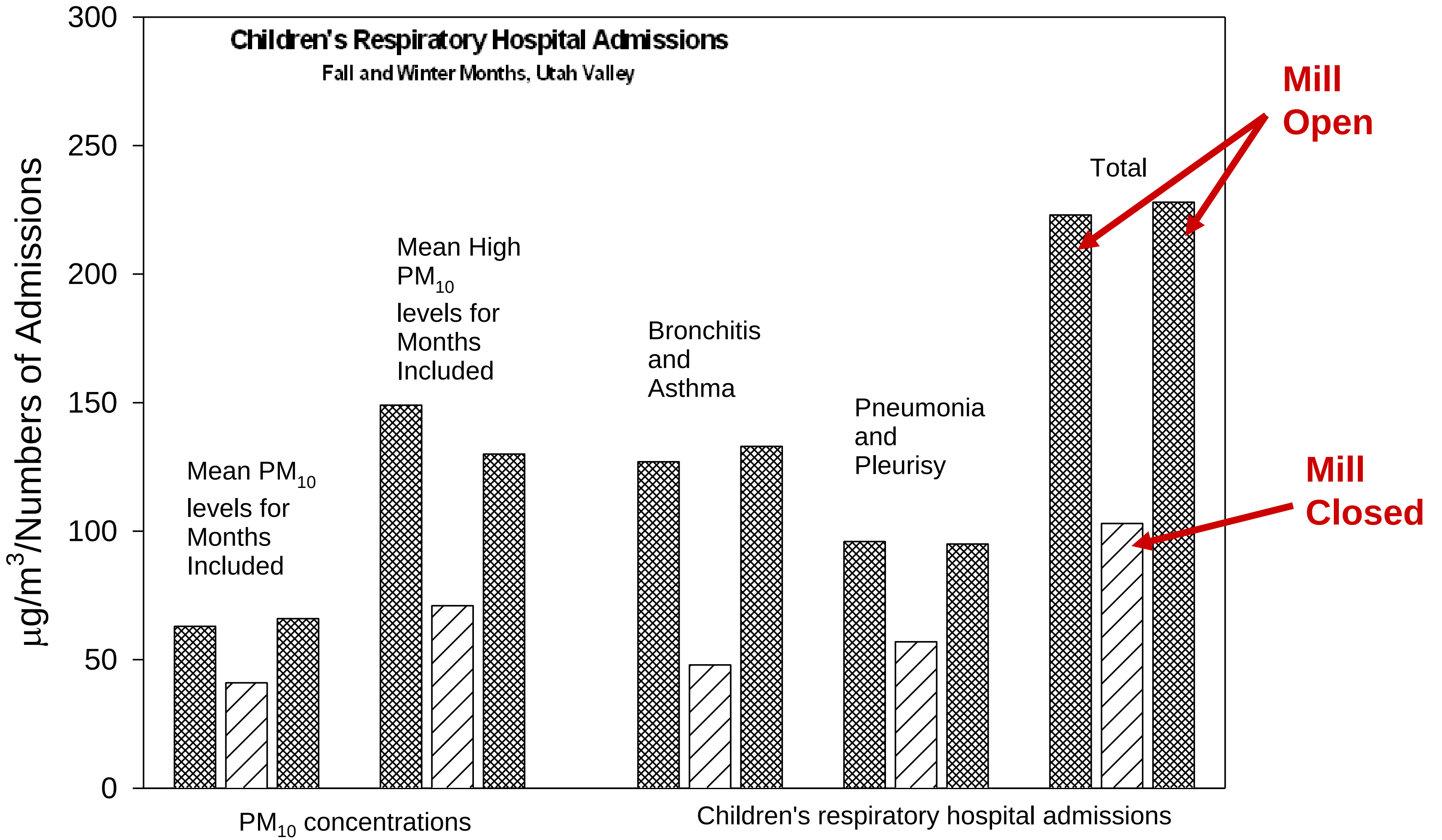


Large difference in air quality when inversions trap air pollution in valley

Utah Valley: Clean day

Utah Valley: Dirty day (PM_{10} = 220 μg/m^3)

When the steel mill was open, total children's hospital admissions for respiratory conditions **approx. doubled.**



Sources: Pope. Am J Pub Health.1989; Pope. Arch Environ Health. 1991

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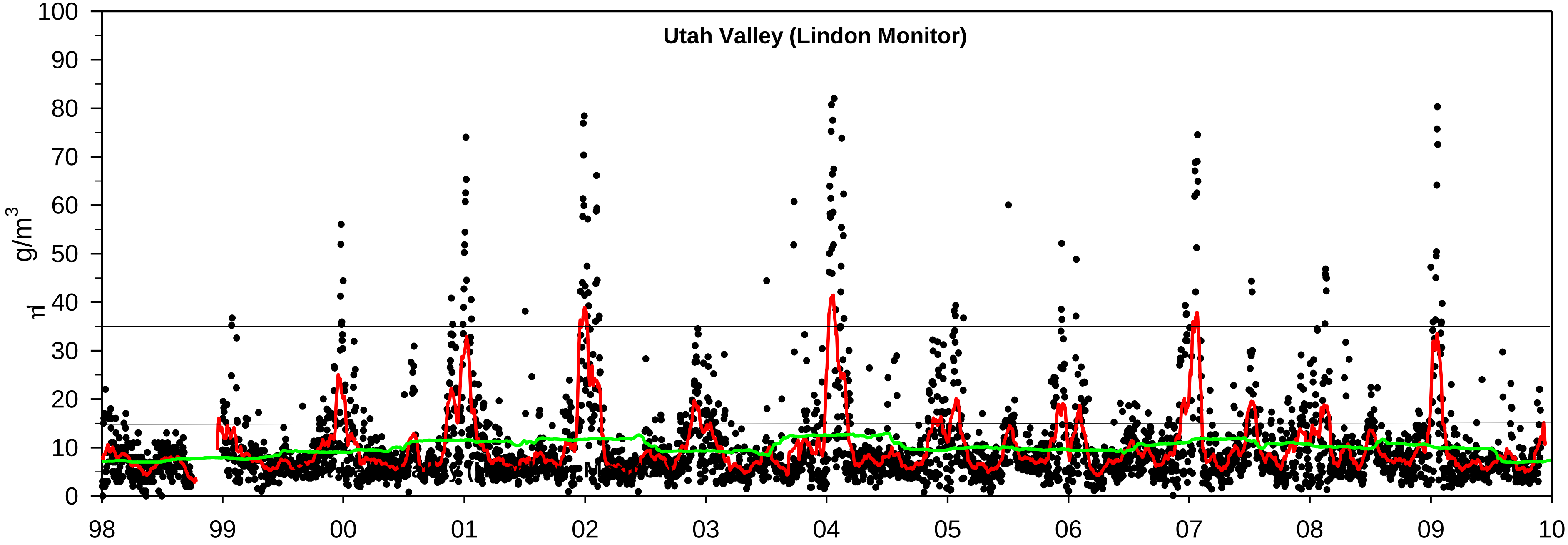
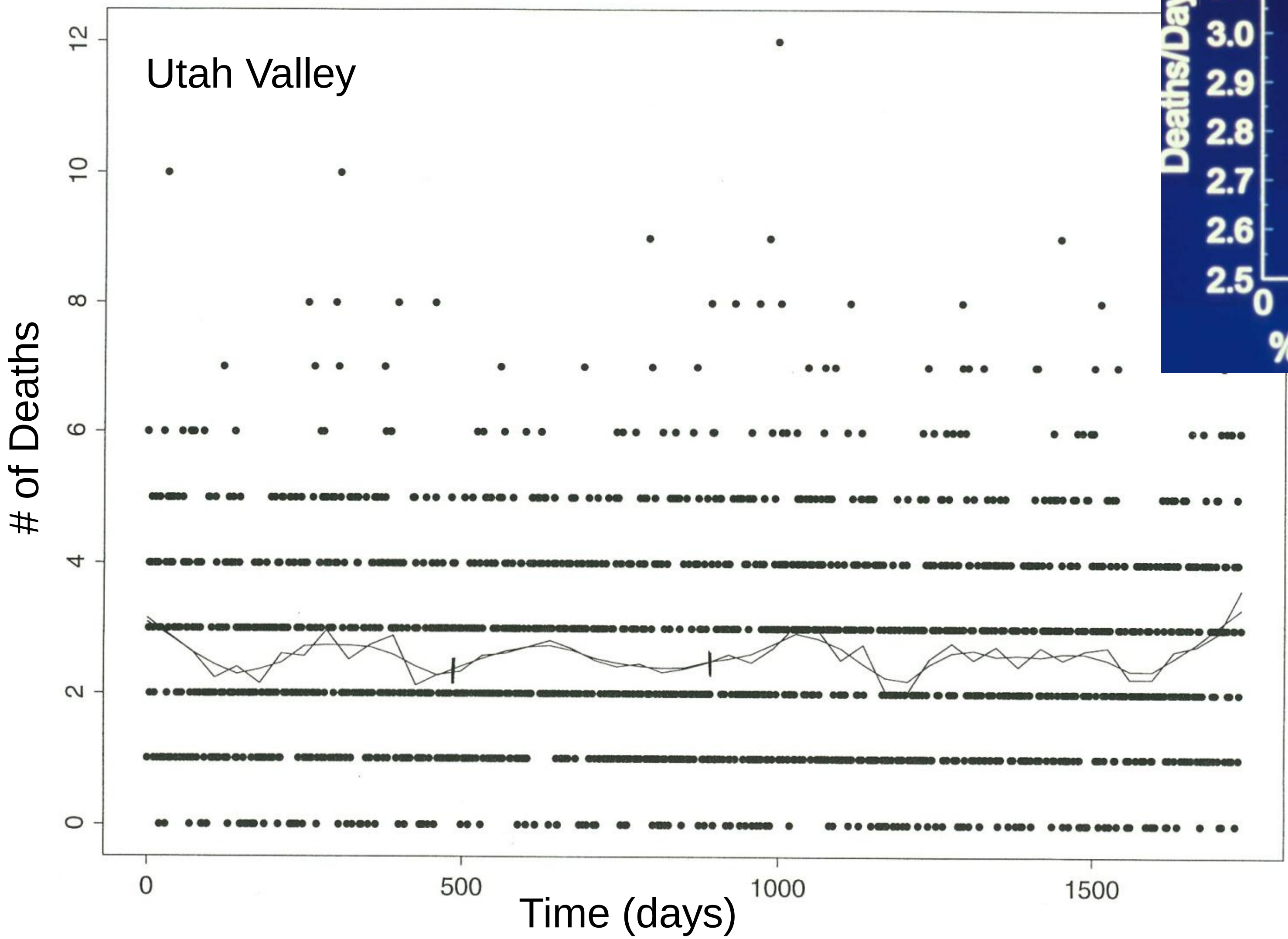
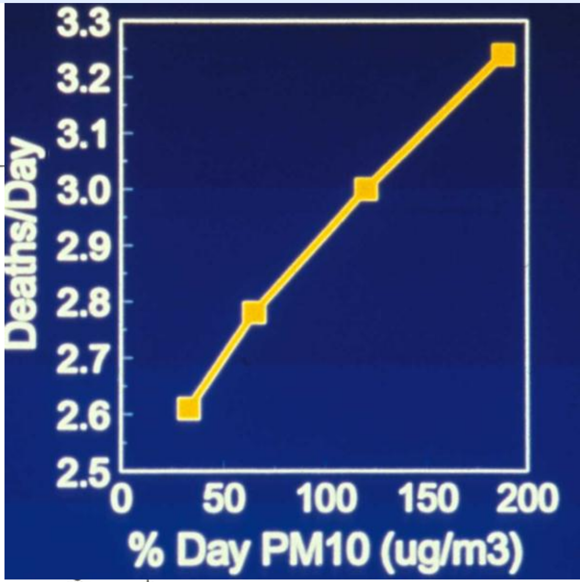
Health studies take advantage of **highly variable** air pollution levels that result from inversions.



$PM_{2.5}$ concentrations January 1 1998-December 12 2009. Black dots, 24-hr $PM_{2.5}$; Red line, 30-day moving average $PM_{2.5}$; Green line, 1-yr moving average $PM_{2.5}$.

Daily changes in air pollution → **daily death counts**





Poisson Regression

Count data (non-negative integer values). Counts of independent and random occurrences classically modeled as being generated by a Poisson process with a Poisson distribution:

$$\text{Prob}(Y = r) = e^{(-\lambda)} \frac{\lambda^r}{r!}$$

Note: λ = mean and variance. If λ is constant across time, we have a stationary Poisson process. If λ changes over time due to changes in pollution (P), time trends, temperature, etc., this non-stationary Poisson process can model as:

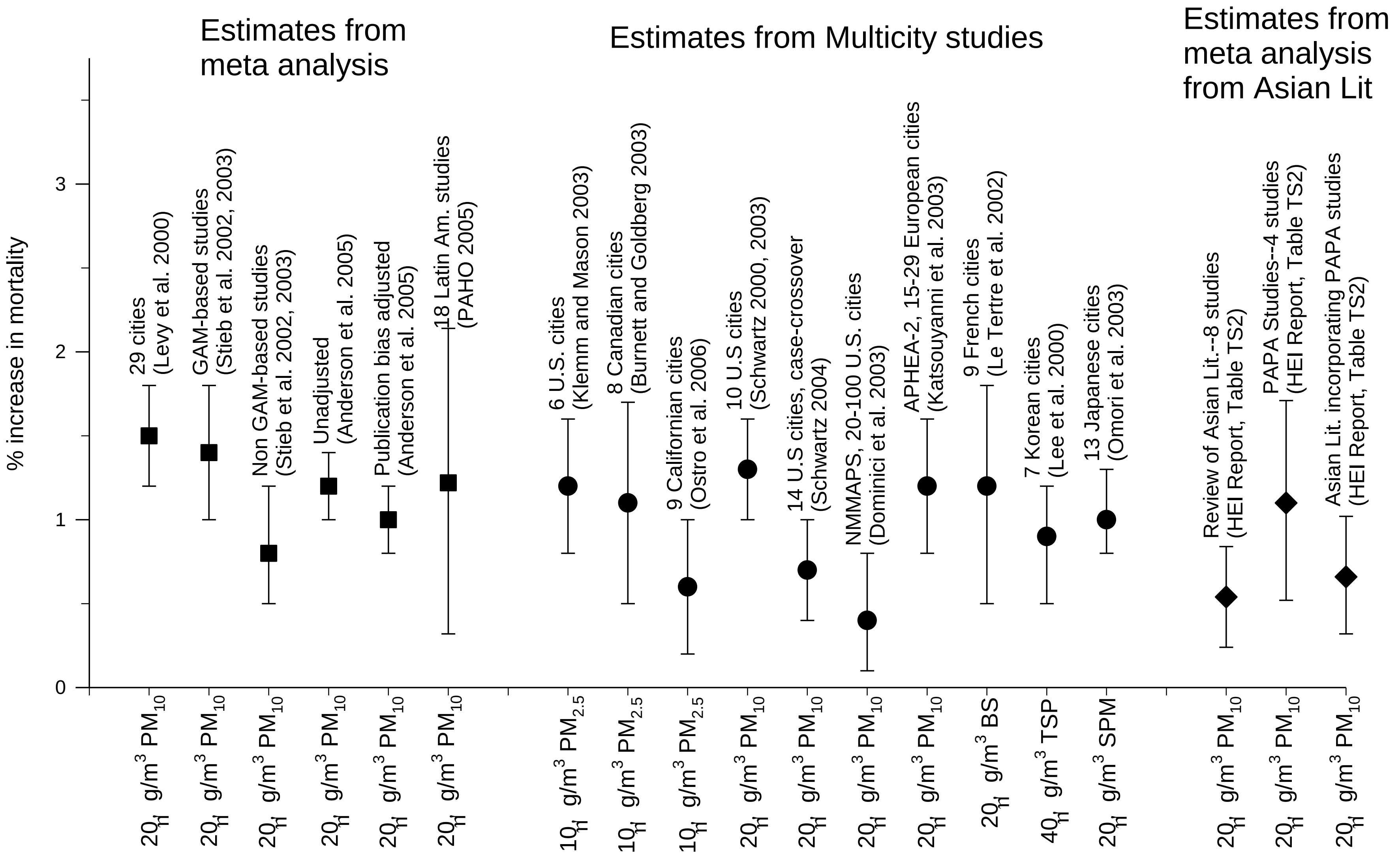
$$\ln \lambda_t = \alpha + \beta(w_0 P_t + w_1 P_{t-1} + w_2 P_{t-2} + \ldots) + s^1(t) + s^2(\text{temp}_t) + \ldots$$

Modeling controversies

- How to construct the lag structure? (MA, PDL, etc.)
- How aggressive do you fit time? (harmonics vs GAMs, df, span, loess, cubic spline, etc.)
- How to control for weather? (smooths of temp & RH, synoptic weather, etc.)

Also: How to combine or integrate information from multiple cities

Daily time-series studies ***of over 200 cities***



10 μg/m^3 $PM_{2.}$ or 20 μg/m^3 PM_{10} → 0.4% to 1.5% increase in relative risk of mortality—Small but remarkably consistent across meta-analyses and multi-city studies.

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Panel studies of asthmatics and non-asthmatics

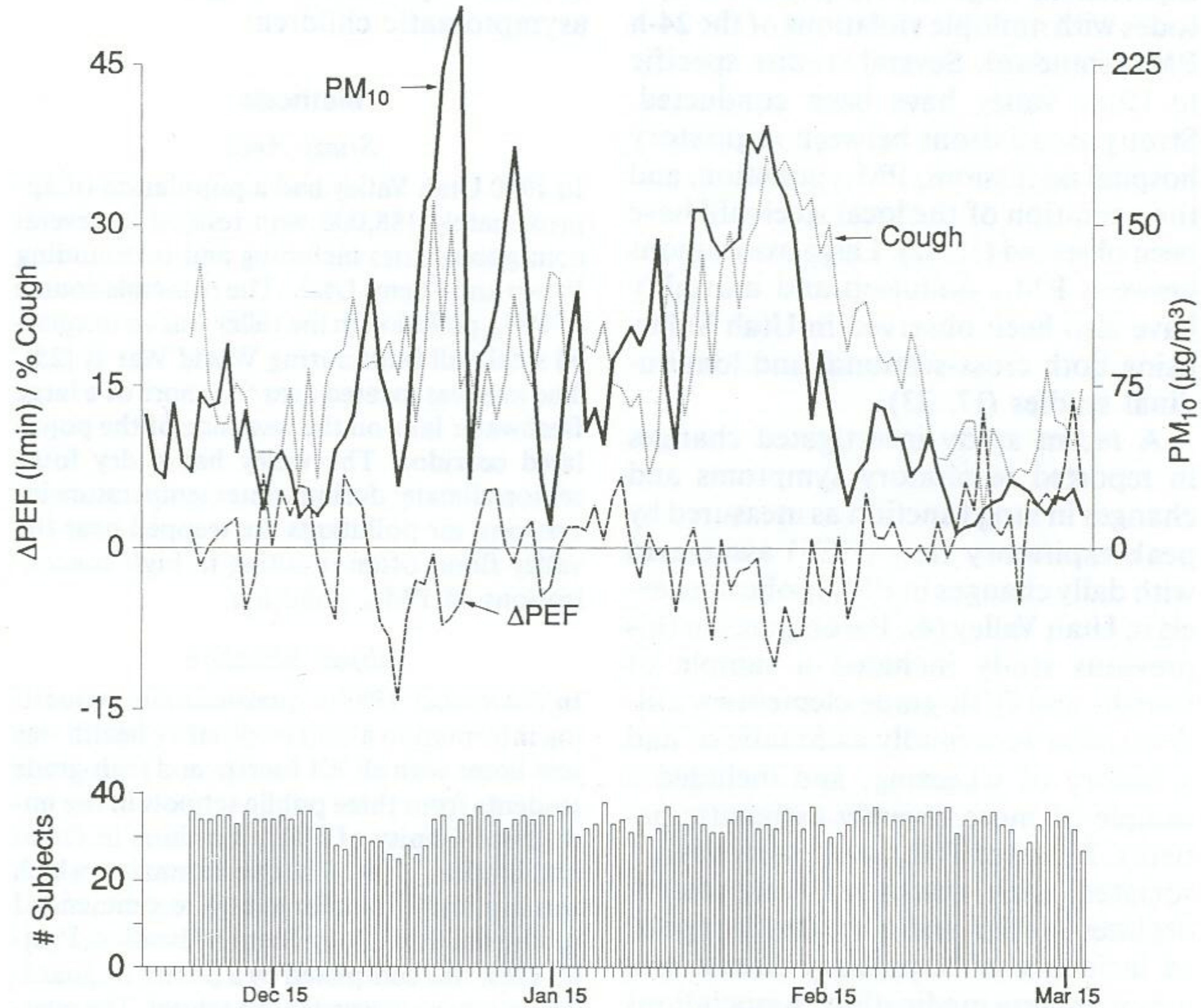

Fig. 1. Daily PM_{10} levels, mean peak expiratory flow deviations (ΔPEF), percentage who reported cough, and number of participants for the symptomatic sample.

Summary of early Utah Valley epidemiological studies

Health effects

- **Increased hospital admissions**
- **Increased respiratory symptoms**
- **Reduced lung function**
- **Increased school absences**
- **Increased respiratory and cardiovascular deaths**

Study References

Pope (1989) Am. J. Public Health
Pope (1991) Arch. Environ. Health

Pope, Dockery, Spengler, Raizenne (1991) Am. Rev. Resp. Dis.
Pope, Dockery (1992) Am. Rev. Resp. Dis.
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Pope, Schwartz, Ransom (1992) Arch. Environ. Health
Pope, Kalkstein (1996) Environ. Health Perspect.
Pope, Hill, Villegas (1999) Environ. Health Perspect.

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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
2006;114:2443-48

Ischemic Heart Disease Events Triggered by Short-Term Exposure to Fine Particulate Air Pollution

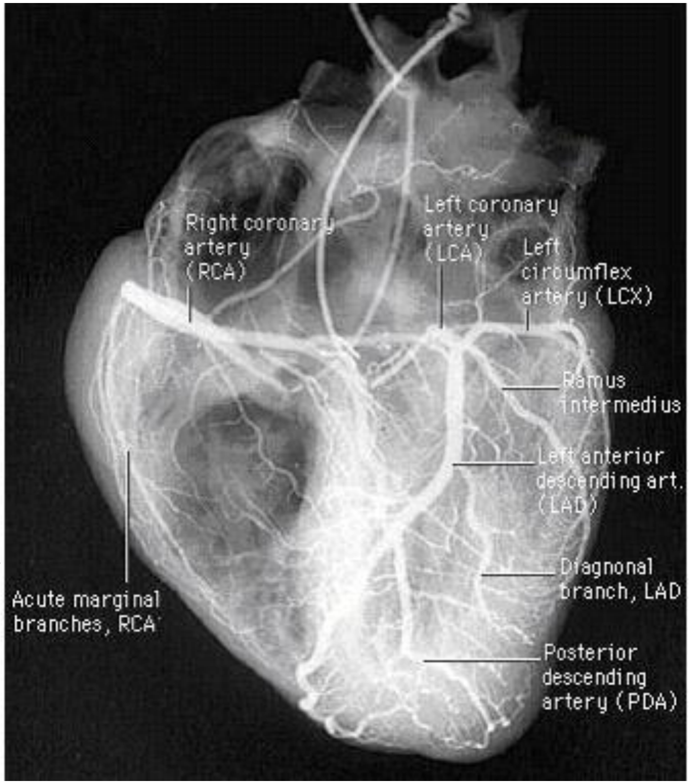
C. Arden Pope III, PhD; Joseph B. Muhlestein, MD; Heidi T. May, MSPH; Dale G. Renlund, MD; Jeffrey L. Anderson, MD; Benjamin D. Horne, PhD, MPH

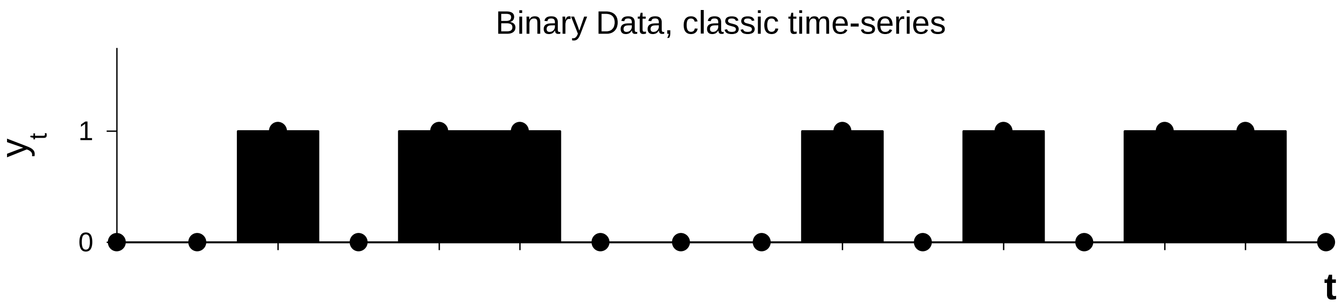

Jeffrey Anderson

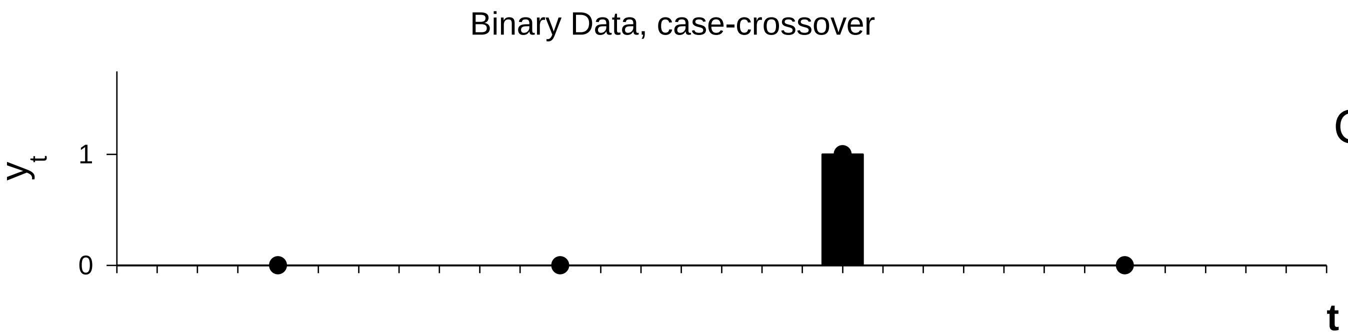
Methods:

Case-crossover study of acute ischemic coronary events (heart attacks and unstable angina) in 12,865 well-defined and followed up cardiac patients who lived on Utah's Wasatch Front

…and who underwent coronary angiography







Conditional Logistic Reg.

Each subject serves as his/her own control.

Control for subject-specific effects, day of week, season, time-trends, etc.—by matching

Conditional logistic regression:

$$\ln\left(\frac{\text{Prob}(Y_t = 1)}{1 - \text{Prob}(Y_t = 1)}\right) =$$

$$\alpha_1 + \alpha_2 + \alpha_3 + \ldots + \alpha_{12,865} + \beta(w_0 P_t + w_1 P_{t-1} + w_2 P_{t-2} + \ldots)$$

Control by matching for:

All cross-subject differences

(in this case, 12,865 subject-level fixed effects),

Season and/or month of year,

Time trends,

Day of week

Modeling controversies: How to select control or referent periods. Time stratified referent selection approach (avoids bias that can occur due to time trends in exposure) (**Holly Janes, Lianne Sheppard, Thomas Lumley** Statistics in Medicine and Epidemiology 2005)

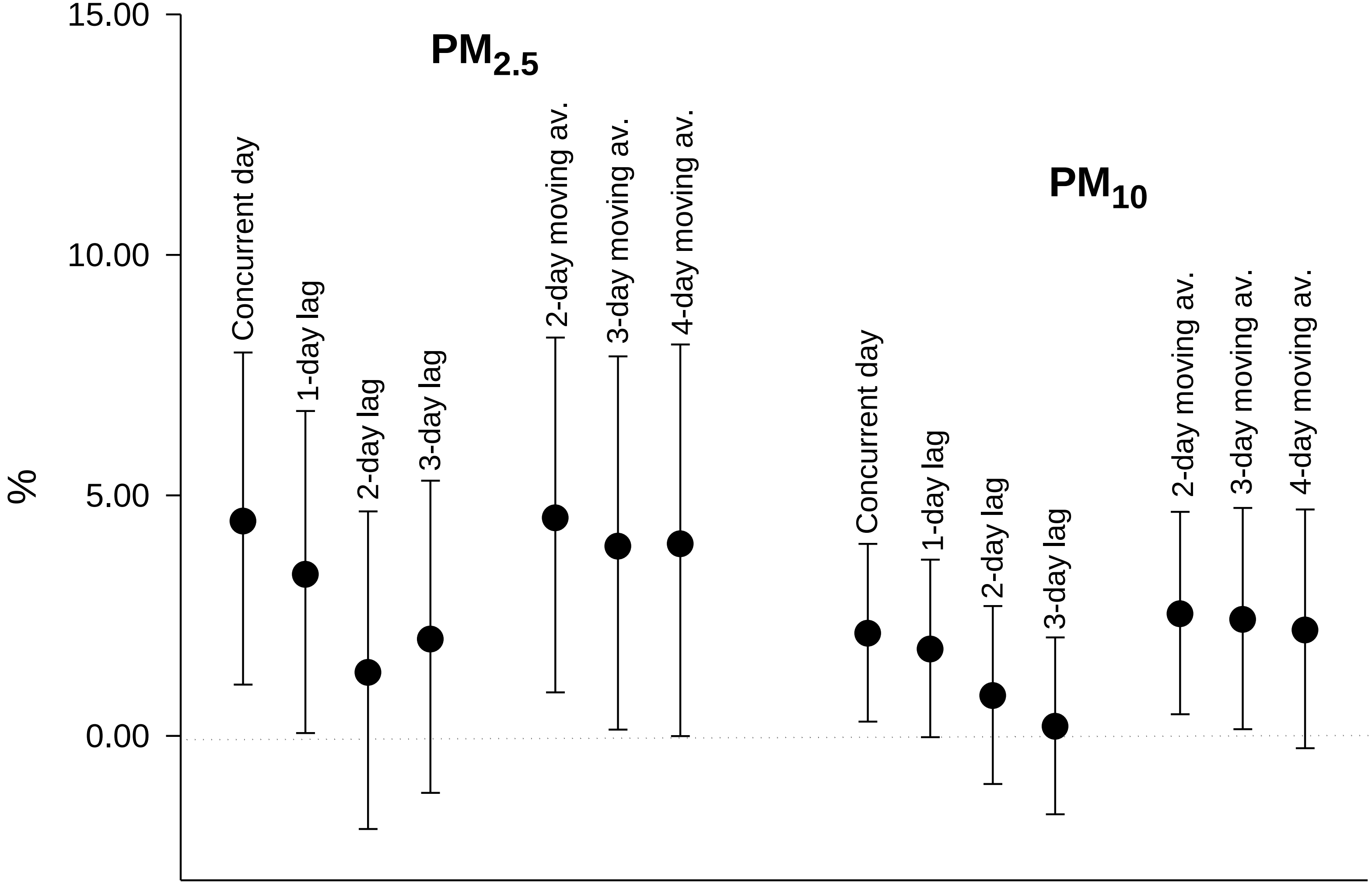


Figure 1. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 $\mu g/m^3$ of $PM_{2.5}$, or PM_{10} for different lag structures.

Short-term PM exposures contributed to acute coronary events, especially among patients with underlying coronary artery disease.

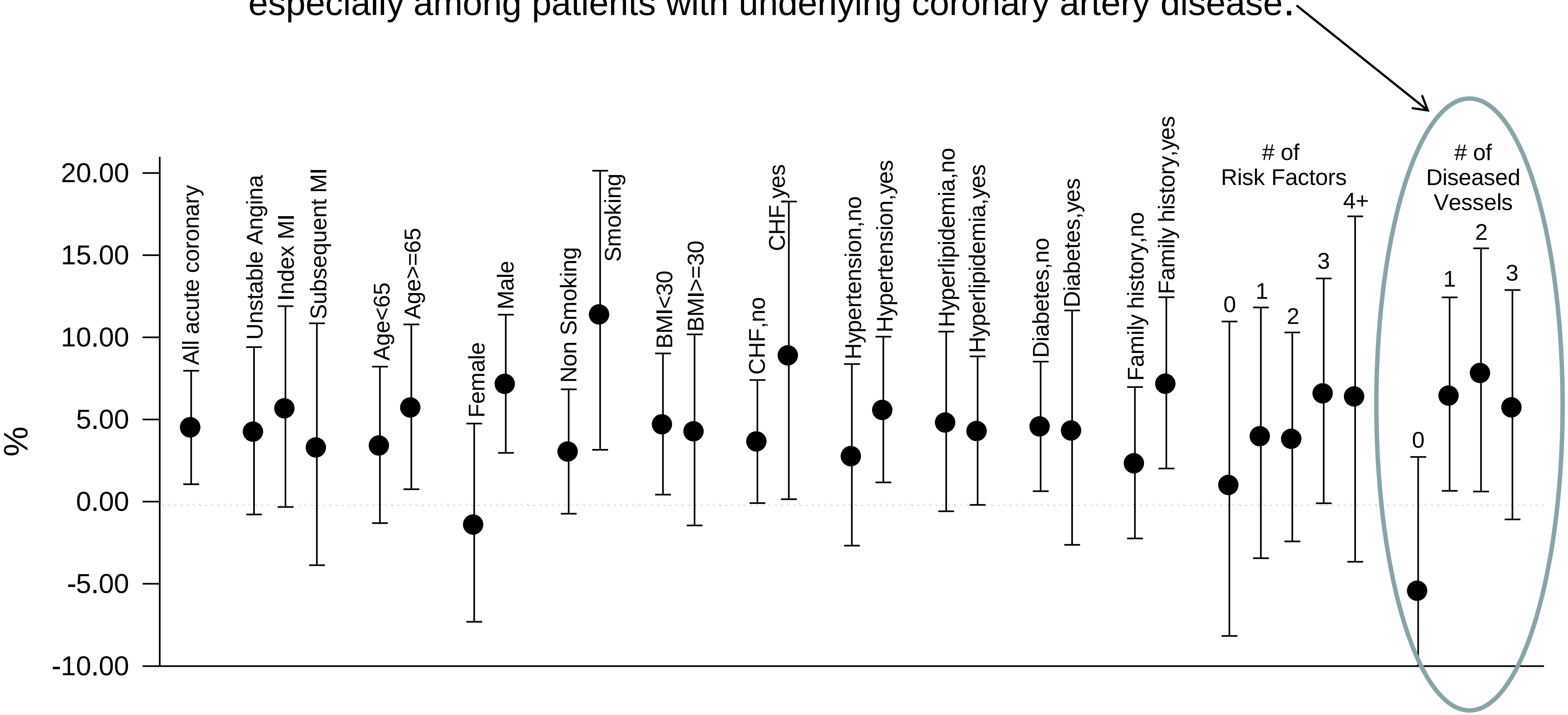


Figure 2. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 $\mu g/m^3$ of $PM_{2.5}$, stratified by various characteristics.

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Any Questions?

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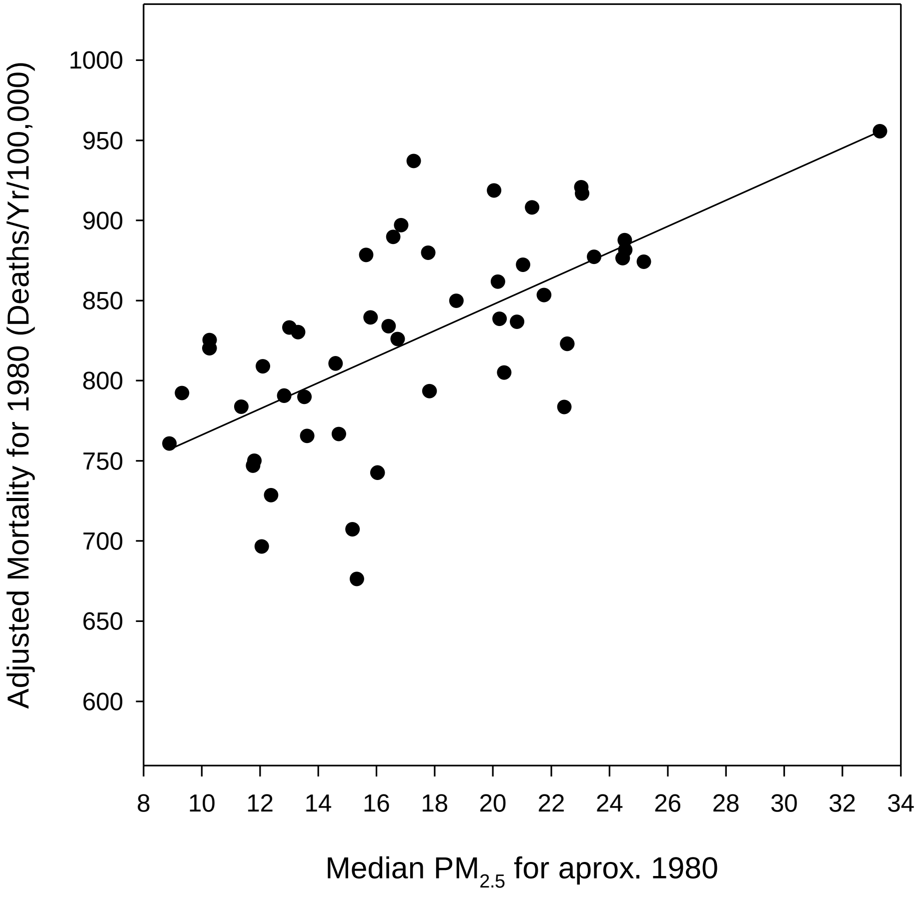
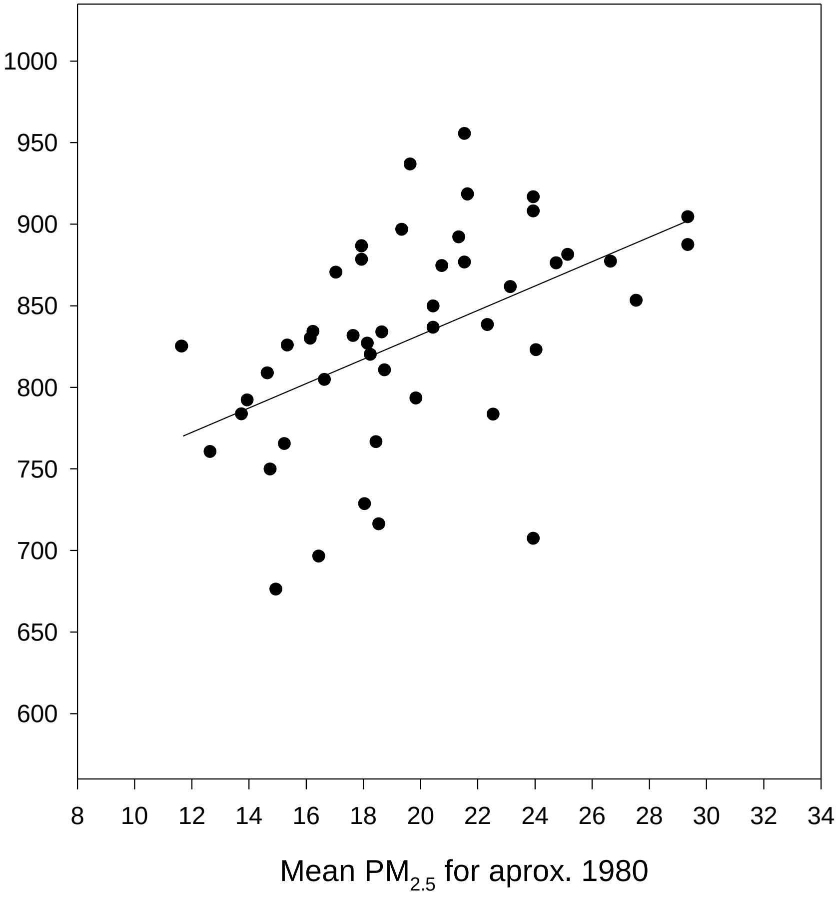
Age-, sex-, and race- adjusted population-based mortality rates in U.S. cities for 1980 plotted over various indices of particulate air pollution (From Pope 2000).





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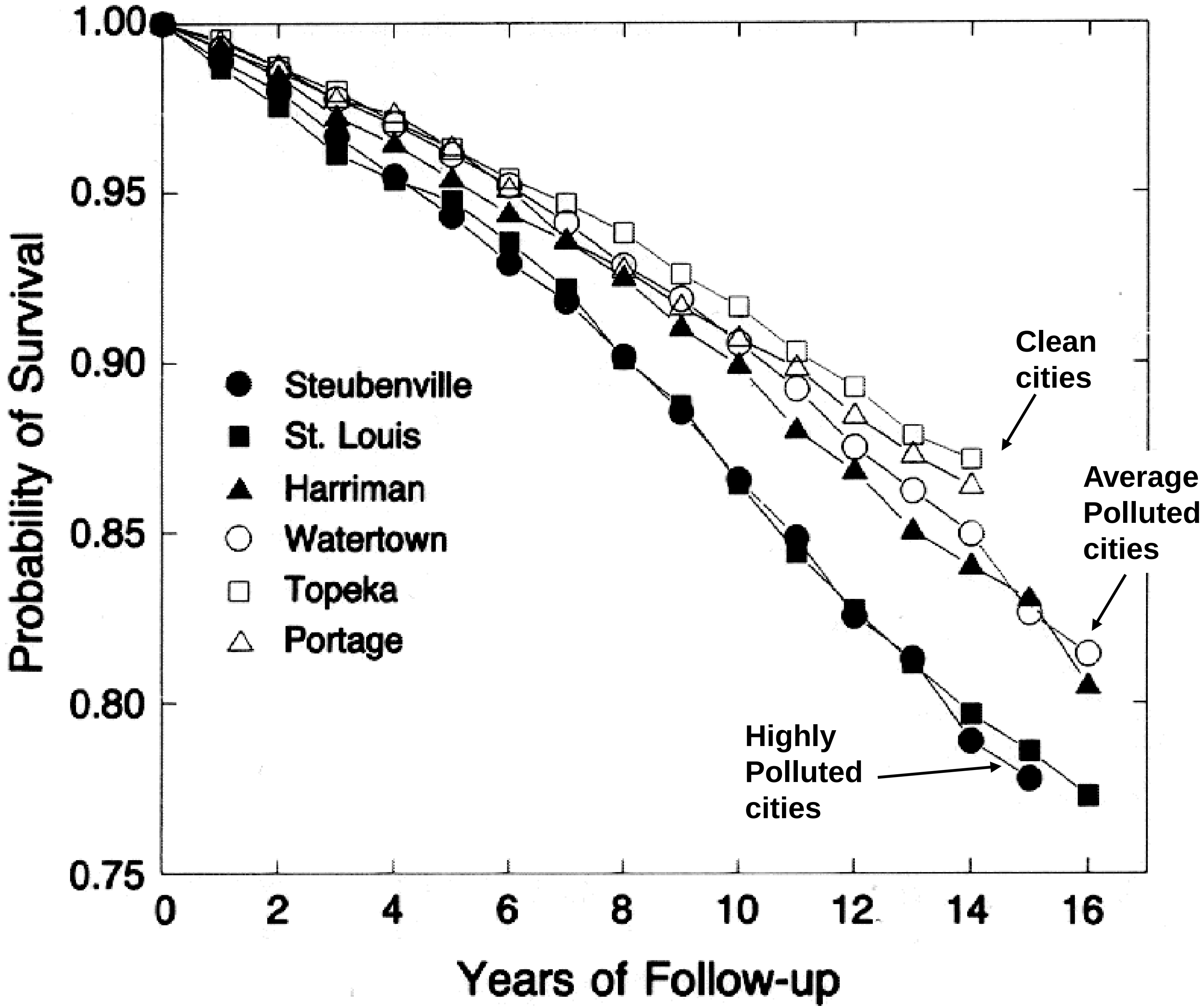
An Association Between Air Pollution and Mortality in Six U.S. Cities

The NEW ENGLAND JOURNAL of MEDICINE 1993

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE.

Methods:

- 14-16 yr prospective follow-up of 8,111 adults living in six U.S. cities.
- Monitoring of TSP PM_{10}, $PM_{2.5}$, SO_4, H^+, SO_2, NO_2, O_3 .
- Data analyzed using survival analysis, including Cox Proportional Hazards Models.
- Controlled for individual differences in: age, sex, smoking, BMI, education, occupational exposure.



Probability of Survival
1.00
0.95
0.90
0.85
0.80
0.75
0
2
4
6
8
10
12
14
16
Years of Follow-up
Steubenville
St. Louis
Harriman
Watertown
Topeka
Portage
Clean cities
Average Polluted cities
Highly Polluted cities

Cox Proportional Hazards Survival Model

Cohort studies of outdoor air pollution have commonly used the CPH Model to relate survival experience to exposure while simultaneously controlling for other well known mortality risk factors. The model has the form

$$\lambda_i^{(l)}(t) = \lambda_0^{(l)}(t)\, exp\left(\beta^T x_i^{(l)}(t)\right)$$

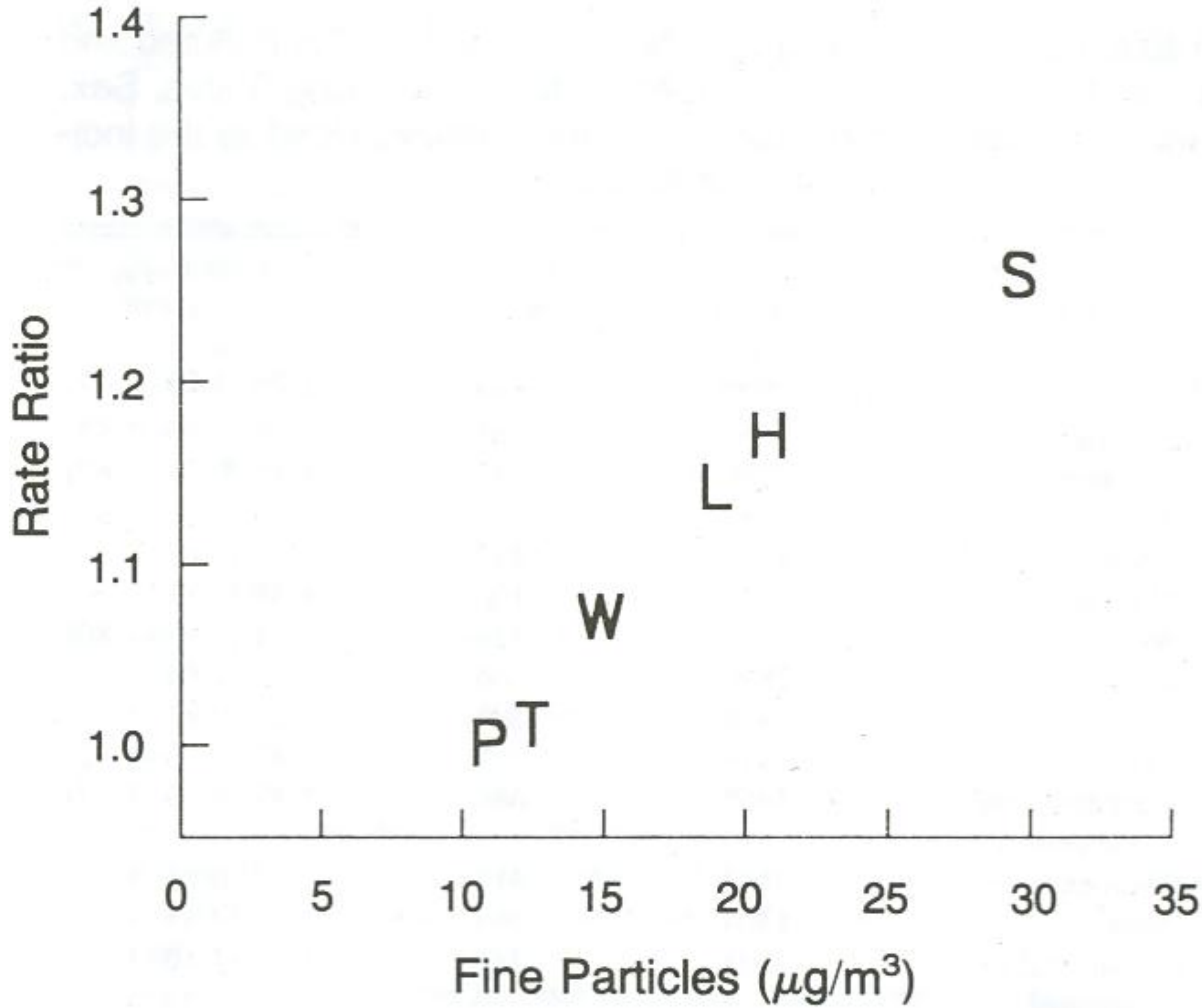
Hazard function or instantaneous probability of death for the *i*th subject in the *l*th strata.

Baseline hazard function, common to all subjects within a strata.

Regression equation that modulates the baseline hazard. The vector $X_i^{(l)}$ contains the risk factor information related to the hazard function by the regression vector β which can vary in time.

Adjusted risk ratios (and 95% CIs) for cigarette smoking and $PM_{2.5}$

Cause of Death	Current Smoker, 25 Pack years	Most vs. Least Polluted City
All	2.00 (1.51-2.65)	**1.26** (1.08-1.47)
Lung Cancer	8.00 (2.97-21.6)	**1.37** (0.81-2.31)
Cardio-pulmonary	2.30 (1.56-3.41)	**1.37** (1.11-1.68)
All other	1.46 (0.89-2.39)	**1.01** (0.79-1.30)



Rate Ratio
1.4
1.3
1.2
1.1
1.0
S
H
L
W
T
P
0
5
10
15
20
25
30
35
Fine Particles (μg/m³)

Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults

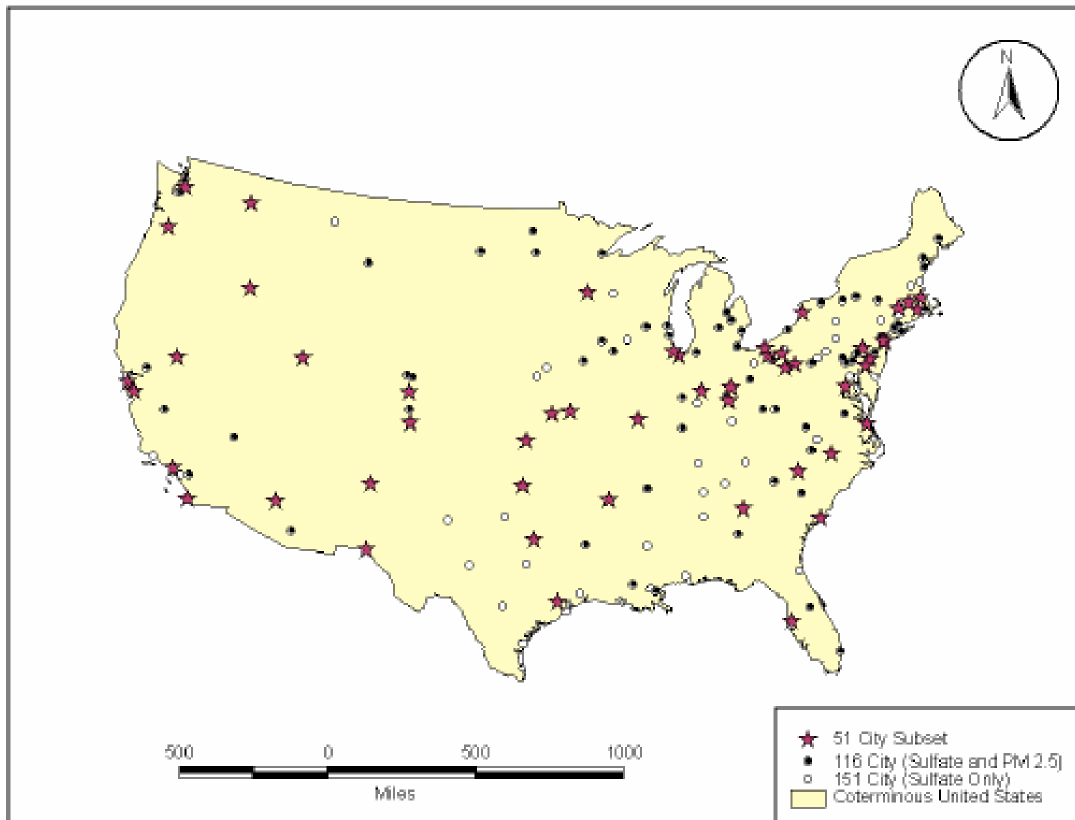
Michael Thun

Pope CA III, Thun MJ, Namboodiri MM,
Dockery DW, Evans JS, Speizer FE, Heath CW Jr.

AMERICAN JOURNAL OF Respiratory and Critical Care Medicine® 1995

Clark Heath

Methods: Linked and analyzed ambient air pollution data from 51-151 U.S. metro areas with risk factor data for over 500,000 adults enrolled in the ACS-CPSII cohort.



Adjusted mortality risk ratios (and 95% CIs) for cigarette smoking the range of sulfates and fine particles

Cause of Death	Current Smoker	Sulfates	Fine Particles
All	2.07 (1.75-2.43)	1.15 (1.09-1.22)	1.17 (1.09-1.26)
Lung Cancer	9.73 (5.96-15.9)	1.36 (1.11-1.66)	1.03 (0.80-1.33)
Cardio-Pulmonary	2.28 (1.79-2.91)	1.26 (1.16-1.37)	1.31 (1.17-1.46)
All other	1.54 (1.19-1.99)	1.01 (0.92-1.11)	1.07 (0.92-1.24)



Dan Krewski
Rick Burnett
Mark Goldberg
and 28 others

HEI

SPECIAL REPORT

HEALTH
EFFECTS
INSTITUTE

July 2000

Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

A Special Report of the Institute's Particle Epidemiology Reanalysis Project

JAMA®
The Journal of the American Medical Association
March 6, 2002—Vol 287, No. 9

Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution

C. Arden Pope III, PhD
Richard T. Burnett, PhD
Michael J. Thun, MD
Eugenia E. Calle, PhD
Daniel Krewski, PhD
Kazuhiko Ito, PhD
George D. Thurston, ScD

Context Associations have been found between day-to-day particulate ai
and increased risk of various adverse health outcomes, including cardiopulmc
tality. However, studies of health effects of long-term particulate air pollu
been less conclusive.

Objective To assess the relationship between long-term exposure to fir
late air pollution and all-cause, lung cancer, and cardiopulmonary mortalit

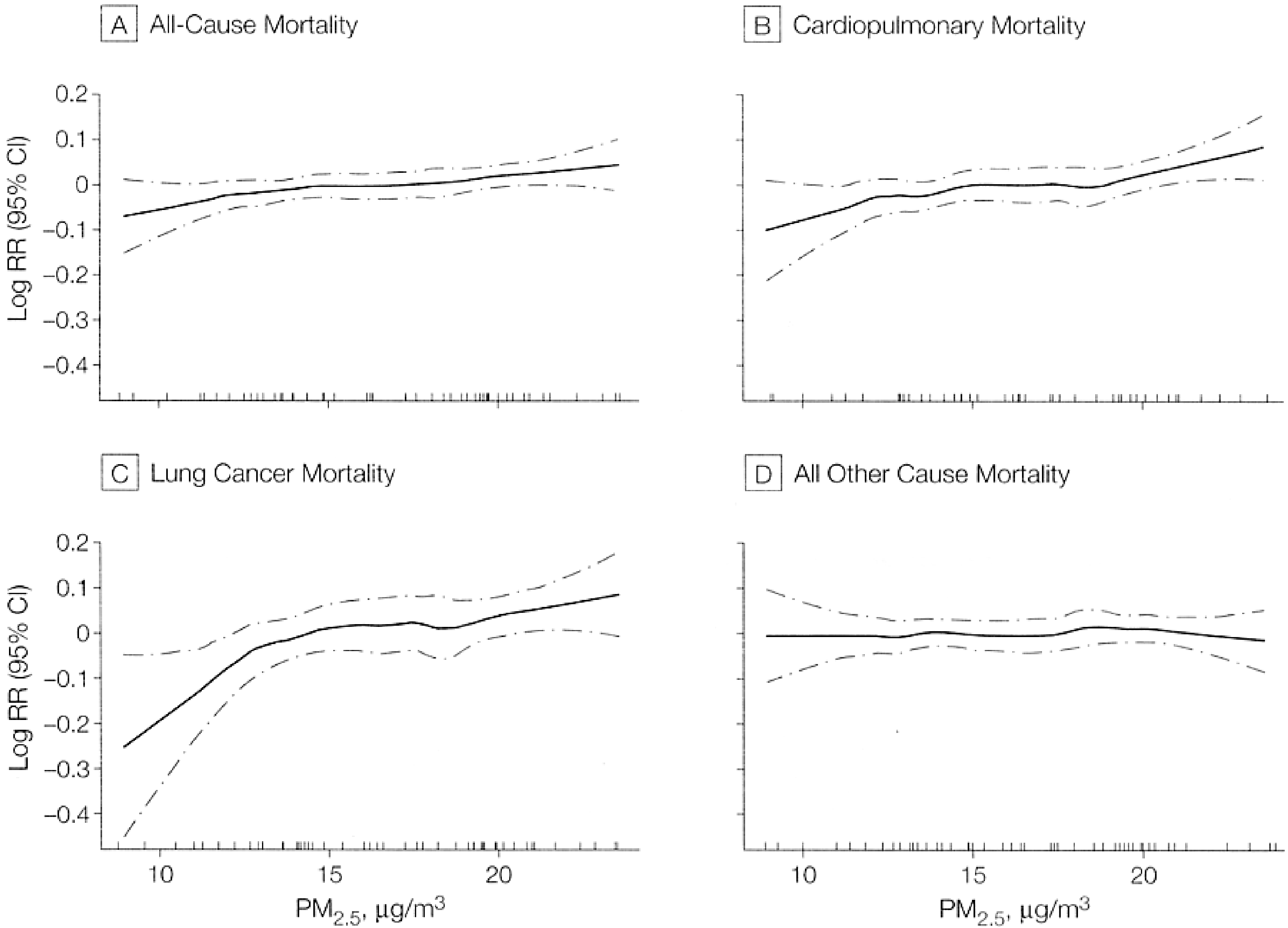
Design, Setting, and Participants Vital status and cause of death data
lected by the American Cancer Society as part of the Cancer Prevention II stu
going prospective mortality study, which enrolled approximately 1.2 million adu







Figure 2. Nonparametric Smoothed Exposure Response Relationship



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

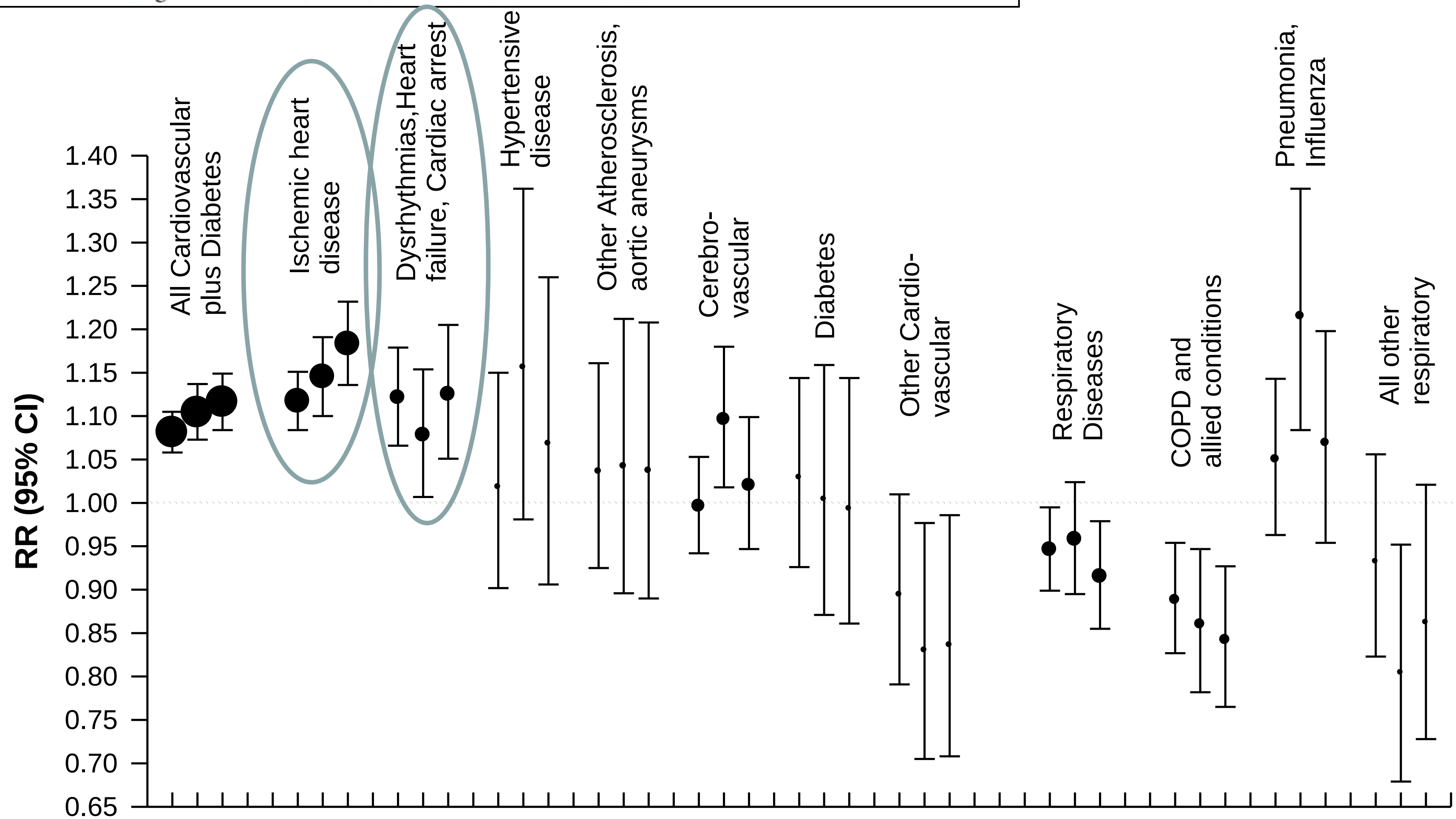
2004;109:71-

Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution

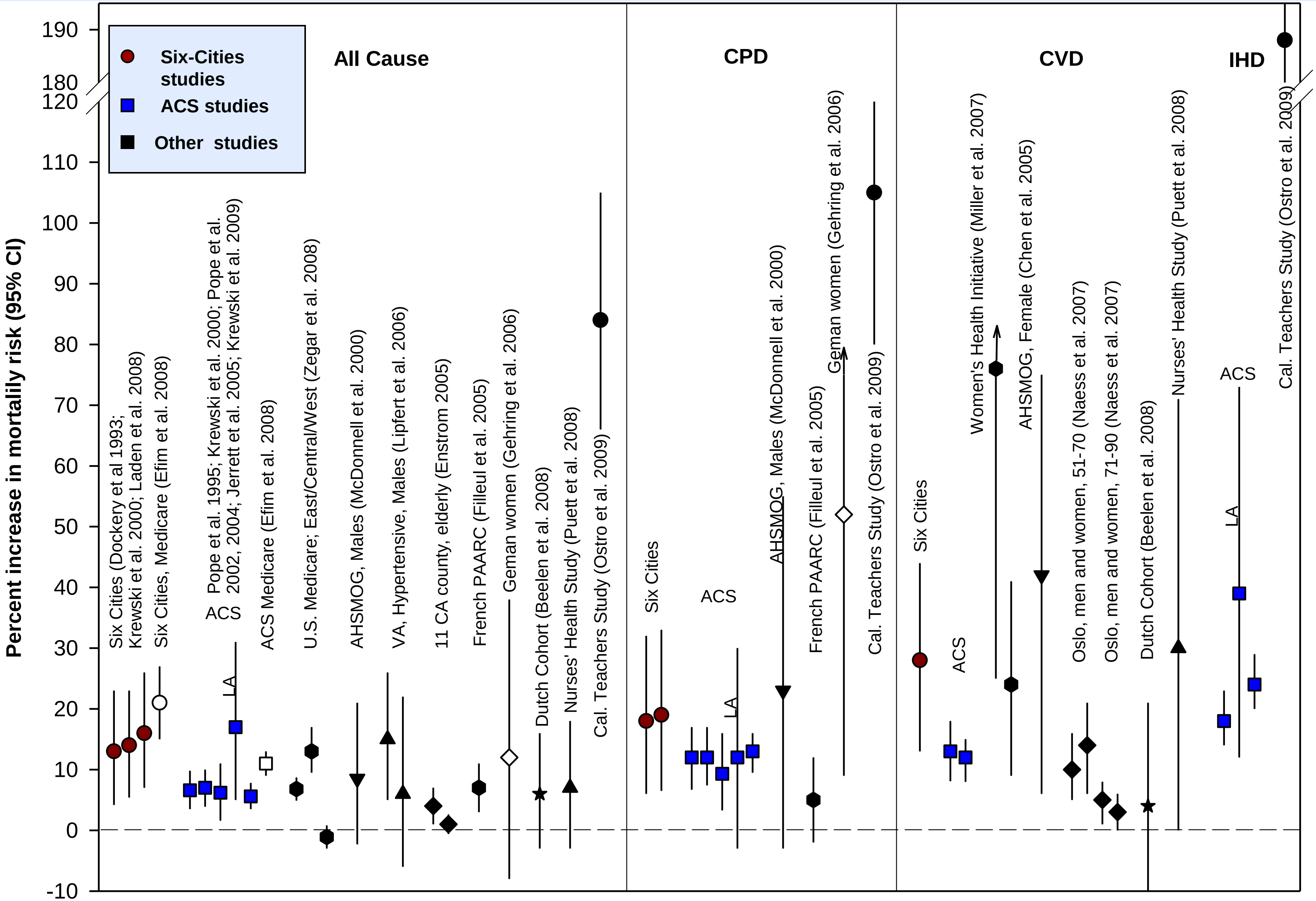
Epidemiological Evidence of General Pathophysiological Pathways of Disease

C. Arden Pope III, PhD; Richard T. Burnett, PhD; George D. Thurston, ScD; Michael J. Thun, MD; Eugenia E. Calle, PhD; Daniel Krewski, PhD; John J. Godleski, MD

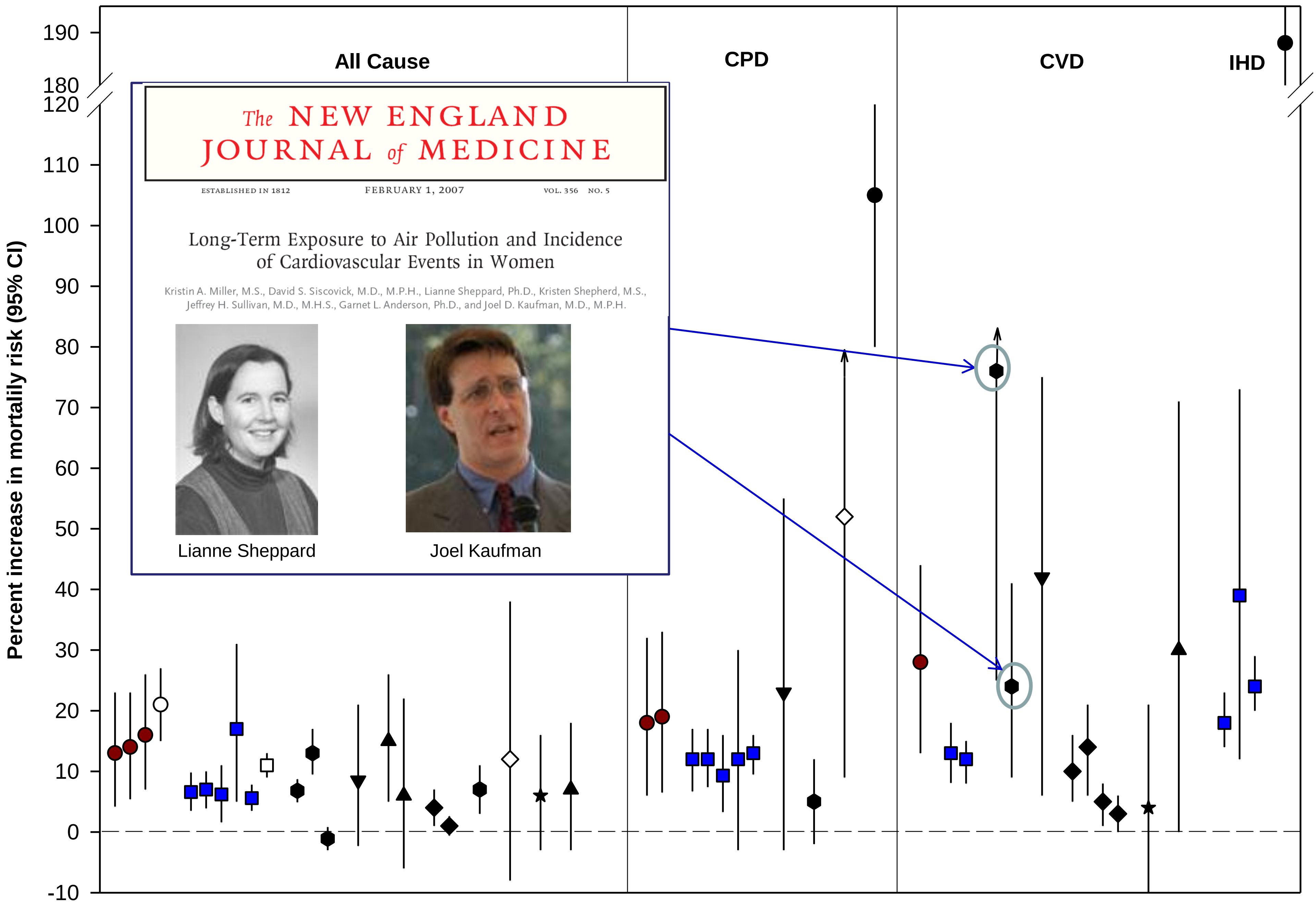
John Godleski

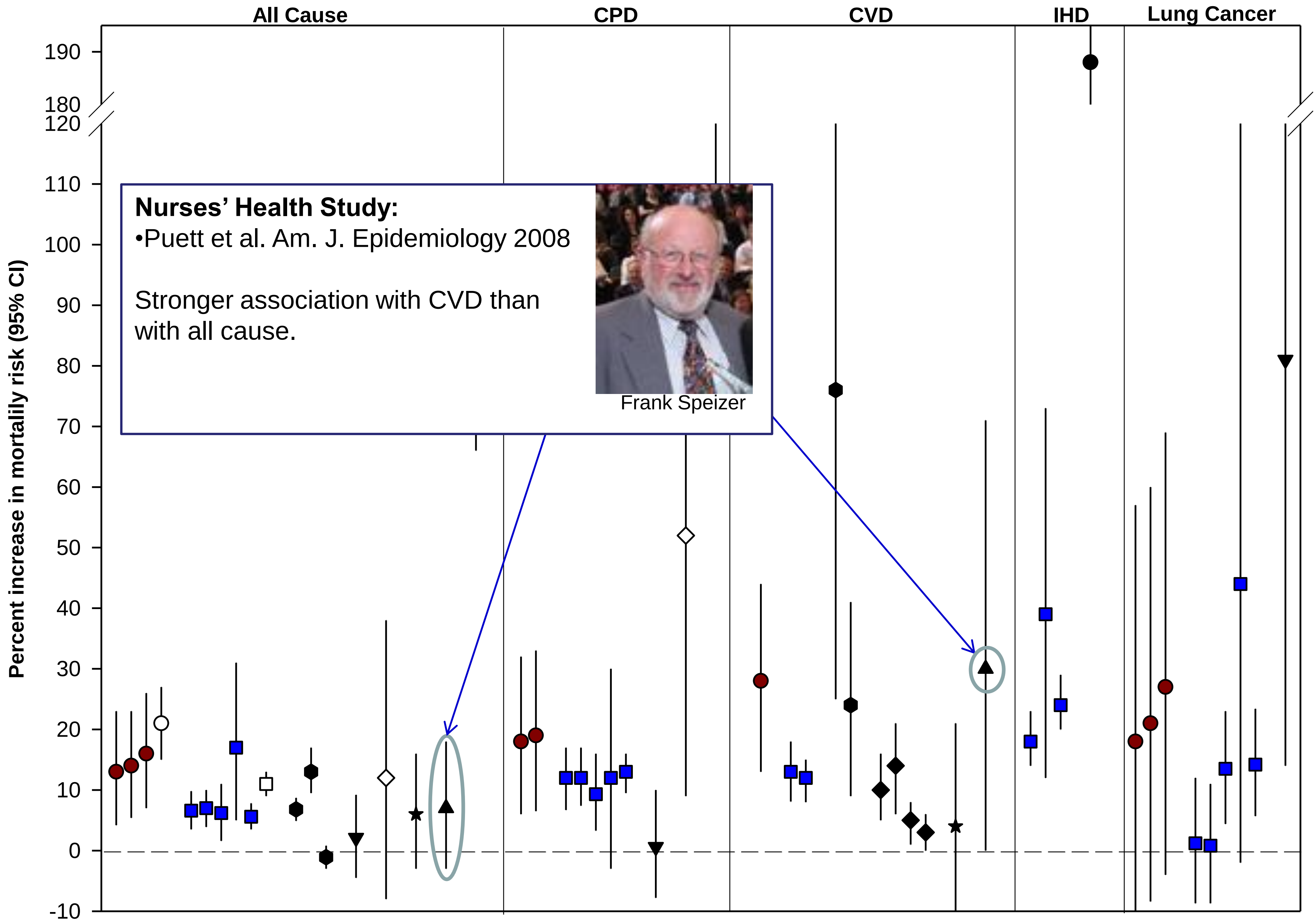


Other cohort studies have shown associations between exposure to fine PM and increased risk of cardiovascular death.



Women’s Health Initiative Study





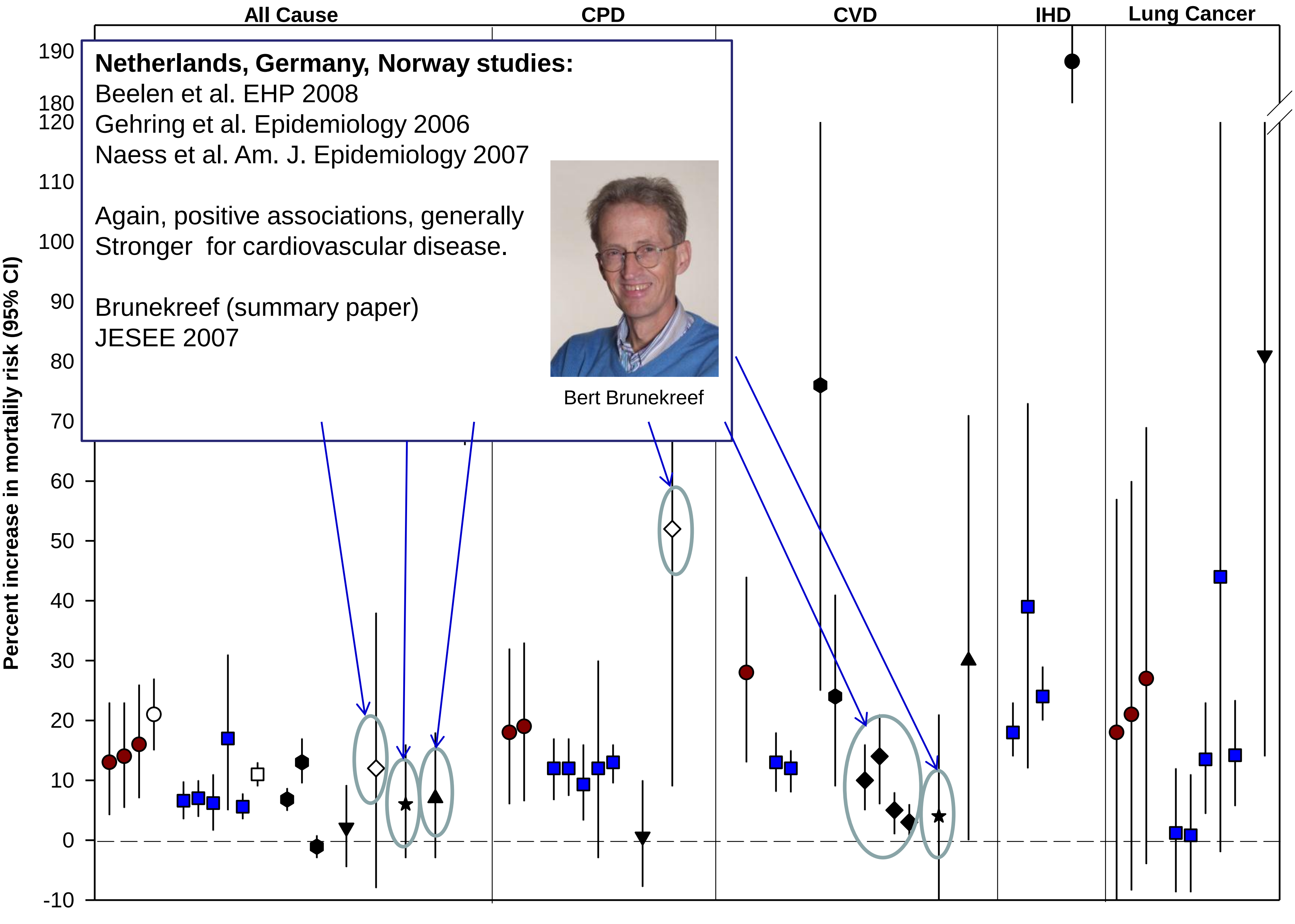
All Cause
CPD
CVD
IHD
Lung Cancer
Percent increase in mortality risk (95% CI)
190
180
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Nurses' Health Study:
•Puett et al. Am. J. Epidemiology 2008
Stronger association with CVD than with all cause.
Frank Speizer

Netherlands, Germany, Norway studies:
Beelen et al. EHP 2008
Gehring et al. Epidemiology 2006
Naess et al. Am. J. Epidemiology 2007

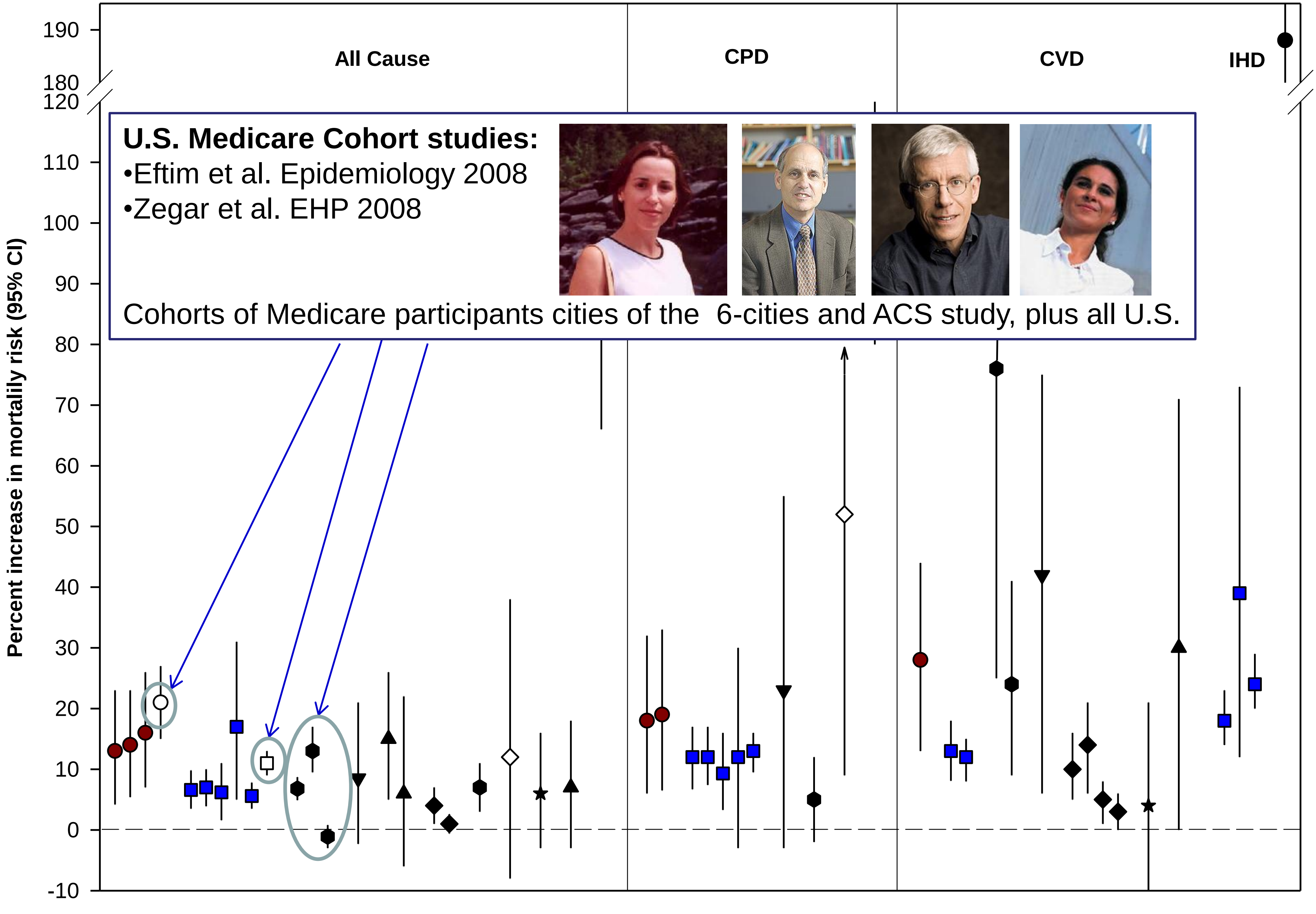
Again, positive associations, generally
Stronger for cardiovascular disease.

Brunekreef (summary paper)
JESEE 2007

Bert Brunekreef



U.S. Medicare Cohort Studies



U.S. Medicare Cohort studies:

- Eftim et al. Epidemiology 2008
- Zegar et al. EHP 2008

Cohorts of Medicare participants cities of the 6-cities and ACS study, plus all U.S.

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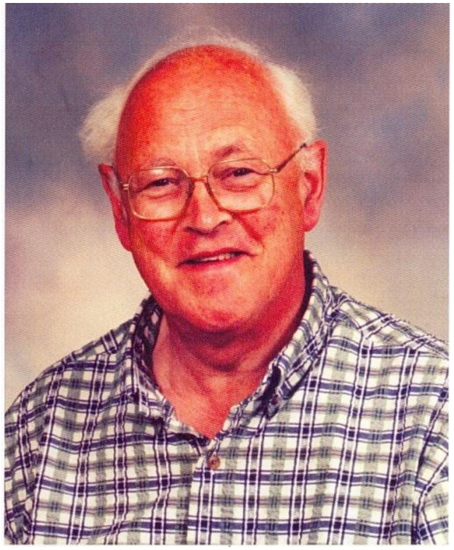
- Population-based cross-sectional
- Cohort-based mortality
- Cohort- and panel-based morbidity
- Case-control studies

Intervention/natural experiment (months-years)

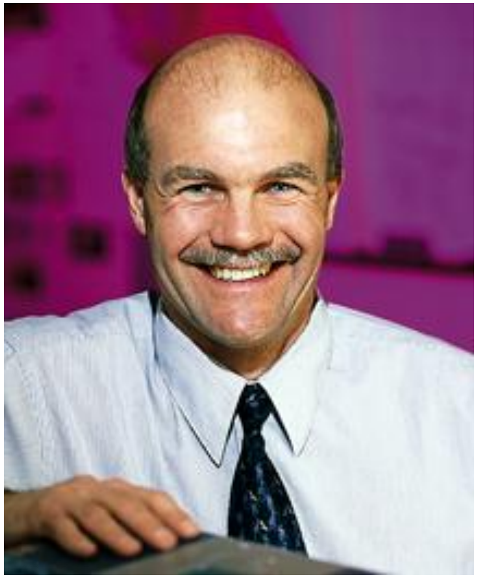
Controlled experimental human and animal

Southern California Children's Health Study

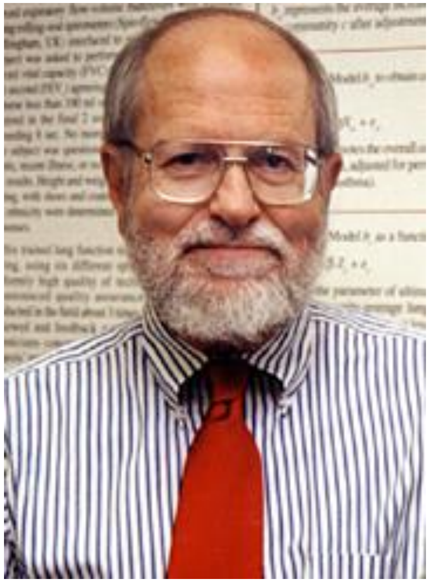
Effects of air pollution on children's health, especially lung function growth.



David Bates, Advisor

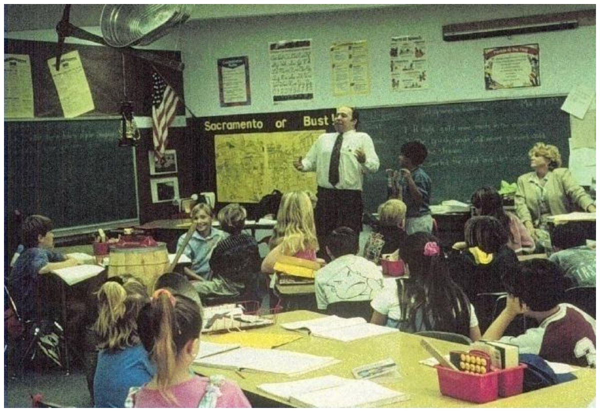


W. James Gauderman



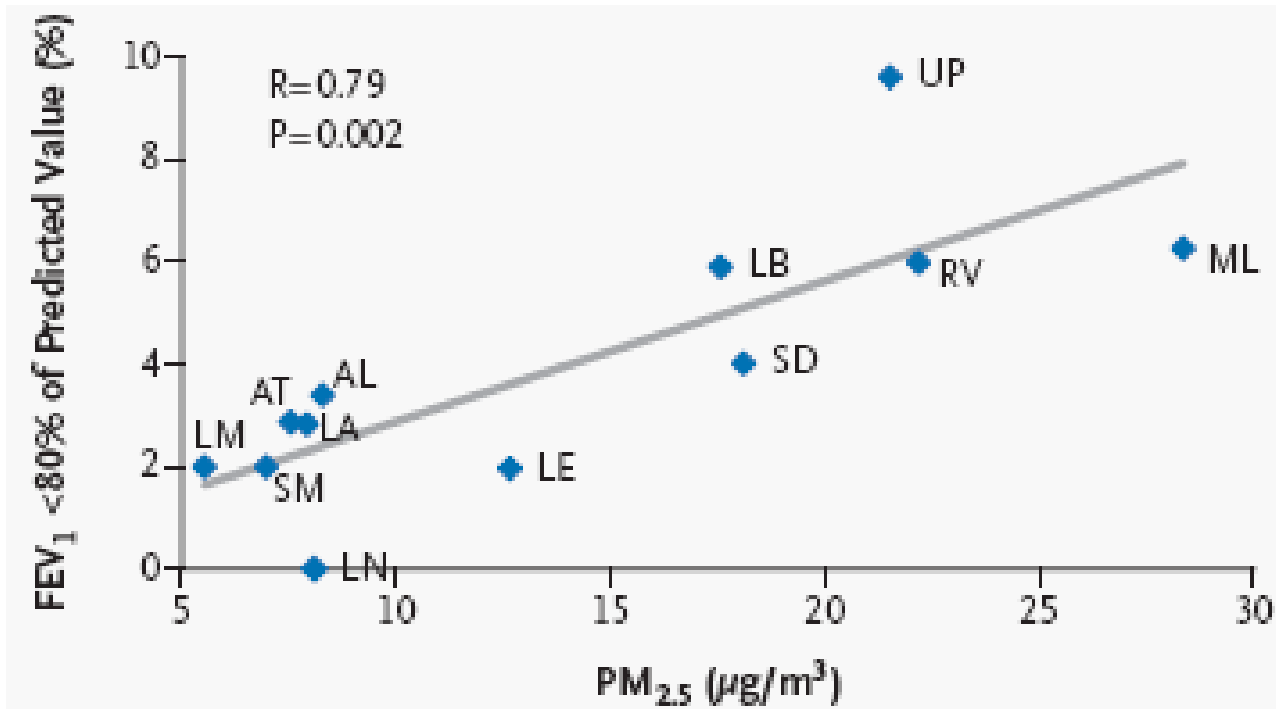
John Peters

Southern California Children's Health Study, has shown that **air pollution impacts lung development in children.**



THE LANCET

Gauderman et al. 2007



Children living in cities with higher air pollution and living near major traffic sources showed greater deficits in lung function growth.

This presentation not organized chronologically, but methodologically

Studies of short-term exposure (hours-days)

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The NEW ENGLAND JOURNAL of MEDICINE

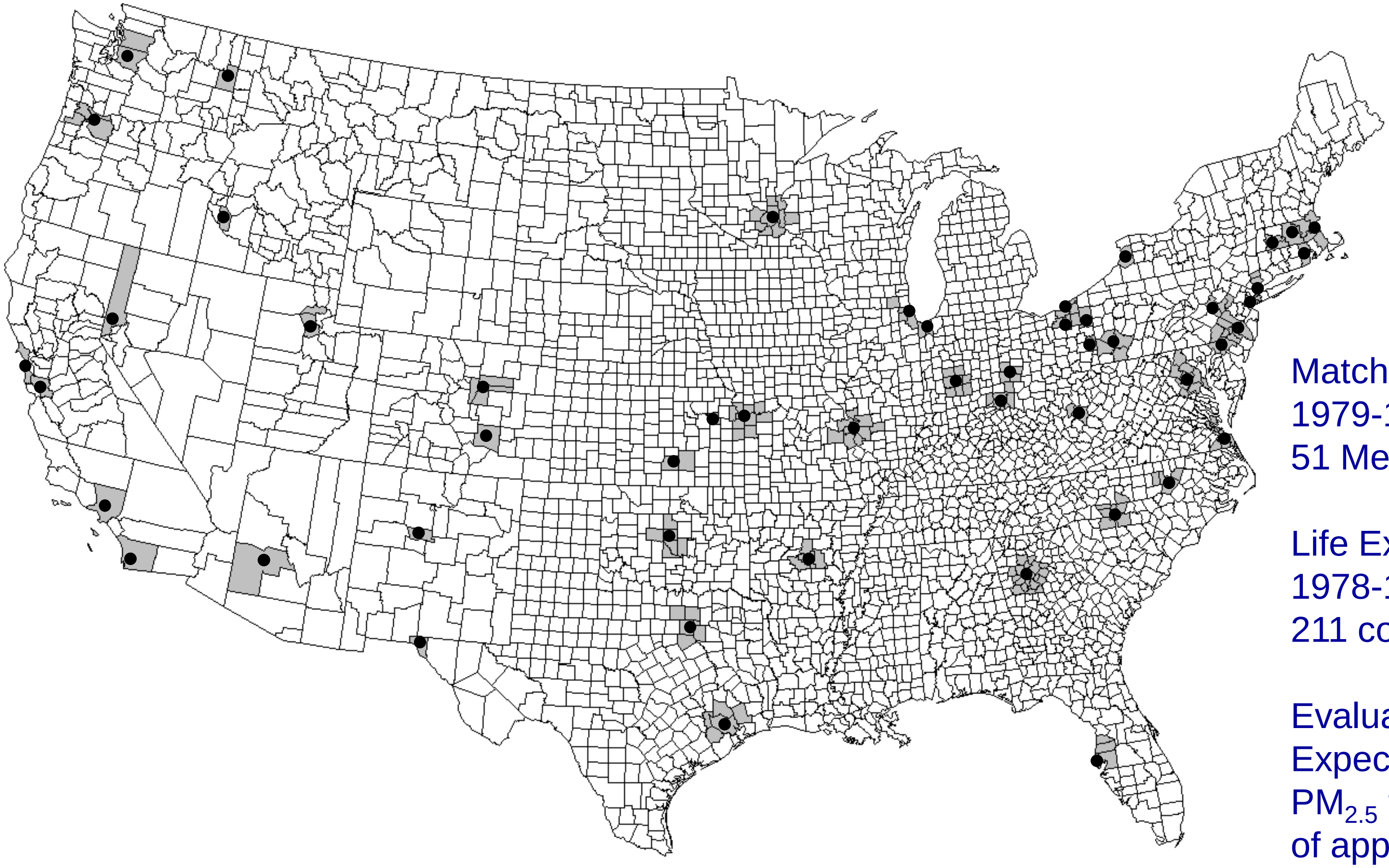
Fine-Particulate Air Pollution and Life Expectancy in the United States

C. Arden Pope, III, Ph.D., Majid Ezzati, Ph.D., and Douglas W. Dockery, Sc.D.

January 22, 2009

Majid Ezzati

Doug Dockery



Matching $PM_{2.5}$ data for 1979-1983 and 1999-2000 in 51 Metro Areas

Life Expectancy data for 1978-1982 and 1997-2001 in 211 counties in 51 Metro areas

Evaluate changes in Life Expectancy with changes in $PM_{2.5}$ for the 2-decade period of approximately 1980-2000.

Covariates included in the regression models

Changes in socio-economic and demographic variables (from U.S. Census Data):

- Per capita income
- Population
- 5-yr in-migration
- High-school graduates
- Urban population
- Black proportion of population
- Hispanic proportion of population

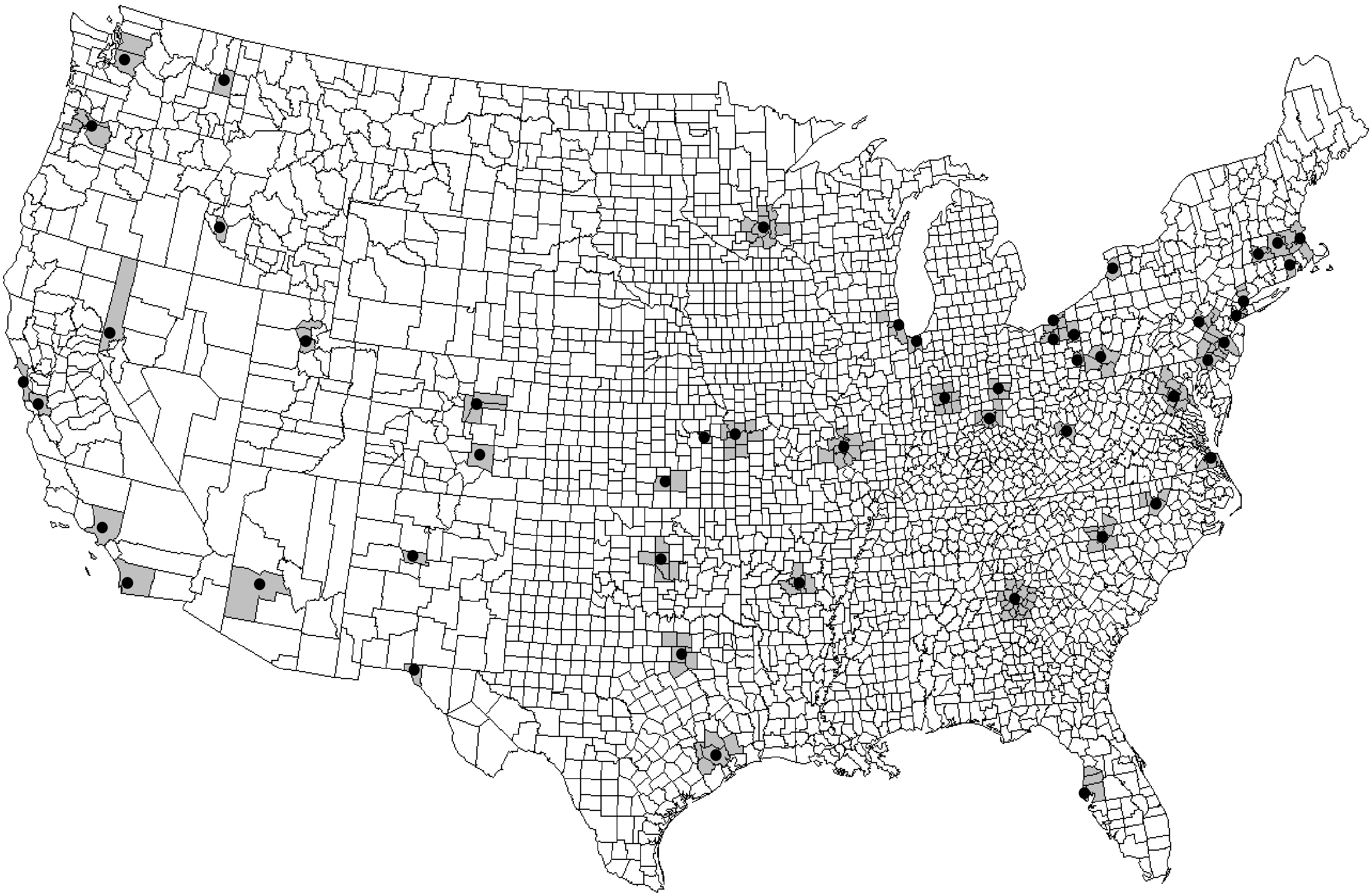
Proxy cigarette smoking variables—available for all 211 counties

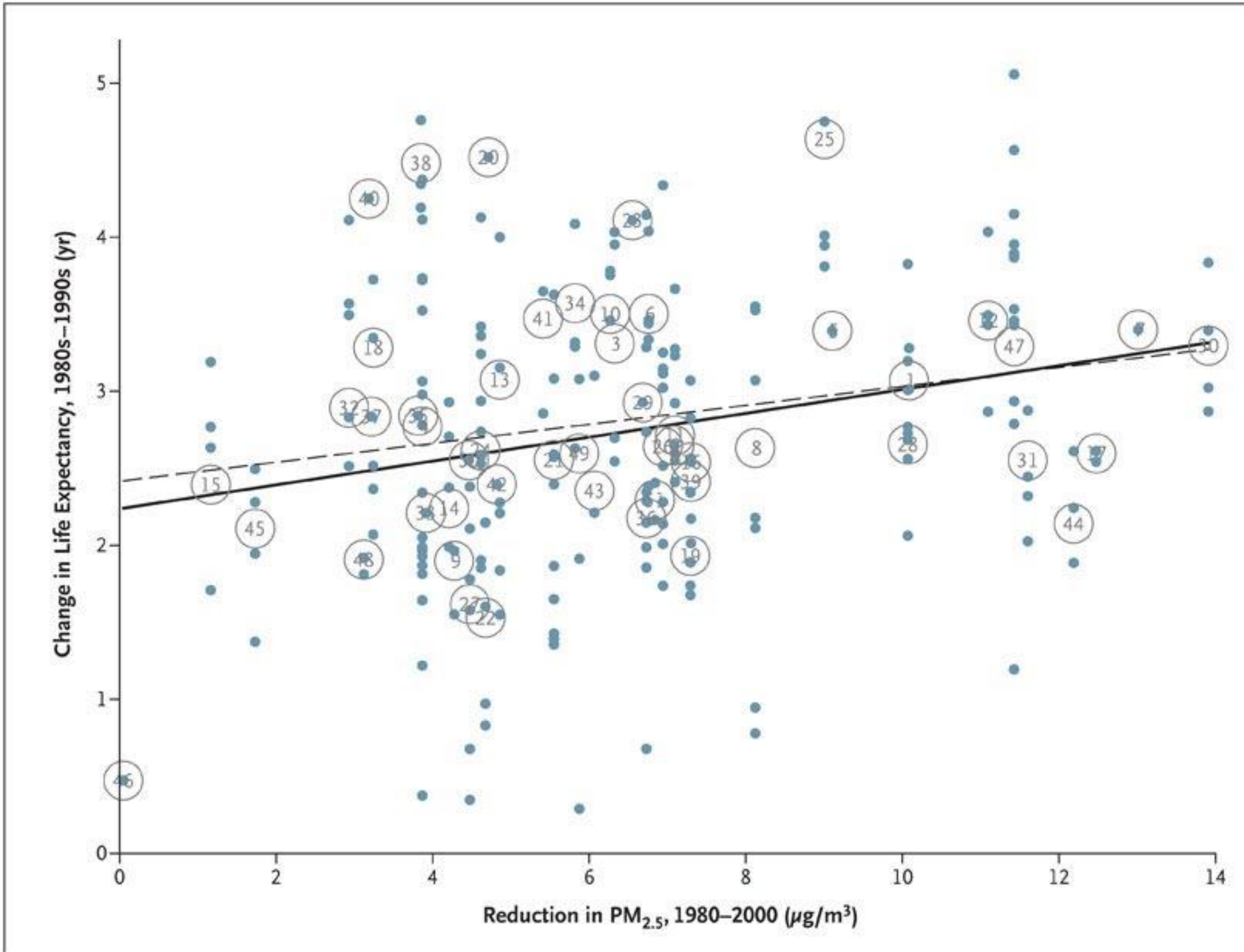
- COPD mortality rates
- Lung Cancer mortality rates

Survey-based metro-area estimates of smoking prevalence

- National Health Interview Survey (1978-1980)
- Behavioral Risk Factor Surveillance System (1998-2000)
- Matching data available for only 24 of 51 metro areas

- Clustered standard errors (clustered by the 51 metro areas) were estimated for all models except for analysis that included only the 51 largest counties in each metro area.





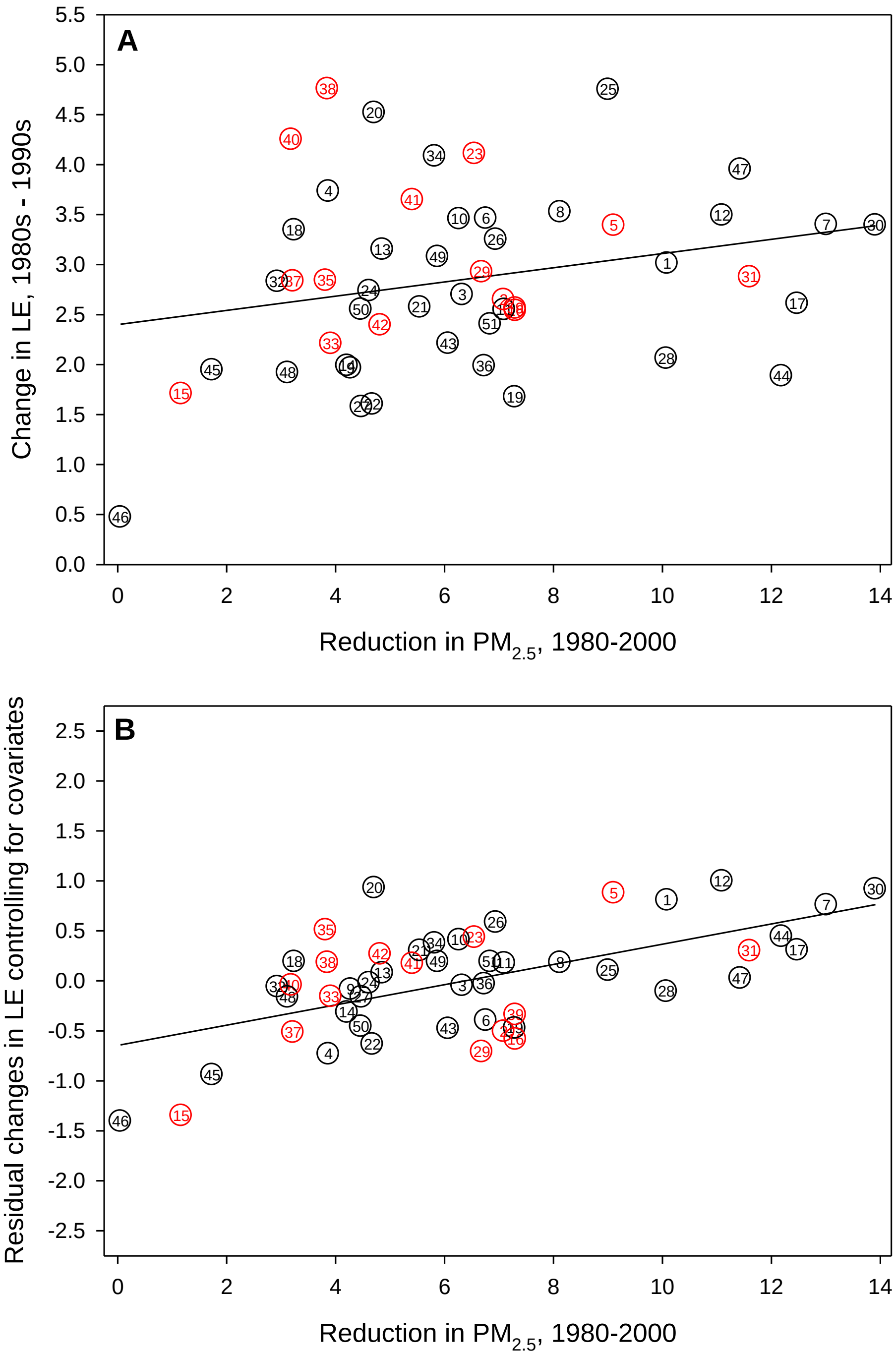
Change in Life Expectancy, 1980s–1990s (yr)
Reduction in PM2.5, 1980–2000 (μg/m3)
0
1
2
3
4
5
0
2
4
6
8
10
12
14

A 10 µg/m^3 decrease in $PM_{2.5}$ was associated with a **7.3 (± 2.4) month** increase in life expectancy.

Table 2. Results of Selected Regression Models, Including Estimates of the Increase in Life Expectancy Associated with a Reduction in $PM_{2.5}$ of 10 µg per Cubic Meter, Adjusted for Socioeconomic, Demographic, and Proxy Indicators for Prevalence of Smoking.*

Variable	Model 1	Model 2	Model 3	Model 4	Model 5†	Model 6‡	Model 7‡
				years			
Intercept	2.25±0.21§	0.80±0.19§	1.78±0.27§	1.75±0.27§	2.02±0.34§	1.71±0.51§	2.09±0.36§
Reduction in $PM_{2.5}$ (10 µg/m^3)	0.72±0.29¶	0.83±0.20§	0.60±0.20§	0.61±0.20§	0.55±0.24¶	1.01±0.25§	0.95±0.23§
Change in income (in thousands of $)	—	0.17±0.02§	0.13±0.02§	0.13±0.01§	0.11±0.02§	0.15±0.04§	0.11±0.02§
Change in population (in hundreds of thousands)	—	0.08±0.02§	0.05±0.02§	0.06±0.02§	0.05±0.02§	0.04±0.02	0.05±0.02¶
Change in 5-yr in-migration (proportion of population)‖**	—	0.19±0.79	1.28±0.80	—	—	−0.02±1.83	—
Change in high-school graduates (proportion of population)‖	—	0.17±0.56	−0.11±0.53	—	—	−0.90±0.86	—
Change in urban residence (proportion of population)‖	—	−0.76±0.32¶	−0.40±0.25	—	—	0.03±1.88	—
Change in black population (proportion of population)‖††	—	−1.94±0.58§	−2.74±0.58§	−2.70±0.64§	−2.95±0.78§	−5.06±2.12§	−5.98±1.99§
Change in Hispanic population (proportion of population)‖††	—	1.46±1.23	1.33±1.10	—	—	2.44±2.22	—
Change in lung-cancer mortality rate (no./10,000 population)	—	—	−0.07±0.02§	−0.06±0.02§	−0.07±0.03¶	0.01±0.03	0.02±0.03
Change in COPD mortality rate (no./10,000 population)	—	—	−0.07±0.02§	−0.08±0.02§	−0.09±0.03§	−0.15±0.06§	−0.19±0.05§
No. of county units	211	211	211	211	127	51	51
R^2‡‡	0.05	0.47	0.55	0.53	0.60	0.76	0.74

This increase in life expectancy persisted even after controlling for socio-economic, demographic, or smoking variables



A
B
Change in LE, 1980s - 1990s
Residual changes in LE controlling for covariates
Reduction in PM2.5, 1980-2000

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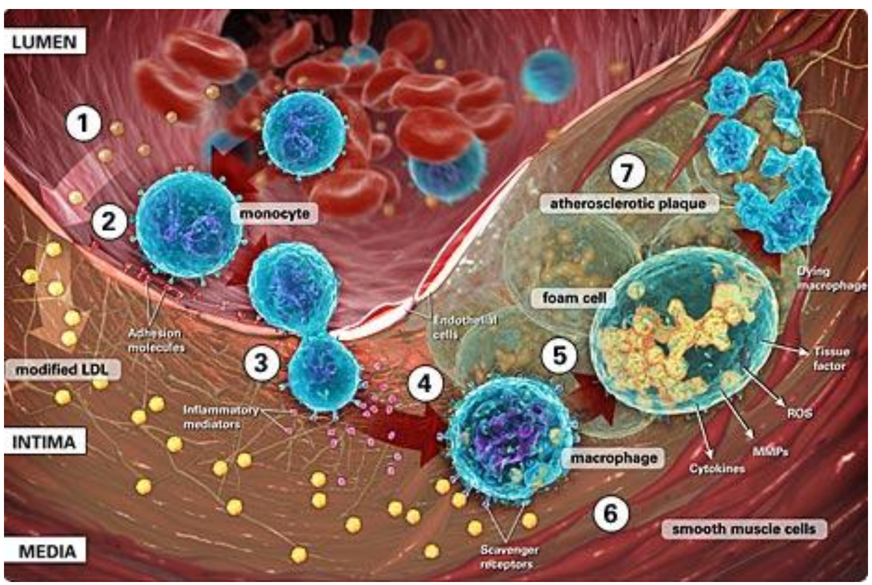
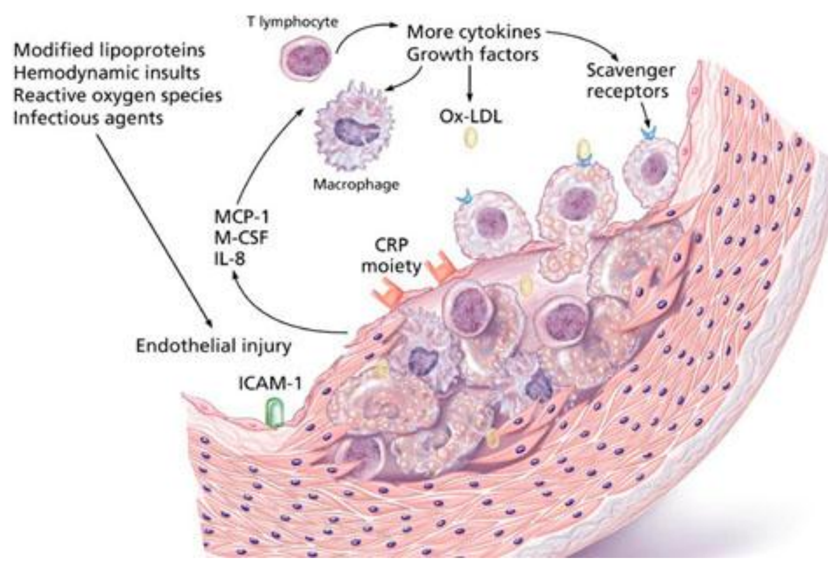
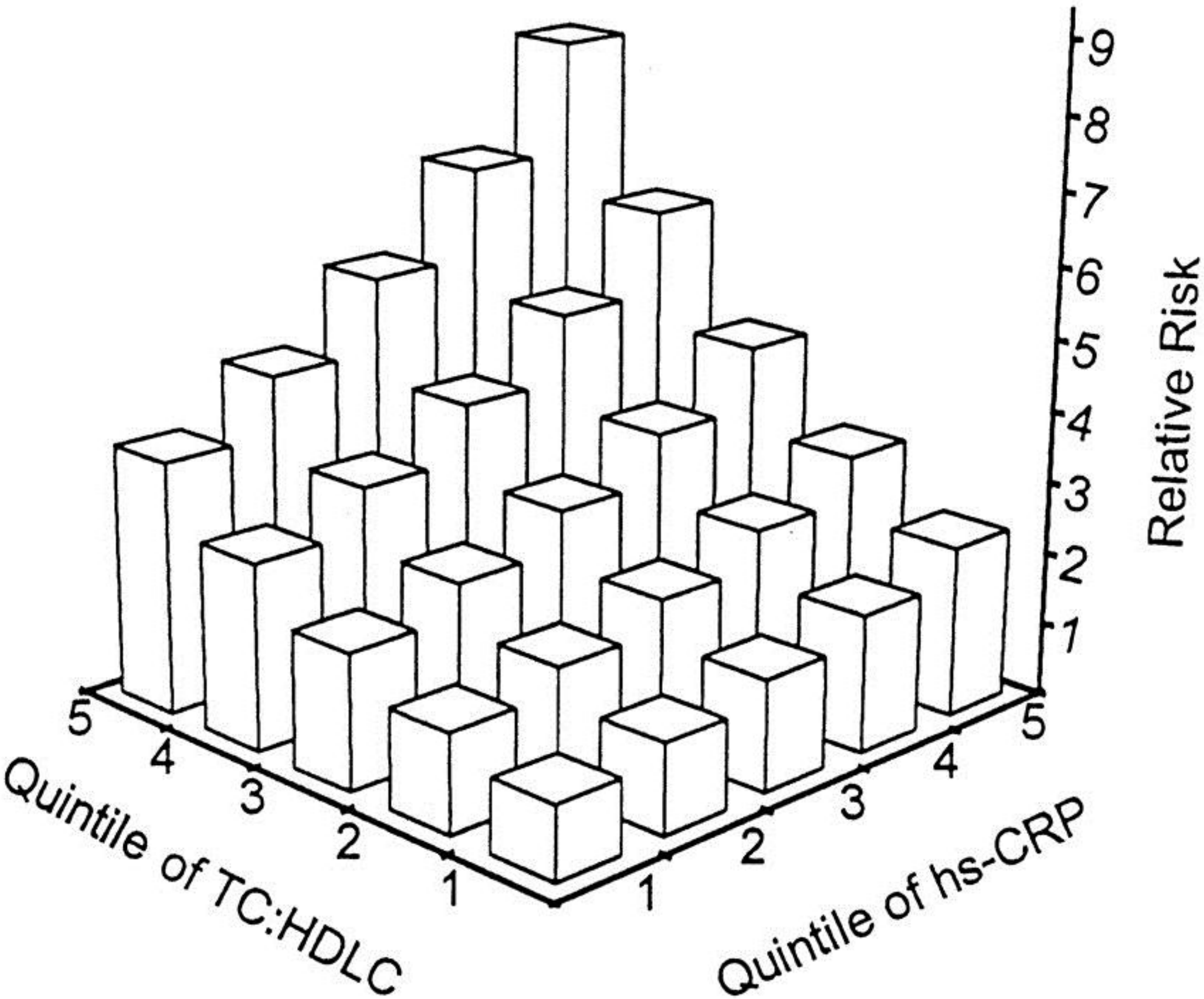
Cardiovascular disease as part of chronic and acute inflammatory processes.

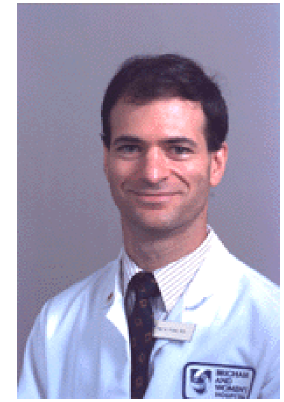
By the early 2000s, there was increasingly compelling evidence that inflammation is a major accomplice with LDL cholesterol in the initiation and progression of atherosclerosis.

Furthermore, inflammation contributes to acute thrombotic complications of atherosclerosis, increasing the risk of making atherosclerotic plaques more vulnerable to rupture, clotting, and precipitating acute cardiovascular or cerebrovascular events (MI or ischemic stroke).









Paul Ridker

Interactive effects of hs-CRP (marker of inflammation) and blood lipids.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Ridker PM. 2001;103:1813-1818.

Fine Particulate exposure

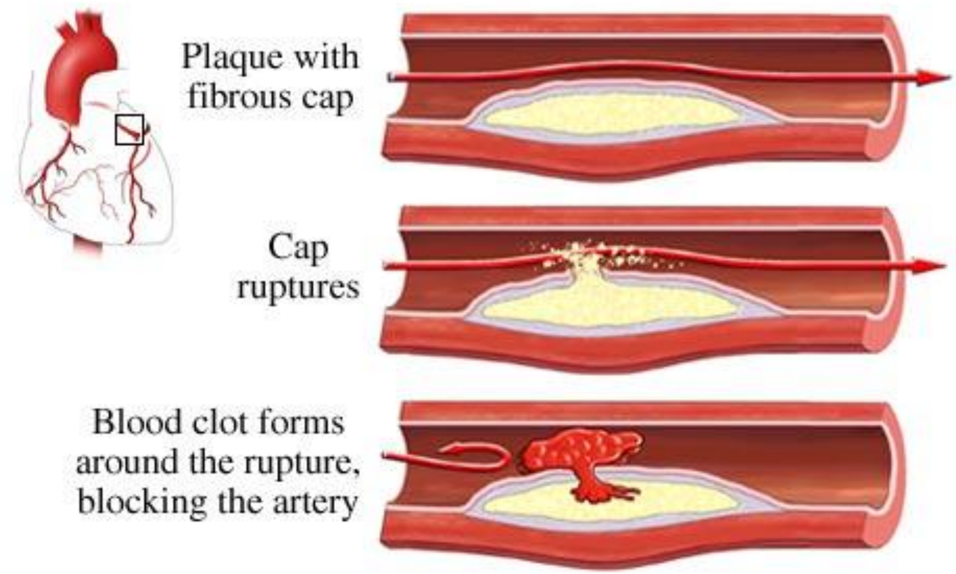
↓

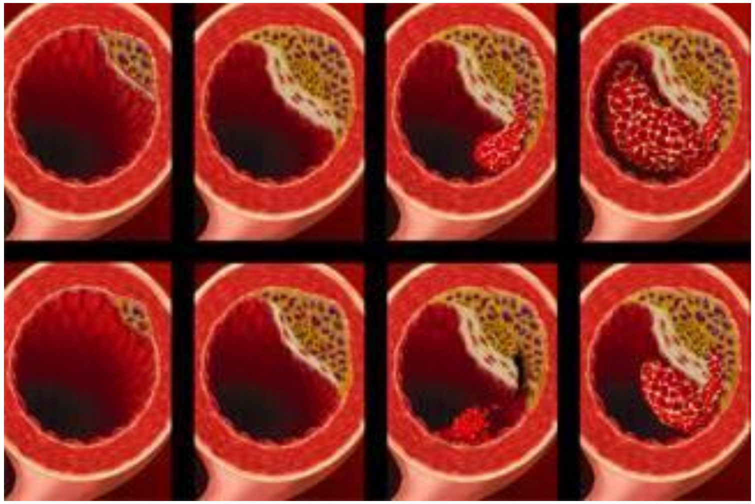
Pulmonary and systemic inflammation and oxidative stress

(along with blood lipids)

↓

Progression and destabilization of atherosclerotic plaques





Experimental evidence of biological effects of PM extracted from filters
(Ghio, Costa, Devlin, Kennedy, Frampton, Dye, et al. 1998-2004)

- Acute airway injury and inflammation in rats and humans
- *In vitro* oxidative stress and release of proinflammatory mediators by cultured respiratory epithelial cells
- Differential toxicities of PM when the mill was operating versus when it was not (metals content and mixtures?)

A series of studies by van Eeden, Hogg, Suwa et al. (1997-2002) suggest:

PM exposure

↓

Pulmonary inflammation

↓

Systemic inflammatory responses (including release of inflammatory mediators, bone marrow stimulation and release of leukocytes and platelets)

↓

Progression and destabilization of atherosclerotic plaques

Stephan van Eeden

In rabbits naturally prone to develop atherosclerosis they found that:

PM exposure

↓↓

Accelerated progression of atherosclerotic plaques with greater vulnerability to plaque rupture

James Hogg

Sun QH

Lippmann M

Sun et al. (*JAMA* 2005)

apoE$^{-/-}$ mouse

Representative Photomicrographs of Aortic Arch Sections

Normal Chow

Clean Filtered Air | **PM Polluted Air**

High-Fat Chow

Clean Filtered Air | **PM Polluted Air**

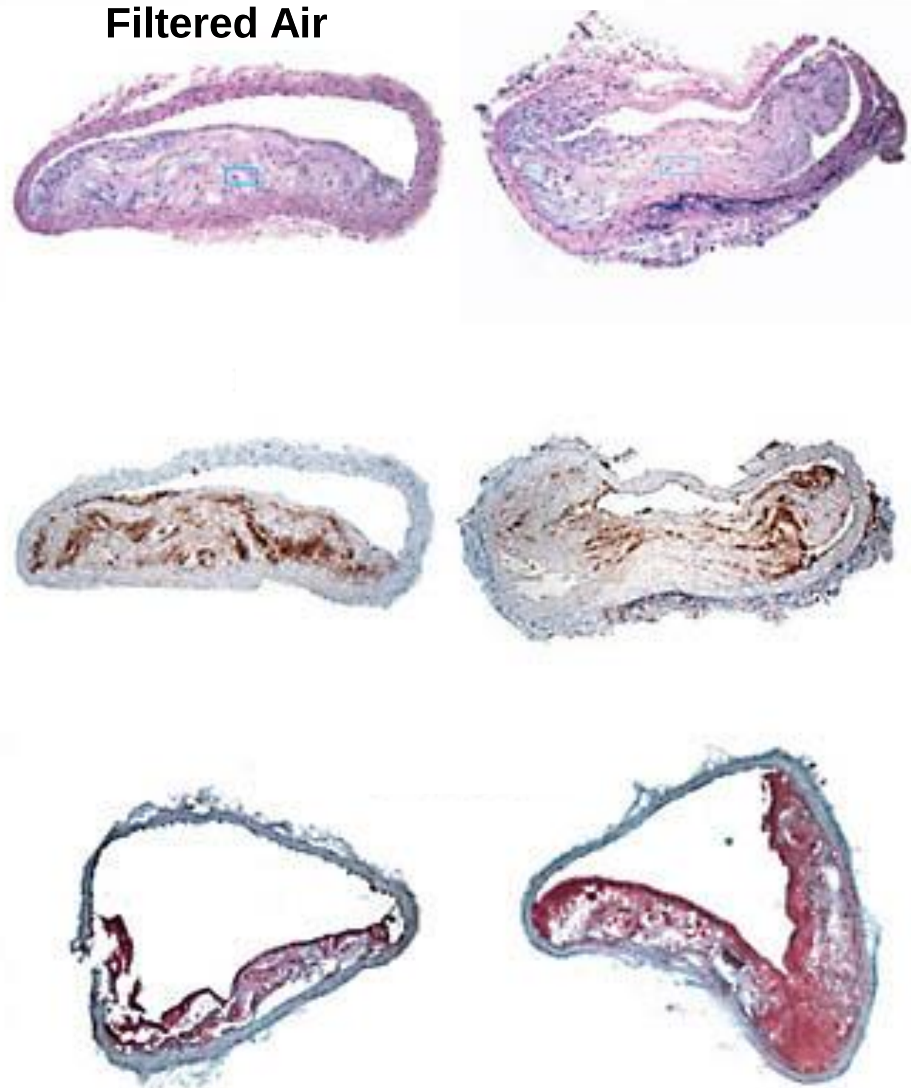


Table 1. Stylized outline of studies on air pollution and health.

General Study Designs	Examples	Time-scale	Selected Sample of Effects of Elevated Exposures	Common Statistical Modeling Approaches
Episode	Meuse Valley 1930[73] Donora 1948[74] London 1952[75,76]	Days	↑ episode-related cardiovascular disease and respiratory illness and death	Simple Comparative Stats, Graphs
Population-based time-series	Meta analysis[27] Large multi-city mortality[28-31] Large multi-city hospitalizations[77]	Days	↑ daily cardiovascular disease and respiratory mortality and hospitalization counts	Poisson reg., (GAMs, smooths for time , weather etc.)
Panel-based acute exposure	Review resp. effects[19] Review CVD effects[54] HRV/Inflammation[78,79]	Hours-days	↑ respiratory symptoms ↓ pulmonary function ↑ markers of inflammation ↓ heart rate variability	Linear and Logistic Reg., (fixed effects, temporal autocorr., etc.)
Case-crossover	Multi-c Ischem		ar disease	Conditional Logistic Reg.
Population-based cross-sectional	U.S. m			Linear regression
Cohort-based mortality	Harvar Americ Wome Medica Europe		ality	Survival Analyses, Cox Proportional Hazards models (random effect, spatial autocorr., etc.)
Cohort- and panel-based morbidity	Swiss c Harvar So. Cal Athero		herosclerosis	Various regression modeling strategies (fixed effects, mixed models. . .)
Case-control studies	Czech Lung C AMI tr Italy DVT[94]		↑ acute myocardial infarction ↑ risk of deep vein thrombosis	Conditional Logistic Reg.
Intervention/natural experiment	Utah Valley, steel mill[18] Dublin coal ban[65] Hong Kong Sulfur[66] Copper smelter strike[64] Cook stove intervention[95] U.S. Life Expectancy[67]	Months to years	Various intervention-related improvements in morbidity, mortality and/or life expectancy	Various comparative stats and regression models
Controlled experimental human studies and animal toxicology	Human instillation[96] Human chamber[97,98] Tox, rabbits[99] Tox, hamsters[100,101] Tox, dogs[102] Tox, mice[103-105]	Variety, usually hours to weeks	Growing complementary evidence of adverse cardiopulmonary health effects of air pollution	Various comparative stats and regression models

Many studies using various study designs and approaches with companion statistical modeling approaches and techniques have provided remarkably coherent evidence.

Table 6. Overall Summary of Epidemiological Evidence of the Cardiovascular Effects of $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure at Ambient Levels

Health Outcomes	Short-Term Exposure (Days)	Longer-Term Exposure (Months to Years)
Clinical cardiovascular end points from epidemiological studies at ambient pollution concentrations		
Cardiovascular mortality	↑ ↑ ↑	↑ ↑ ↑
Cardiovascular hospitalizations	↑ ↑ ↑	↑
Ischemic heart disease*	↑ ↑ ↑	↑ ↑ ↑
Heart failure*	↑ ↑	↑
Ischemic stroke*	↑ ↑	↑
Vascular diseases	↑	↑†
Cardiac arrhythmia/cardiac arrest	↑	↑
Subclinical cardiovascular end points and/or surrogate measures in human studies		
Surrogate markers of atherosclerosis	N/A	↑
Systemic inflammation	↑ ↑	↑
Systemic oxidative stress	↑	
Endothelial cell activation/ blood coagulation	↑ ↑	↑
Vascular/endothelial dysfunction	↑ ↑	
BP	↑ ↑	
Altered HRV	↑ ↑ ↑	↑
Cardiac ischemia	↑	
Arrhythmias	↑	

Table 7. Summary of Level of Evidence Supporting Global Biological Pathways and Specific Mechanisms Whereby $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure Can Affect the Cardiovascular System

	Animal Studies	Human Studies
General "intermediary" pathways whereby PM inhalation can instigate extrapulmonary effects on the cardiovascular system		
Pathway 1: Instigation of systemic proinflammatory responses	↑ ↑ ↑	↑ ↑ ↑
Pathway 2: Alterations in systemic ANS balance/activity	↑	↑ ↑
Pathway 3: PM and/or associated constituents directly reaching the systemic circulation	↑	↑
Specific biological mechanisms directly responsible for triggering cardiovascular events		
Vascular dysfunction or vasoconstriction	↑ ↑ ↑	↑ ↑
Enhanced thrombosis or coagulation potential	↑ ↑	↑ ↑
Elevated arterial BP	↑ ↑	↑ ↑
Enhanced atherosclerosis or plaque vulnerability	↑ ↑	↑
Arrhythmias	↑	↑

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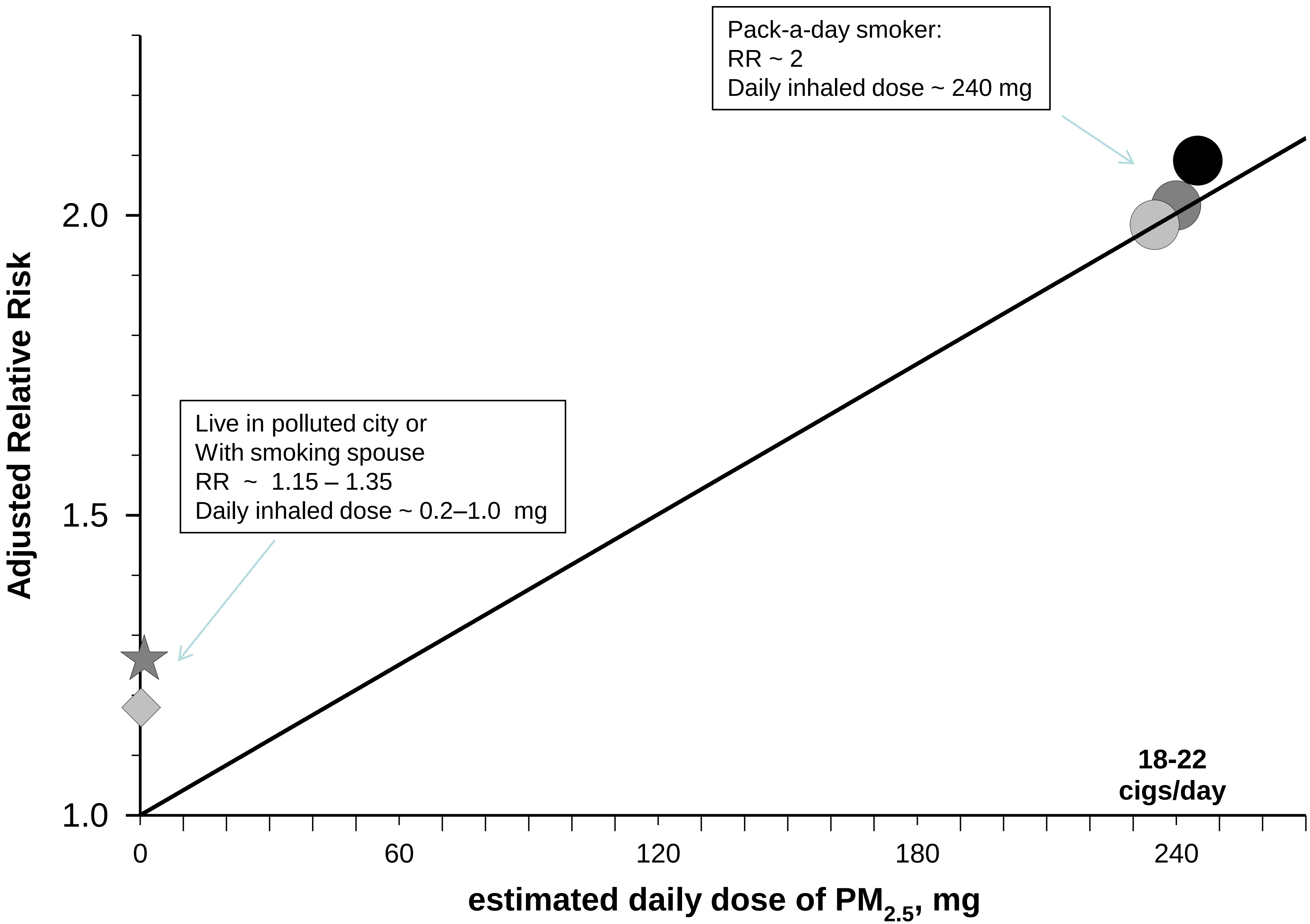
Pack-a-day smoker:
RR ~ 2
Daily inhaled dose ~ 240 mg
Live in polluted city or
With smoking spouse
RR ~ 1.15 – 1.35
Daily inhaled dose ~ 0.2–1.0 mg
2.0
1.5
1.0
Adjusted Relative Risk
18-22
cigs/day
0
60
120
180
240
estimated daily dose of $PM_{2.5}$, mg

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Pope, Burnett, Krewski, et al. 2009.

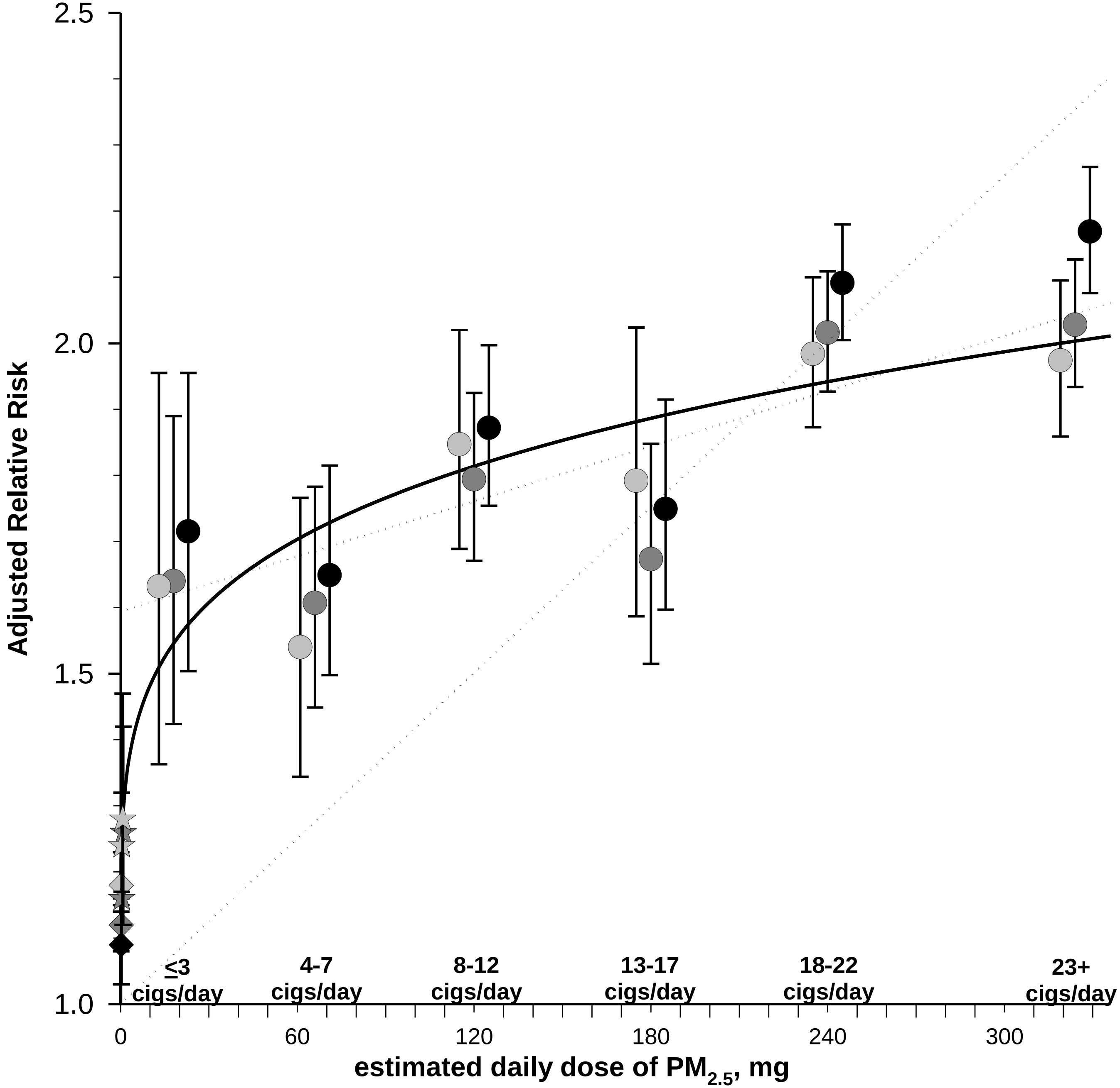

Figure 1. Adjusted relative risks (and 95% CIs) of IHD (light gray), CVD (dark gray), and CPD (black) mortality plotted over estimated daily dose of $PM_{2.5}$ from different increments of current cigarette smoking. Diamonds represent comparable mortality risk estimates for $PM_{2.5}$ from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General's report and from the INTERHEART study.

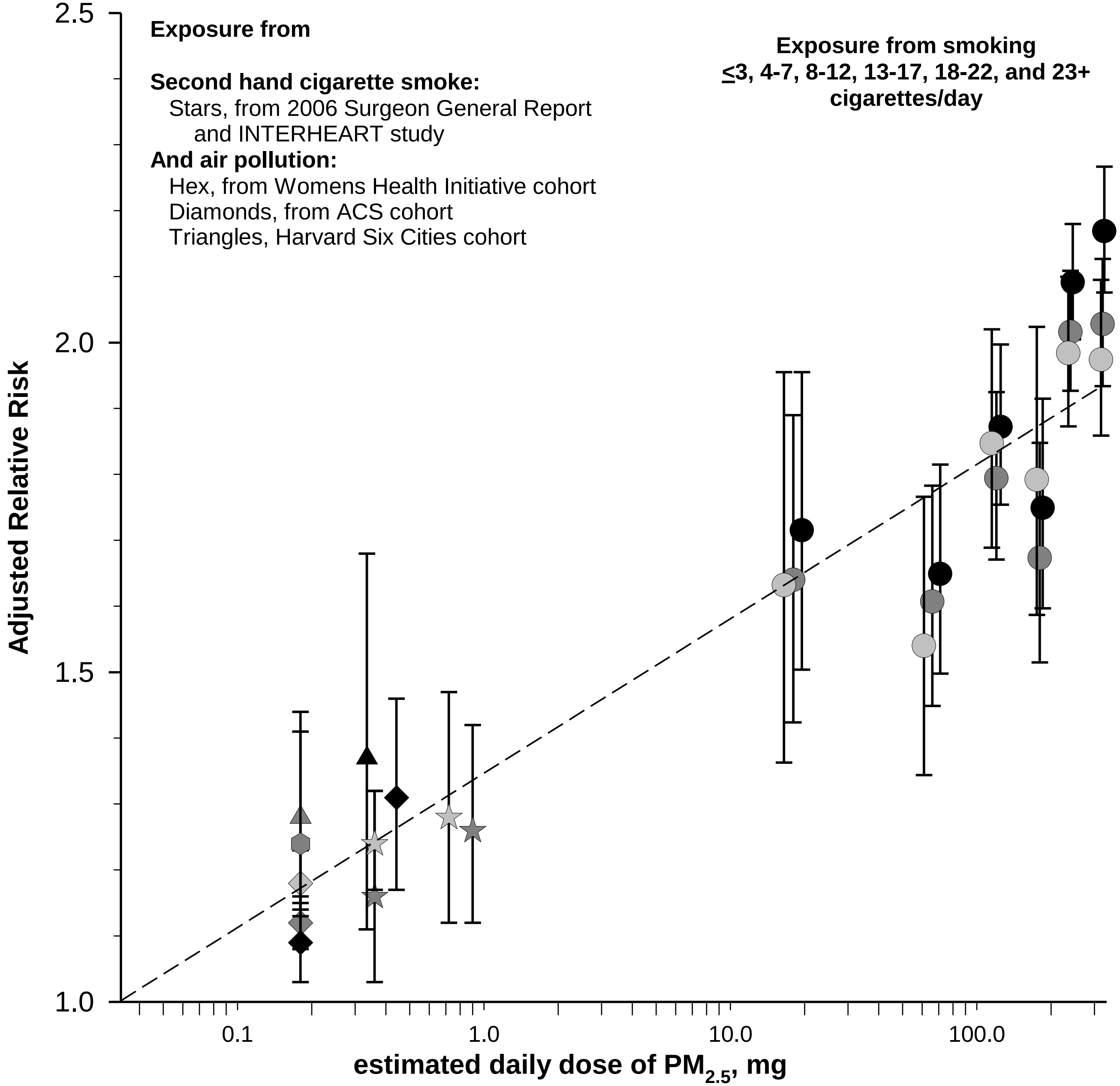

Figure 2. Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular (dark gray), and cardiopulmonary (black) mortality plotted over baseline estimated daily dose (using a log scale) of $PM_{2.5}$ from current cigarette smoking (relative to never smokers), SHS, and air pollution.