Human Health Effects of Air Pollution: Statistics and Public Policy

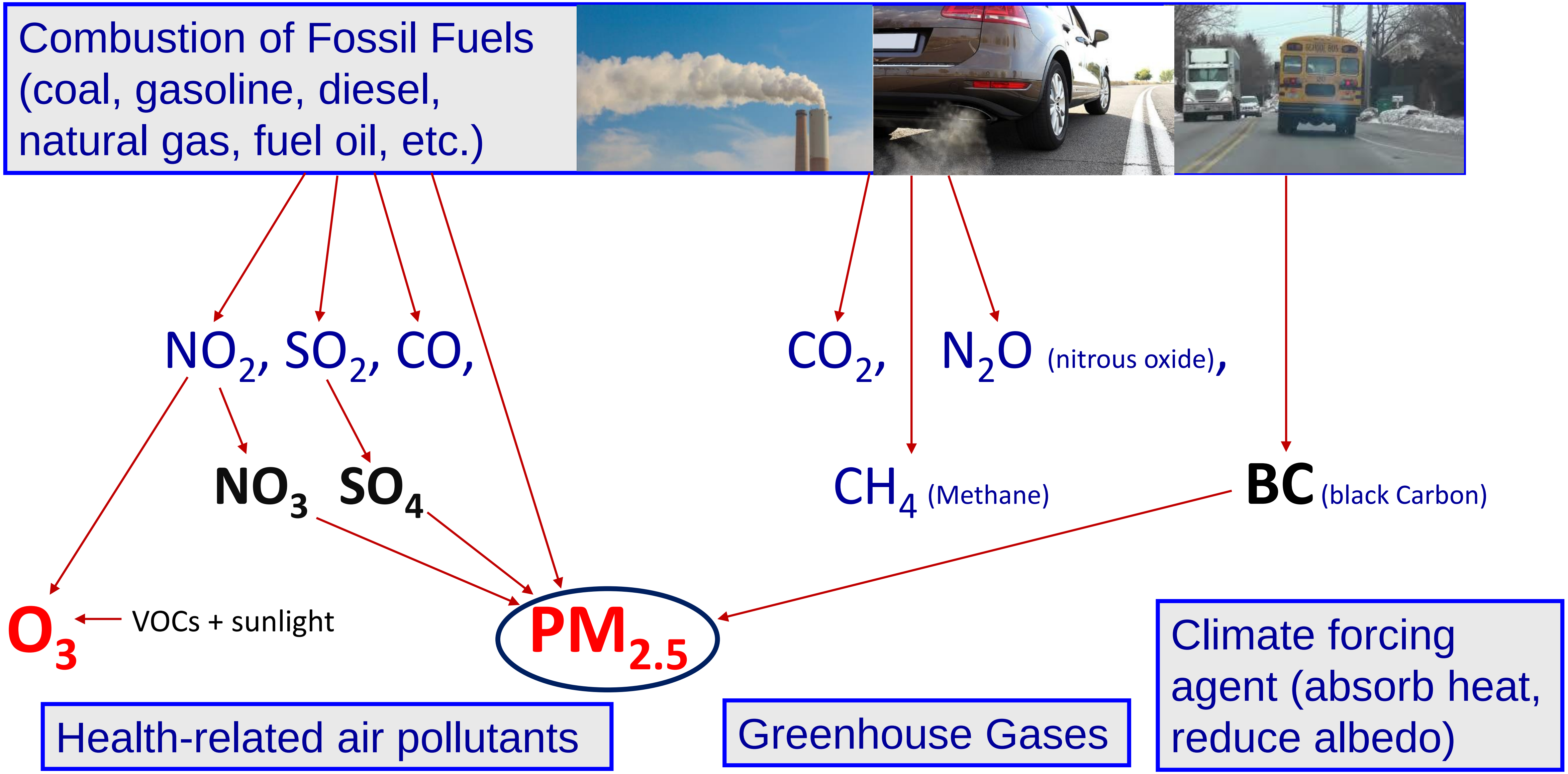
C. Arden Pope III, PhD
Mary Lou Fulton Professor of Economics
Brigham Young University

International Conference on Health Policy Statistics

Leveraging Data to Shape the Future

January 6 - 8, 2020 • San Diego, California

Common link between air pollutants and greenhouse gases:

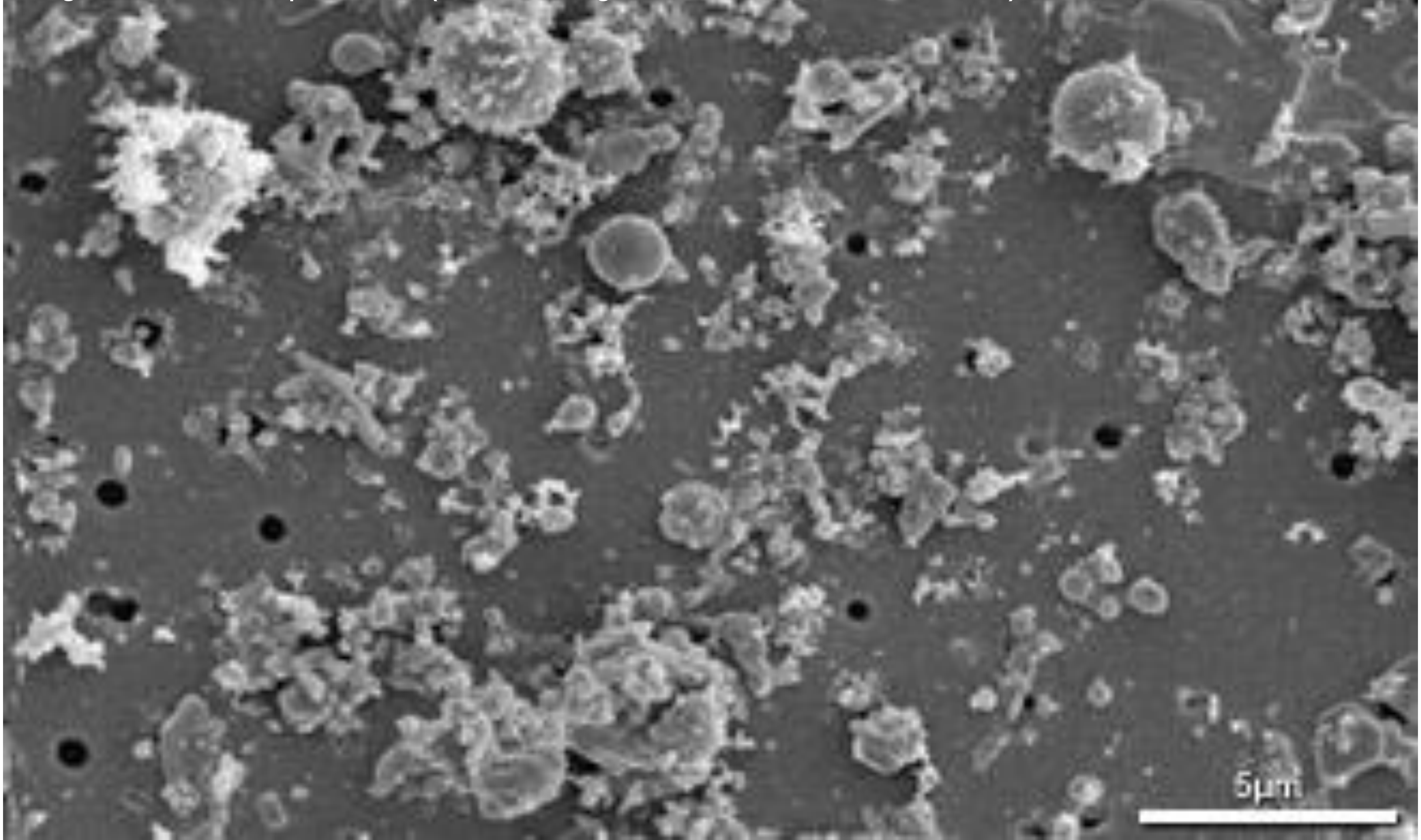


Salt Lake City, Utah

India--New Delhi (India Gate), Agra (Taj Mahal), Lucknow, Chandigarh, Jaipur

Beijing, China

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



Stylized outline of epidemiologic study designs of air pollution and health

General statistical approaches

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

Intervention/natural experiment/quasi-experimental

Controlled experimental human and animal

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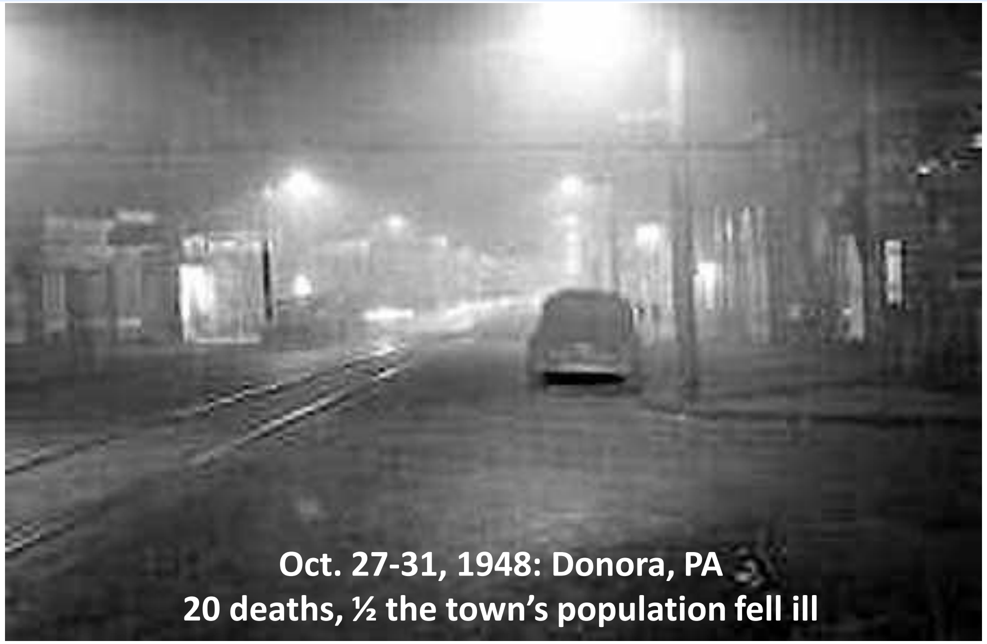
General statistical approaches

Simple comparative statistics. Graphics, etc.

Compare relative number of deaths or hospitalizations or incidence of disease

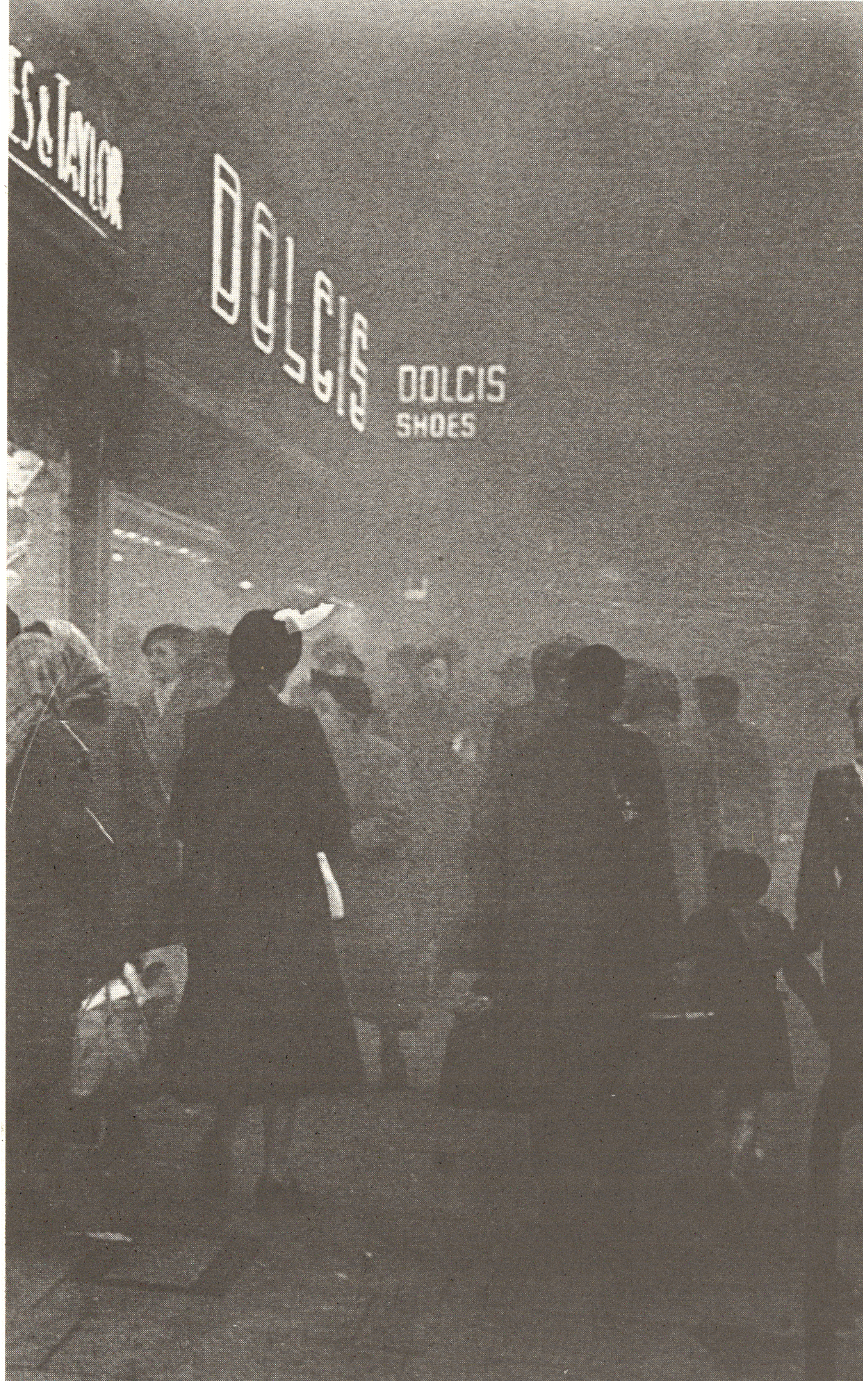
Dec. 1-5, 1930: Meuse Valley, *Belgium*
60 deaths (10x expected)



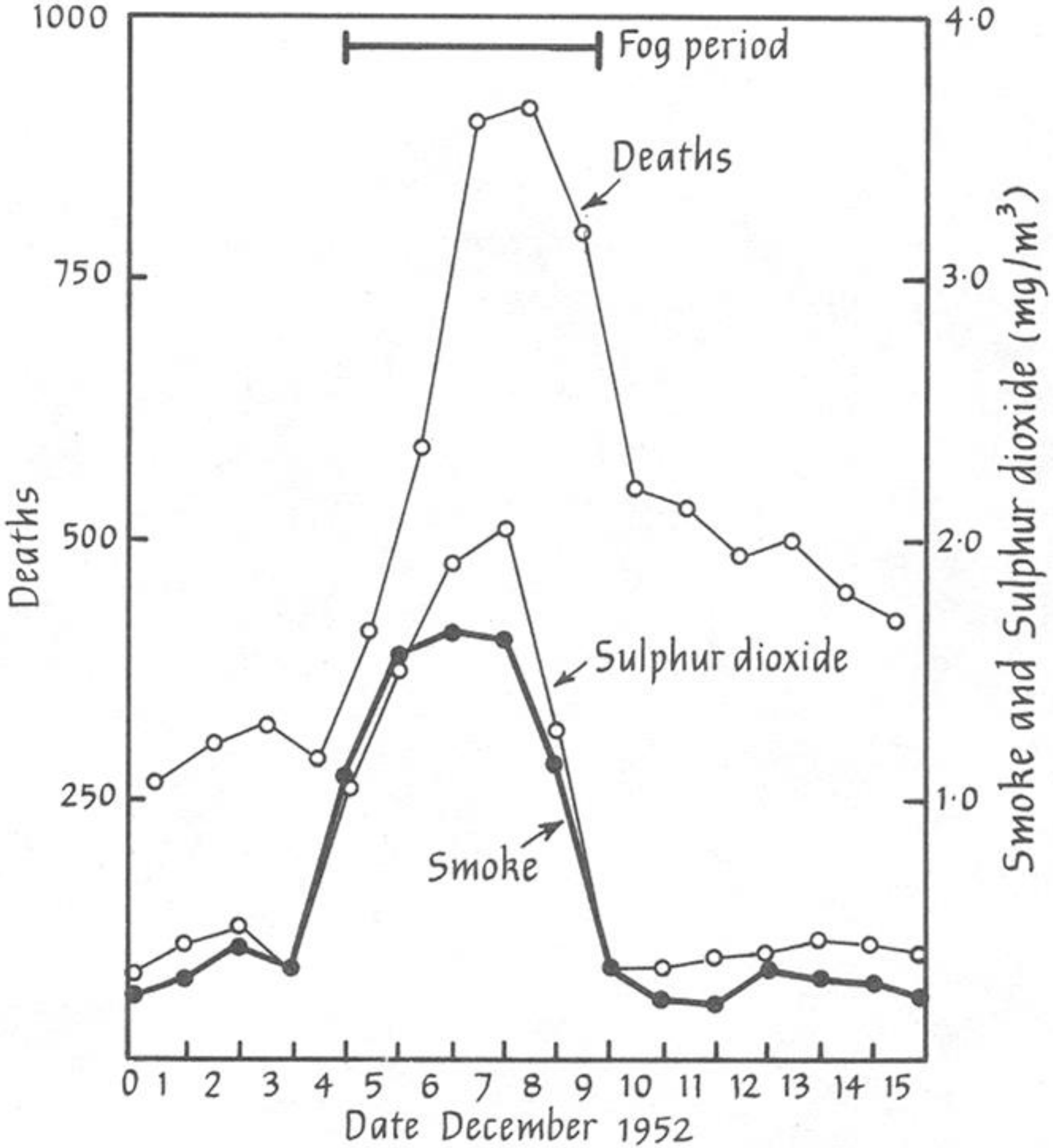
Oct. 27-31, 1948: Donora, PA
20 deaths, ½ the town's population fell ill

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, Methuen 1987

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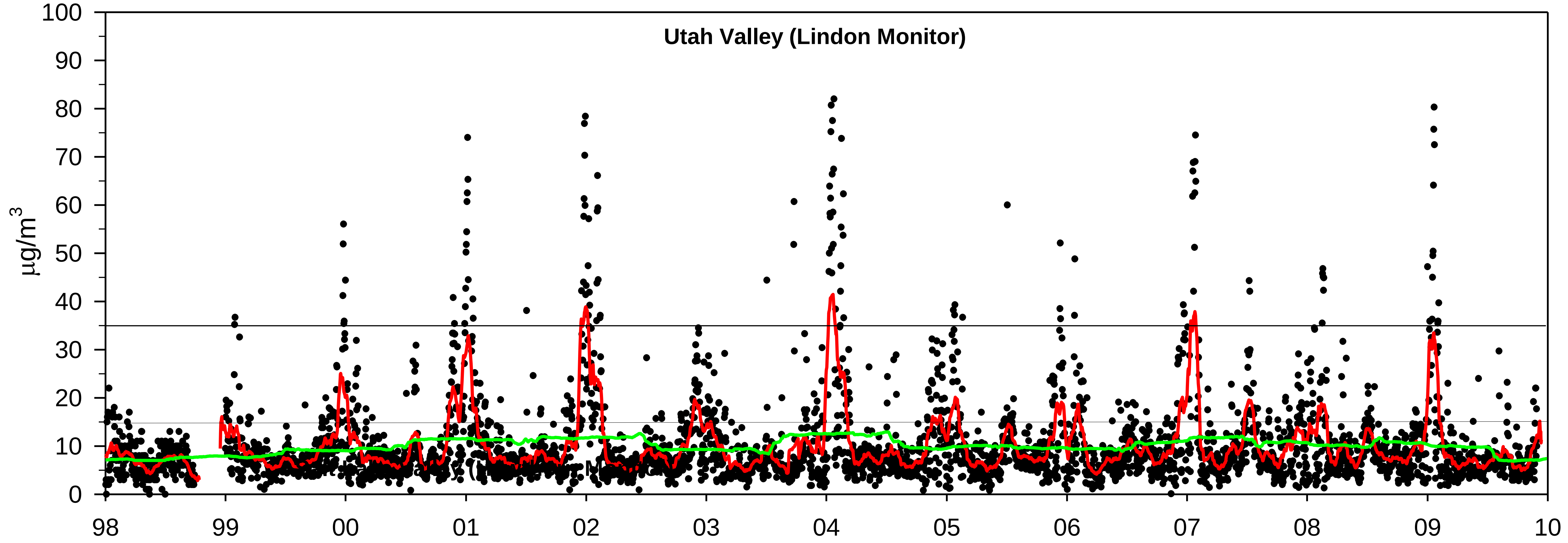
Filtered OLS regression

Single city, Poisson regression

Poisson Regression with non-parametric/flexible smooths

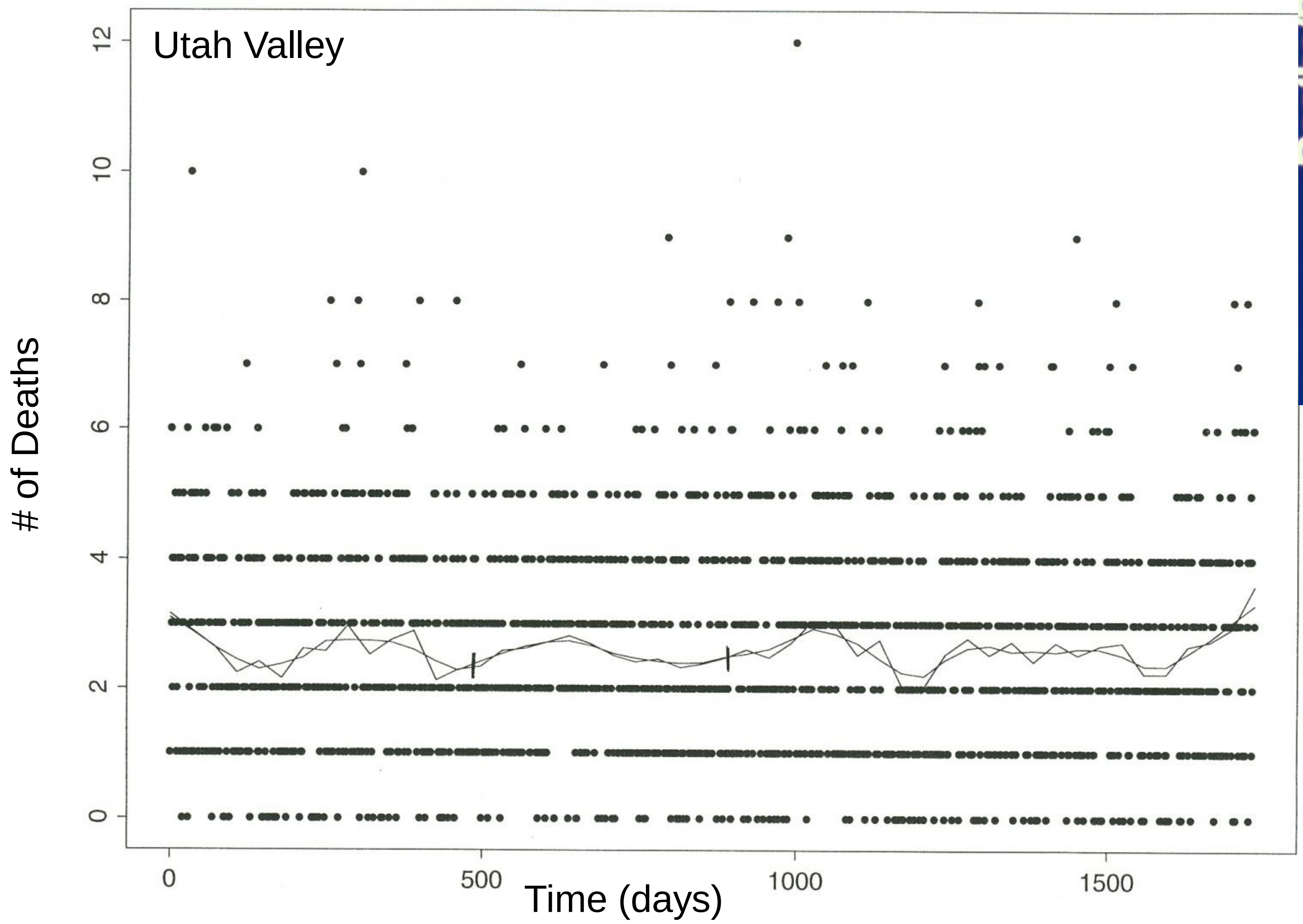
Multi-city Bayesian hierarchical models

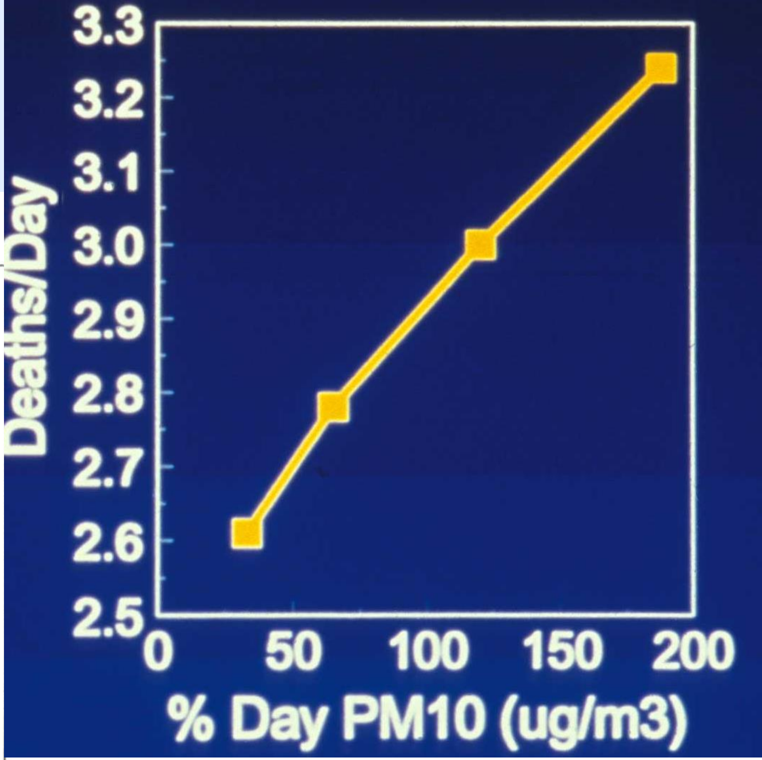
Time-series studies take advantage of **highly variable** air pollution levels



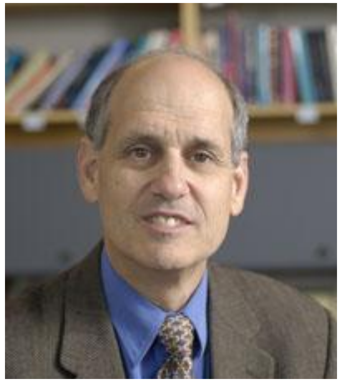
$PM_{2.5}$ concentrations January 1 1998-December 12 2009. Black dots, 24-hr $PM_{2.5}$; Red line, 30-day moving average $PM_{2.5}$; Green line, 1-yr moving average $PM_{2.5}$.

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





Joel Schwartz, PhD
Harvard



Scott Zeger, PhD
Johns Hopkins

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:

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

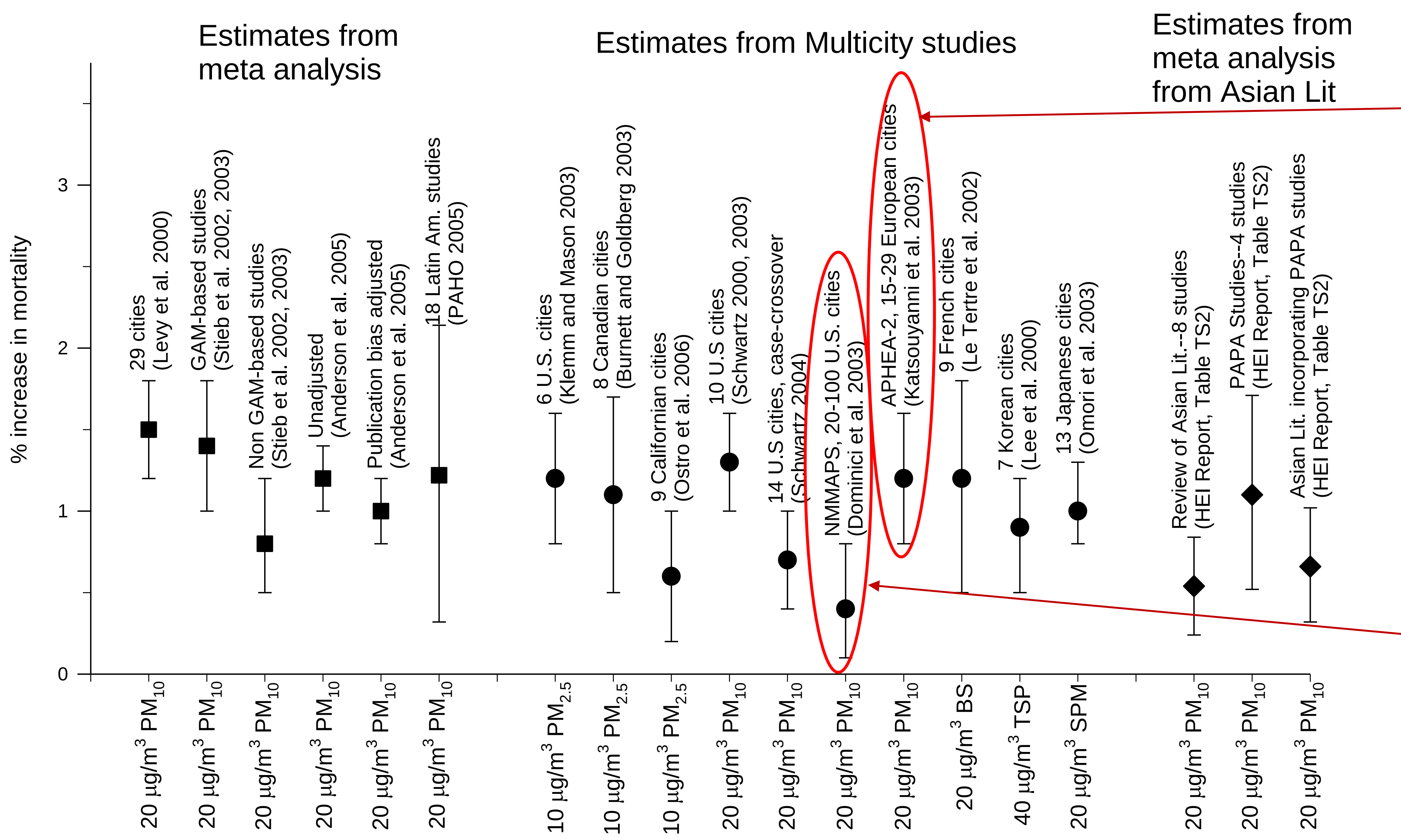
How to construct the lag structure? (MA, PDL, etc.)

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***



Klea Katsouyanni, PhD
U of Athens, King's College London

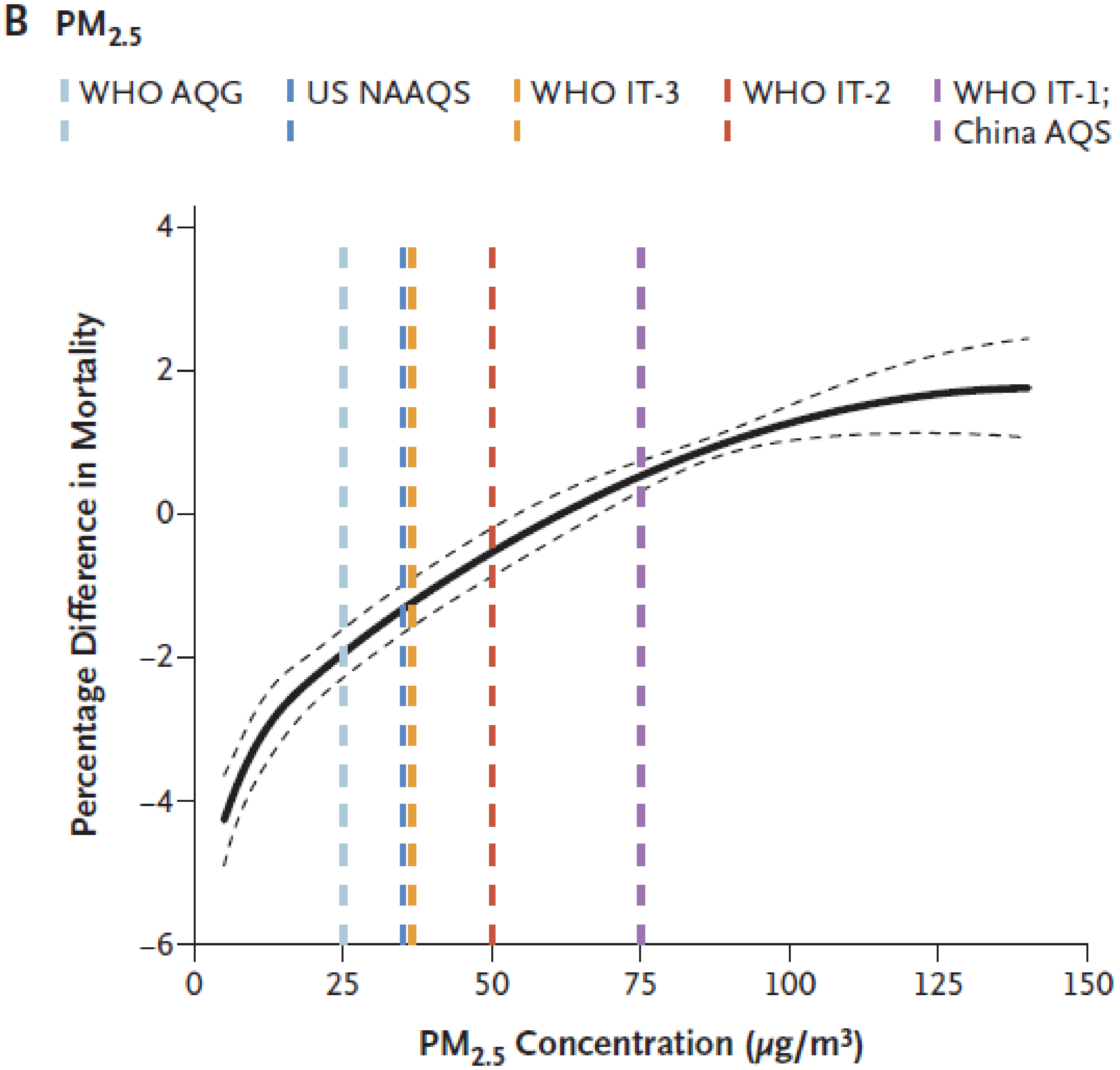
Jonathan Samet, MD
Johns Hopkins, USC

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 22, 2019 VOL. 381 NO. 8

Ambient Particulate Air Pollution And Daily Mortality in 652 Cities.

Liu et al. Aug. 22, 2019.

Figure 3, Panel B. Pooled concentration-response curves for the associations of 2-day moving average concentrations of $PM_{2.5}$ with daily all-cause mortality.



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Intervention/natural experiment/quasi-experimental

Controlled experimental human and animal

General statistical approaches

Fixed and/or random effects Gaussian or Logistic style models that often address autocorrelation

Examples: Daily measure pulmonary function, or respiratory symptoms in panels of children.

Panel studies of asthmatics and non-asthmatics

Pope and Dockery. Acute Health Effects of PM10 Pollution on Symptomatic and Asymptomatic Children.

AMERICAN REVIEW OF
RESPIRATORY DISEASE®

1992

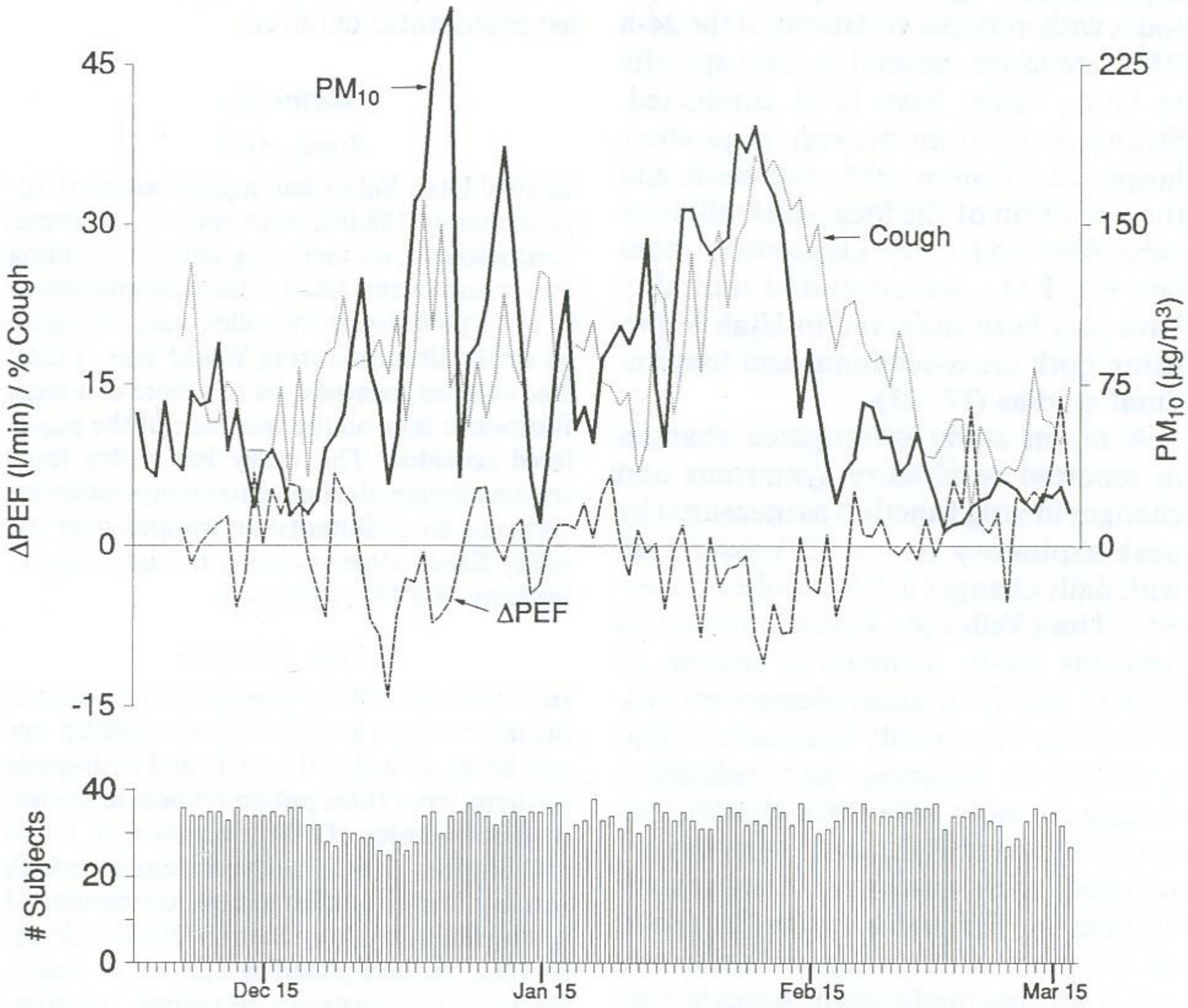

Fig. 1. Daily PM_{10} levels, mean peak expiratory flow deviations (ΔPEF), percentage who reported cough, and number of participants for the symptomatic sample.

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General statistical approaches

Conditional logistic regression with clever matching strategies that control for cross-subject differences by matched, versus statistical modeling.

Quasi-experimental feel

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

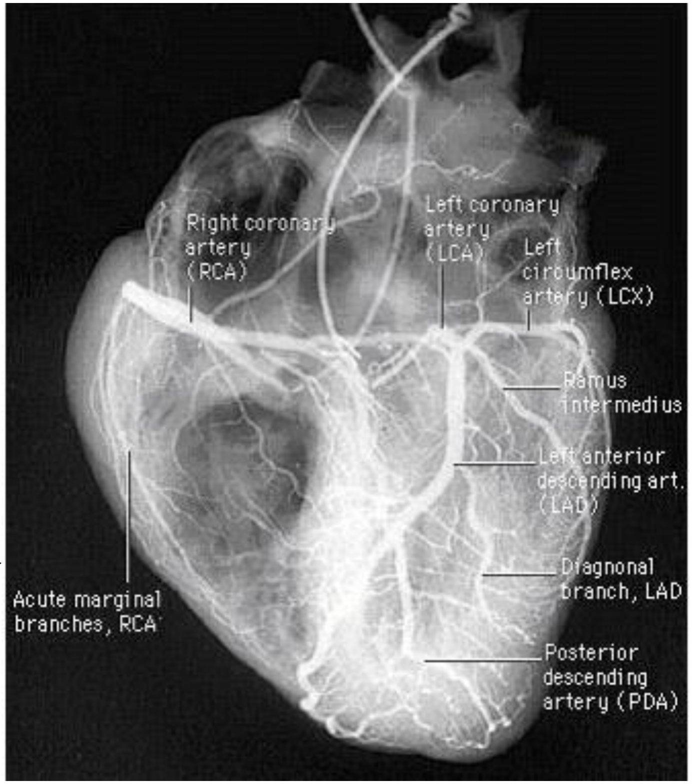
Jeffrey Anderson

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

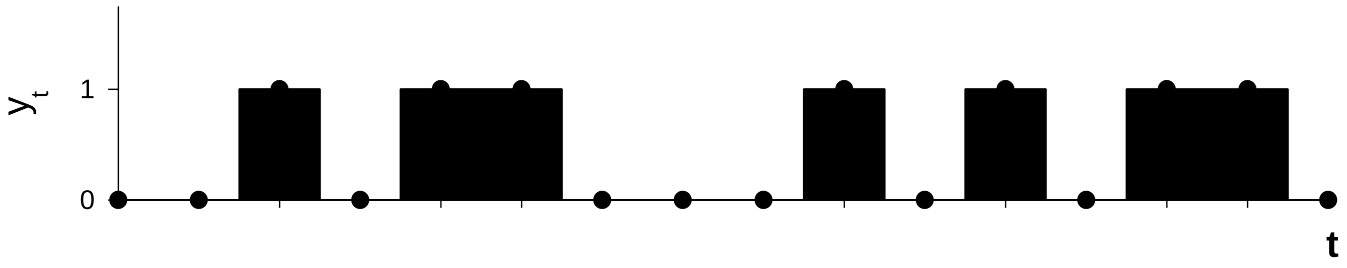
C. Arden Pope III, PhD; Joseph B. Muhlestein, MD; Heidi T. May, MSPH; Dale G. Renlund, MD; Jeffrey L. Anderson, MD; Benjamin D. Horne, PhD, MPH

Methods:

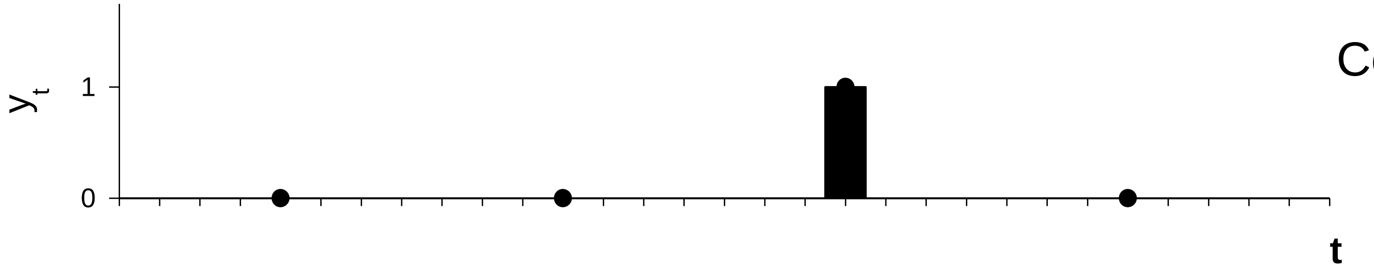
- Case-crossover study of acute ischemic coronary events (heart attacks and unstable angina) in 12,865 well-defined and followed up cardiac patients who lived on Utah's Wasatch Front
- …and who underwent coronary angiography



Binary Data, classic time-series



Binary Data, case-crossover



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)

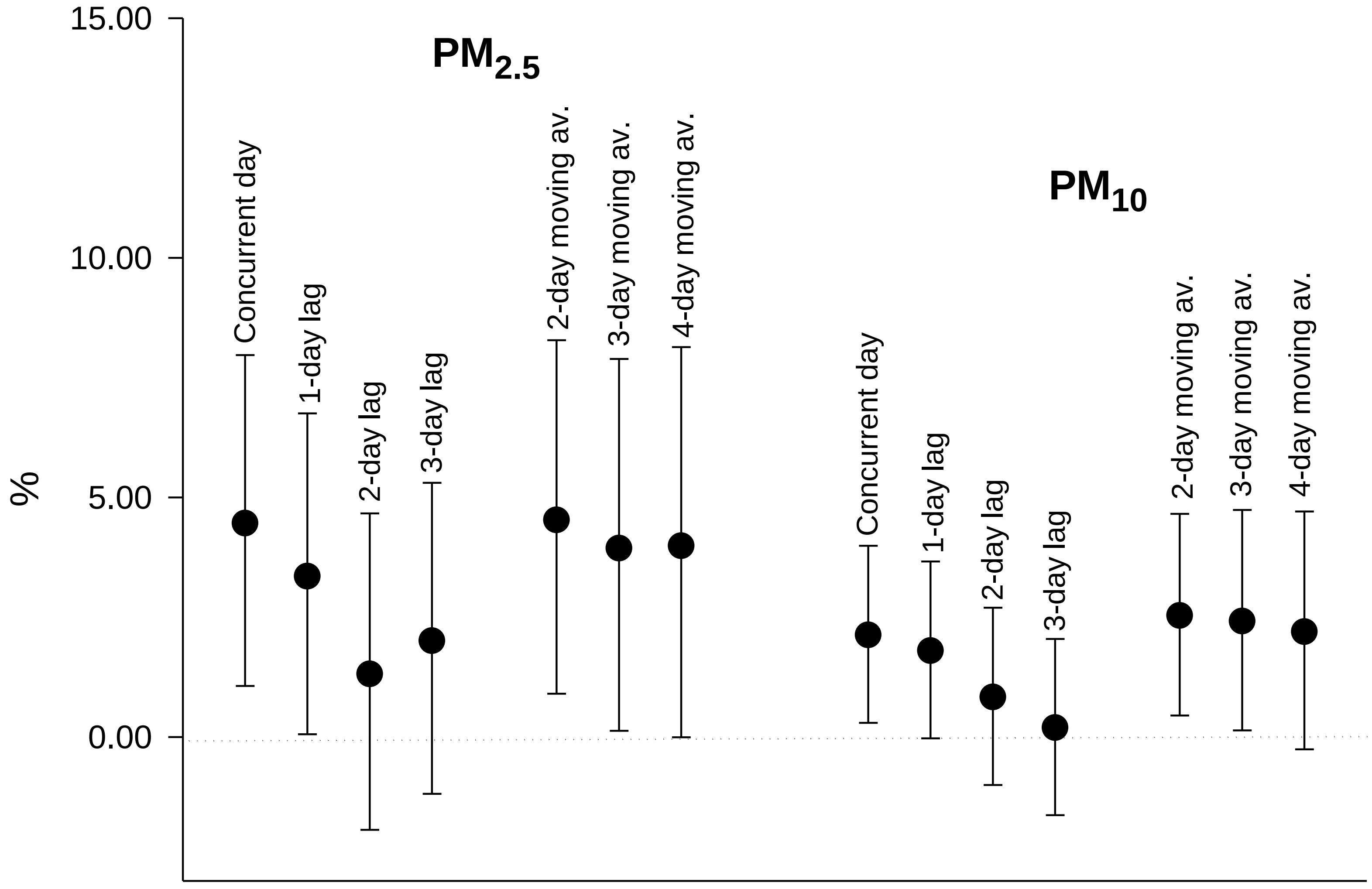


Figure 1. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 $\mu g/m^3$ of $PM_{2.5}$, or PM_{10} for different lag structures.

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

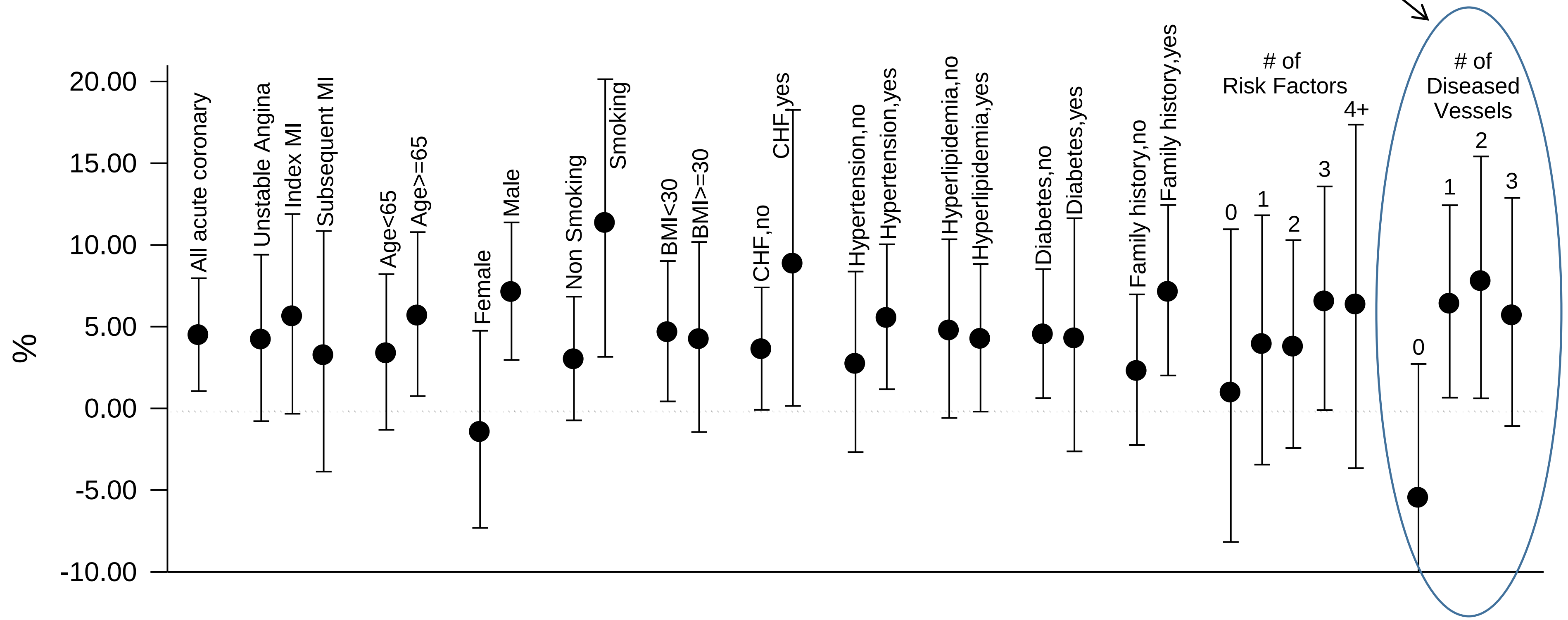


Figure 2. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 $\mu g/m^3$ of $PM_{2.5}$, stratified by various characteristics.

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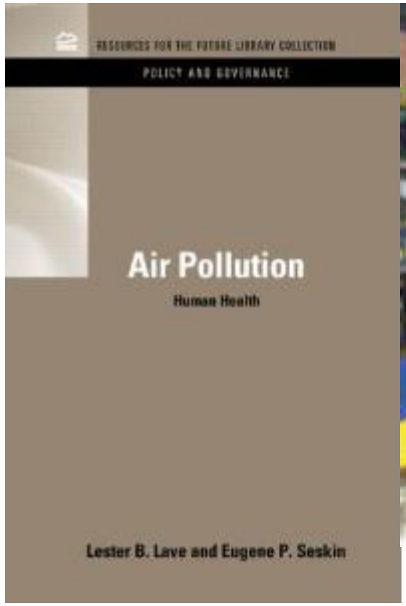
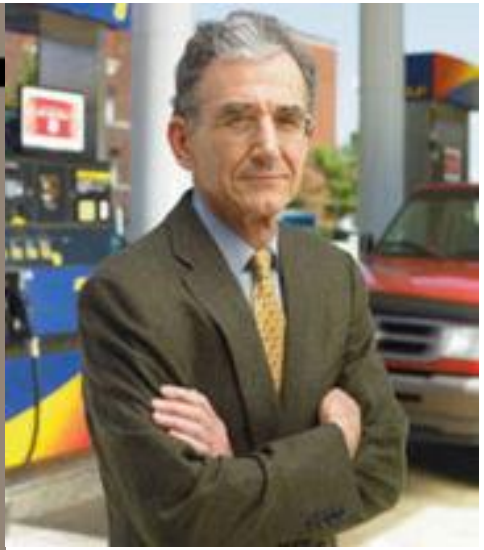
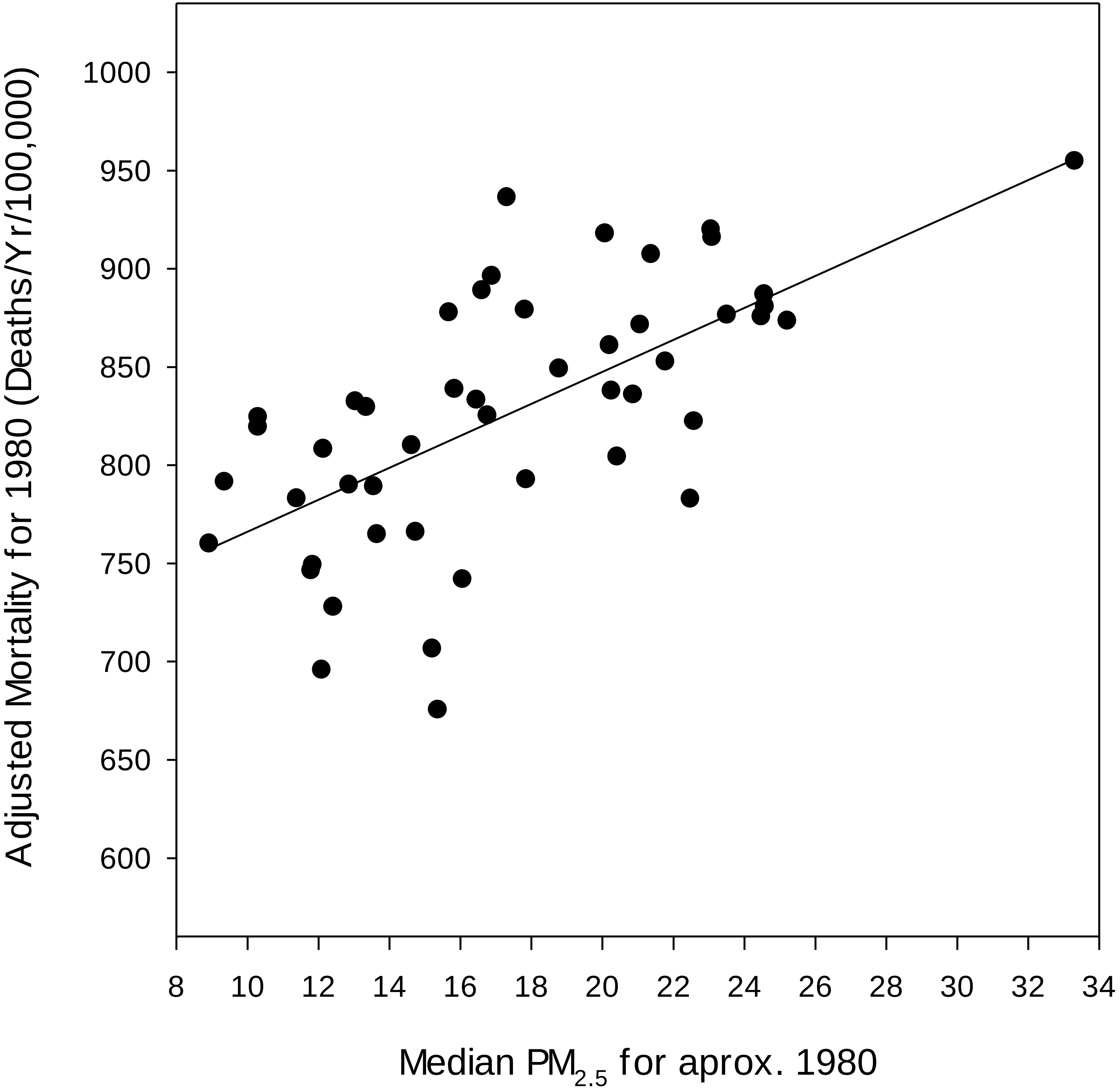
Controlled experimental human and animal

General statistical approaches

Weighted OLS/GLS regression models, etc.







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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General statistical approaches

Survival analyses,

Cox Proportional Hazard regression models,

etc.

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

The NEW ENGLAND JOURNAL of MEDICINE

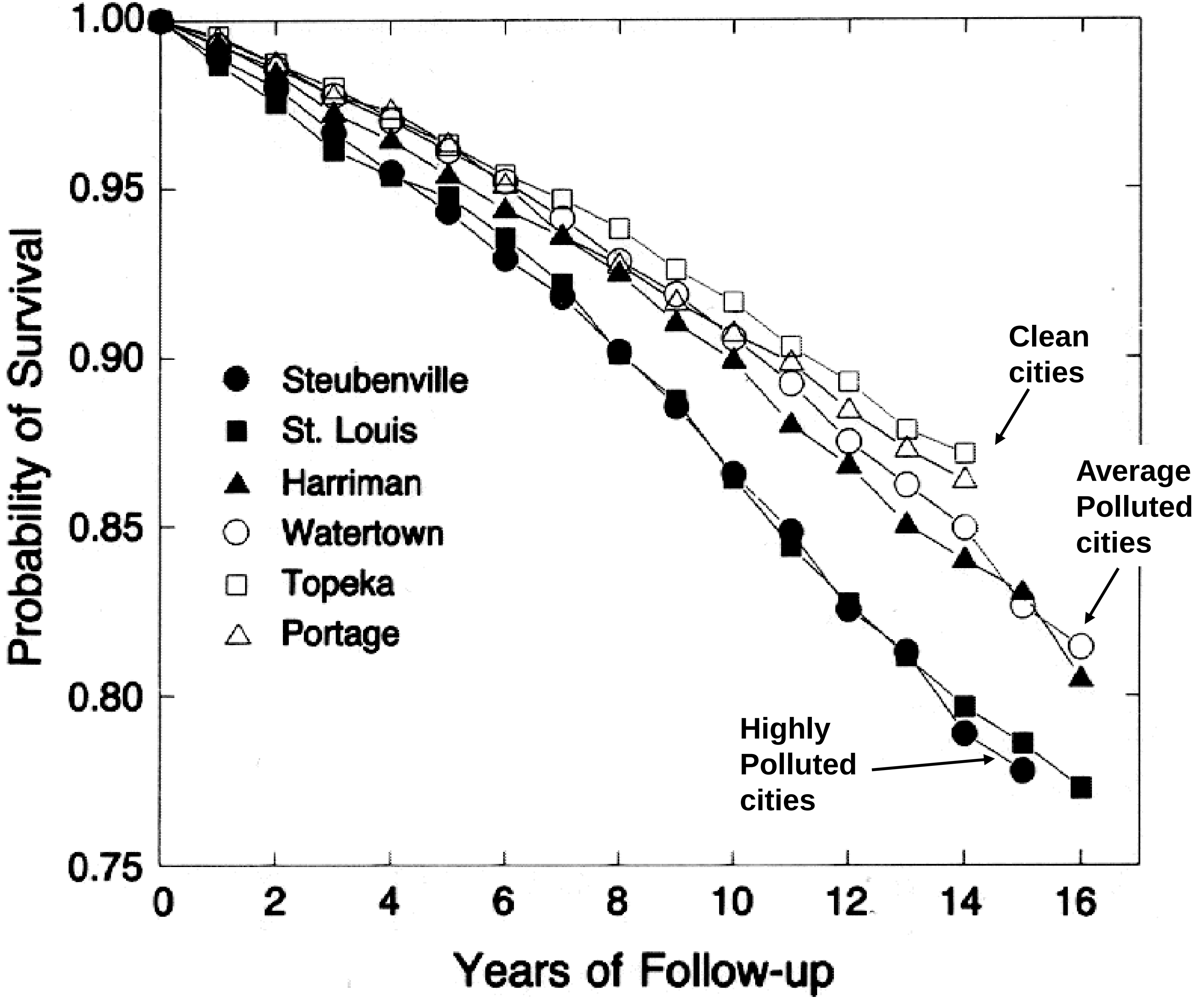
Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE.


Doug Dockery, ScD
Harvard


Frank Speizer, ScD
Harvard

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, etc.



1.00
0.95
0.90
0.85
0.80
0.75
Probability of Survival
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

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

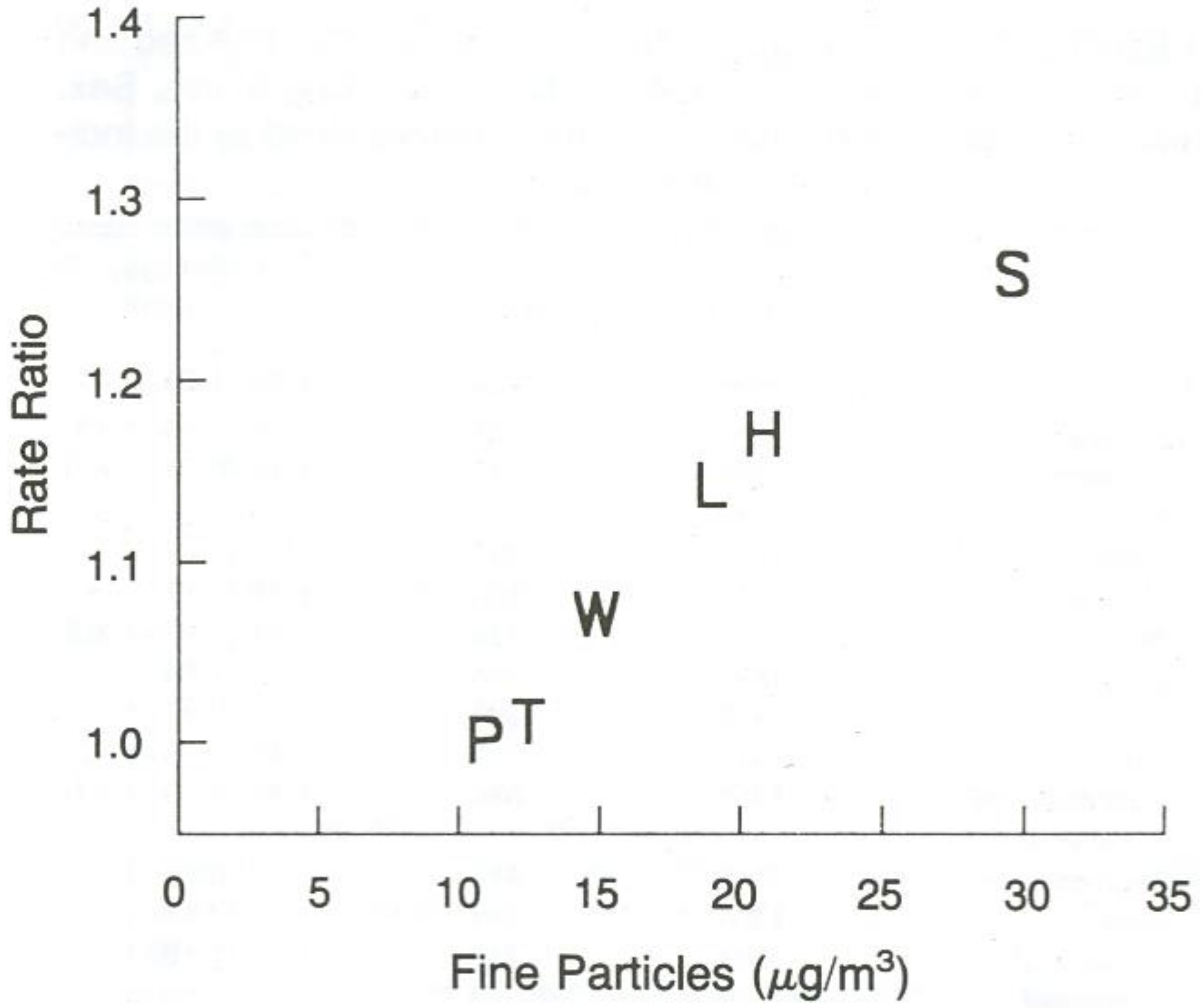
Hazard function or instantaneous probability of death for the *i*th subject in the *l*th strata.

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 Hazard 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)



1.4
1.3
1.2
1.1
1.0
Rate Ratio
S
H
L
W
P
T
0
5
10
15
20
25
30
35
Fine Particles (μg/m^3)

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







Richard Burnett, Phd
Health Canada/U. Ottawa

Extended the basic Cox PH model allow random effects, spatial autocorrelation, and semi-non-parametric spatial smoothing.

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

More statistical modeling controversies

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

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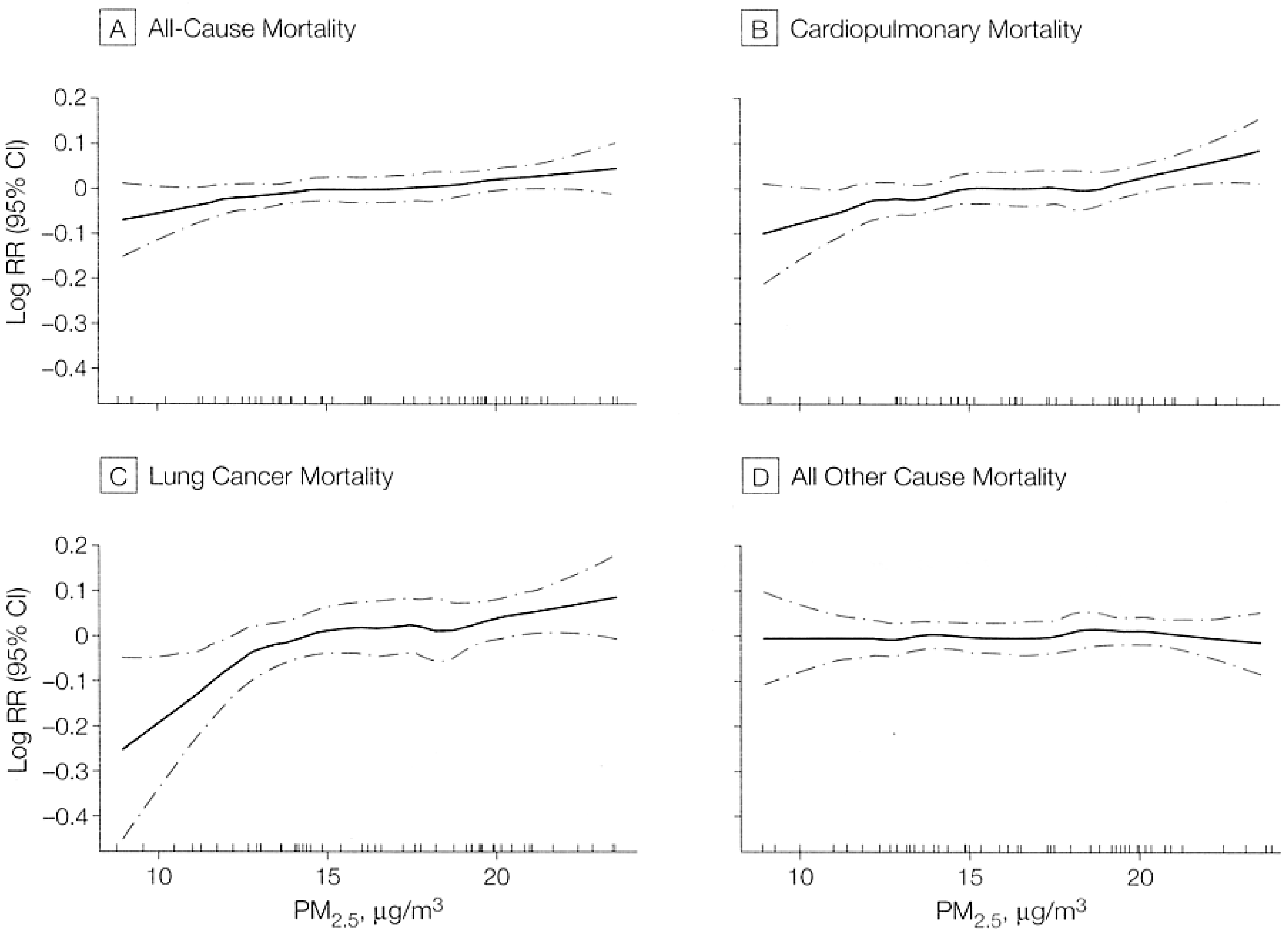
Baseline hazard function, common to all subjects within a strata.

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.

Figure 2. Nonparametric Smoothed Exposure Response Relationship



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 29, 2017 VOL. 376 NO. 26

Air Pollution and Mortality in the Medicare Population

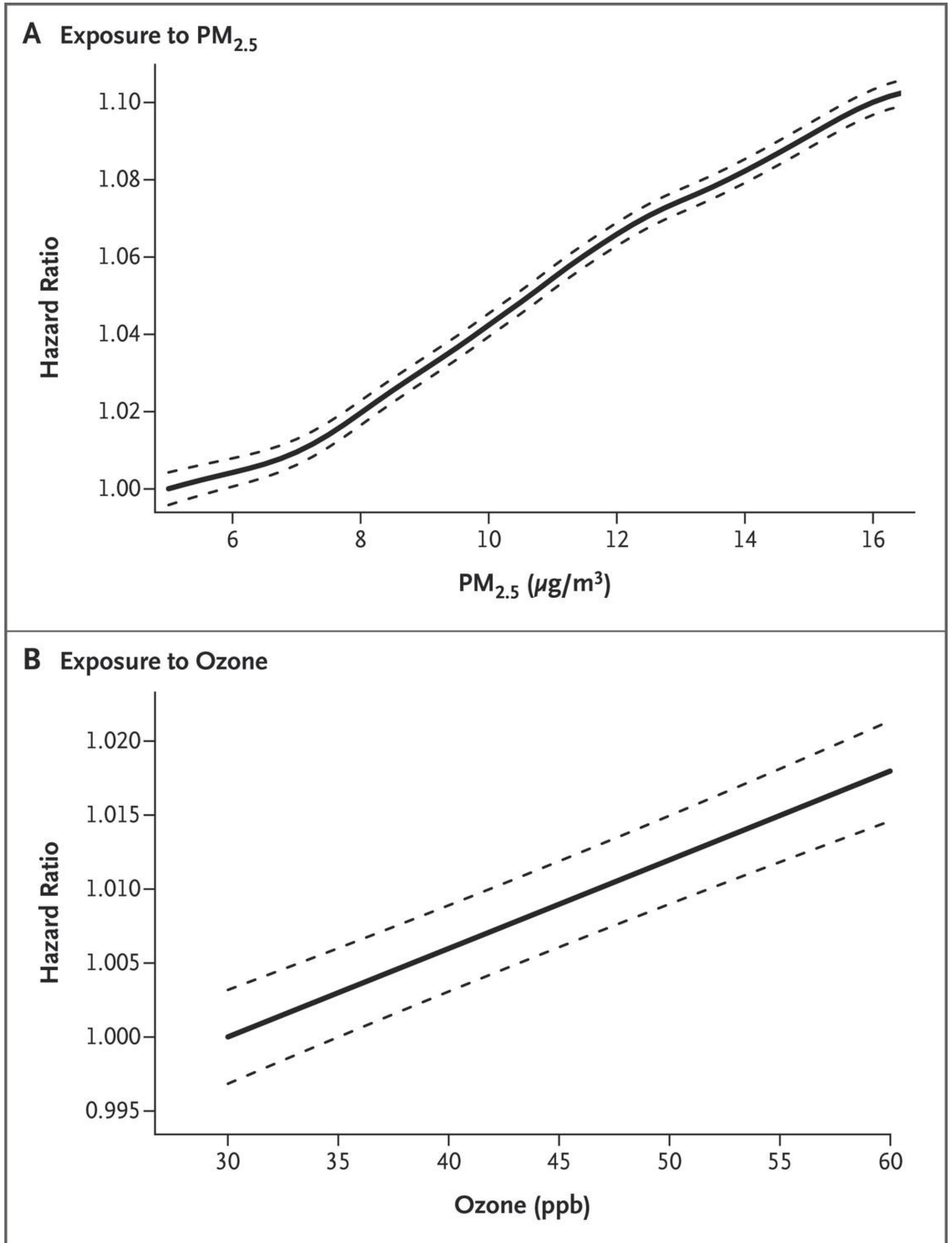
Qian Di, M.S., Yan Wang, M.S., Antonella Zanobetti, Ph.D., Yun Wang, Ph.D., Petros Koutrakis, Ph.D., Christine Choirat, Ph.D., Francesca Dominici, Ph.D., and Joel D. Schwartz, Ph.D.

- 60,925,443 Medicare beneficiaries
- Followed up from 2000-2012
- 460,310,521 person-yrs follow-up

10 μg/m^3 increase in $PM_{2.5}$

↓

7.3% (95% CI 7.1-7.5)
increase in all-cause mortality



Review and Meta-Analysis

Pope, Coleman, Pond, Burnett.
Fine Particulate Air Pollution and Human Mortality: 25+ Years of Cohort Studies.

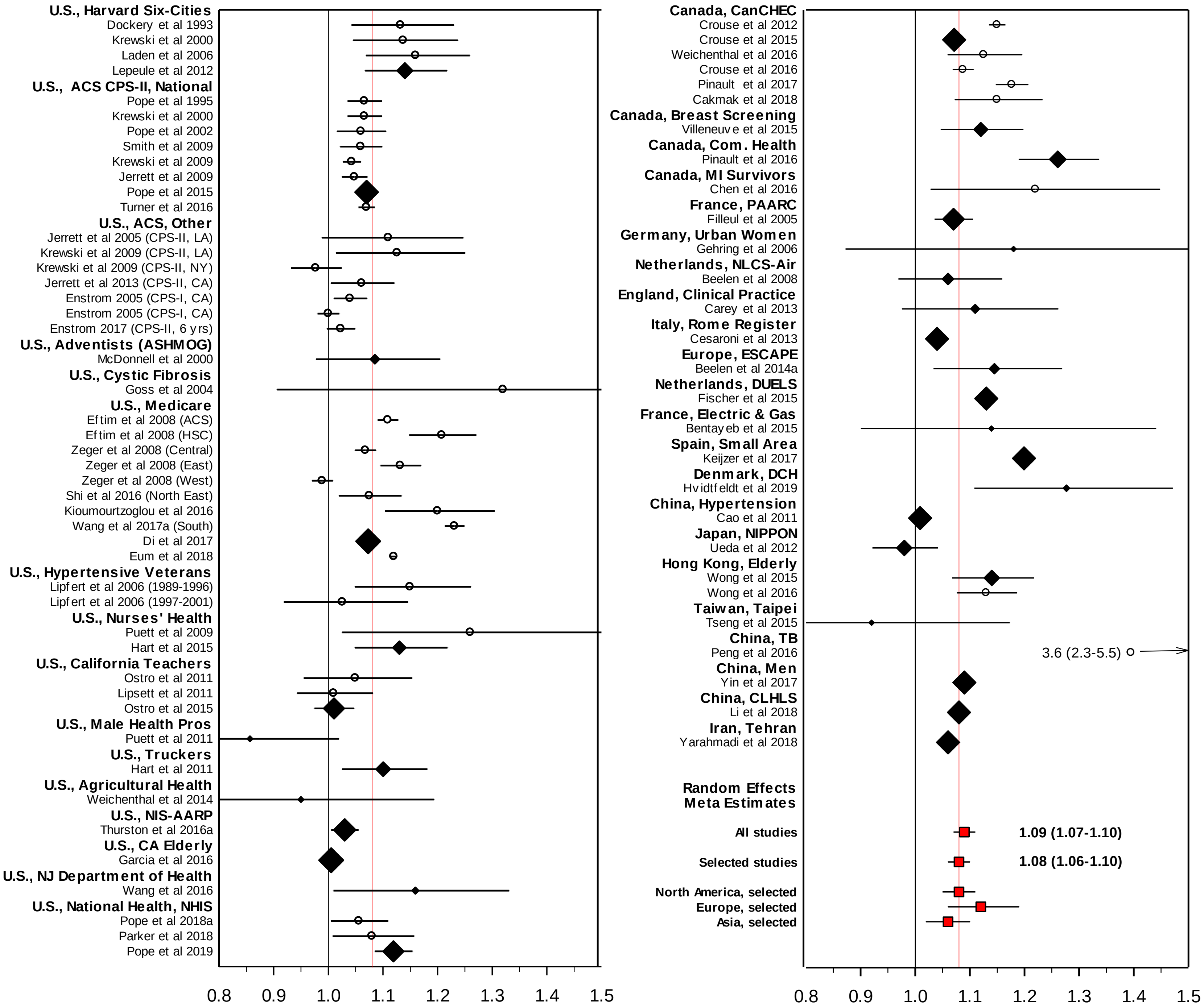
environmental research

2019 (in press)

All studies: 75
Selected studies: 33

Note: These estimates come now from areas with wide ranges of pollution—very low in Canada, high in China.

All-Cause Mortality



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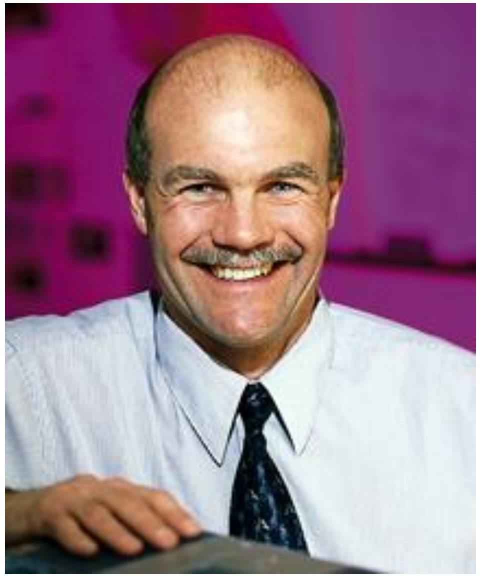
General statistical approaches

California Children's Health study

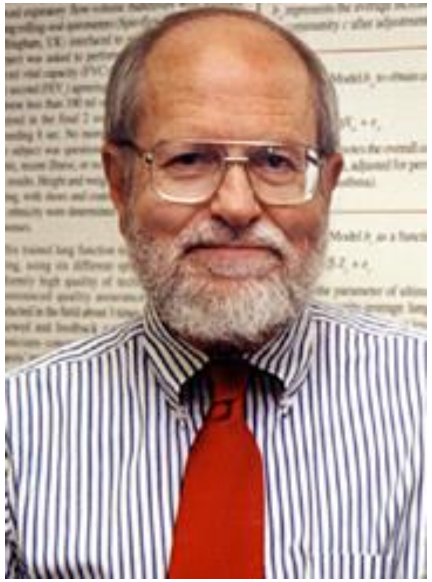
Southern California Children’s Health Study

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



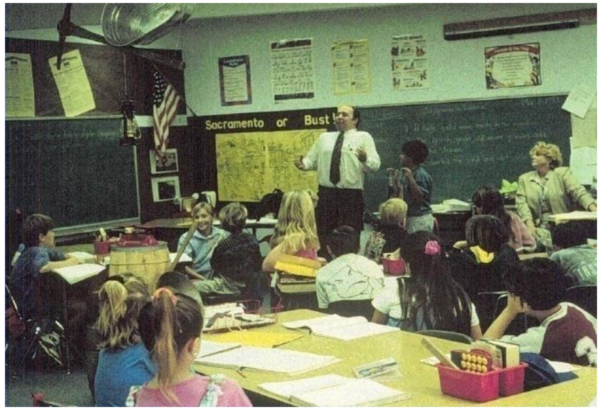
W. James Gauderman

Kiros T. Burhane



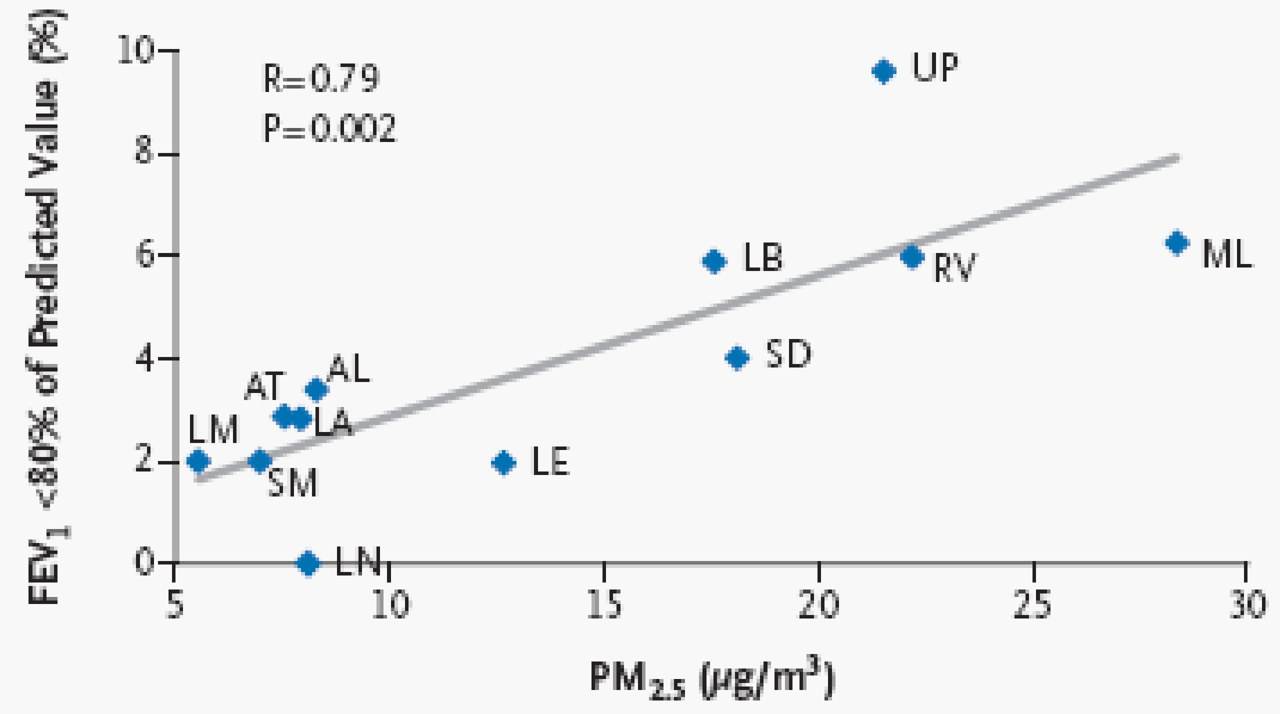
John Peters

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.

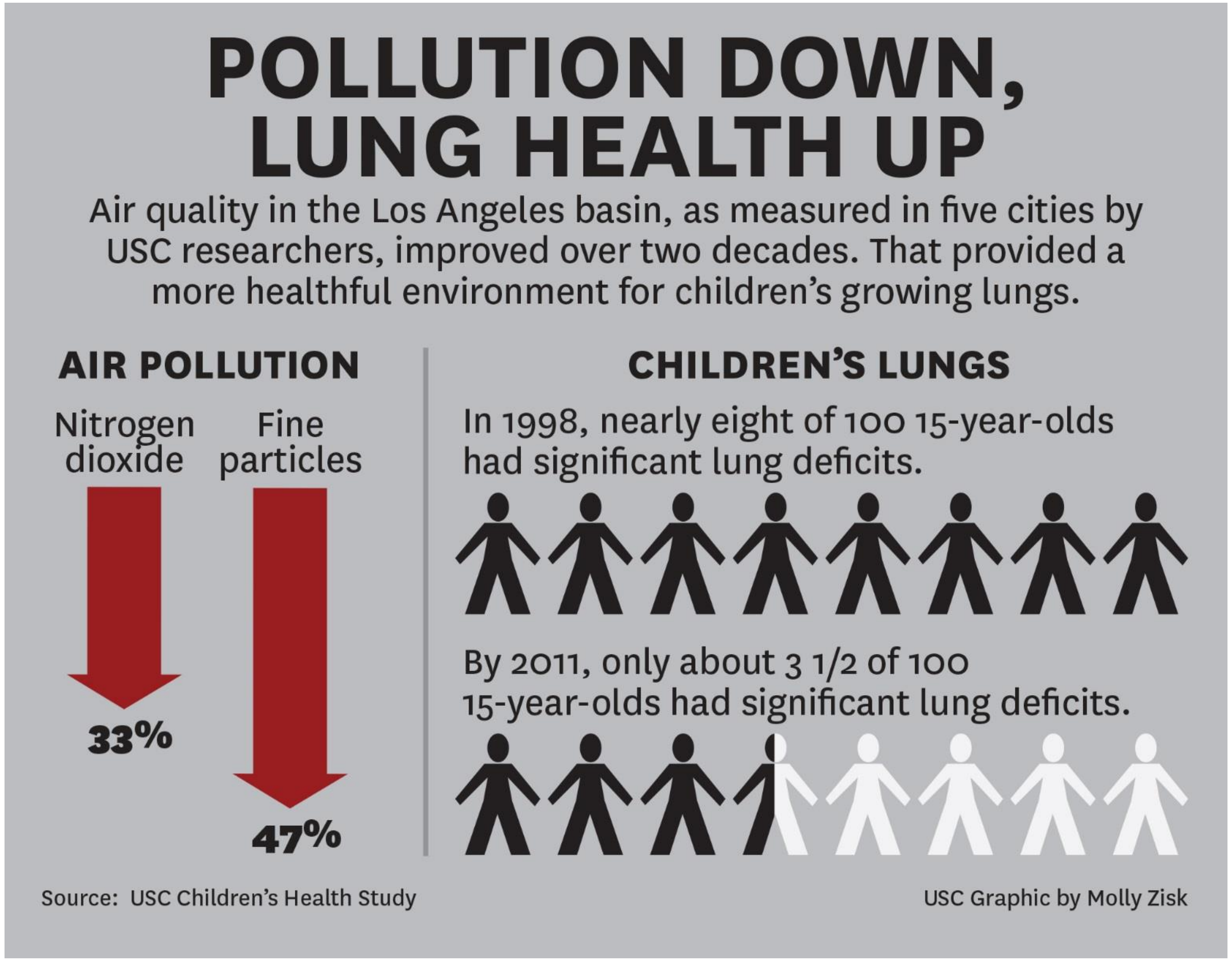
JAMA®
The Journal of the American Medical Association

April 2016

Original Investigation

Association of Changes in Air Quality With Bronchitic Symptoms in Children in California, 1993-2012

Kiros Berhane, PhD; Chih-Chieh Chang, PhD; Rob McConnell, MD; W. James Gauderman, PhD; Edward Avol, MS; Ed Rapappport, MPH; Robert Urman, PhD; Fred Lurmann, MS; Frank Gilliland, MD, PhD




Kiros T. Burhane, PhD USC

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General statistical approaches

Many statistical approaches including:

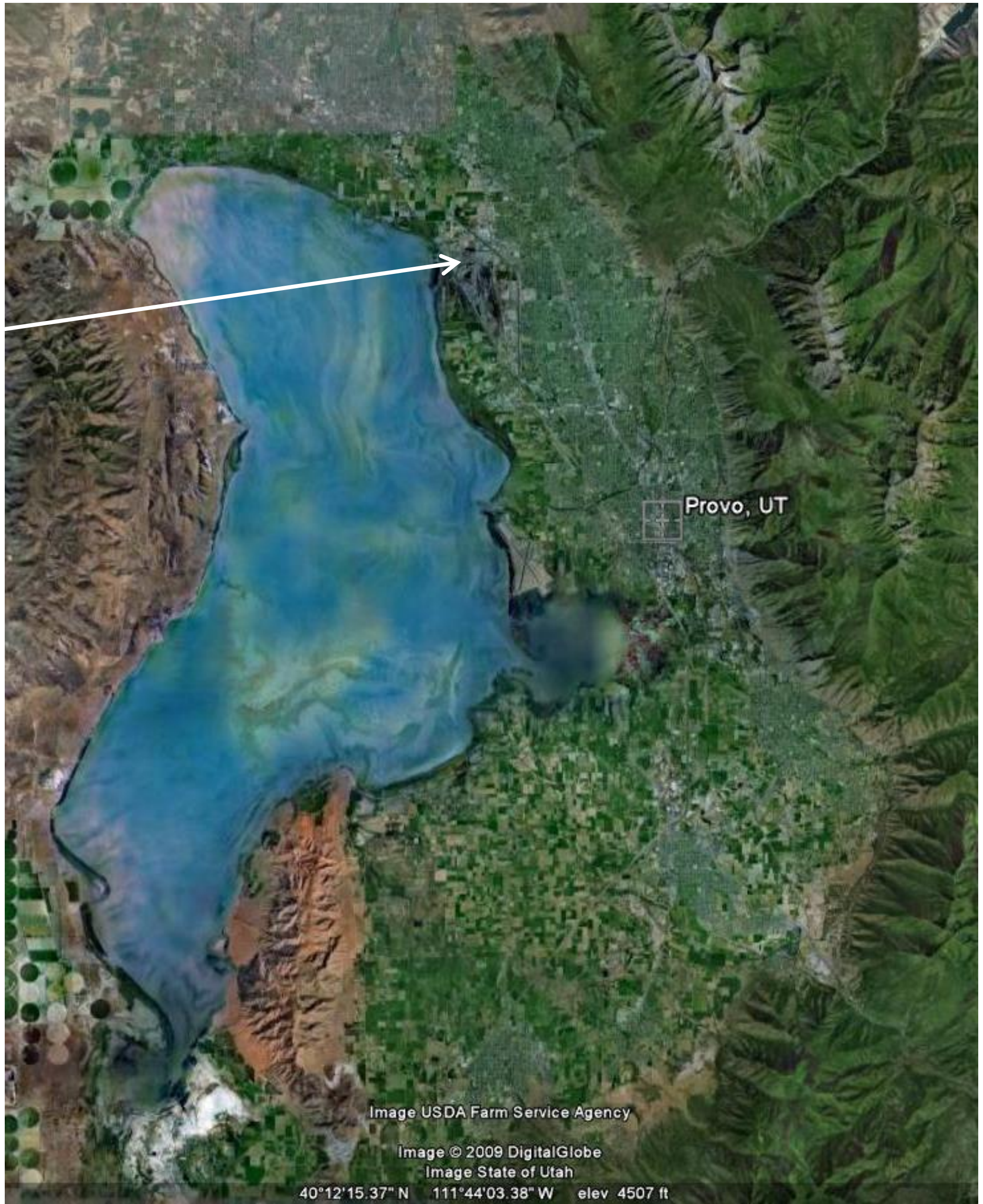
- Comparative stats,
- Diff-in-Diff
- Inverse Probability weighting/doubly robust
- Propensity score Weighting
- Regression discontinuity
- Instrumental variables

Etc.

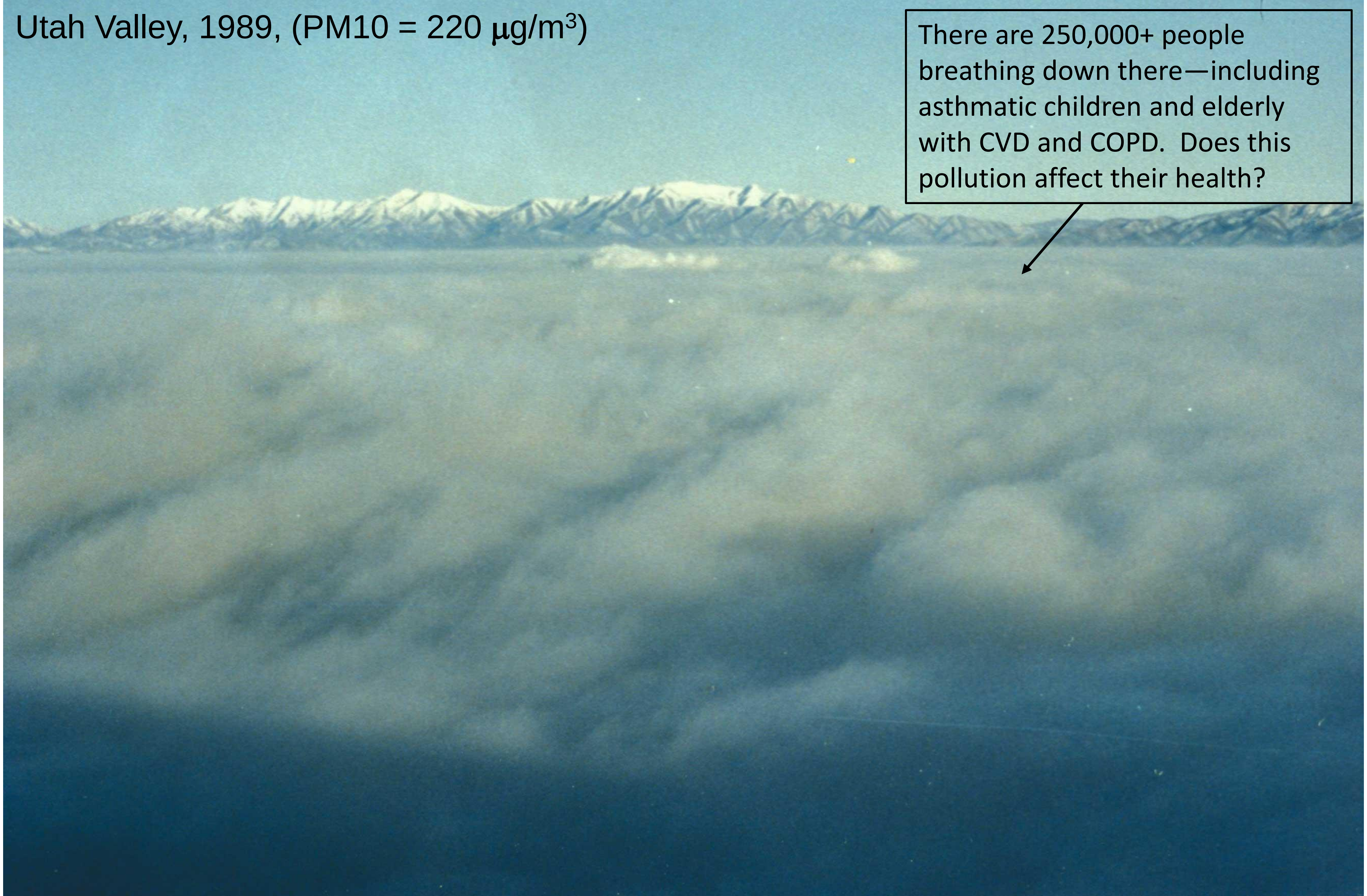
**Efforts at more design-based, causal modeling.

Utah Valley, 1980s

- **Winter inversions trap local pollution**
- **Natural test chamber**

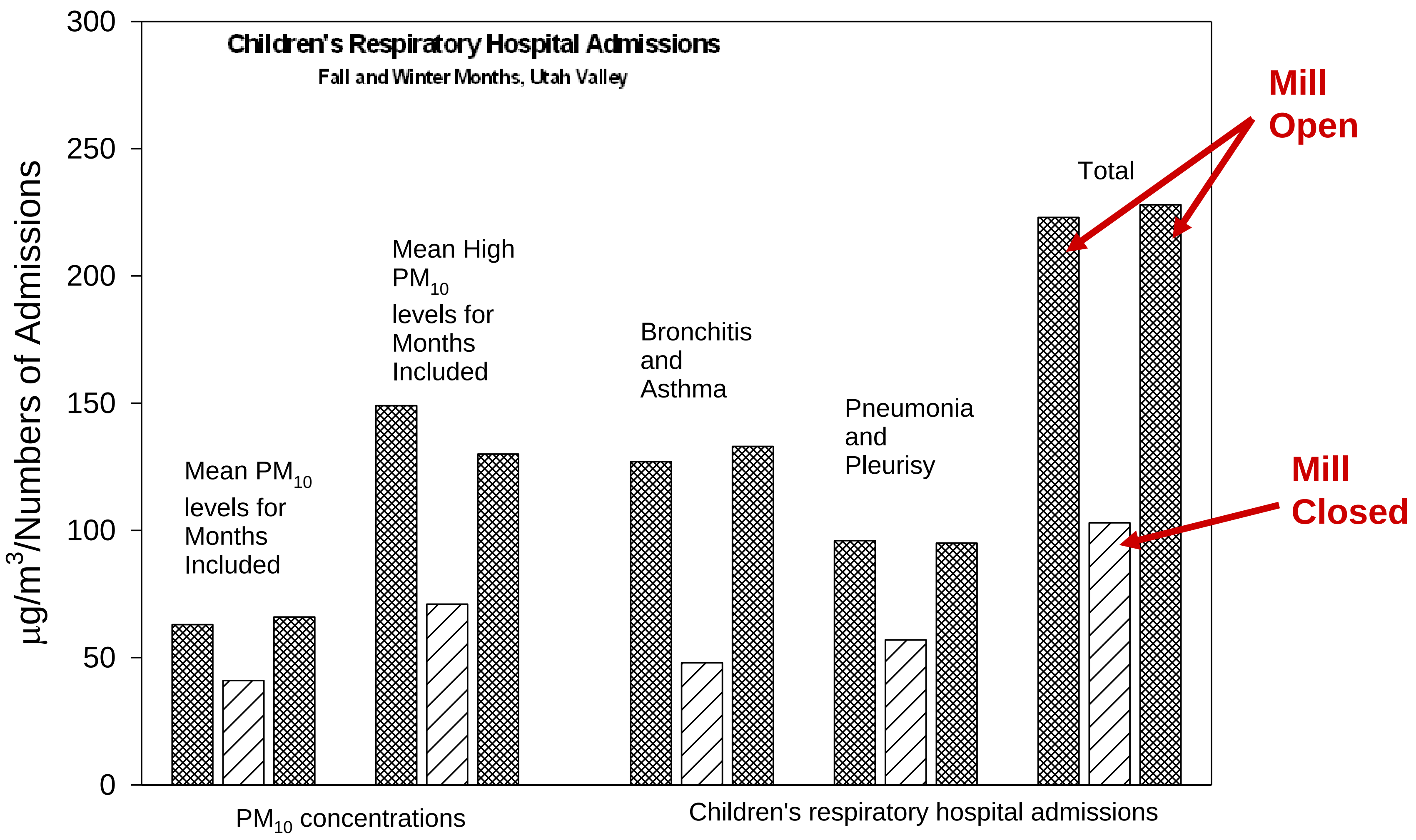


- **Local Steel mill contributed ~50% $PM_{2.5}$**
- **Shut down July 1986-August 1987**
- **Natural Experiment**



Utah Valley, 1989, (PM10 = 220 μg/m3)
There are 250,000+ people breathing down there—including asthmatic children and elderly with CVD and COPD. Does this pollution affect their health?

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

The NEW ENGLAND JOURNAL of MEDICINE

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

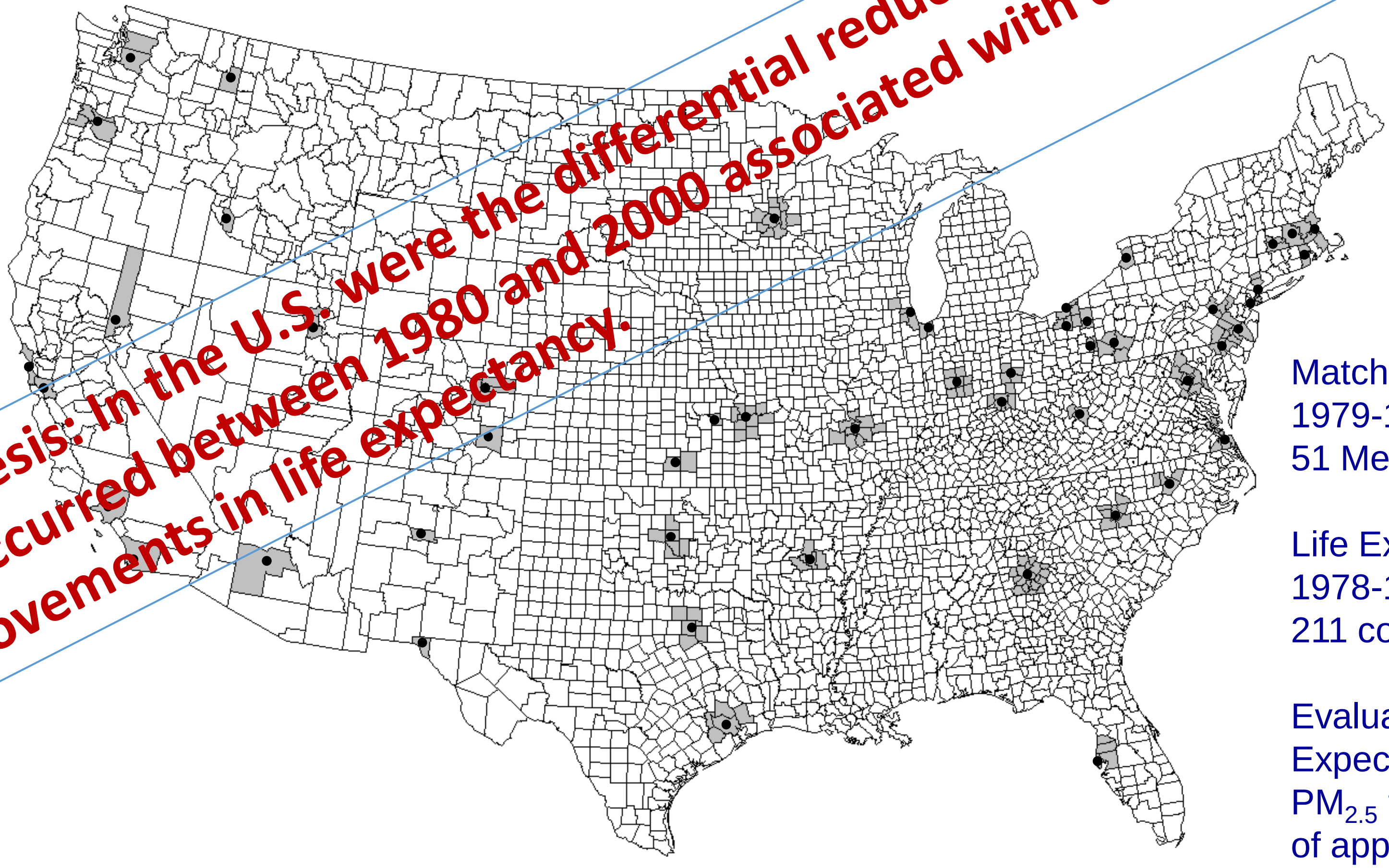
C. Arden Pope, III, Ph.D., Majid Ezzati, Ph.D., and Douglas W. Dockery, Sc.D.

January 22, 2009

Majid Ezzati, PhD
Imperial College London

Francesca Dominici, PhD
Harvard

Hypothesis: In the U.S. were the differential reductions in pollution that occurred between 1980 and 2000 associated with differential improvements in life expectancy.



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

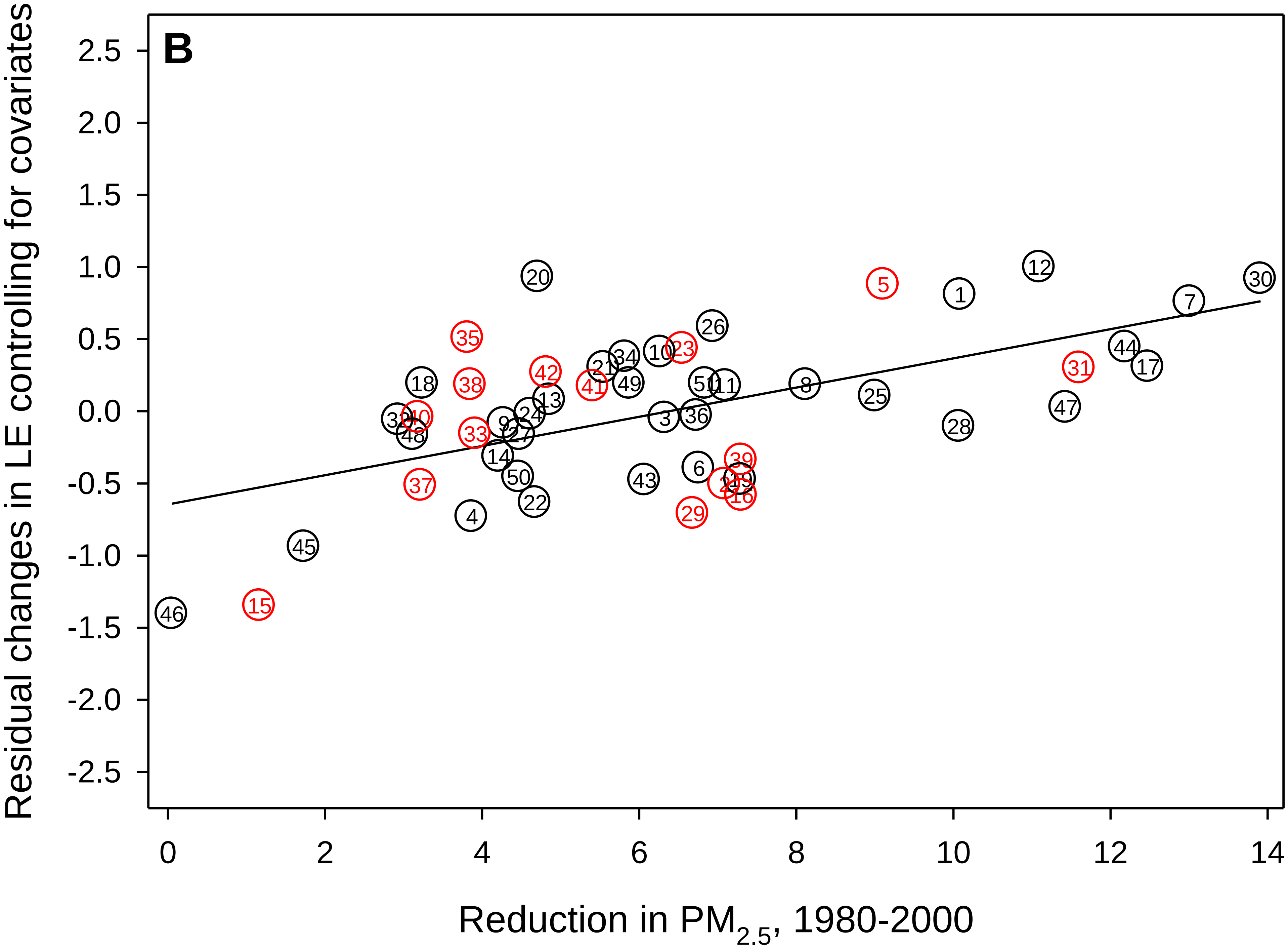
Evaluate changes in Life Expectancy with changes in $PM_{2.5}$ for the 2-decade period of approximately 1980-2000.

10 μg/m^3 decrease in $PM_{2.5}$ associated with a **one year** increase in life expectancy.

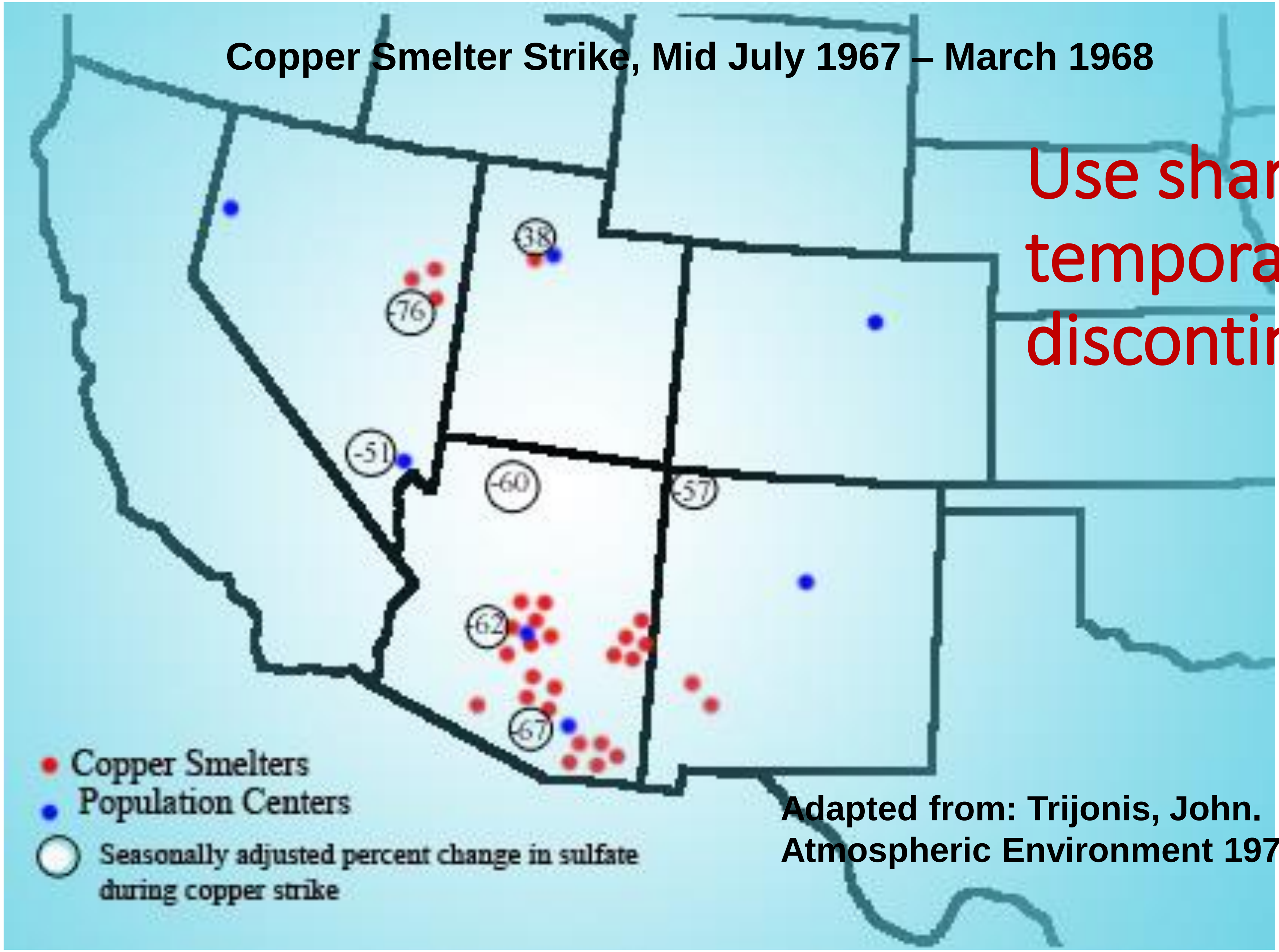
Table 2. Results of Selected Regression Models, Including Estimates of the Increase in Life Expectancy Associated with a Reduction in $PM_{2.5}$ of 10 μg per Cubic Meter, Adjusted for Socioeconomic, Demographic, and Proxy Indicators for Prevalence of Smoking.*

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


B
Residual changes in LE controlling for covariates
Reduction in $PM_{2.5}$, 1980-2000
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
0
2
4
6
8
10
12
14

Copper Smelter Strike, Mid July 1967 – March 1968



Use sharp temporal discontinuities

Adapted from: Trijonis, John. Atmospheric Environment 1979

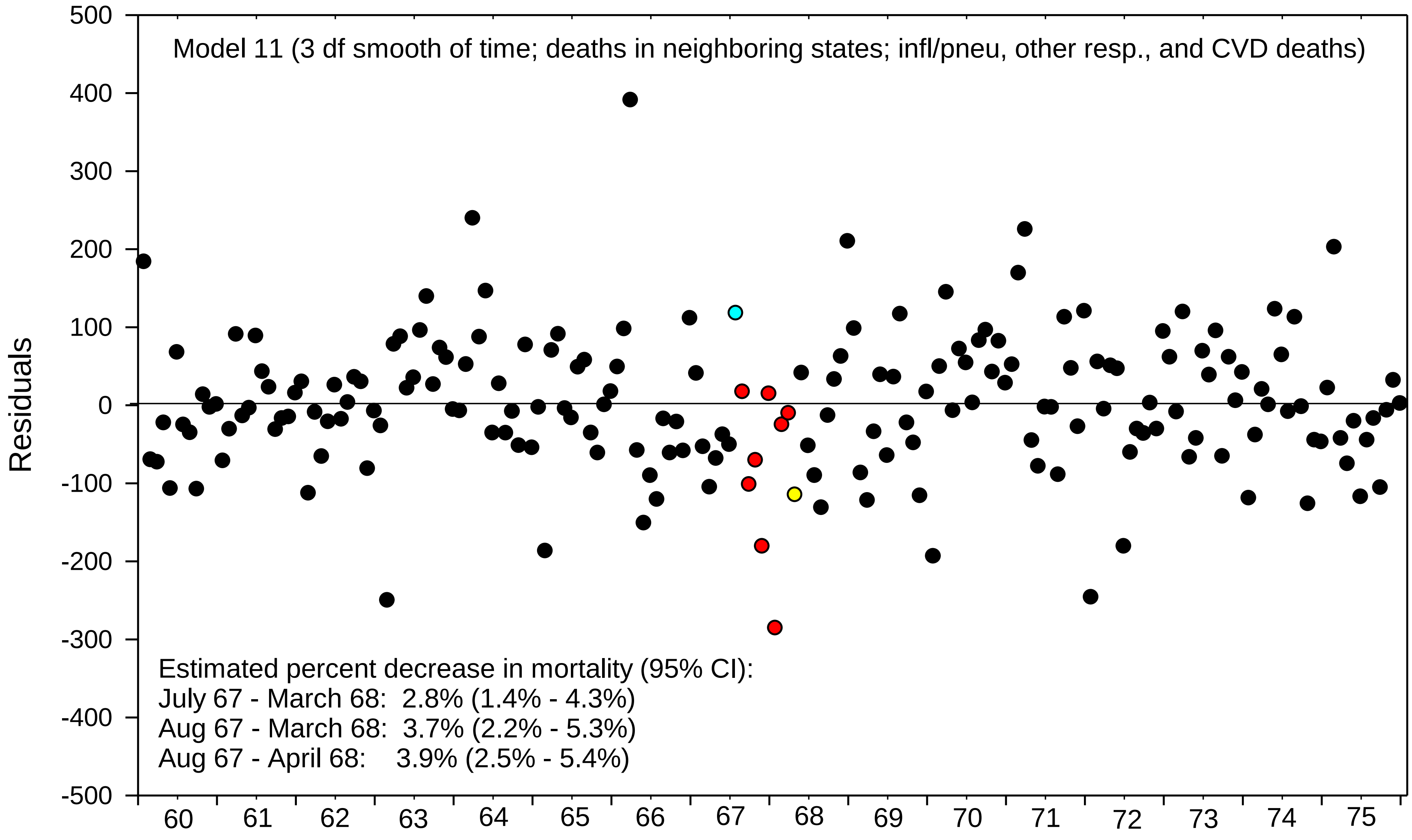
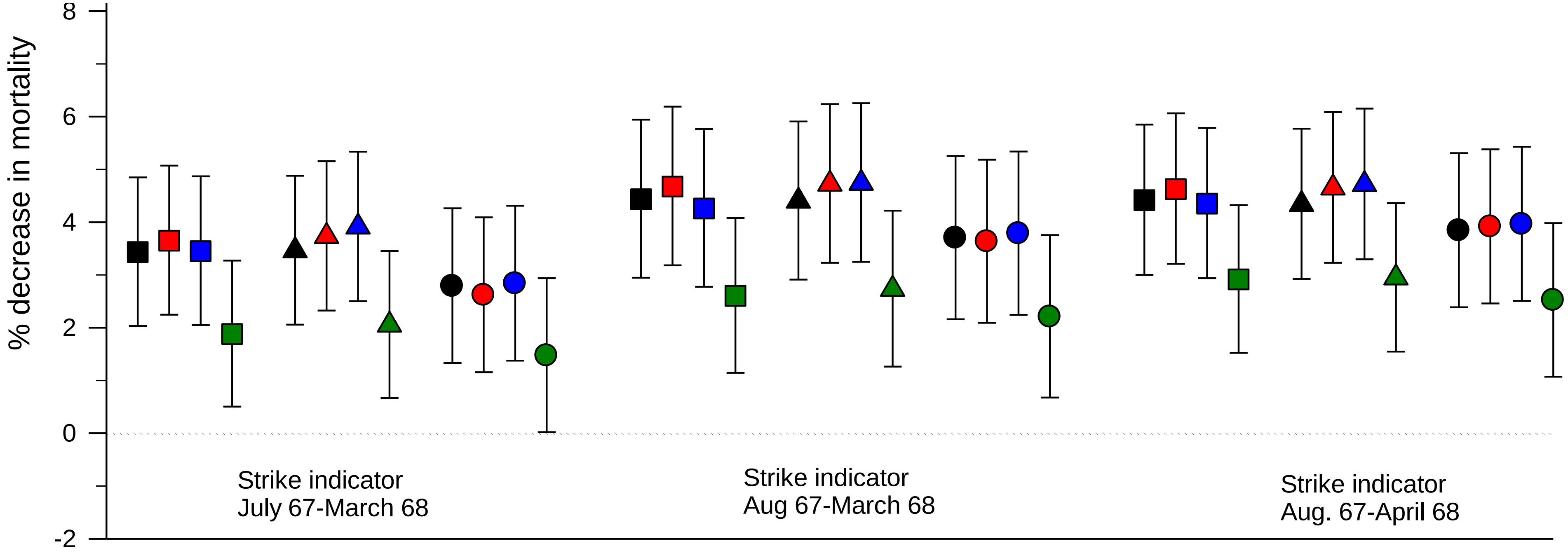


Figure 3a. Residual plot of model 11. The blue dot indicates the month when strike began mid month (July 1967). Red dots indicate full strike months (Aug. 1967-March 1968). Yellow dot indicates first end-of-strike month (April 1968).

Mortality Effects of a Copper Smelter Strike and Reduced Ambient Sulfate Particulate Matter Air Pollution

C. Arden Pope III, Douglas L. Rodermund, Matthew M. Gee

Environmental Health Perspectives
2007



Evidence on the impact of sustained exposure to air pollution on life expectancy from China's Huai River policy

2013

Yuyu Chen[a,1], Avraham Ebenstein[b,1], Michael Greenstone[c,d,1,2], and Hongbin Li[e,1]

PNAS
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

Fig. 1. The cities shown are the locations of the Disease Surveillance Points. Cities north of the solid line were covered by the home heating policy.

Use sharp spatial discontinuities

Key estimated equations:

$$TSP_j = \alpha_0 + \alpha_1 N_j + \alpha_2 f(L_j) + X_j \kappa + \nu_j \qquad [2a]$$

$$Y_j = \delta_0 + \delta_1 N_j + \delta_2 f(L_j) + X_j \phi + u_j, \qquad [2b]$$

Mortality or Life expectancy for city j.

Indicator variable equal to 1 for locations North of Huai River line

Polynomial in degrees North of Huai River line

Other demographic and city characteristics that may effect mortality

$$Y_j = \beta_0 + \beta_1 T\hat{S}P_j + \beta_2 f(L_j) + X_j \Gamma + \varepsilon_j, \qquad [2c]$$

Or estimate 2a as the first step in a two stage least-squares (2SLS) and then estimated 2c above as the second stage equation.

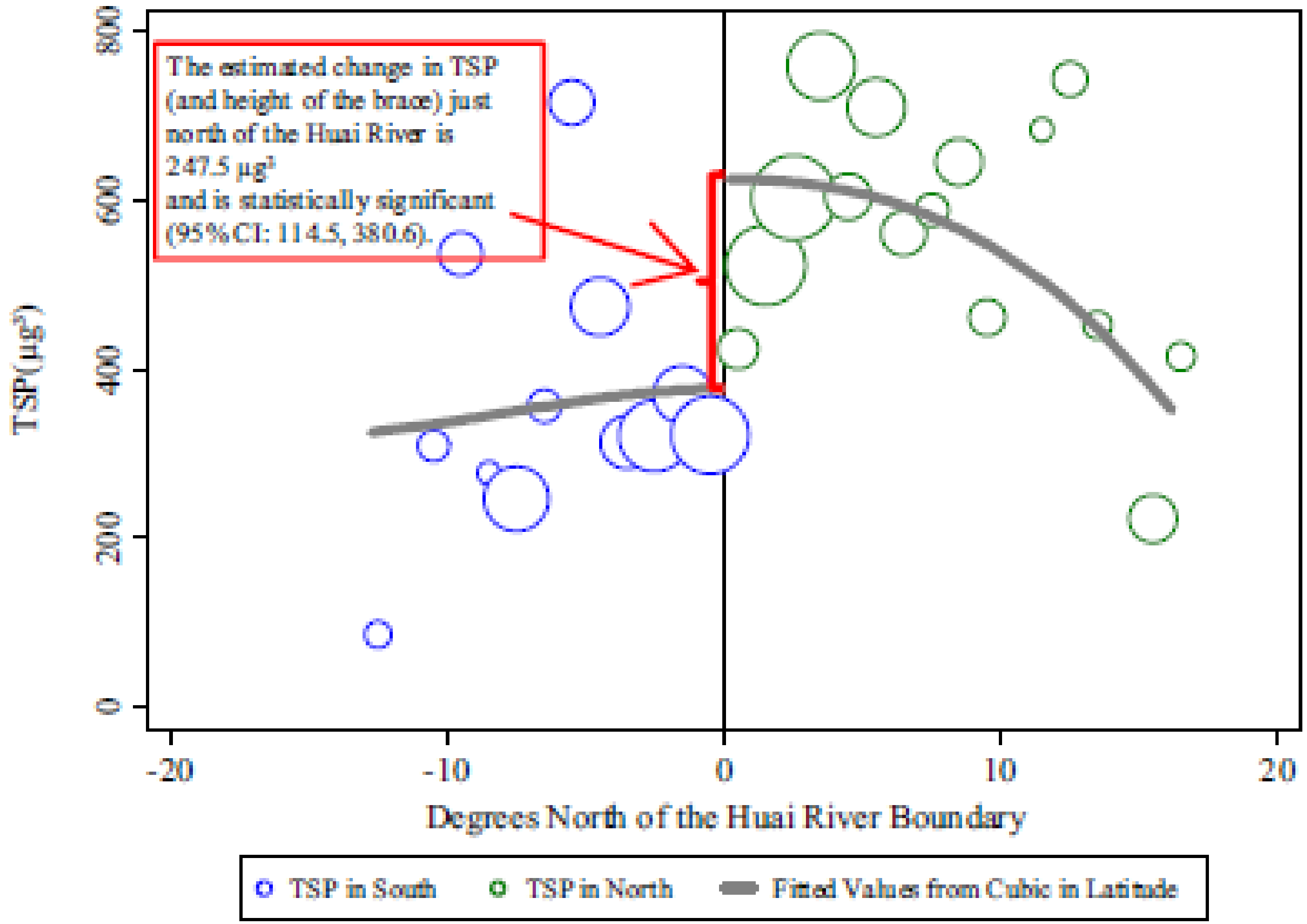


Fig. 2. Each observation (circle) is generated by averaging TSPs across the Disease Surveillance Point locations within a 1° latitude range, weighted by the population at each location. The size of the circle is in proportion to the total population at DSP locations within the 1° latitude range. The plotted line reports the fitted values from a regression of TSPs on a cubic polynomial in latitude using the sample of DSP locations, weighted by the population at each location.

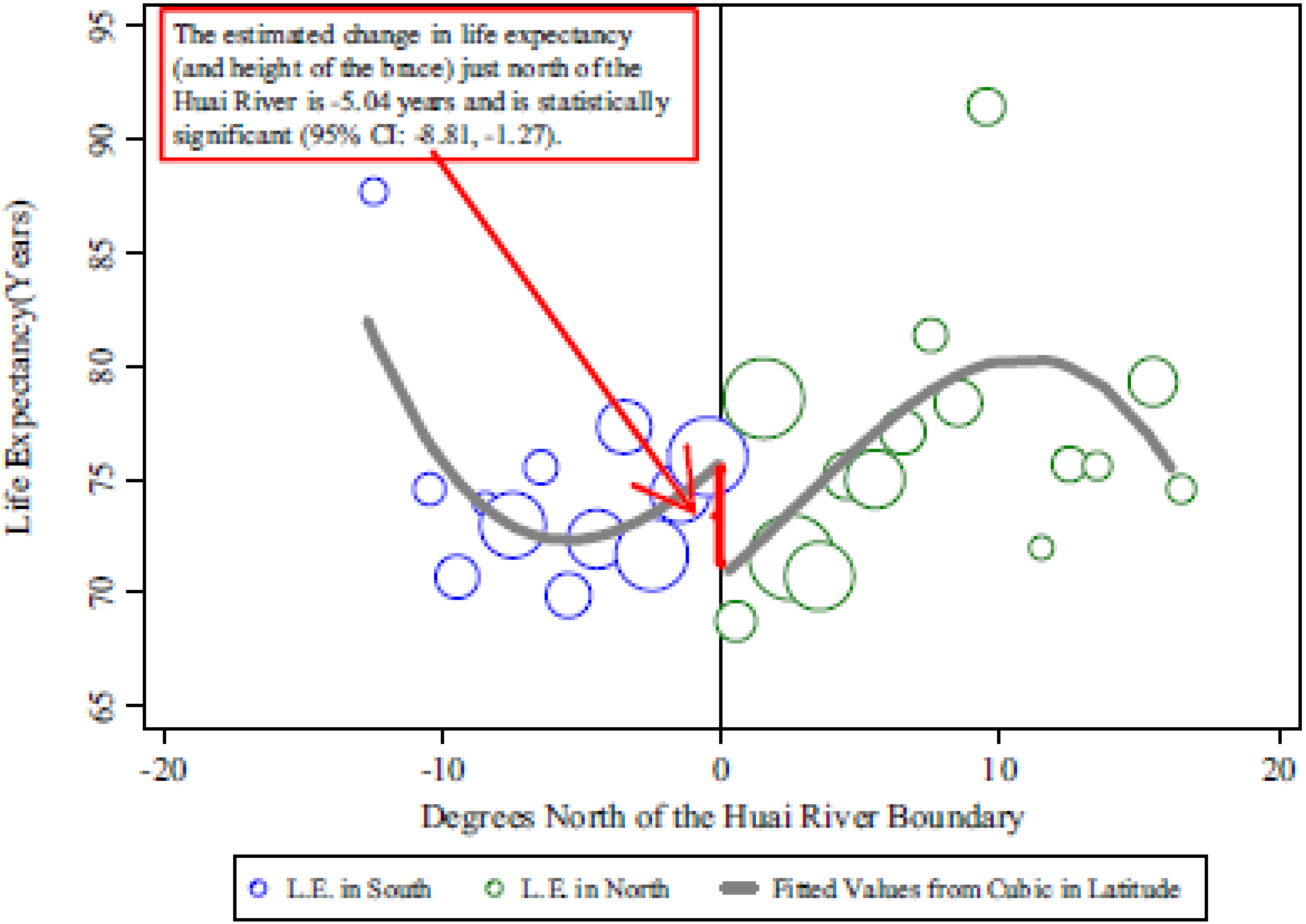


Fig. 3. The plotted line reports the fitted values from a regression of life expectancy on a cubic in latitude using the sample of DSP locations, weighted by the population at each location.

Stylized outline of epidemiologic study designs of air pollution and health

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**

Intervention/natural experiment/quasi-experimental

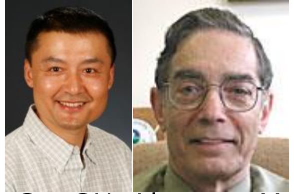
Controlled experimental human and animal

General statistical approaches

Generally simpler statistical modeling—

Data are less observational with more control by statistical strategy and design.

Sun et al. (*JAMA* 2005)


Sun QH   Lippmann M

$apoE^{-/-}$ mouse

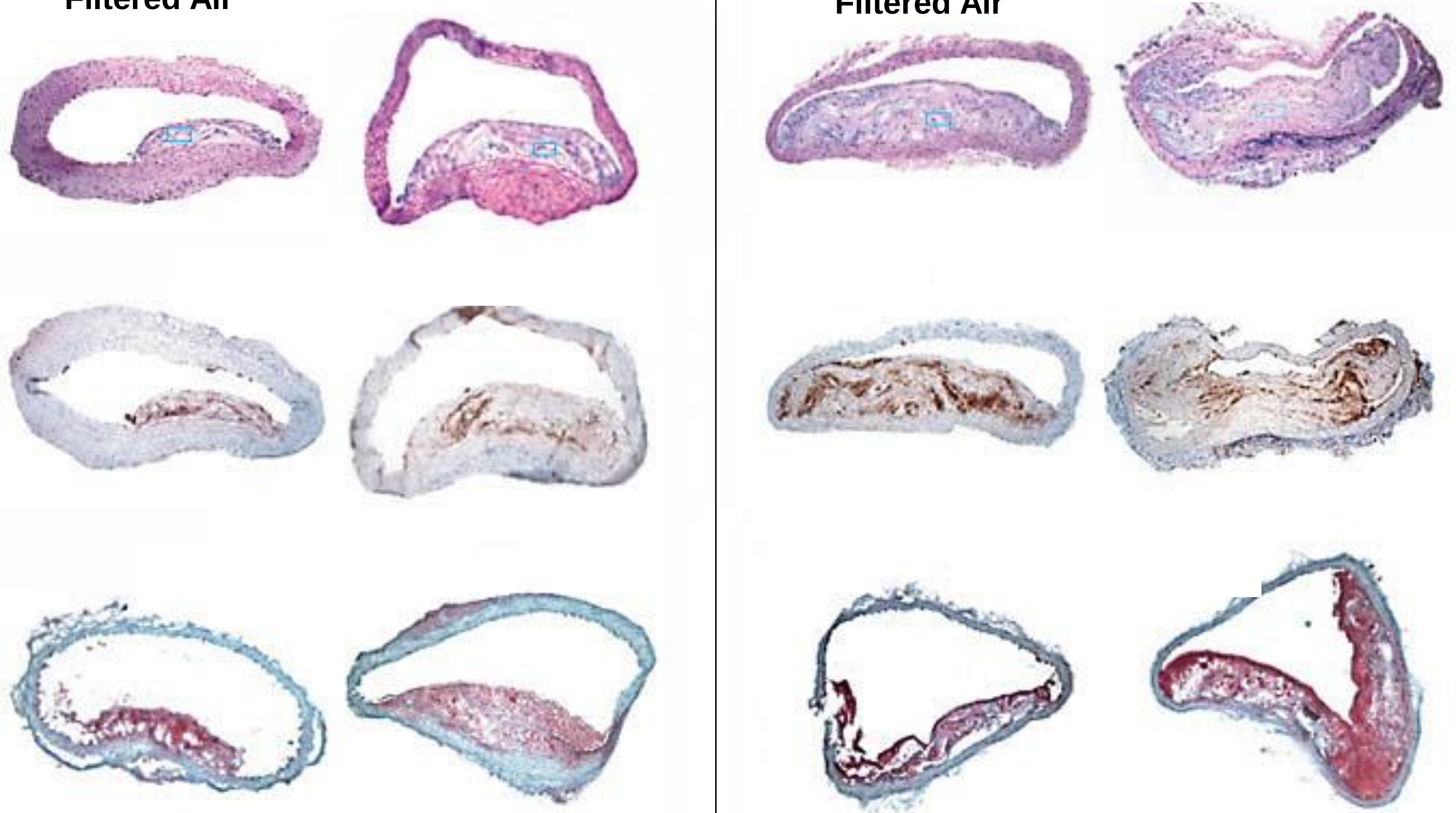
Representative Photomicrographs
of Aortic Arch Sections

Normal Chow

Clean Filtered Air | PM Polluted Air

High-Fat Chow

Clean Filtered Air | PM Polluted Air



Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

2016

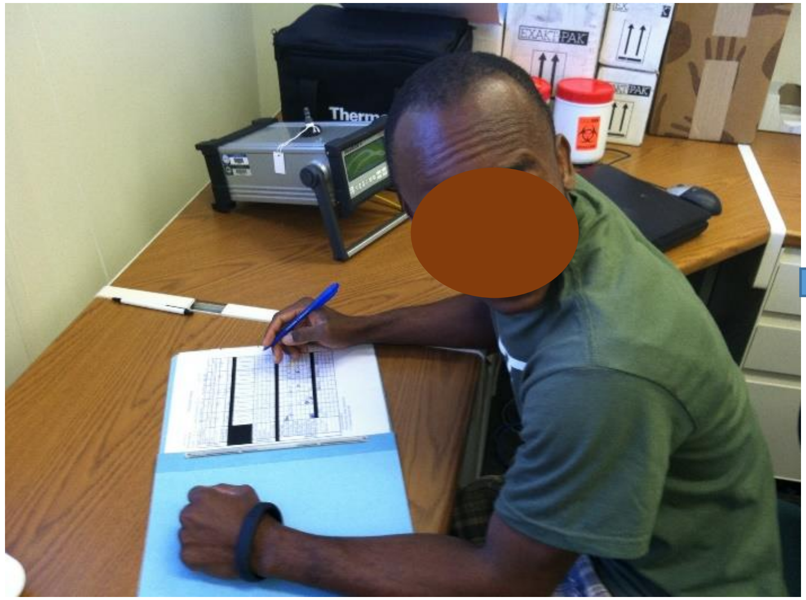
Aruni Bhatnagar, PhD FAHA
U of Louisville

Tim O'Toole, PhD
U of Louisville

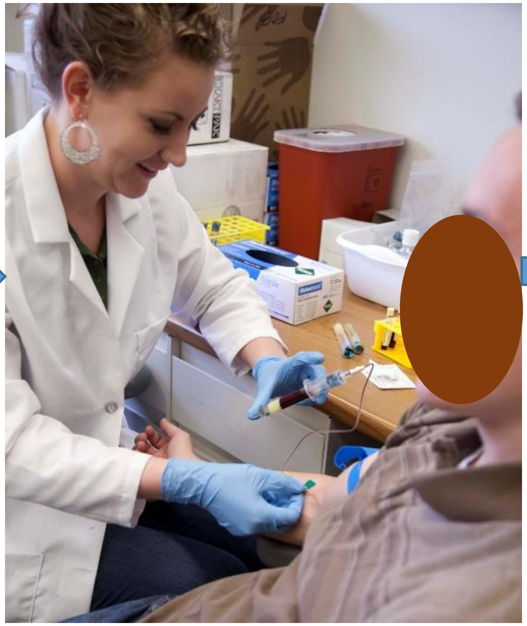
Cellular Biology

Exposure to Fine Particulate Air Pollution Is Associated With Endothelial Injury and Systemic Inflammation

C. Arden Pope III, Aruni Bhatnagar, James P. McCracken, Wesley Abplanalp, Daniel J. Conklin, Timothy O'Toole



Enroll research subjects including 72 young, healthy, non-smoking adults from BYU/Provo. (Note DataRAM $PM_{2.5}$ monitor).



Multiple blood draws during relatively clean and polluted periods over 3 yrs.

Process blood, ship to UofL.

Microparticles and immune cells quantified using a multi-laser flow cytometer (Becton Dickinson LSR II) at UofL

Eve technologies
Your Partner in Research

An array of **42 human cytokines** and an array of **2 markers of endothelial adhesion (sICAM-1 and sVCAM-1)** were measured from frozen plasma aliquots by analytic services at **Eve Technologies** (Calgary, Alberta, Canada) using multiplexing laser bead technology.

Statistical Analysis

- Fixed-effects regression models
- Subject-mean-adjusted regression
- Graphical analysis
- Sensitivity analysis

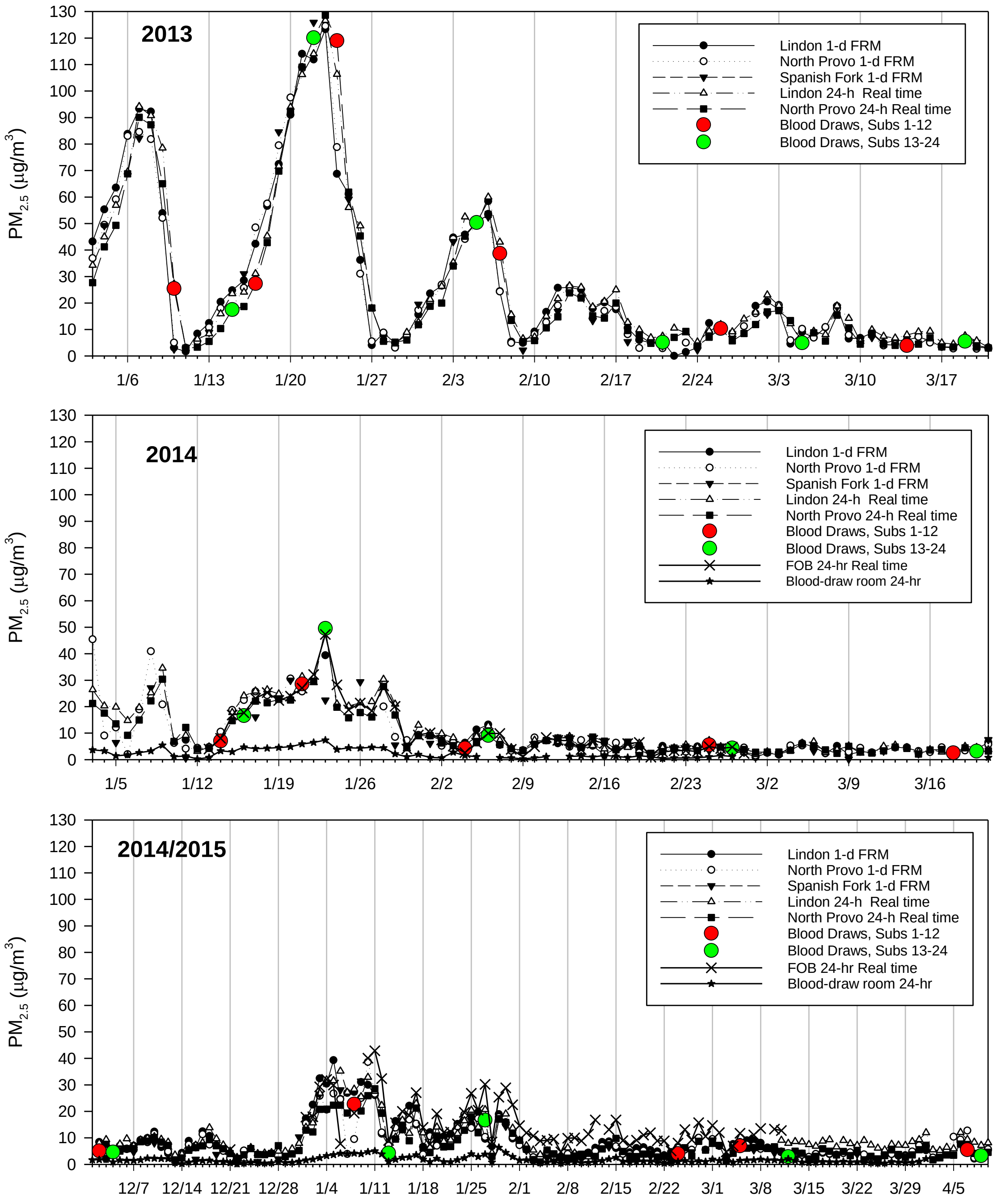


Figure 1. $PM_{2.5}$ concentrations and blood-draw dates plotted during study periods.

Table 2. Description and Summary Statistics of Microparticles and Immune Cells and Regression Coefficients for $PM_{2.5}$ From the Subject Mean–Adjusted Regression Models

Outcome Variables	Phenotype	No. of obs.	Mean*	SD	Coefficient (×10; SE)	*P* Value	R^2
Microparticles							
MP, EPC	$CD34^+/CD31^+$	332	22.03	21.68	−0.09 (0.34)	0.796	0.00
MP, Platelet	$CD41^+$	332	37.37	34.94	−1.33 (0.55)	0.017	0.02
MP, Endothelial	$CD31^+/CD41^-$	332	6.76	10.14	1.00 (0.16)	<0.001	0.11
MP, Lung endothelial	$CD31^+/CD41^-/CD143^+$	331	2.82	4.48	0.42 (0.07)	<0.001	0.10
MP, Nonlung endothelial	$CD31^+/CD41^-/CD143^-$	331	3.88	6.40	0.56 (0.10)	<0.001	0.09
MP, Venous endothelial	$CD31^+/CD41^-/EphB4^+$	329	2.55	5.54	0.48 (0.09)	<0.001	0.09
MP, Lung venous endothelial	$CD31^+/CD41^-/EphB4^+/CD143^+$	329	2.06	4.57	0.39 (0.07)	<0.001	0.08
MP, Arterial endothelial	$CD31^+/CD41^-/EphrinB2^+$	331	3.68	5.03	0.37 (0.07)	<0.001	0.07
MP, Lung arterial endothelial	$CD31^+/CD41^-/EphrinB2^+/CD143^+$	331	3.27	4.56	0.31 (0.07)	<0.001	0.06
MP, Activated endothelial	$CD62^+$	332	17.91	16.11	−0.63 (0.26)	0.014	0.02
MP, Lung-activated endothelial	$CD62^+/CD143^+$	332	3.93	4.25	0.005 (0.06)	0.943	0.00
MP, Venous-activated endothelial	$CD62^+/EphB4^+$	332	4.40	6.67	−0.02 (0.10)	0.876	0.00
MP, Lung venous–activated endothelial	$CD62^+/EphB4^+/CD143^+$	329	3.57	3.80	−0.002 (0.06)	0.980	0.00
MP, Arterial-activated endothelial	$CD62^+$/ $EphrinB2^+$	330	5.17	5.03	0.03 (0.08)	0.702	0.00
MP, Lung arterial–activated endothelial	$CD62^+$/ $EphrinB2^+/CD143^+$	330	4.52	4.47	0.05 (0.07)	0.518	0.00
Immune cells							
Monocytes	$CD14^+$	365	22 503	15 535	863.99 (185.95)	<0.001	0.06
Natural killer cells	$CD16^+$	365	17 530	16 784	660.22 (182.24)	<0.001	0.03
Helper T cells	$CD4^+$	365	72 604	42 633	2151.75 (504.36)	<0.001	0.05
Killer T cells	$CD8^+$	365	39 259	24 421	1038.21 (323.52)	0.001	0.03
B cells	$CD19^+$	365	18 242	22 527	−310.72 (304.33)	0.308	0.00
Platelet–monocyte aggregates	$CD45^+/CD41^+$	368	4.71	5.62	0.20 (0.09)	0.020	0.01

EPC indicates endothelial progenitor cells; MP, microparticles; and PM, fine particulate matter <2.5 μm in aerodynamic diameter.
*Per volume of the analytic tube. All microparticle subpopulations were <1 μm and Annexin V^+.

Elevated circulating endothelial microparticles indicative of endothelial cell apoptosis and endothelial injury.

Evidence of subclinical damage to the blood vessels.

Elevated circulating monocytes and T, but not B, lymphocytes—Suggestive of a non-specific or innate ... response and not a sp... response involving antibodies targ...

Evidence of non-specific inflammatory immune response.

Weaker but sig. association with platelet-monocyte aggregates

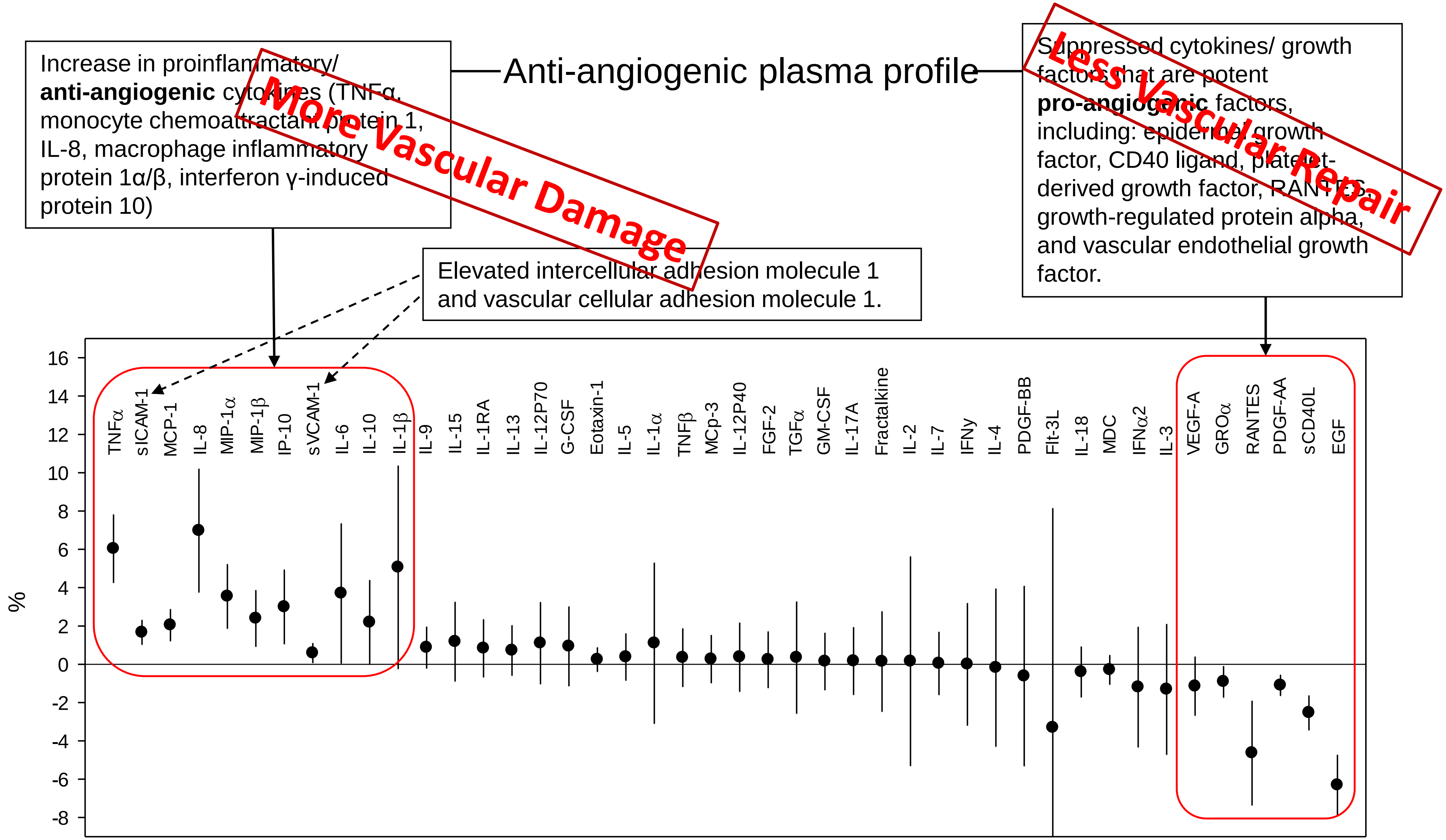


Figure 3. Percent change (and 95% CIs) in analyte per 10 $\mu g/m^3$ increase in $PM_{2.5}$ relative to mean value of analyte. Estimates come from subject-mean adjusted regressions. The results are ordered from left to right based on t-values--resulting in the most statistically signifiant possitive associations being on the left and the most statistially significant negative associations being on the right.

Stylized outline of epidemiologic study designs of air pollution and health

General statistical approaches

Studies of short-term exposure (hours-days)

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- **Cohort- and panel-based morbidity**

Intervention/natural experiment/quasi-experimental

Controlled experimental human and animal

Many study designs, statistical approaches . . .

Has led to compelling evidence that exposure to air pollution has adverse health effects.

In 2015 air pollution was estimated to be the 4th to 6th largest risk factor contributing to GBD for both men and women.

THE LANCET
Volume 376 · Number 9734 · Pages 1-68 · July 3-9, 2010
www.thelancet.com

The Global Burden of Disease 2015

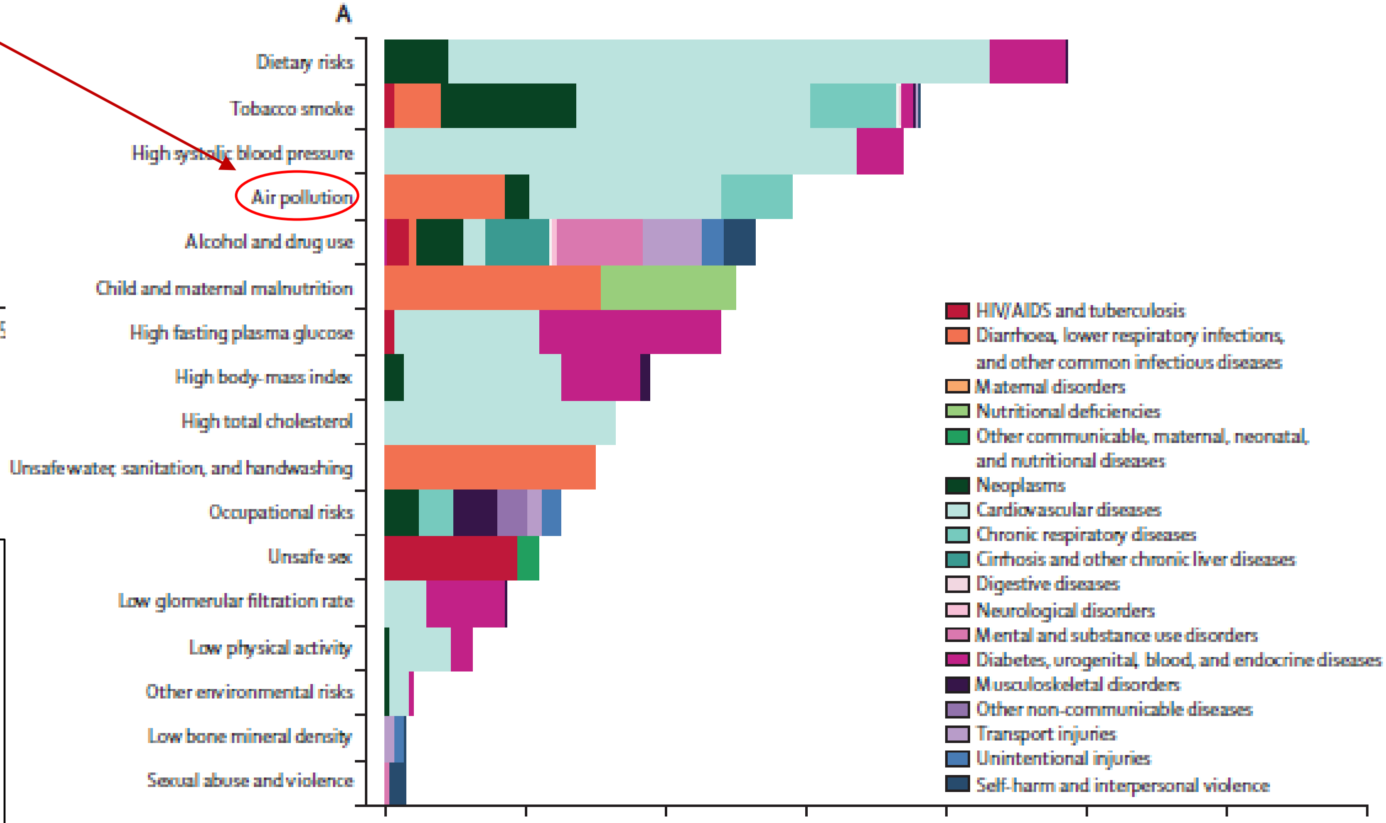

Figure 1. Global DALYs attributable to risk factors for (B) women, and (A) men in 2015.

DALYs=disability adjusted life years.

Clean versus polluted air is among our public policy and economic choices.

- Clean air is an <u>economic good</u> that contributes to human well-being, human capital, and positive environmental amenities.
- The “production” of clean air can contribute to economic prosperity, human well being, and improved public health.