State of the Science for—

Air Pollution-Related Chronic Health Effects Research

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Air Pollution Exposure and Health
RTP, NC

Long-term exposure and mortality

1970s-

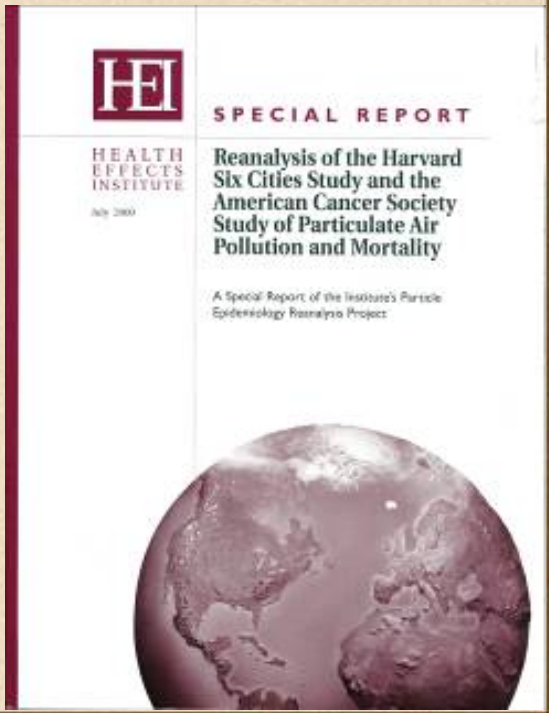
- Population-based cross-sectional studies reported associations between long-term average fine PM and mortality rates.
- These studies discounted—couldn't control for smoking and other individual risk factors.

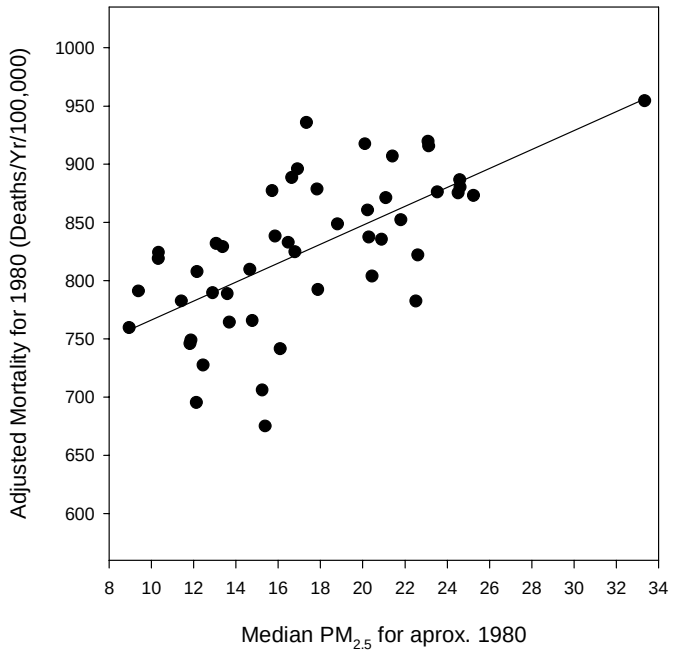
1993, 1995

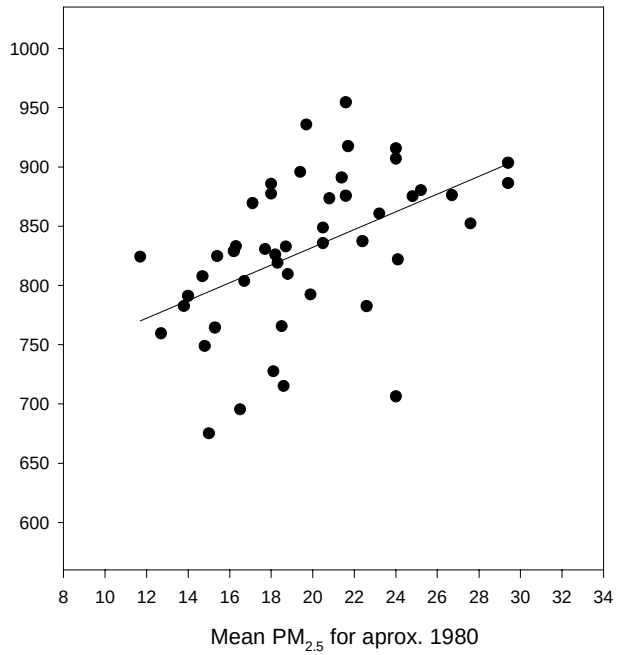
- Harvard Six-Cities and ACS Prospective Cohort studies were reported.
- Long-term fine PM exposure was associated with mortality even after controlling for cigarette smoking and other individual risk factors.

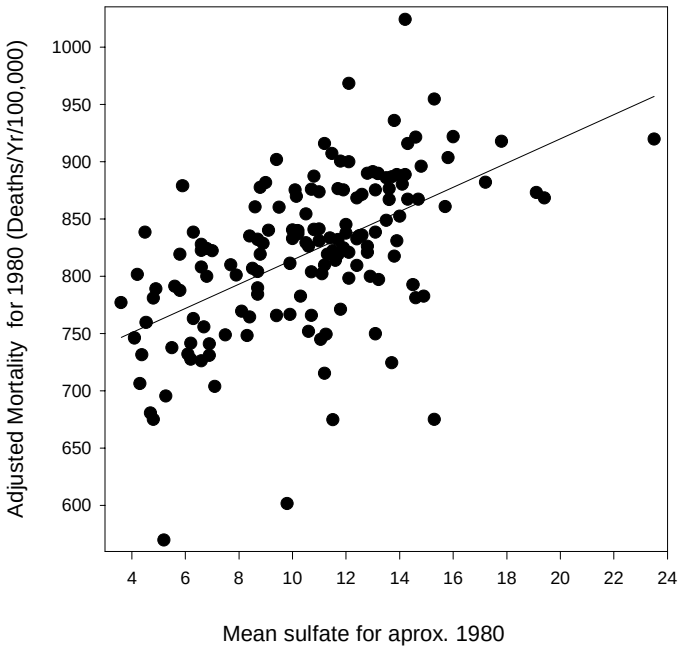
1997-2006

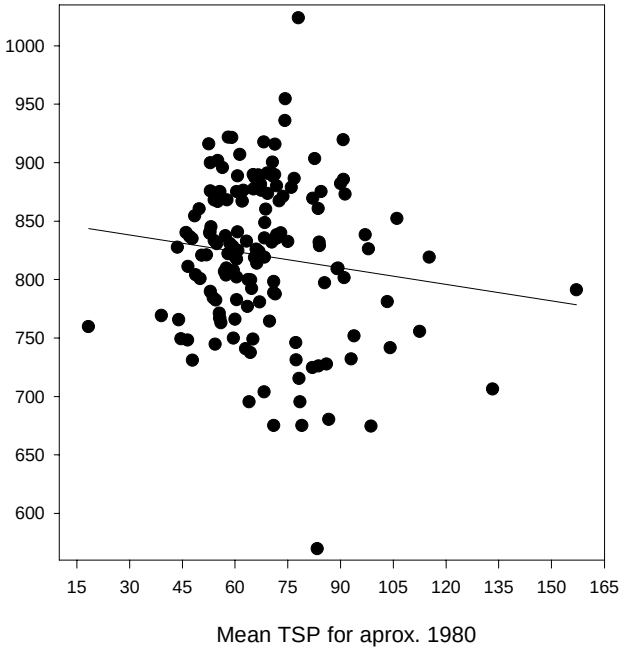
- HEI reanalyzes Six-cities and ACS studies
- Other extended analyses of Six-Cities & ACS
- Several other independent studies reported.





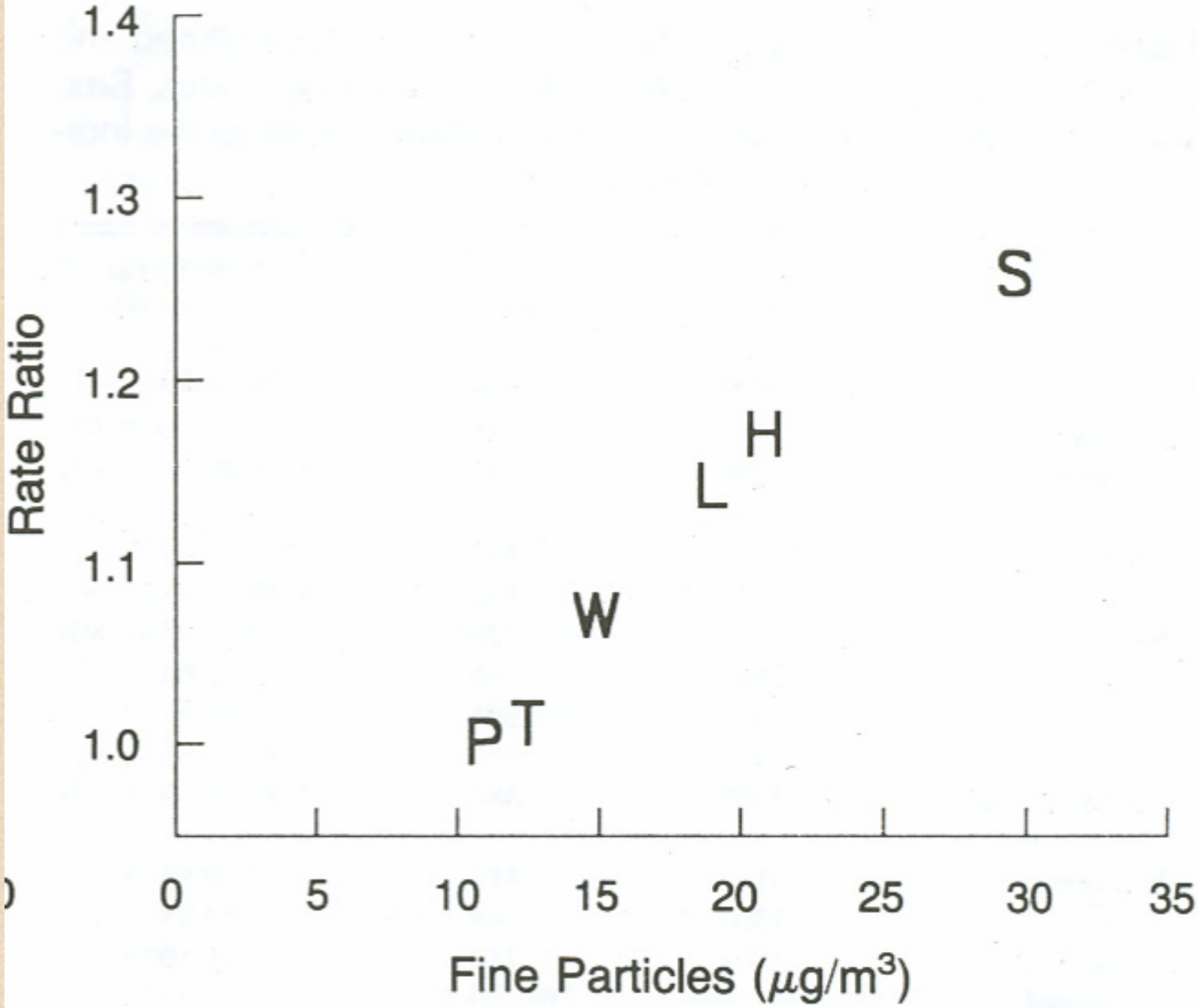




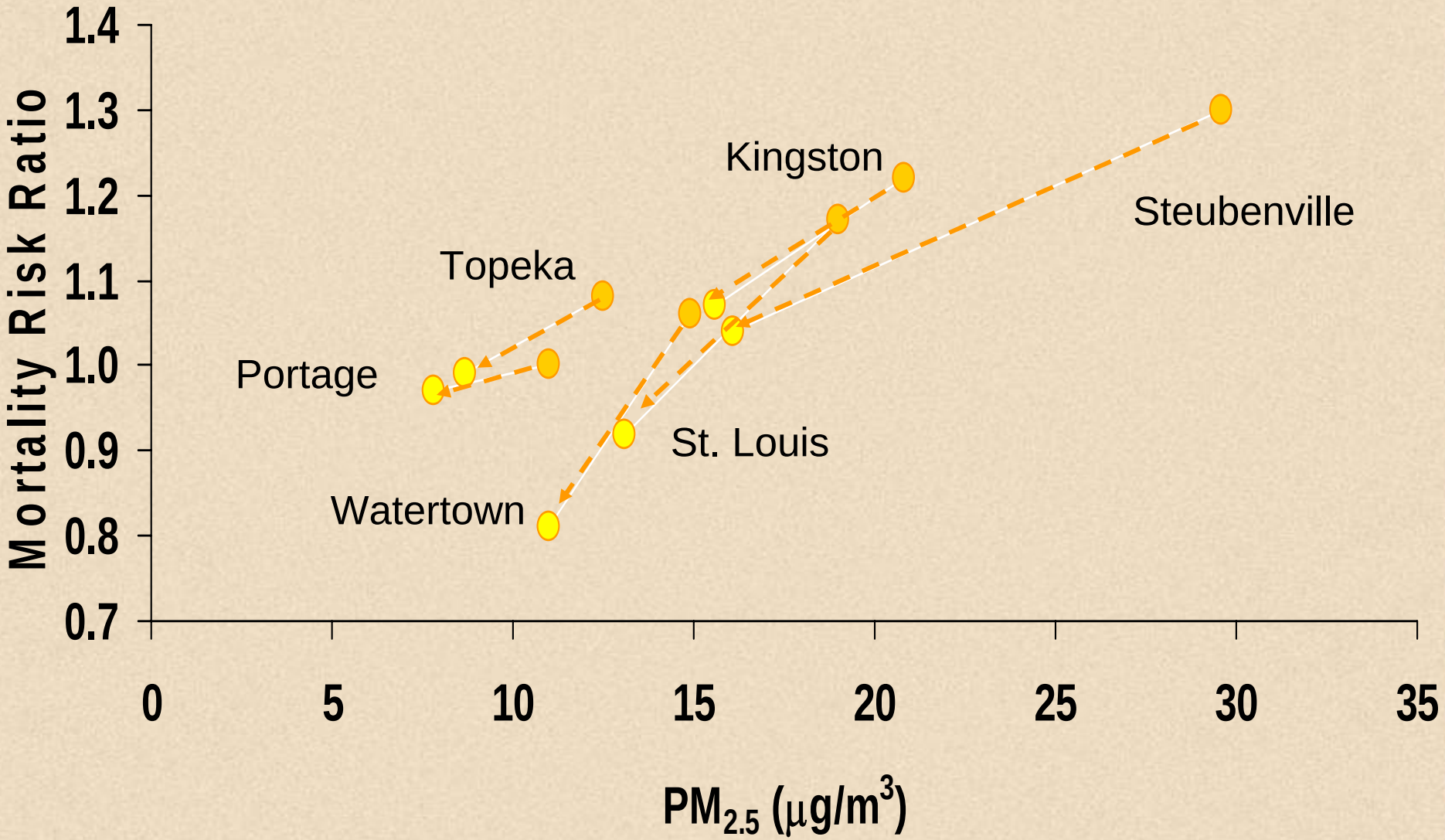


Age-, sex-, and race- adjusted population-based mortality rates in U.S. cities for 1980 plotted over various indices of particulate air pollution (From Pope 2000).

NOTE: Mortality rates associated with $PM_{2.5}$ and SO_4 but not TSP.


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

Six Cities Cohort Follow-up



Laden et al, 2006

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

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Context Associations have been found between day-to-day particulate ai and increased risk of various adverse health outcomes, including cardiopulmo 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

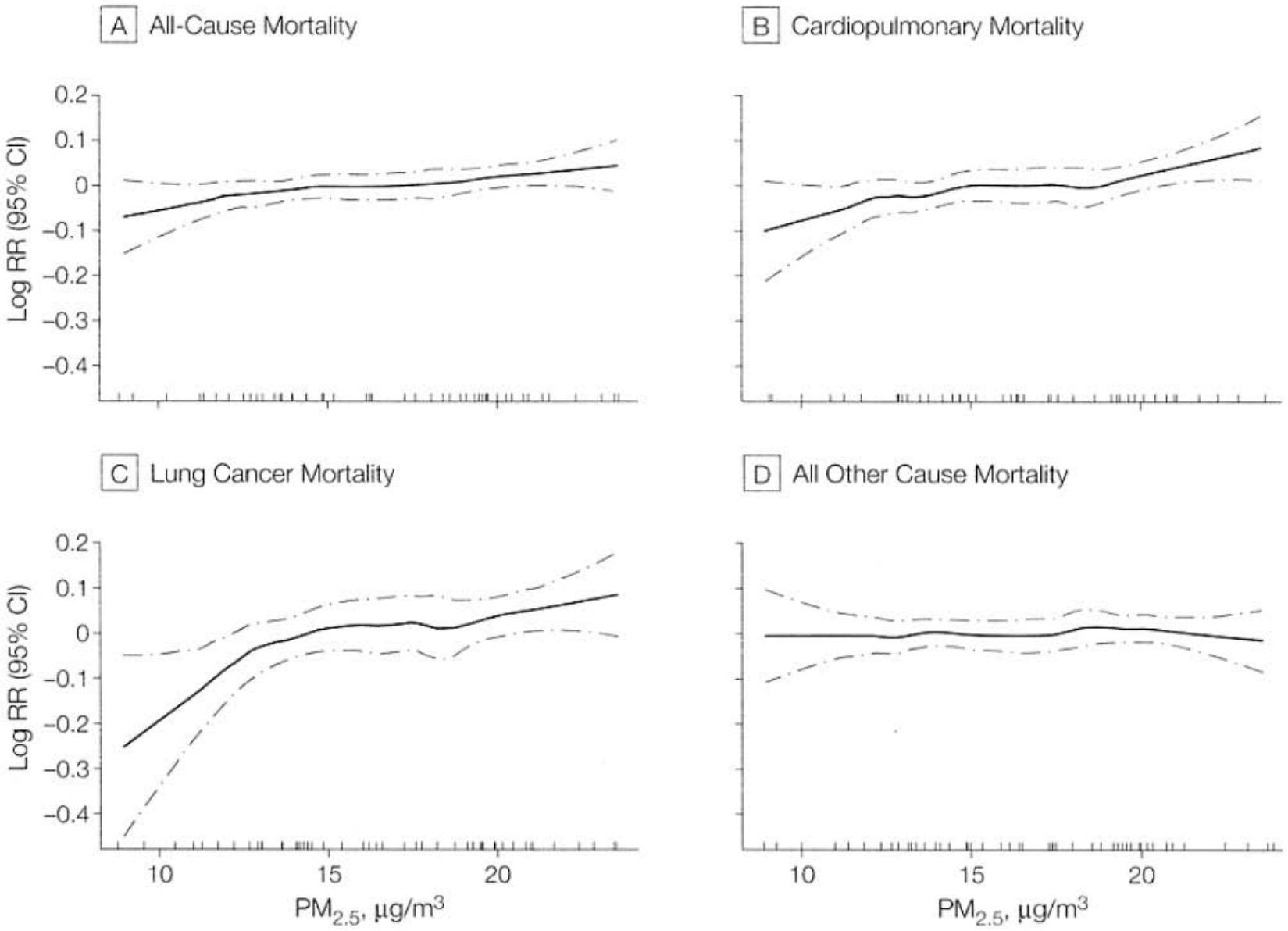
Design, Setting, and Participants Vital status and cause of death data lected by the American Cancer Society as part of the Cancer Prevention II stu going prospective mortality study, which enrolled approximately 1.2 million adu Participants completed a questionnaire detailing individual risk factor data (age

Table 2. Adjusted Mortality Relative Risk (RR) Associated With a 10-μg/m^3 Change in Fine Particles Measuring Less Than 2.5 μm in Diameter

	Adjusted RR (95% CI)*		
Cause of Mortality	1979-1983	1999-2000	Average
All-cause	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.11)
Cardiopulmonary	1.06 (1.02-1.10)	1.08 (1.02-1.14)	1.09 (1.03-1.16)
Lung cancer	1.08 (1.01-1.16)	1.13 (1.04-1.22)	1.14 (1.04-1.23)
All other cause	1.01 (0.97-1.05)	1.01 (0.97-1.06)	1.01 (0.95-1.06)

*Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. CI indicates confidence interval.

Figure 2. Nonparametric Smoothed Exposure Response Relationship



Vertical lines along x-axes indicate rug or frequency plot of mean fine particulate pollution; $PM_{2.5}$, mean fine particles measuring less than 2.5 µm in diameter; RR, relative risk; and CI, confidence interval.

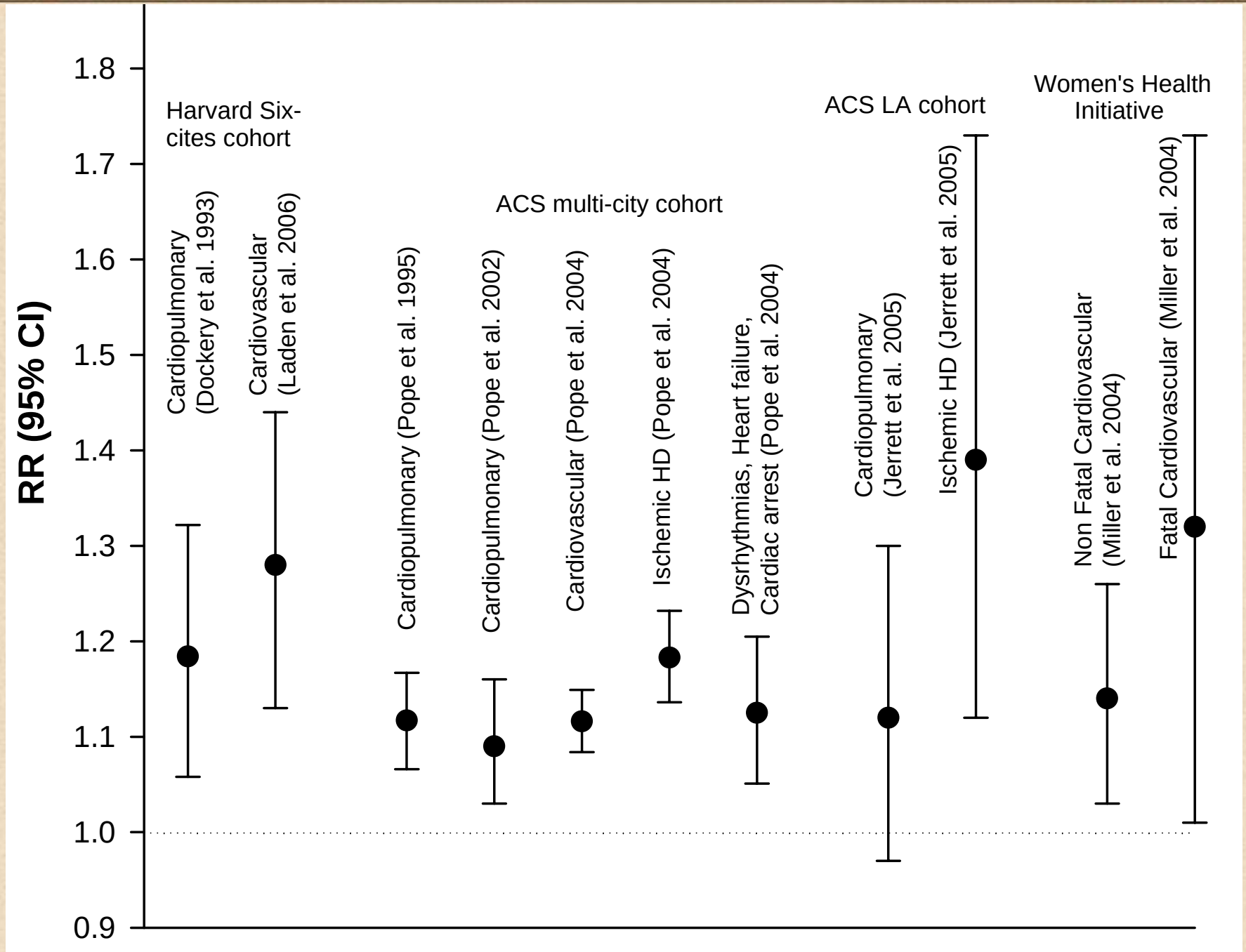


Figure 3. RR for CV mortality associated with a 10-μg/m^3 in long-term $PM_{2.5}$.

Table 2. Comparison of percentage increase (and 95% CI) in relative risk of mortality associated with long-term particulate exposure.

Study	Primary Sources	Exposure Increment	Percent Increases in Relative Risk of Mortality (95% CI)		
			All Cause	Cardiopulmonary	Lung Cancer
Harvard Six Cities, original	Dockery et al. 1993[26]	10 μg/m^3 $PM_{2.5}$	13 (4.2, 23)	18 (6.0, 32)	18 (−11, 57)
Harvard Six Cities, HEI reanalysis	Krewski et al. 2000[177]	10 μg/m^3 $PM_{2.5}$	14 (5.4, 23)	19 (6.5, 33)	21 (−8.4, 60)
Harvard Six Cities, extended analysis	Laden et al. 2006[184]	10 μg/m^3 $PM_{2.5}$	16 (7, 26)	28 (13, 44)[a]	27 (−4, 69)
ACS, original	Pope et al. 1995[27]	10 μg/m^3 $PM_{2.5}$	6.6 (3.5, 9.8)	12 (6.7,17)	1.2 (−8.7, 12)
ACS, HEI reanalysis	Krewski et al. 2000[177]	10 μg/m^3 $PM_{2.5}$	7.0 (3.9, 10)	12 (7.4, 17)	0.8 (−8.7, 11)
ACS, extended analysis	Pope et al. 2002[179]	10 μg/m^3 $PM_{2.5}$	6.2 (1.6, 11)	9.3 (3.3, 16)	13.5 (4.4, 23)
	Pope et al. 2004[180]			12 (8, 15)[a]	
ACS adjusted using various education weighting schemes	Dockery et al. 1993[26]	10 μg/m^3 $PM_{2.5}$	8–11	12–14	3–24
	Pope et al. 2002[179]				
	Krewski et al. 2000[177]				
ACS intrametro Los Angeles	Jerrett et al. 2005[181]	10 μg/m^3 $PM_{2.5}$	17 (5, 30)	12 (−3, 30)	44 (−2, 211)
Postneonatal infant mortality, U.S.	Woodruff et al. 1997[185]	20 μg/m^3 PM_{10}	8.0 (4, 14)	–	–
Postneonatal infant mortality, CA	Woodruff et al. 2006[186]	10 μg/m^3 $PM_{2.5}$	7.0 (−7, 24)	113 (12, 305)[c]	–
AHSMOG[b]	Abbey et al. 1999[187]	20 μg/m^3 PM_{10}	2.1 (−4.5, 9.2)	0.6 (−7.8, 10)	81 (14, 186)
AHSMOG, males only	McDonnell et al. 2000[188]	10 μg/m^3 $PM_{2.5}$	8.5 (−2.3, 21)	23 (−3, 55)	39 (−21, 150)
AHSMOG, females only	Chen et al. 2005[189]	10 μg/m^3 $PM_{2.5}$	–	42 (6, 90)[a]	–
Women's Health Initiative	Miller et al. 2004[190]	10 μg/m^3 $PM_{2.5}$	–	32 (1, 73)[a]	
VA, preliminary	Lipfert et al. 2000, 2003[190,192]	10 μg/m^3 $PM_{2.5}$	0.3 (NS)[d]	–	–
VA, extended	Lipfert et al. 2006[193]	10 μg/m^3 $PM_{2.5}$	15 (5, 26)[e]	–	–
11 CA counties, elderly	Enstrom 2005[194]	10 μg/m^3 $PM_{2.5}$	1 (−0.6, 2.6)	–	–
Netherlands	Hoek et al. 2002[195]	10 μg/m^3 BS	17 (−24, 78)	34 (−32, 164)	–
Netherlands	Hoek et al. 2002[195]	Near major road	41 (−6, 112)	95 (9, 251)	–
Hamilton, Ontario, Canada	Finkelstein et al. 2004[197]	Near major road	18 (2, 38)	–	–
French PAARC	Filleul et al. 2005[198]	10 μg/m^3 BS	7 (3, 10)[f]	5 (−2,12)[f]	3 (−8,15)[f]
Cystic fibrosis	Goss et al. 2004[200]	10 μg/m^3 $PM_{2.5}$	32 (−9, 99)	–	–

10 μg/m^3 $PM_{2.5}$ → approximately 6% to 17% increase in relative risk of mortality, with some outliers.

Generally bigger effects on cardiopulmonary/cardiovascular disease mortality.

Time scales of exposure

- Are the excess deaths observed in the short-term studies due primarily to mortality displacement (harvesting)?
- Why are the PM-mortality effect estimates from the long-term studies so much larger than from the short-term studies?
- Can we learn more about the dynamic exposure-response relationship by integrating evidence from long-term, intermediate, and short-term time scales?

Table 3. Comparison of estimated excess risk of mortality estimates for different time scales of exposure.

Study	Primary Sources	Time Scale of Exposure	% Change in Risk of Mortality Associated with an Increment of 10 μg/m³ $PM_{2.5}$ or 20 μg/m³ PM_{10} or BS			
			All Cause	Cardiovascular/ cardiopulmonary	Respiratory	Lung Cancer
Daily time series	Table 1	1–3 days	0.4–1.4	0.6–1.1	0.6–1.4	–
10 U.S. cities, time series, extended distributed lag	Schwartz 2000[213]	1 day	1.3	–	–	–
		2 days	2.1	–	–	–
		5 days	2.6	–	–	–
10 European cities, time series, extended distributed lag	Zanobetti et al. 2002[215]	2 days	1.4	–	–	–
		40 days	3.3	–	–	–
10 European cities, time series, extended distributed lag	Zanobetti et al. 2003[216]	2 days	–	1.4	1.5	–
		20 days	–	2.7	3.4	–
		30 days	–	3.5	5.3	–
		40 days	–	4.0	8.6	–
Dublin daily time series, extended distributed lag	Goodman et al. 2004[217]	1 day	0.8	0.8	1.8	–
		40 days	2.2	2.2	7.2	–
Dublin intervention	Clancy et al. 2002[203]	months to year	3.2	5.7	8.7	–
Utah Valley, time series and intervention	Pope et al. 1992[20]	5 days	3.1	3.6	7.5	–
		13 months	4.3	–	–	–
Harvard Six-Cities, extended analysis	Laden et al. 2006[184]	1–8 yr	14	–	–	–
Prospective cohort studies	Dockery et al. 1993[28] Pope et al. 2002[179]	10+ yr	6–17	9–28	–	14–44

The PM-mortality effect estimates are consistently larger for longer time scales of exposure.

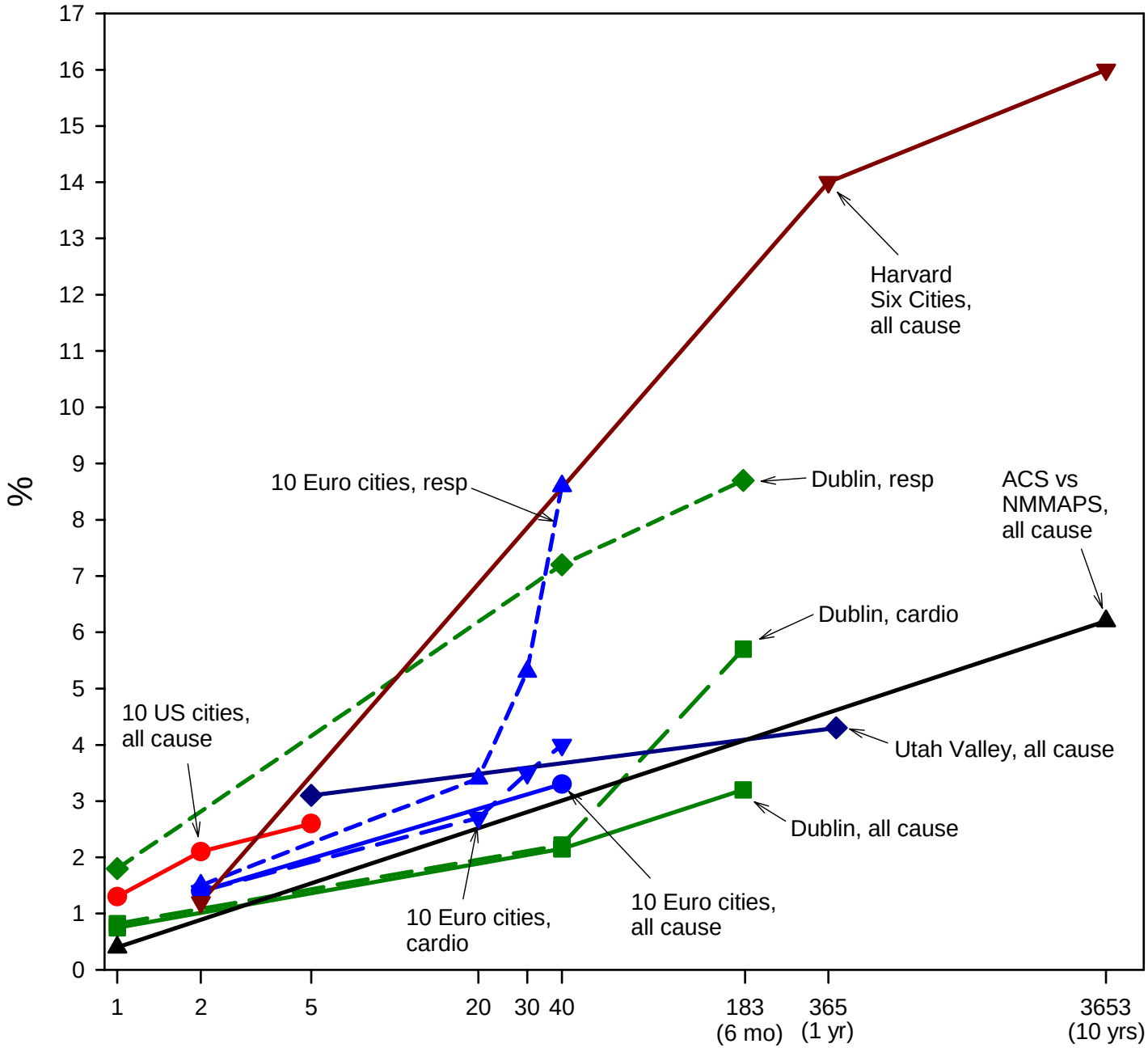
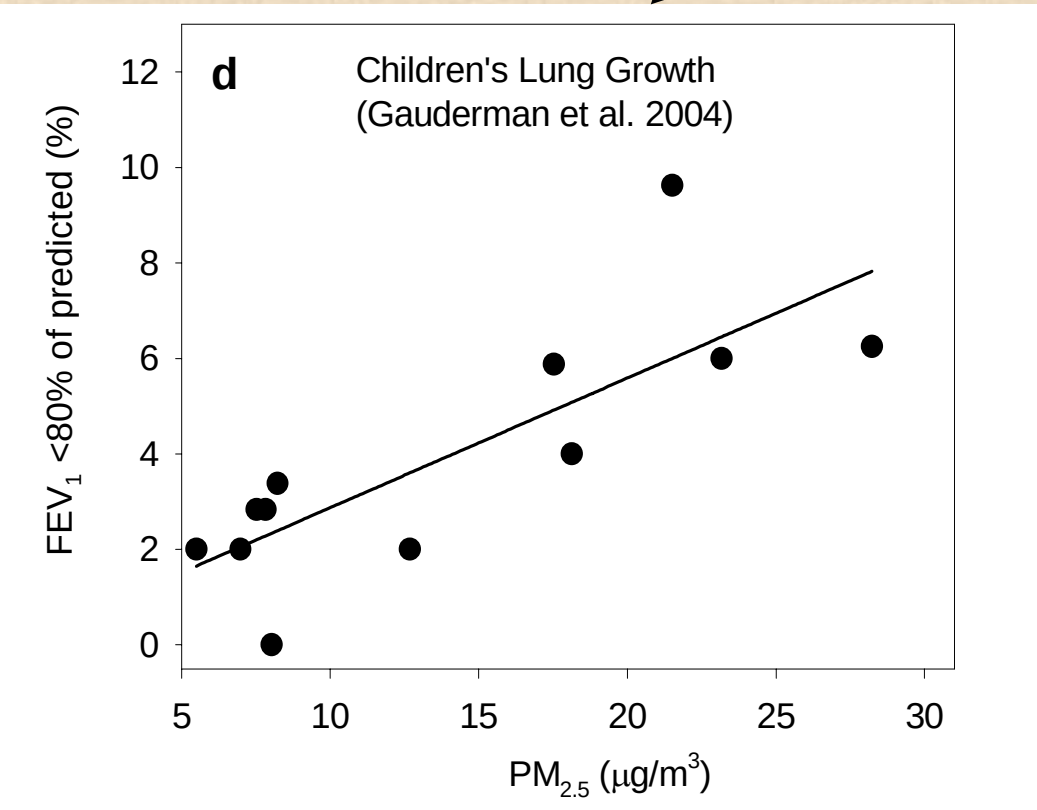


Figure 1. Comparison of % change in risk of mortality associated with an increment of 10 μg/m^3 $PM_{2.5}$ or 20 μg/m^3 PM_{10} or BS estimated for different time scales of exposure (approximate number of days, log scale).

Long-term PM exposure and Respiratory disease:

- Pulmonary retention of fine PM and small airway remodeling contributing to COPD (Brauer et al. 2001; Churg et al. 2003)
- Deficits in lung function (Ackermann-Liebrich et al. 1997)
- Increased symptoms of obstructive airway disease (chronic cough, bronchitis, chest illness)
- Deficits in rate of lung function growth in children (Gauderman et al. 2004)



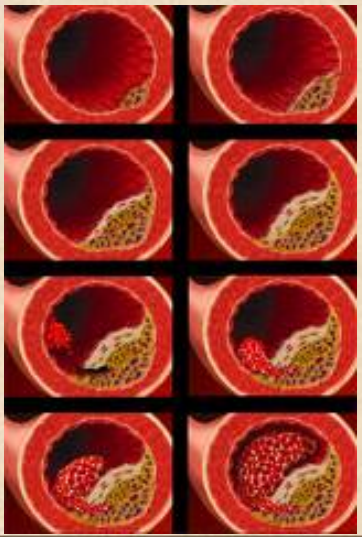
Long-term PM exposure and Cardiovascular disease:

Pulmonary/Systemic Oxidative Stress/Inflammation and Accelerated Atherosclerosis

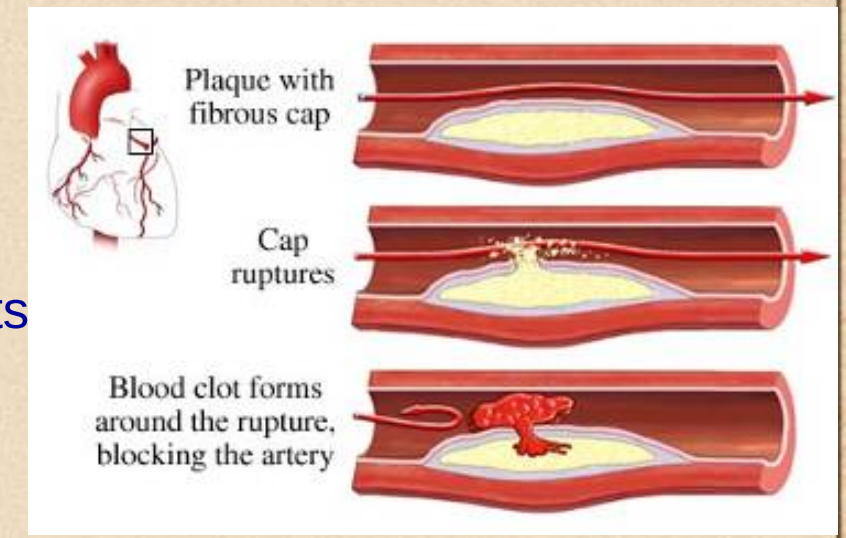
➢Inflammation (and blood lipids) contribute to the initiation and progression of atherosclerosis.

➢Long-term PM exposure → pulmonary/systemic oxidative stress→ low to moderate grade inflammation → initiate and accelerate atherosclerosis.

➢Short-term PM exposures and related inflammation may contribute 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).



Inflammation/Accelerated Atherosclerosis is supported by evidence that:

Long-term PM exposure associated with:

- Ischemic heart disease mortality (Pope et al. 2004; Jarrett et al. 2005; Miller et al. 2004)
- Blood markers of cardiovascular risk (fibrinogen levels, counts of platelets and WBCs) (Schwartz 2001)
- Subclinical chronic inflammatory lung injury (Souza et al. 1998)
- Subclinical atherosclerosis (carotid intima-media thickness, CIMT) (Kunzli et al. 2005)

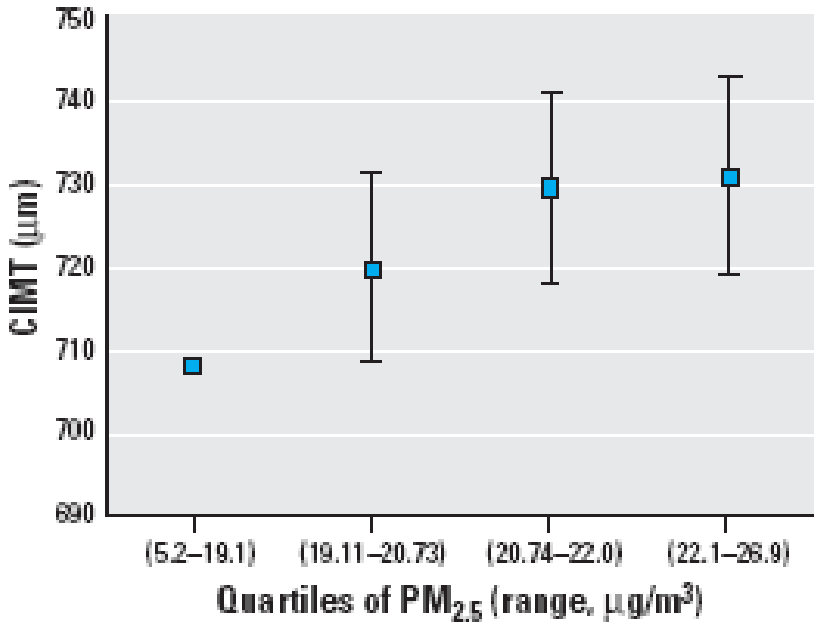


Figure 2. Mean CIMT ± 1 SE among quartiles of the $PM_{2.5}$ distribution. The *y*-axis shows mean CIMT levels at the population average of the adjustment covariates (age, sex, education, and income). The first quartile is the reference group.

A series of Sub-chronic 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

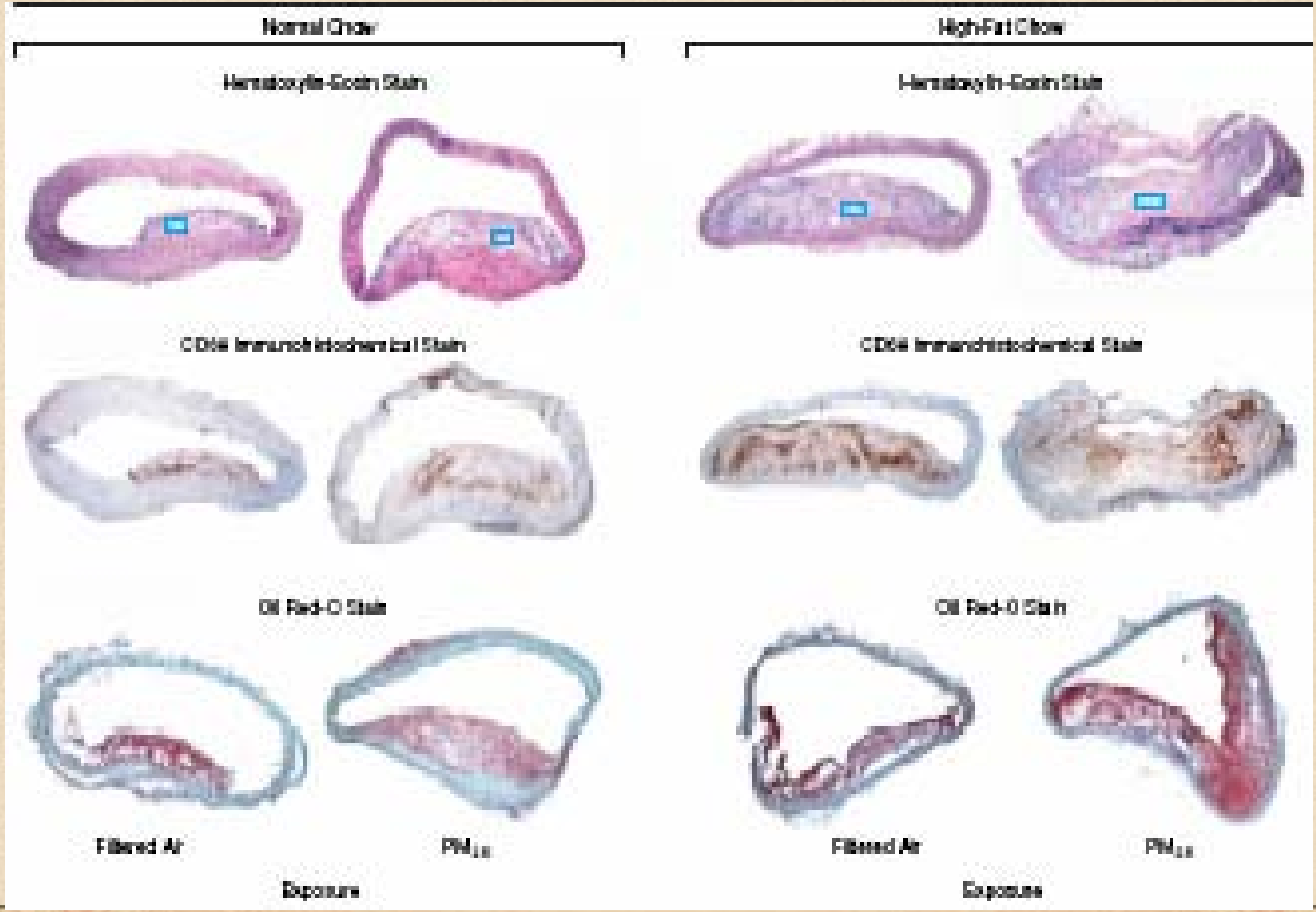
James Hogg

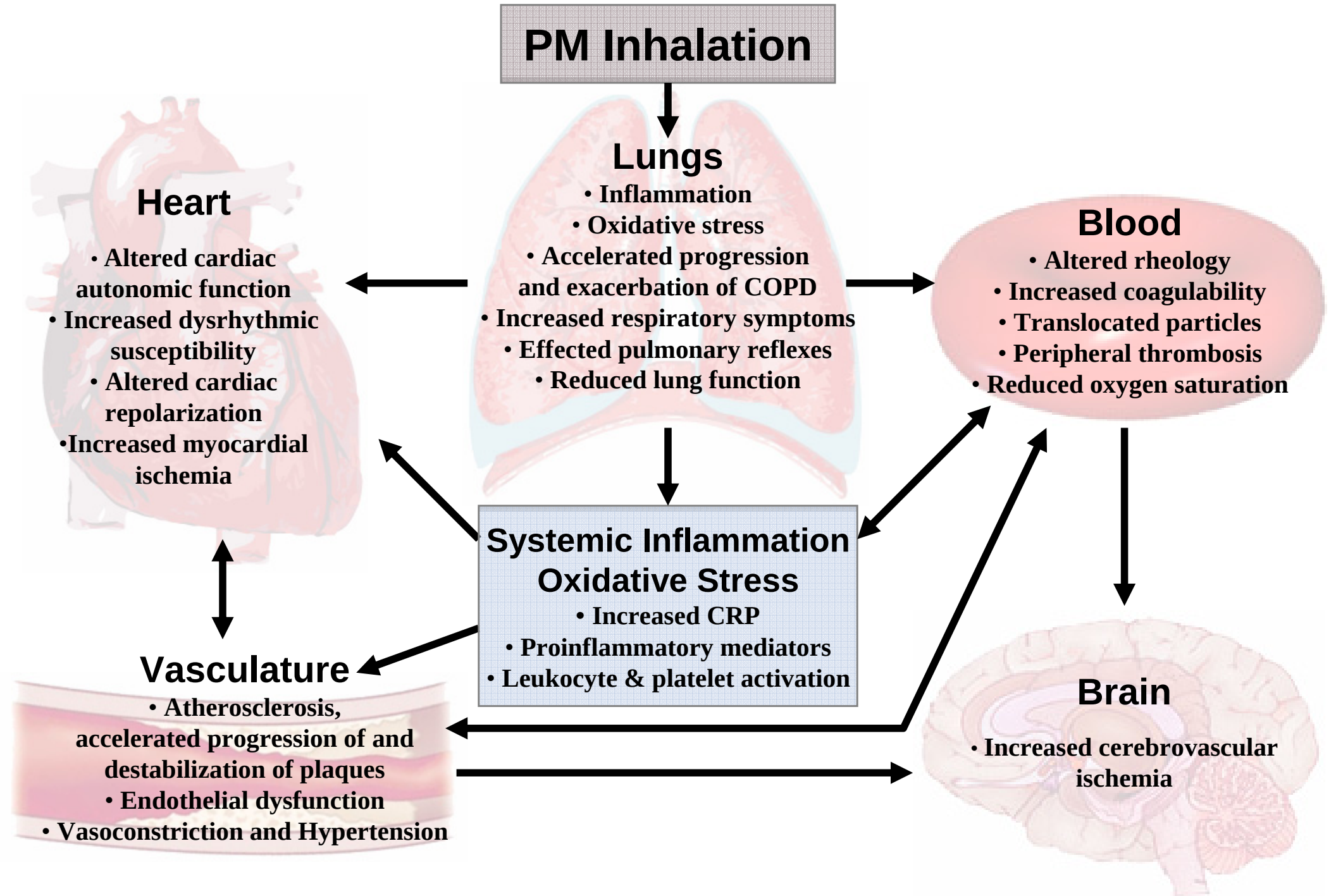
Sun et al. *JAMA* 2005

A hyperlipidemic (ApoE-deficient) sub-chronic mouse model:

$PM_{2.5}$ (85-110 μg/m^3) → vascular inflammation and atherosclerosis

Representative Photomicrographs of Aortic Arch Sections





There are multiple mechanistic pathways have complex interactions and interdependencies

Pope et al. Ischemic Heart Disease Events Triggered by Short-Term Exposure to Fine Particulate Air Pollution. *Circulation* (in press).

Methods:

Case-crossover study design was used to analyze ischemic heart disease events in 12,865 patients who lived on Utah's Wasatch Front.

Patients were drawn from a large, ongoing registry of patients who underwent coronary arteriography and were followed longitudinally.

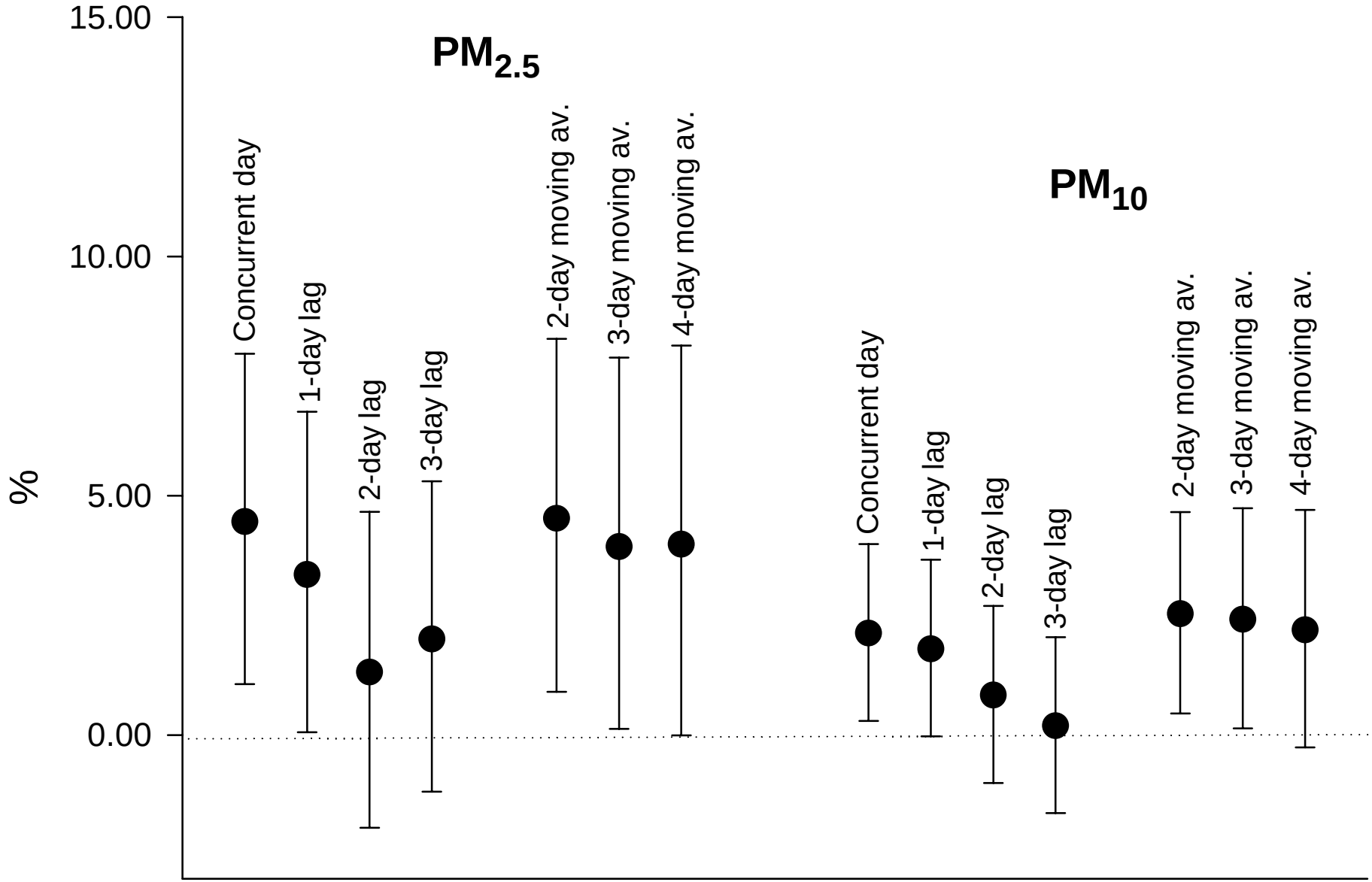


Figure 1. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 μg/m^3 of $PM_{2.5}$, or PM_{10} for different lag structures.

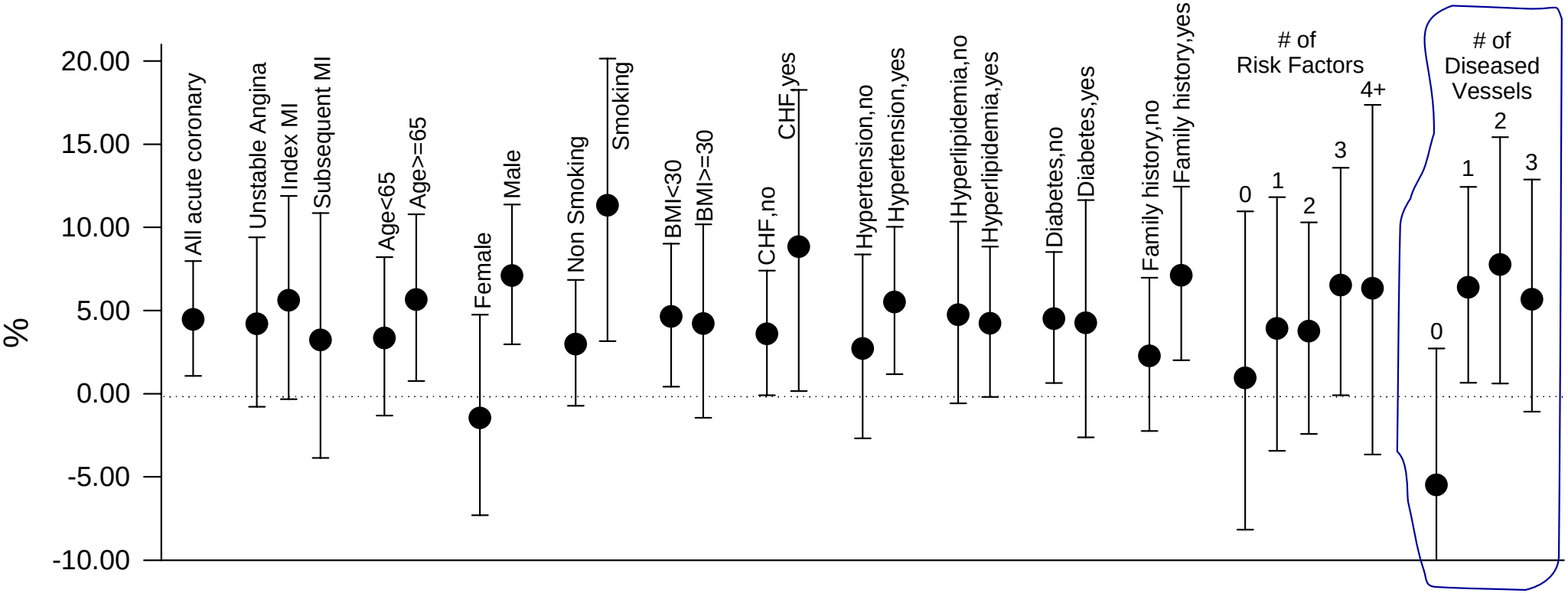


Figure 2. Percent increase in risk (and 95% CI) of acute coronary events associated with 10 μg/m^3 of $PM_{2.5}$, stratified by various characteristics.