2006 A&WMA Critical Review—

Health Effects of Fine Particulate Air Pollution: *Lines that Connect*

C. Arden Pope III
Brigham Young University

Douglas W. Dockery
Harvard School of Public Health

Brief outline of PM Science and Public Policy History

SCIENCE	U.S. PUBLIC POLICY
1930s-1950s Early Episode studies	1955, 1963 Early national legislation
1960s-1980s Ecological mortality and inhalation tox. studies	1967, 1970, 1971 Clean Air Act, amendments, NAAQS
1989-mid 1990s Intriguing new results from several epidemiologic studies	1987 PM standards revised, TSP--PM_{10}
1997- Vedal's "Lines that Divide" ➢ Growth in PM and health effects research	1997-2002 Promulgation of $PM_{2.5}$ standards, Legal challenges argued and largely resolved
2006 **"Lines that Connect"** Gaps and skepticism	2006 New proposed standards for $PM_{2.5}$ and $PM_{10-2.5}$

Outline of 2006 Crit. Rev.

- Characteristics of PM (skip in presentation)
- Lines that connect
  1. Short-term exposure and mortality
  2. Long-term exposure and mortality
  3. Time-scales of exposure
  4. Shape of concentration-response function
  5. Cardiovascular disease
  6. Biological plausibility
- Gaps in Knowledge and reasons for skepticism
- Conclusions

Line 1. Short-term exposure and mortality--outline

1930s-mid 1980s.

- Episode and misc. studies.

Late 1980s-1990s.

- Early formal daily-time series studies reported and replicated.
- Use of increasingly rigorous time-series modeling techniques
- Explosion of single-city studies

1997-2006

- Continued development of time-series modeling (including discovery and partial resolution of problems with some early S+ estimated GAM models).
- Use and further development of the case-crossover design
- **Meta analyses**
- **Multi-city daily time-series and case-crossover studies**

Table 1. Comparison of pooled estimated percentage increase (and 95% confidence or posterior interval, CI, or *t* value) in relative risk of mortality estimated across meta-analyses and multicity studies of short-term (daily) changes in exposure.

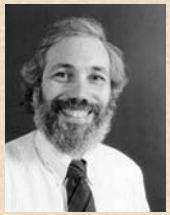
Study		Primary Sources	Exposure Increment	Percent Increases in Relative Risk of Mortality (95% CI)		
				All Cause	Cardiovascular	Respiratory
Meta-analysis of 29 *studies*		Levy et al. 2000[134]	20 μg/m³ PM_{10}	1.5 (1.2, 1.75)[a]	–	–
Meta-analysis: GAM-based studies		Stieb et al. 2002, 2003[135,136]	20 μg/m³ PM_{10}	1.4 (1.0, 1.8)[a]	–	–
Non GAM-based studies				0.8 (0.5, 1.2)	–	–
Metaestimate from single-city studies, adjusted for publication bias		Anderson et al. 2005[137]	20 μg/m³ PM_{10}	1.2 (1.0, 1.4)[a]	–	–
				1.0 (0.8, 1.2)[a]	–	–
Metaestimates from COMEAP report to the U.K. Department of Health on Cardiovascular Disease and Air Pollution		COMEAP 2006[138]	20 μg/m³ PM_{10}	–	1.8 (1.4, 2.4)	
			10 μg/m³ $PM_{2.5}$	–	1.4 (0.7, 2.2)	–
U.S. 6 cities	(12+ studies, 170+ cities)	Klemm and Mason 2003[142]	10 μg/m³ $PM_{2.5}$	1.2 (0.8, 1.6)	1.3 (0.3, 2.4)[b]	0.6 (−2.9, 4.2)[c]
Canadian 8 cities		Burnett and Goldberg 2003[144]	10 μg/m³ $PM_{2.5}$	1.1 (t = 3.4)	–	–
Californian 9 cities		Ostro et al. 2006[145]	10 μg/m³ $PM_{2.5}$	0.6 (0.2, 1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
U.S. 10 cities		Schwartz 2000, 2003[146,148]	20 μg/m³ PM_{10}	1.3 (1.0, 1.6)	–	–
U.S. 14-city case-crossover		Schwartz 2004[149]	20 μg/m³ PM_{10}	0.7 (0.4, 1.0)	–	–
NMMAPS 20–100 U.S. cities		Dominici et al. 2003[153]	20 μg/m³ PM_{10}	0.4 (0.2, 0.8)	0.6 (0.3, 1.0)[d]	–
APHEA-2 15–29 European cities		Katsouyanni et al. 2003[162]	20 μg/m³ PM_{10}	1.2 (0.8, 1.4)	–	–
APHEA-2 29 European cities		Analitis et al. 2006[163]	20 μg/m³ PM_{10}	–	1.5 (0.9, 2.1)	1.2 (0.4, 1.9)
Australia 3-cities		Simpson et al. 2005[165]	10 μg/m³ $PM_{2.5}$	0.9 (−0.7, 2.5)	–	–
French 9 cities		Le Tertre et al. 2002[164]	20 μg/m³ BS	1.2 (0.5, 1.8)[a]	1.2 (0.2, 2.2)[a]	1.1 (−1.4, 3.2)[a]
Korean 7 cities		Lee et al. 2000[166]	40 μg/m³ TSP	0.9 (0.5, 1.2)[a]	–	–
Japanese 13-cities, age >65 yr		Omori et al. 2003[167]	20 μg/m³ SPM	1.0 (.8, 1.3)	1.1 (0.7, 1.5)	1.4 (0.9, 2.1)

[a]Includes GAM-based analyses with potentially inadequate convergence; [b]Ischemic heart disease deaths; [c]Chronic obstructive pulmonary disease deaths; [d]Cardiovascular and respiratory deaths combined.

10 μg/m³ $PM_{2.5}$ or 20 μg/m³ PM_{10} → 0.4% to 1.5% increase in relative risk of mortality—Small but remarkably consistent across meta-analyses and multi-city studies.

Line 1. Short-term exposure and mortality --conclusions

- Elevated PM exposure of a few days results in small increased risk of mortality.
- Uncertainties in estimating such small effects legitimately create some doubts or concerns regarding these estimates.
- Nevertheless, these effects have been observed:
  - in many cities
  - by different researchers
  - using time-series methods
  - case-crossover designs
  - in large multi-city studies with reduced potential for selection or publication bias.


Joel Schwartz


Jonathan Samet


Scott Zeger


Richard Burnett


Francesca Dominici


Antonella Zanobetti


Bart Ostro


Ross Anderson


Pat Kinney


Lucas Neas


George Thurston


Xiping Xu


Mark Goldberg


Michelle Bell


Jong-Tae Lee, **et al.**

Line 2. Long-term exposure and mortality--outline

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.

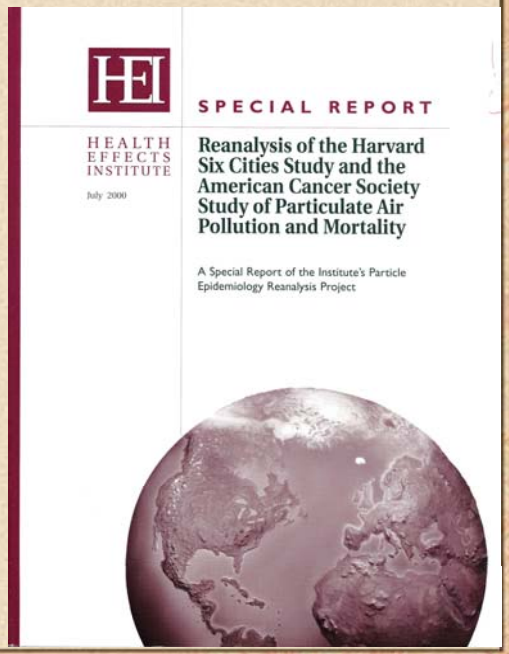


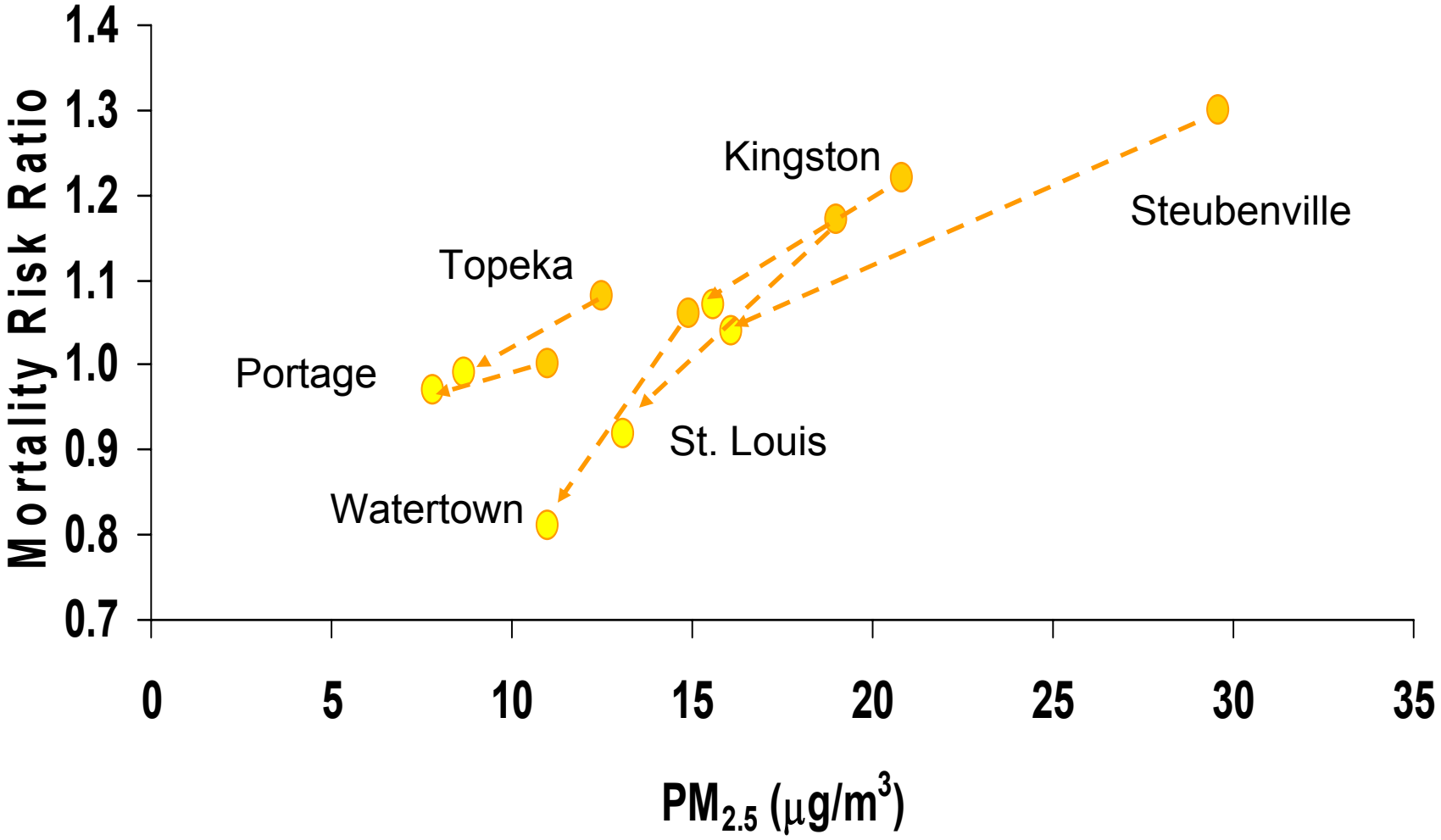
Table 2. Comparison of percentage increase (and 95% CI) in relative risk of mortality associated with long-term particulate exposure.

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/m³ $PM_{2.5}$	13 (4.2, 23)	18 (6.0, 32)	18 (−11, 57)
Harvard Six Cities, HEI reanalysis	Krewski et al. 2000[177]	10 μg/m³ $PM_{2.5}$	14 (5.4, 23)	19 (6.5, 33)	21 (−8.4, 60)
Harvard Six Cities, extended analysis	Laden et al. 2006[184]	10 μg/m³ $PM_{2.5}$	16 (7, 26)	28 (13, 44)[a]	27 (−4, 69)
ACS, original	Pope et al. 1995[27]	10 μg/m³ $PM_{2.5}$	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/m³ $PM_{2.5}$	7.0 (3.9, 10)	12 (7.4, 17)	0.8 (−8.7, 11)
ACS, extended analysis	Pope et al. 2002[179] Pope et al. 2004[180]	10 μg/m³ $PM_{2.5}$	6.2 (1.6, 11)	9.3 (3.3, 16) 12 (8, 15)[a]	13.5 (4.4, 23)
ACS adjusted using various education weighting schemes	Dockery et al. 1993[26] Pope et al. 2002[179] Krewski et al. 2000[177]	10 μg/m³ $PM_{2.5}$	8–11	12–14	3–24
ACS intrametro Los Angeles	Jerrett et al. 2005[181]	10 μg/m³ $PM_{2.5}$	17 (5, 30)	12 (−3, 30)	44 (−2, 211)
Postneonatal infant mortality, U.S.	Woodruff et al. 1997[185]	20 μg/m³ PM_{10}	8.0 (4, 14)	–	–
Postneonatal infant mortality, CA	Woodruff et al. 2006[186]	10 μg/m³ $PM_{2.5}$	7.0 (−7, 24)	113 (12, 305)[c]	–
AHSMOG[b]	Abbey et al. 1999[187]	20 μg/m³ 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/m³ $PM_{2.5}$	8.5 (−2.3, 21)	23 (−3, 55)	39 (−21, 150)
AHSMOG, females only	Chen et al. 2005[189]	10 μg/m³ $PM_{2.5}$	–	42 (6, 90)[a]	–
Women's Health Initiative	Miller et al. 2004[190]	10 μg/m³ $PM_{2.5}$	–	32 (1, 73)[a]	
VA, preliminary	Lipfert et al. 2000, 2003[190,192]	10 μg/m³ $PM_{2.5}$	0.3 (NS)[d]	–	–
VA, extended	Lipfert et al. 2006[193]	10 μg/m³ $PM_{2.5}$	15 (5, 26)[e]	–	–
11 CA counties, elderly	Enstrom 2005[194]	10 μg/m³ $PM_{2.5}$	1 (−0.6, 2.6)	–	–
Netherlands	Hoek et al. 2002[195]	10 μg/m³ 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/m³ BS	7 (3, 10)[f]	5 (−2,12)[f]	3 (−8,15)[f]
Cystic fibrosis	Goss et al. 2004[200]	10 μg/m³ $PM_{2.5}$	32 (−9, 93)	–	–

10 μg/m³ $PM_{2.5}$ → approximately 6% to 17% increase in relative risk of mortality, with some outliers.

Generally bigger effects on cardiopulmonary/cardiovascular disease mortality.

Six Cities Cohort Follow-up



Laden et al, 2006

Line 2. Long-term exposure and mortality-- conclusions

Expanded analyses of Six-Cities and ACS cohorts → robust effect estimates.

Comparable PM-mortality effects have been observed in several other studies including:

- Infant mortality studies (Woodruff et al. 2006)
- Women's Health Initiative (Miller et al. 2004)
- Netherlands (Hoek et al. 2002)
- Hamilton, Canada (Finkelstein et al. 2004)

Mixed results have also been observed in:

- AHSMOG (McDonnell et al. 2000; Chen et al. 2005)
- French PAARC (Filleul et al. 2005)
- VA Cohort (Lipfert et al. 2000, 2003, 2006)
- 11 CA counties (Enstrom 2005)

➢ PM-mortality effect estimates tend to be larger when exposure estimates are based on more focused spatial resolution and/or when local sources of exposure, especially traffic sources, are accounted for.


Daniel Krewski


Richard Burnett


Arden Pope


Michael Jerrett


Doug Dockery


Francine Laden


Tracey Woodruff


Joel Kaufman


Bert Brunekreef


Frederick Lipfert


James E. Enstrom

Line 3. Time scales of exposure --issues

- 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.

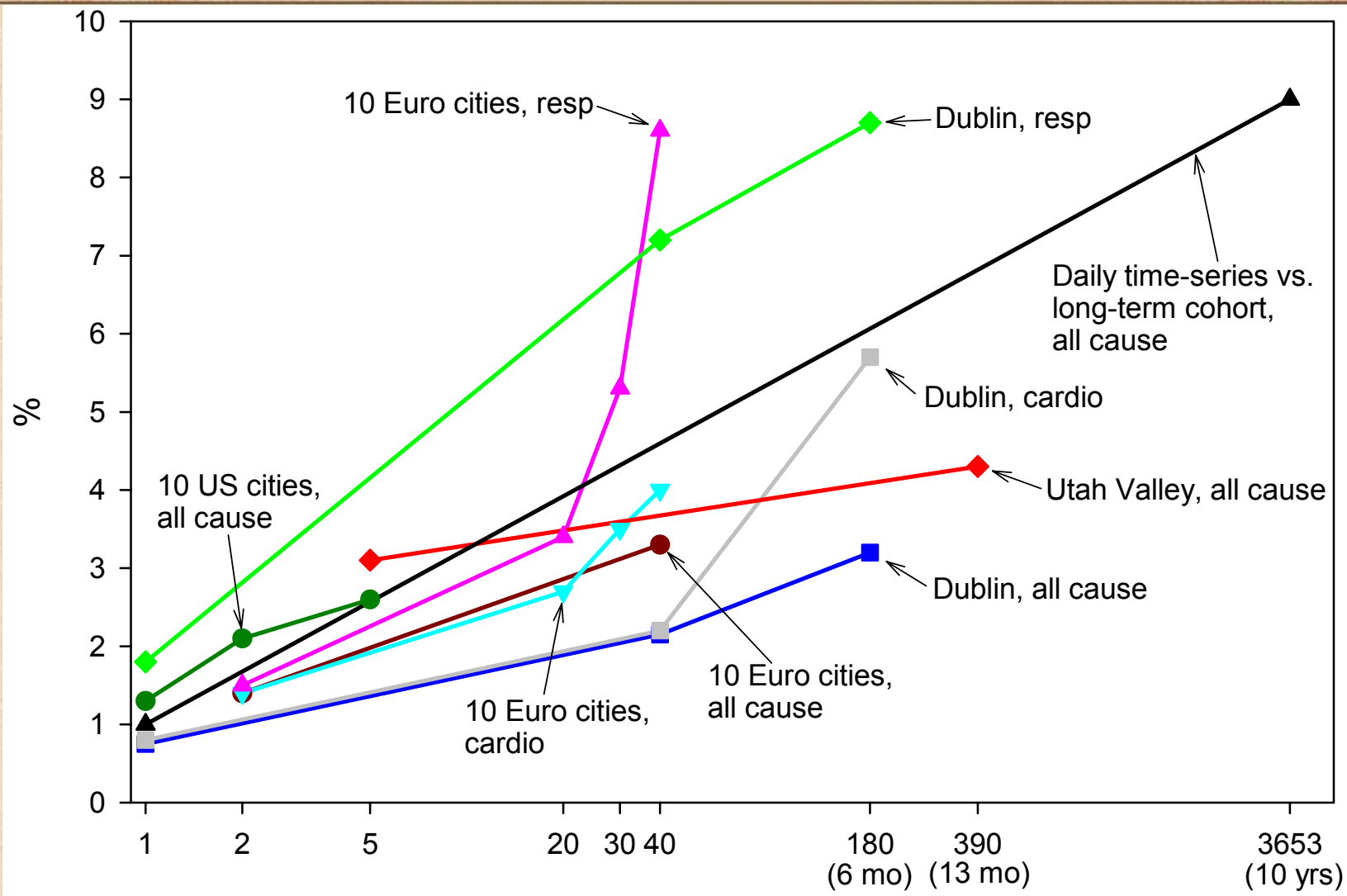


Figure 1. Comparison of % change in risk of mortality associated with an increment of 10 μg/m^3 $PM_{2.5}$ or 20 μg/m^3 PM_{10} or BS estimated for different time scales of exposure (approximate number of days, log scale).

Line 3. Time scales of exposure--conclusions

- Short-term studies are observing more than just harvesting or mortality displacement:

  --little short-term compensatory reduction in deaths

  --larger effects for intermediate and longer-term time scales.

- Adverse health effects are dependent on both exposure concentrations and length of exposure.

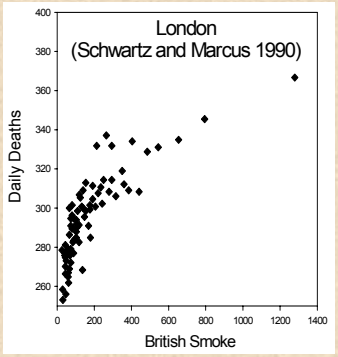
- Long-term exposures have larger more persistent cumulative effects than short-term exposures.

Luke Clancy

Line 4. Shape of concentration-response (C-R) function--outline

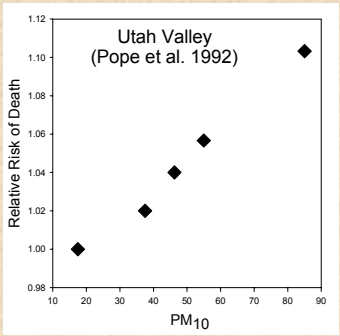
1984, 1990

- Early analyses of concentration-response function.
- Used London mortality data for 14 winters
- C-R function less steep at higher concentrations
- No evidence of a threshold



Early to Mid 1990s

- Many single-city time series studies used quintile (or quartile) analysis, spline functions, or non-parametric smoothing that allowed for flexible fitting C-R function.
- C-R were generally (but not always) near linear with no clear threshold.



1997-2006

- Combined or "meta-smoothed" C-R function estimated using multiple cities—enhancing statistical power and generalizability.
- Extended analyses of C-R function in prospective cohort and related studies.

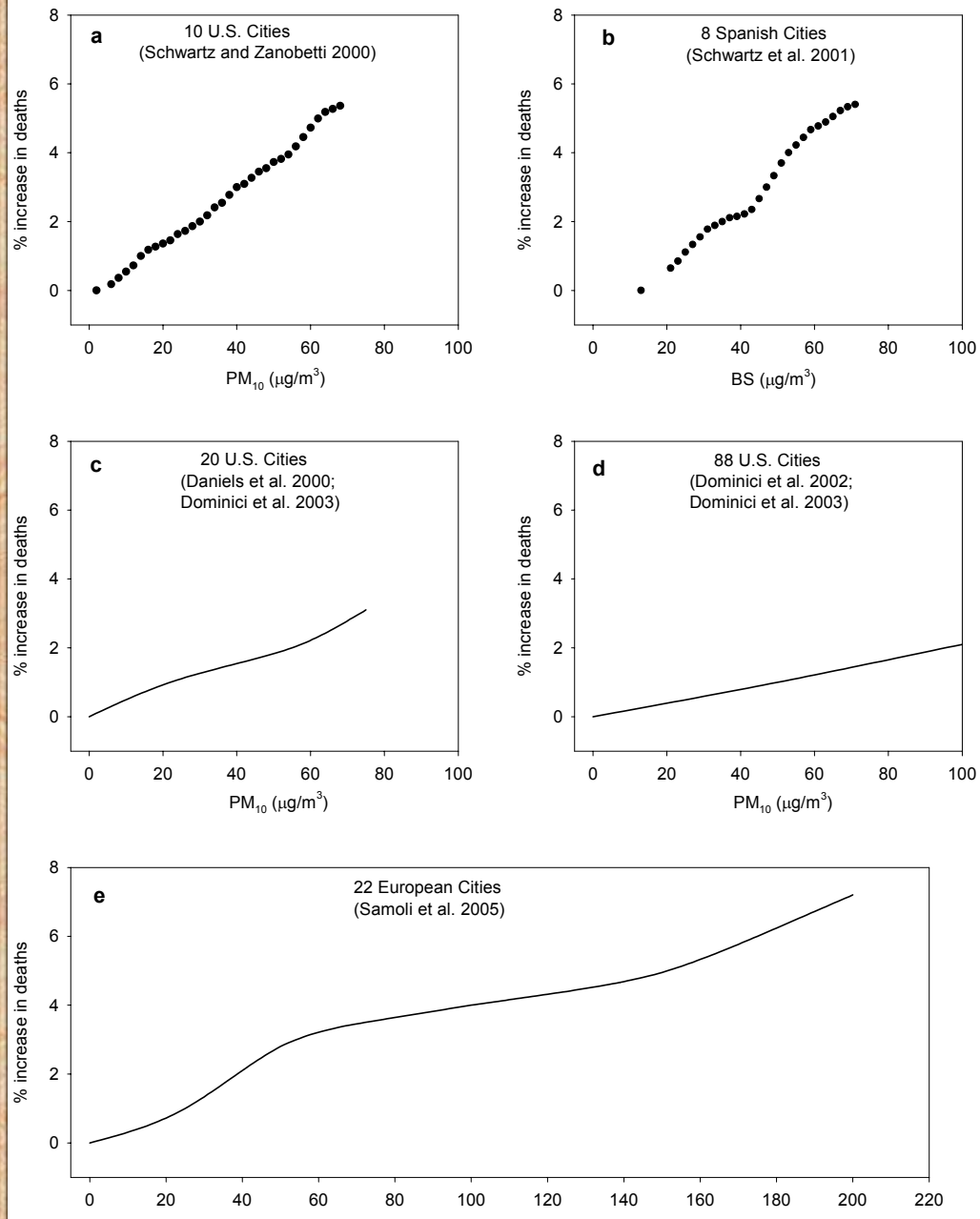


Figure 1. Selected concentration-response relationships estimated from various multi-city daily time-series studies (approximate adaptations from original publications rescaled for comparison purposes).

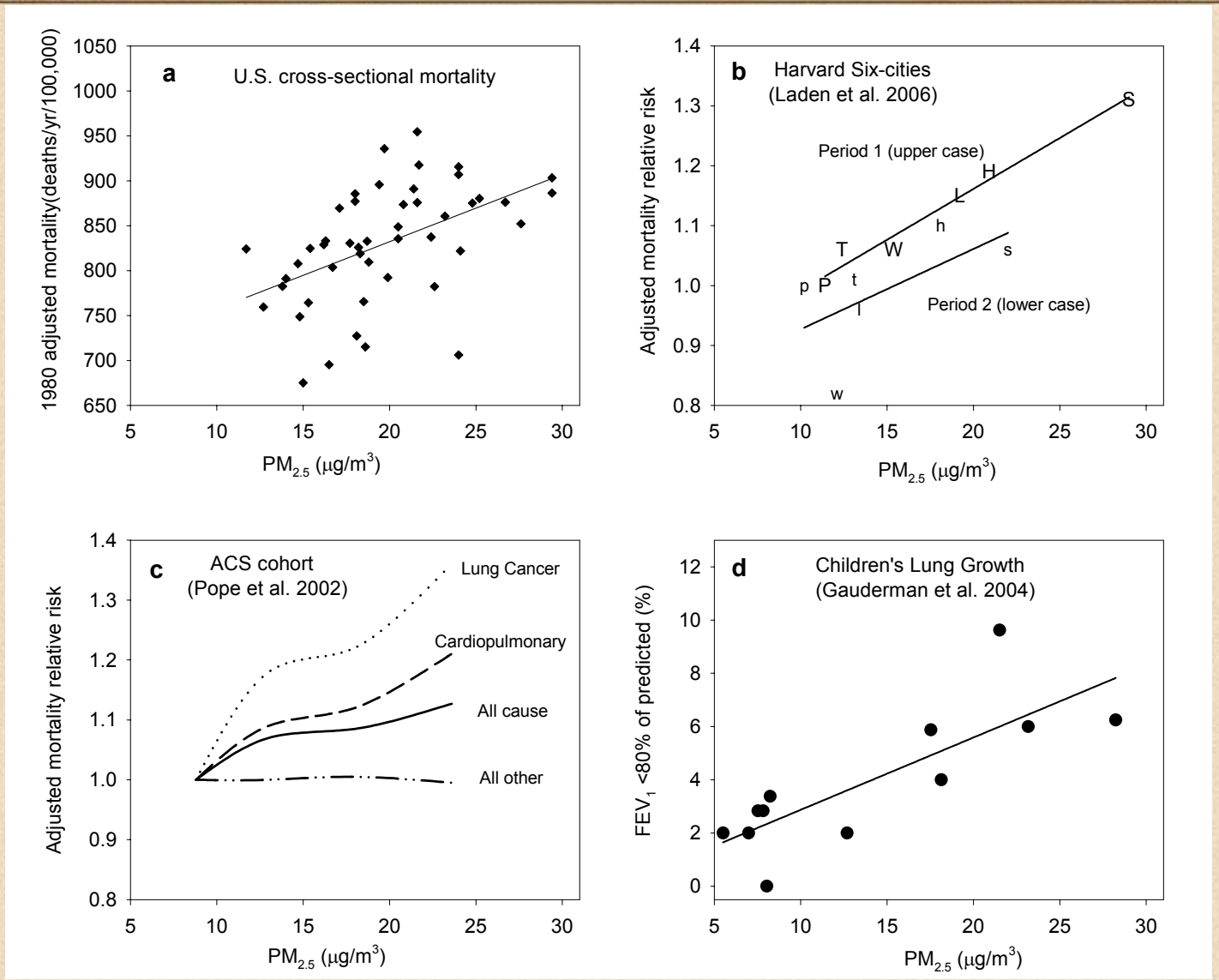


Figure 2. Selected concentration-response relationships estimated from various studies of long-term exposure (approximate adaptations from original publications rescaled for comparison purposes).

Line 5. Cardiovascular disease--outline

1930s-1950s

- Excess deaths in early severe air pollution episodes were due to both respiratory and cardiovascular disorders, often in combination.

Early to Mid 1990s

- Much of the research focused on respiratory disease, but—
- Daily time series studies observed PM associations with deaths and hospitalizations for both respiratory and cardiovascular disease.
- PM was strongly associated with cardiopulmonary mortality in the early prospective cohort studies.

1997-2006

- Dramatic growth in studies of air pollutions and cardiovascular disease.
- Studies of air pollution and cardiovascular disease being published and discussed in the cardiovascular journals.

Outline of cardiovascular and related effects

Long-term PM exposure

- Cardiovascular mortality
- Blood markers of cardiovascular risk (fibrinogen platelets, white blood cells)
- Histopathologic markers of sub-clinical chronic inflammatory lung injury
- Subclinical atherosclerosis (carotid intima-media thickness, CIMT)

Short-term PM exposure

- Cardiovascular mortality
- Cardiovascular hospital admissions
- Stroke mortality and hospital admissions
- MI
- Hypoxemia (S_p0_2)
- HR and HRV
- Various markers of inflammation
- Cardiac arrhythmia/cardiac arrest/sudden cardiac death
- ST-segment depression and cardiac repolarization
- Blood pressure/arterial vasoconstriction/ vascular reactivity and endothelial function

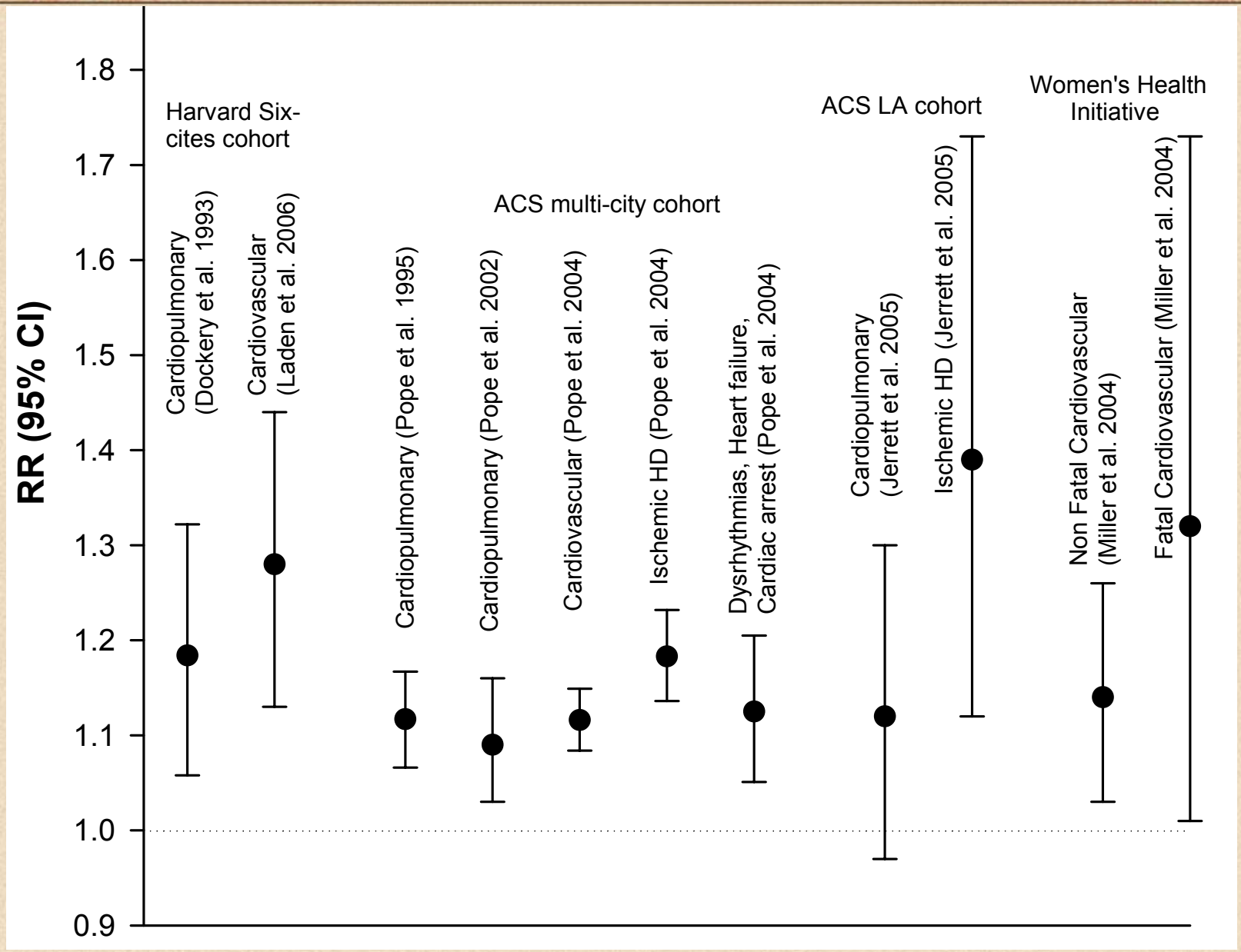


Figure 3. RR for CV mortality associated with a 10-$\mu g/m^3$ in long-term $PM_{2.5}$.

Short-term PM exposure and CV mortality

Table 1. Comparison of pooled estimated percentage increase (and 95% confidence or posterior interval, CI, or *t* value) in relative risk of mortality estimated across meta-analyses and multicity studies of short-term (daily) changes in exposure.

Study	Primary Sources	Exposure Increment	Percent Increases in Relative Risk of Mortality (95% CI)		
			All Cause	Cardiovascular	Respiratory
Meta-analysis of 29 studies	Levy et al. 2000[134]	20 μg/m³ PM_{10}	1.5 (1.2, 1.75)[a]	–	–
Meta-analysis: GAM-based studies	Stieb et al. 2002, 2003[135,136]	20 μg/m³ PM_{10}	1.4 (1.0, 1.8)[a]	–	–
Non GAM-based studies			0.8 (0.5, 1.2)	–	–
Metaestimate from single-city studies,	Anderson et al. 2005[137]	20 μg/m³ PM_{10}	1.2 (1.0, 1.4)[a]	–	–
adjusted for publication bias			1.0 (0.8, 1.2)[a]	–	–
Metaestimates from COMEAP report to the	COMEAP 2006[138]	20 μg/m³ PM_{10}	–	1.8 (1.4, 2.4)	
U.K. Department of Health on		10 μg/m³ $PM_{2.5}$	–	1.4 (0.7, 2.2)	–
Cardiovascular Disease and Air Pollution					
U.S. 6 cities	Klemm and Mason 2003[142]	10 μg/m³ $PM_{2.5}$	1.2 (0.8, 1.6)	1.3 (0.3, 2.4)[b]	0.6 (−2.9, 4.2)[c]
Canadian 8 cities	Burnett and Goldberg 2003[144]	10 μg/m³ $PM_{2.5}$	1.1 (t = 3.4)	–	–
Californian 9 cities	Ostro et al. 2006[145]	10 μg/m³ $PM_{2.5}$	0.6 (0.2, 1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
U.S. 10 cities	Schwartz 2000, 2003[146,148]	20 μg/m³ PM_{10}	1.3 (1.0, 1.6)	–	–
U.S. 14-city case-crossover	Schwartz 2004[149]	20 μg/m³ PM_{10}	0.7 (0.4, 1.0)	–	–
NMMAPS 20–100 U.S. cities	Dominici et al. 2003[153]	20 μg/m³ PM_{10}	0.4 (0.2, 0.8)	0.6 (0.3, 1.0)[d]	–
APHEA-2 15–29 European cities	Katsouyanni et al. 2003[162]	20 μg/m³ PM_{10}	1.2 (0.8, 1.4)	–	–
APHEA-2 29 European cities	Analitis et al. 2006[163]	20 μg/m³ PM_{10}	–	1.5 (0.9, 2.1)	1.2 (0.4, 1.9)
Australia 3-cities	Simpson et al. 2005[165]	10 μg/m³ $PM_{2.5}$	0.9 (−0.7, 2.5)	–	–
French 9 cities	Le Tertre et al. 2002[164]	20 μg/m³ BS	1.2 (0.5, 1.8)[a]	1.2 (0.2, 2.2)[a]	1.1 (−1.4, 3.2)[a]
Korean 7 cities	Lee et al. 2000[166]	40 μg/m³ TSP	0.9 (0.5, 1.2)[a]	–	–
Japanese 13-cities, age >65 yr	Omori et al. 2003[167]	20 μg/m³ SPM	1.0 (.8, 1.3)	1.1 (0.7, 1.5)	1.4 (0.9, 2.1)

[a]Includes GAM-based analyses with potentially inadequate convergence; [b]Ischemic heart disease deaths; [c]Chronic obstructive pulmonary disease deaths; [d]Cardiovascular and respiratory deaths combined.

10 μg/m³ $PM_{2.5}$ or 20 μg/m³ PM_{10} → 0.6% to 1.8% increase in relative risk of cardiovascular mortality—

again remarkably consistent across meta-analyses and multi-city studies.

Table 5. Comparison of pooled estimated percentage increase (and 95% confidence) in relative risk of hospital admission for cardiovascular disease estimated across meta-analyses and multicity studies of short-term (daily) changes in exposure.

Study	Primary Sources	Exposure Increment	% Increase (95% CI)
Cardiac admissions, meta-analysis of 51 estimates	COMEAP 2006[138]	20 μg/m³ PM_{10}	1.8 (1.4, 1.2)
Ischemic heart disease admissions, meta-analysis of 19 estimates	COMEAP 2006[138]	20 μg/m³ PM_{10}	1.6 (1.2, 2.2)
Admission for dysrhythmias, meta-analysis of 7 estimates	COMEAP 2006[138]	20 μg/m³ PM_{10}	1.6 (0.2, 2.8)
Admission for heart failure, meta-analysis of 7 estimates	COMEAP 2006[138]	20 μg/m³ PM_{10}	2.8 (1.0, 4.8)
Cerebrovascular admissions, meta-analysis of 9 estimates	COMEAP 2006[138]	20 μg/m³ PM_{10}	0.8 (0.0, 1.6)
Cardiac admissions, 8 U.S. cities, 65+	Schwartz 1999[285]	20 μg/m³ PM_{10}	2.0 (1.5, 2.5)
Cardiac admissions, 10 U.S. cities, 65+	Zanobetti et al. 2000[286]	20 μg/m³ PM_{10}	2.6 (2.0, 3.0)
Cardiac admissions, 14 U.S. cities, 65+	Samet et al. 2000[287] Schwartz et al. 2003[288]	20 μg/m³ PM_{10}	2.0 (1.5, 2.5)
8 European cities, 65+, cardiac admissions: Ischemic heart admissions	Le Tertre et al. 2002[289]	20 μg/m³ PM_{10}	1.4 (0.8, 2.0) 1.6 (0.6, 2.4)
204 U.S. counties, 65+, CVD admissions	Dominici et al. 2006[290]	10 μg/m³ $PM_{2.5}$	
Heart failure			1.2 (0.8, 1.8)
Heart rhythm			0.6 (0.0, 1.2)
Ischemic heart			0.4 (0.0, 0.9)
Peripheral vascular			0.9 (−0.1, 1.8)
Cerebrovascular			0.8 (0.3, 1.3)

Short-term PM exposure and CV hospital admissions

Notes: We acknowledge Dr. Ross Anderson and Joanna Carrington at the Department of Community Health Sciences, St. George's Hospital Medical School, London, United Kingdom, for help in providing meta-analyses and reviews of the cardiovascular hospitalizations studies.

10 μg/m³ $PM_{2.5}$ or 20 μg/m³ PM_{10} → 0.4% to 2.6% increase in relative risk of cardiovascular hospitalizations—

again remarkably consistent across meta-analyses and multi-city studies.

Line 6. Biological Plausibility

1997

The 1997 Critical Review noted that:

"Weak biological plausibility has been the single largest stumbling block to accepting the association as causal. There is no known mechanism whereby exposure to very low concentrations of inhaled particles would produce such severe outcomes as death, even from respiratory disease, and certainly not from cardiovascular disease."

Sverre Vedal

1997-2006

"It is no longer true that there are no known mechanisms or plausible pathophysiological pathways"

John Godleski

Line 6. Biological Plausibility–Case study of biological effects of exposure to Oil Fly Ash (Ghio et al. 1999)

Case:

- 42-yr-old, never smoker, male, diabetic
- Exposed to aerosolized oil fly ash particles due to cleaning oil-burning stove in home

Within 24 hrs developed:

- Shortness of breath
- Nonproductive cough
- Wheezing

Over weeks:

- Hypoxic respiratory failure
- Abnormal blood indices
- Particle laden macrophages
- Diffuse alveolar damage
- Angina

Evidence that PM-cardiorespiratory effects are biologically plausible?

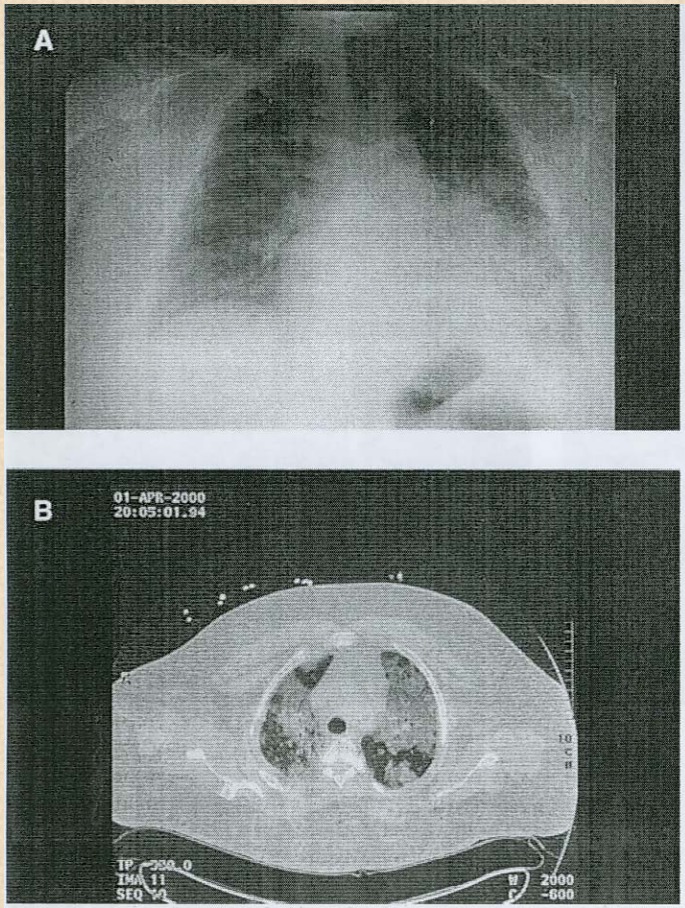


Figure 1. A posteroanterior chest X-ray demonstrated a left lower lobe infiltrate (*A*). Three days later, both the chest X-ray and CT revealed diffuse opacities (ground glass) throughout both lung fields (*B*). Two weeks after discharge, the chest X-ray was normal.

Line 6. Biological Plausibility–Utah Valley PM

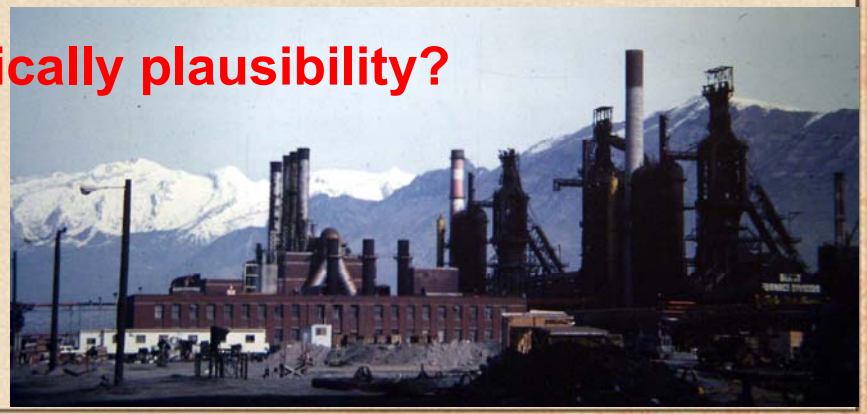
Epidemiological evidence
(Pope et al. 1989-1996)

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

Experimental evidence of biological effects of PM extracted from filters
(Ghio, Kennedy, Frampton, Costa, Dye, Devlin 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?)

Evidence of biologically plausibility?



Line 6. Biological Plausibility–Hypothesized general pathophysiologcial or mechanistic pathways

Much recent research has focused on four interrelated general pathophysiological pathways:

1. Accelerated Progression and exacerbation of COPD
2. Pulmonary/Systemic Oxidative Stress, Inflammation, Accelerated Atherosclerosis
3. Altered Cardiac Autonomic Function
4. Vasculature alterations

Accelerated Progression and exacerbation of COPD

Long-term PM exposure associated with:

- 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)

Short-term PM exposure associated with:

- Exacerbations of respiratory symptoms
- Transient declines in lung function
- Aggravate background inflammation in COPD (MacNee and Donaldson 2000, 2003)

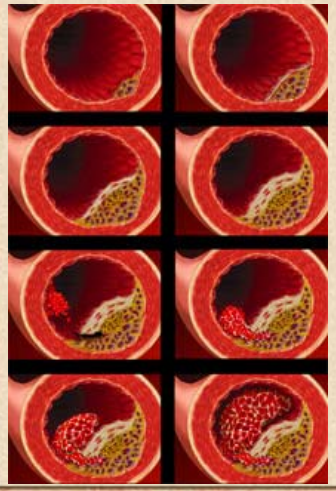
COPD, indicated either by symptoms or deficits in FEV_1, is a substantial risk factor for CVD (van Eeden et al. 2005; Sin et al. 2005)

Pulmonary/Systemic Oxidative Stress/Inflammation and Accelerated Atherosclerosis

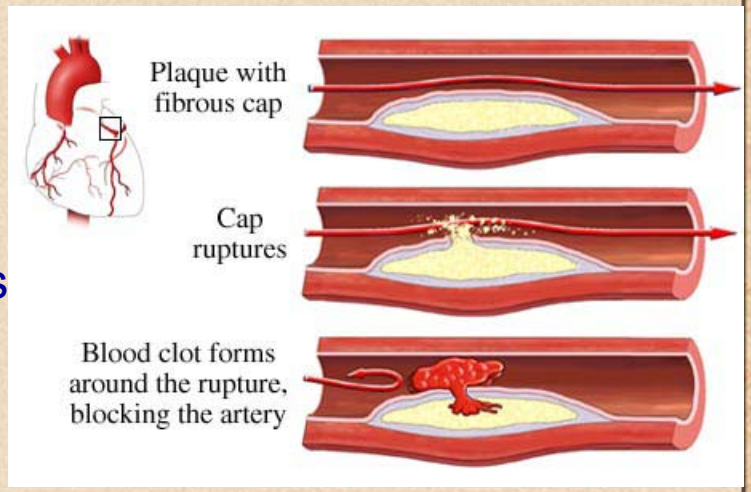
➢Inflammation (and blood lipids) contribute to the initiation and progression of atherosclerosis.

➢Long-term PM exposure → 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).



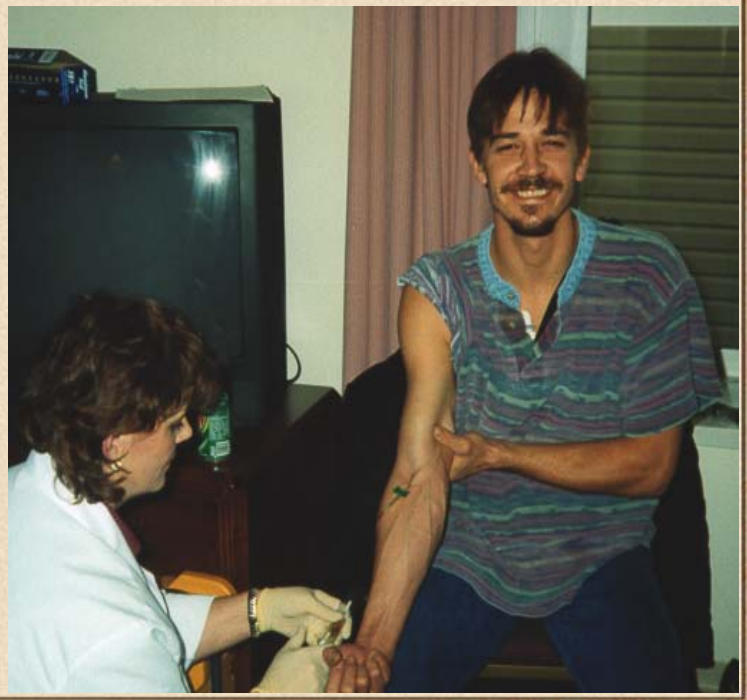
Inflammation/Accelerated Atherosclerosis is supported by evidence that:

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)

Short-term PM exposure associated with:

- CRP/other markers of inflammation and or oxidative stress (Table 4 in Crit. Rev.)
- MI events (Peters et al. 2001; 2004; Zanobetti and Schwartz 2005; Von Klot et al. 2005)
- Ischemic stroke events (Welleninus et al. 2005; Dominici et al. 2006)
- ST-segment depression (Pekkanen et al. 2002; Gold et al. 2005)
- Myocardial ischemia (in dogs) Wellenius et al. 2003)



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

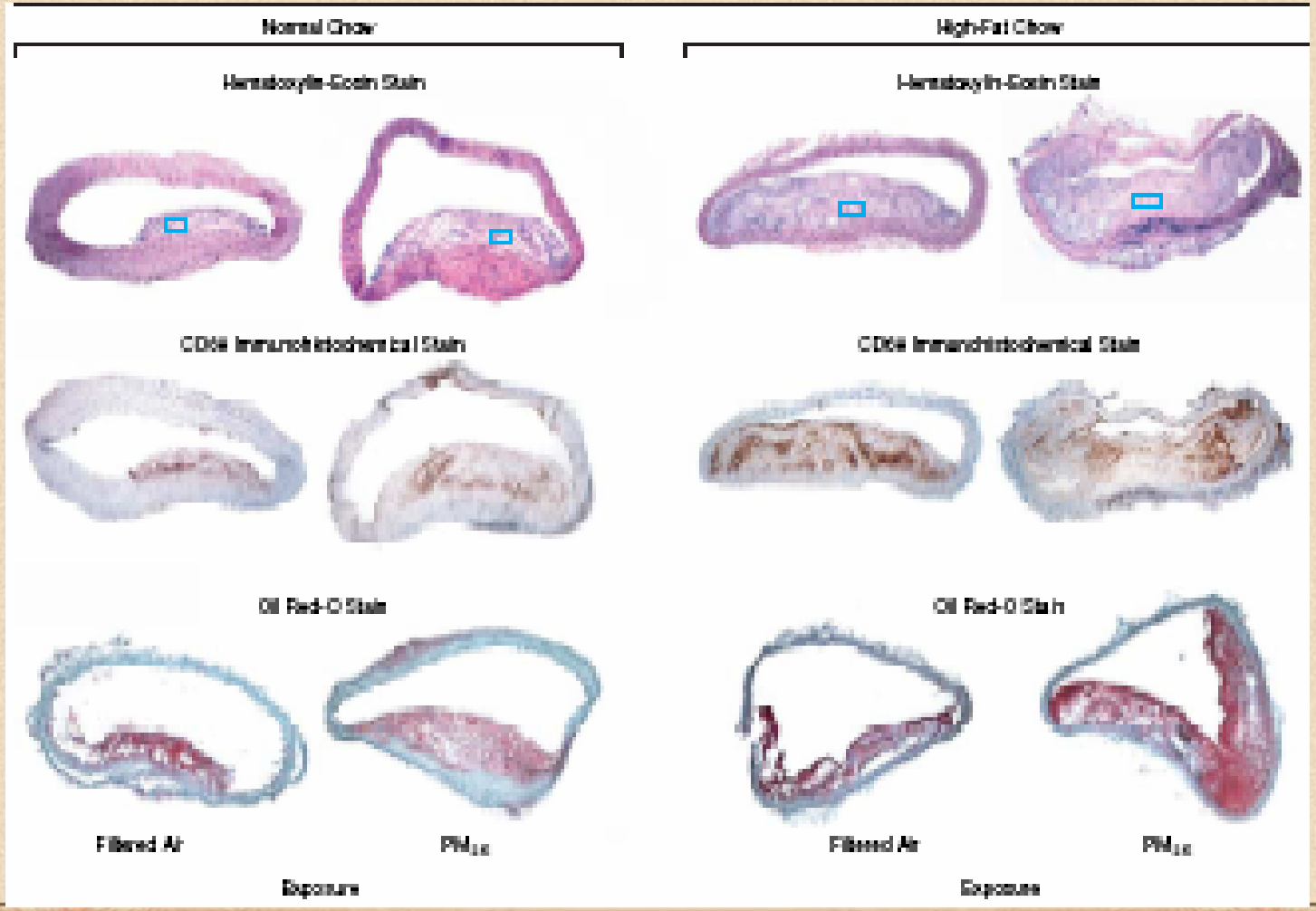
James Hogg

Sun et al. *JAMA* 2005

A hyperlipidemic (ApoE-deficient) mouse model:

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

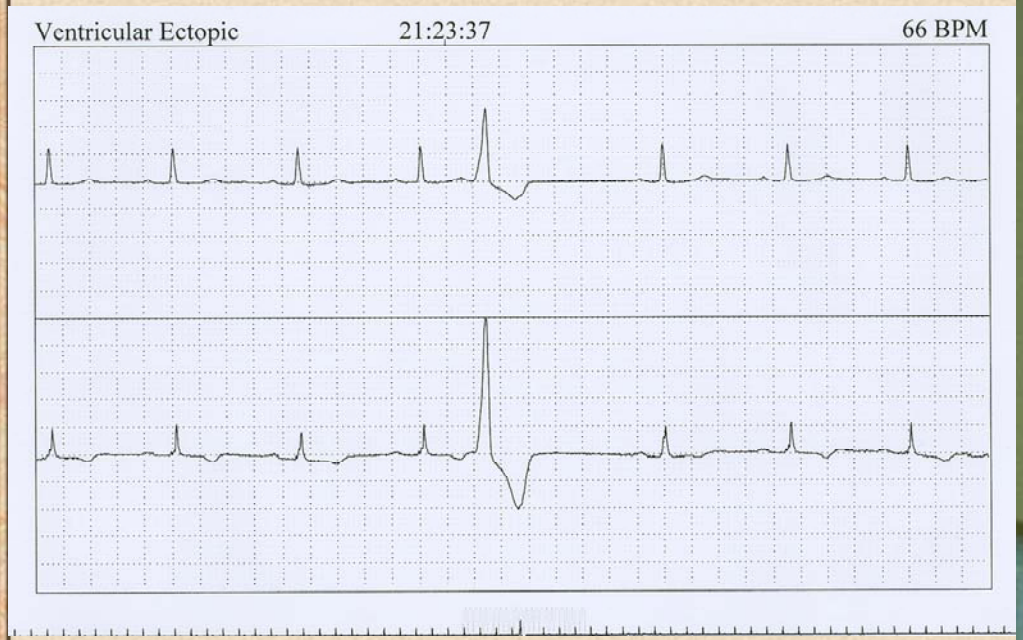
Representative Photomicrographs of Aortic Arch Sections

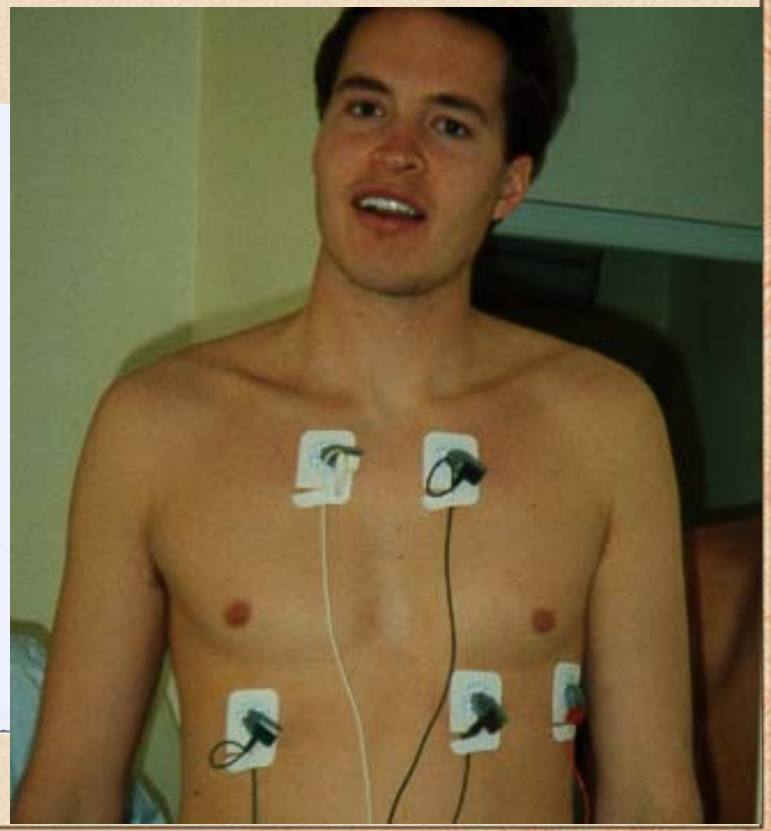


Altered Cardiac Autonomic Function

There is growing recognition of the role of autonomic dysfunction in cardiovascular mortality.

HRV measures provide quantitative, well-defined indicators of cardiac autonomic function





PM associations with HR and HRV

20+ studies

Variety exposures, methods, subjects, etc.

Table 6. HR and HRV and particulate air pollution associations summarized from recent studies.

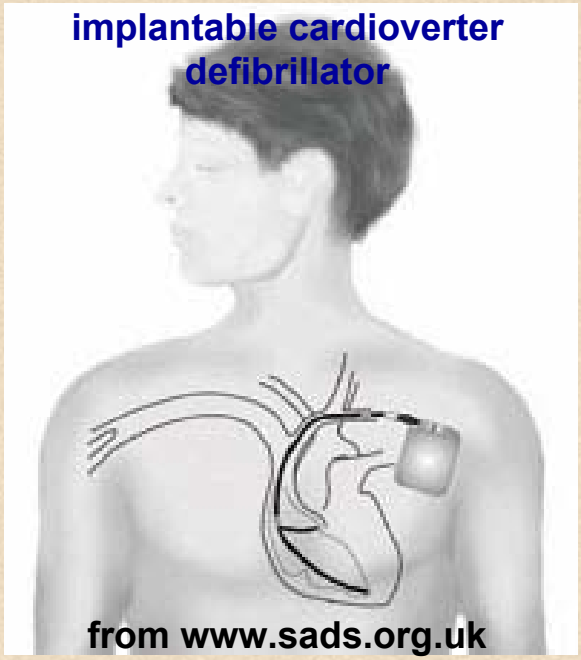
Primary Sources	Type and Duration of Particulate Exposure	Study Subjects (Total observations or study time), Study Area	Length of Analyzed Recordings	Direction of Effect				
				HR	Total, SDNN	ULF, SDANN	VLF, LF	HF, r-MSSD
Pope et al. 1999[291]	24-hr PM_{10}	90 elderly (8760 obs), Utah Valley	3-min	↗				
Peters et al. 1999, 2000[292,293]	Pollution episode	2681 adults, Augsburg, Germany	20-sec	↗				
Liao et al. 1999[294]	24-hr $PM_{2.5}$	26 elderly (wk), Baltimore	6-min		↘		↘	↘
Pope et al. 1999[295]	1- or 2-day PM_{10}	7 elderly (29 person days), Utah Valley	24-hr	↗	↘	↘		↗
Gold et al. 2000[296]	4- and 24-hr $PM_{2.5}$	21 aged 53–81(163 obs), Boston	25-min	↘	↘			↘
Pope et al. 2001[297]	2-hr $PM_{2.5}$, ETS	16 adults (64 2-hr periods) Salt Lake City, UT, airport	2-hr	↘	↘	↘	↘	↘
Creason et al. 2001[298]	24-hr $PM_{2.5}$	65 elderly (4 weeks), Baltimore	6-min				↘	↘
Magari et al. 2001[299]	Up to 9hr $PM_{2.5}$	40 boilermakers, primarily occupational exposure	5-min	↗	↘			
Magari et al. 2002[300]	3-hr $PM_{2.5}$	20 boilermakers, nonworkday exposures	5-min	→	↘			
Devlin et al. 2003[301]	2-hr $PM_{2.5}$, CAPS	10 elderly, 60–80 yr (20 2-hr periods), Chamber	10-min		↘		→	↘
Devlin et al. 2003[301]	2-hr $PM_{2.5}$, CAPS	22 young, 29 yr (20 2-hr periods), Chamber	10-min		→		→	→
Holguin et al. 2003[302]	24-hr $PM_{2.5}$	34 mean age 79 yr (384 obs), Mexico City	5-min				↘	↘
Chan et al. 2004[303]	1- to 4-hr $NC_{0.02-1}$	19 adults (16-hr per subject), Teipei, Taiwan	5-min		↘		↘	↘
Riediker et al. 2004[304]	9-hr $PM_{2.5}$	9 young healthy North Carolina patrol troopers	10-min		↗		→	↗
Pope et al. 2004[305]	24-hr $PM_{2.5}$	88 elderly (250 person days), Utah Valley	24-hr	↘	↘	↘		↘
Liao et al. 2004[306]	24-hr PM_{10}	4899 adults, mean age 62 yr, ARIC study	5-min	↗	↘		→	↘
Park et al. 2005[307] Schwartz et al. 2005[308]	24-hr $PM_{2.5}$	497 adult male, mean age 73 yr, normative aging study in Boston	4-min				↘	↘
Romieu et al. 2005[309]	24-hr $PM_{2.5}$	50 elderly nursing home residents, Mexico City	6-min		↘		↘	↘
Chuang et al. 2005[310]	1- to 4-hr $PM_{0.8-1}$	26 CHD/hypertensive patients in Taipei, Taiwan	5-min		↘			↘

Altered Cardiac Autonomic Function

In addition to HR and HRV, PM associated with:

- **Cardiac Arrythmia (based on ICD records)**
  (Peters, et al. 2000; Dockery et al. 2005)

- **Cardiac repolarization**
  (Henneberger et al. 2005)



- **Changes in cardiac rhythm or function in animal models (Godleski et al. 2000; Watkinson et al. 2001; Wellenius et al. 2002; Wichers et al. 2004)**

Vasculature Alterations

There is evidence that:

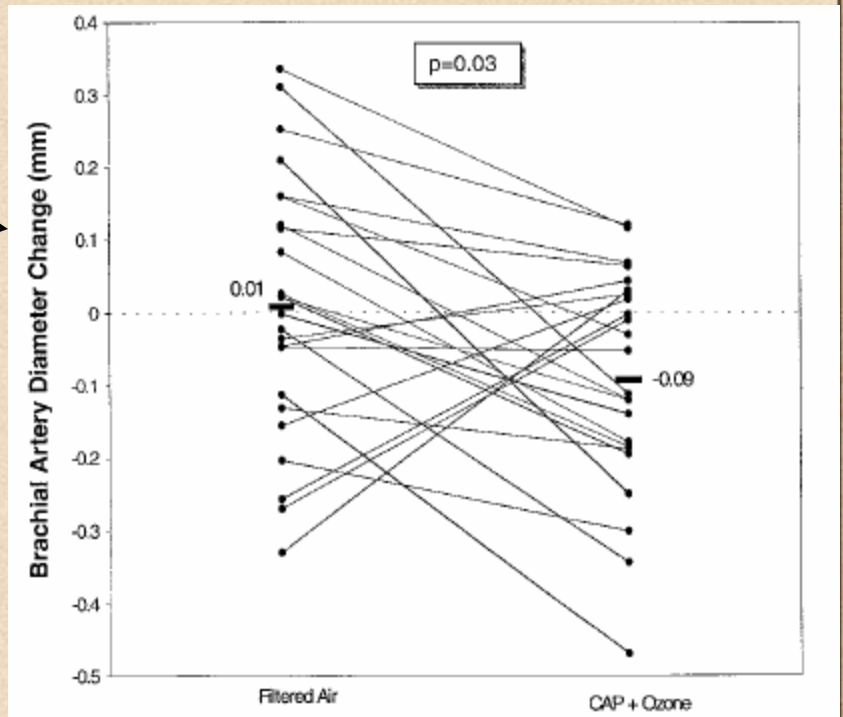
- PM-induced pulmonary inflammation plays a role in activating the vascular endothelium and
- Alterations in vascular tone and endothelial function are important PM-related mechanisms.

In humans, PM exposure has been associated with:

- Arterial vasoconstriction (Brook et al. 2002)
- Impaired vascular reactivity and endothelial function in diabetics (O'Neil et al. 2005)
- Increased blood pressure (Linn and Gong 2001; Zanobetti et al. 2004)

In animals, PM exposure has been associated with:

- Increased vasoconstriction (Batalha et al. 2002)
- Increased circulating levels of endothelin (Vincent et al. 2001; Bouthillier 1998)



Brachial artery diameter vasoconstriction observed in 28 of 34 subjects exposed to ~150 $\mu g/m^3$ $PM_{2.5}$ + 120 ppb O_3

In addition to

- Accelerated Progression and exacerbation of COPD
- Pulmonary/Systemic Oxidative Stress Inflammation/Accelerated Atherosclerosis
- Altered Cardiac Autonomic Function
- Vasculature alterations

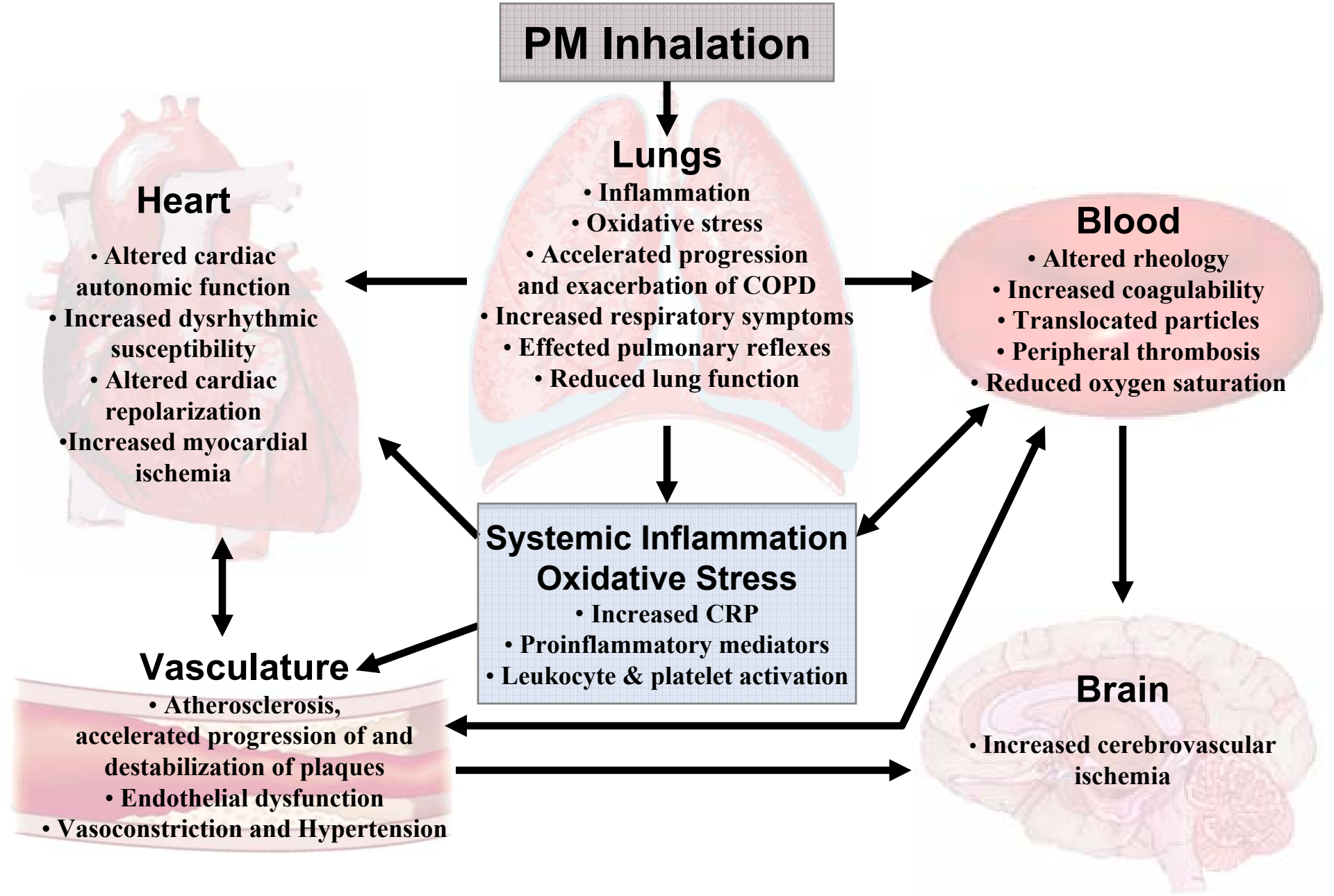
Other mechanistic pathways include:

- Translocation of particles
- Modulated host defenses and immunity
- Hypoxemia

It is unlikely that any single pathway is responsible.

Gunter Oberdorster

Judith Zelikoff



There are multiple mechanistic pathways have complex interactions and interdependencies

Gaps in Knowledge--Susceptibility

Various characteristics have been shown to influence susceptibility including:

- Preexisting respiratory or cardiovascular disease
- Diabetes
- Medication use
- Age, Gender, Race
- Socioeconomic status
- Health care availability
- Educational attainment
- Housing characteristics
- Outdoor activity
- Genetic differences

We still need a better understanding of who's most at risk or susceptible.

Gaps in Knowledge—Infant/Birth Outcomes

There is substantial evidence that PM exposure in children is associated with:

- Deficits in lung function and lung function growth
- Respiratory illness and symptoms
- Respiratory hospitalization

Also evidence that PM exposure increases the risk of

- infant mortality--especially postneonatal respiratory mortality

There remain serious gaps regarding potential effects on

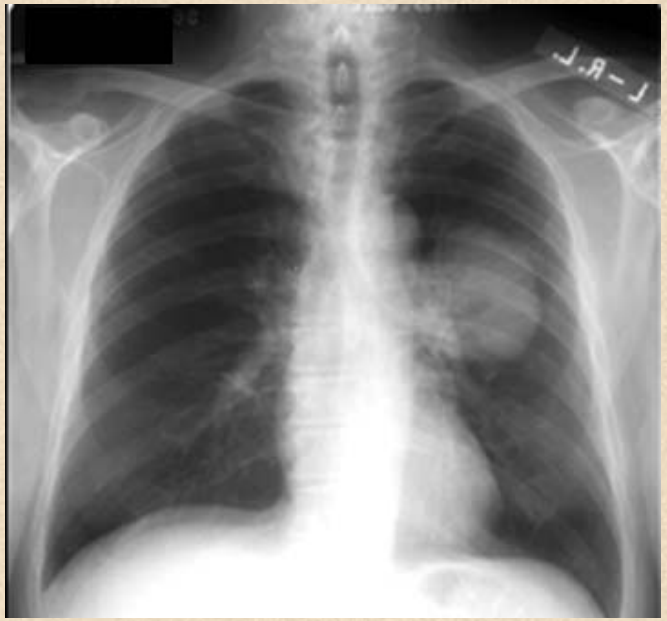
- Fetal growth
- Premature birth
- Related birth outcomes

Gaps in Knowledge—Lung Cancer

Available evidence suggests small PM-related increased lung cancer risk

but,

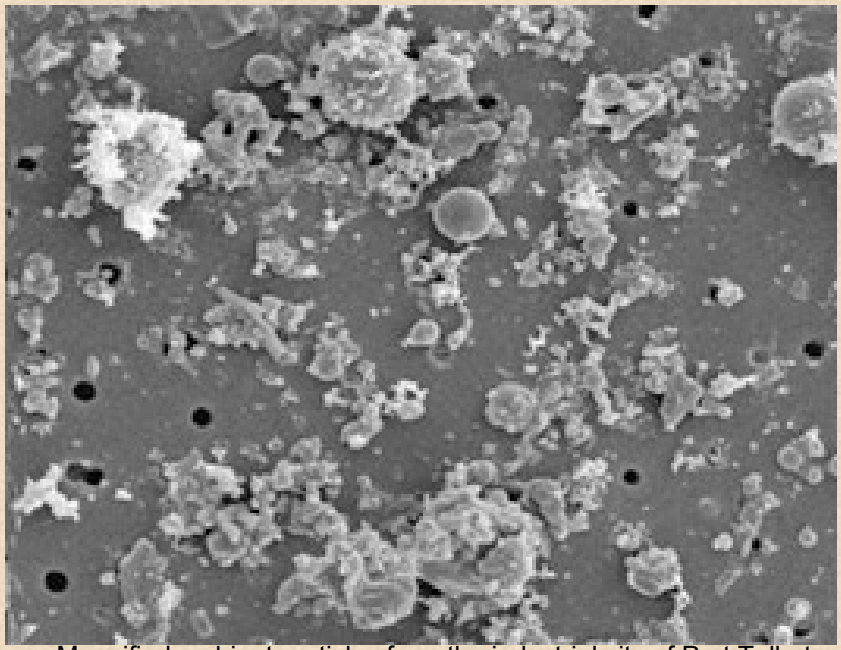
Substantial uncertainty remains. . .



Gaps in Knowledge—Relative toxicity and role of sources and copollutants

- Little evidence that a single source or component of PM is solely responsible for health effects, but the relative importance of:
  - particle size
  - secondary inorganic PM
  - solubility
  - metal content
  - surface area and reactivity
  - and other characteristics

need much additional study.



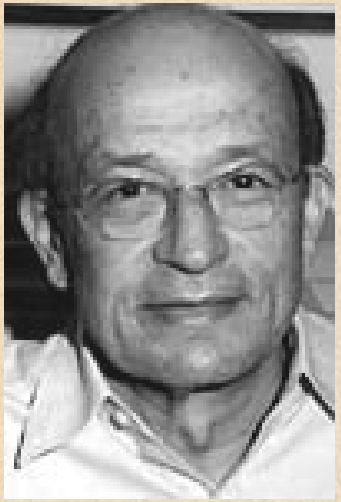
Magnified ambient particles from the industrial city of Port Talbot, England. (www.nasa.gov/vision/earth/environment)

- Further study is also needed to understand the relative importance of various sources and related copollutants

Continued Skepticism

- Need healthy skepticism.
- Is the evidence adequate to establish costly health-based air quality standards?
- Some skepticism seems to be motivated at least in part by *pro forma* opposition to public policy efforts to regulate PM.
- But, there are important scientific issues that are not fully resolved such as concerns about
  - potential confounding,
  - measurement error,
  - model building and selection.

Joel Schwartz (See Regulation 2003; CEI 2003)



Suresh Moolgavka, (See *Regul. Toxicol. Pharmacol.* 2005; *Inhal. Toxicol.* 2006)

Also concerns about consistency across the toxicological, clinical, and epidemiological evidence? But . . .

Many dedicated and skilled interdisciplinary researchers have been/are addressing these issues.


David Bates

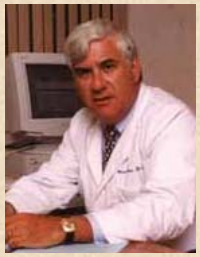

Frank Speizer


Mort Lippmann


Robert Devlin


Joe Mauderly


Dan Costa


Mark Utell

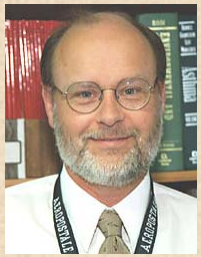

Andy Ghio


Petros Koutrakis


Diane Gold


Michael Brauer


Annette Peters


Mark Frampton


Anthony Seaton


Beatriz Gonzalez-Flecha


Richard Verrier


Flemming Cassee


Ursula Ackermann-Liebrich


Paulo Saldiva


Ira Tager


Henry Gong


Murray Mittleman

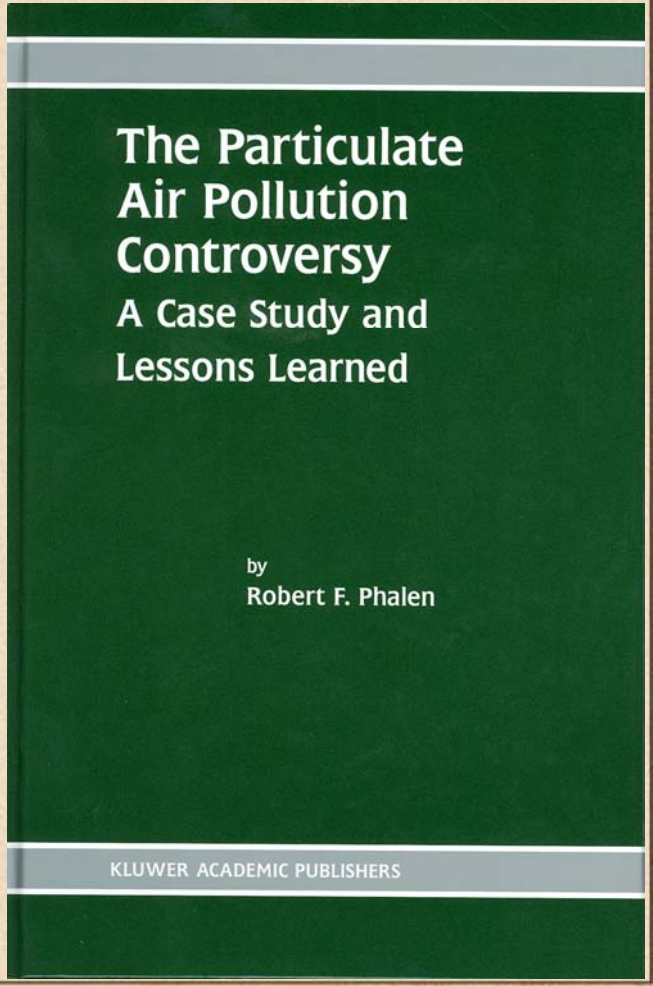

Marie O'Neill


Paige Tolbert

et al.

Another reason for skepticism

- Scientific efforts have taken place within the context of contentious and controversial debate about public health policy, environmental regulations
- Such conditions present both challenges and opportunities to researchers
- These conditions are not always most conducive to deliberate, objective, scientific inquiry
- The extent to which politics, pressure groups, special interests, and funding opportunities and sources influence the science and how it is interpreted is unknown
- But these influences may contribute to our skepticism



Conclusions I

- Recent research has increased our understanding about PM health effects.
- There's been progress evaluating PM effects for different time-scales of exposure and in the exploration of the shape of the concentration-response function.
- The emerging evidence of PM-related cardiovascular health effects and the growing knowledge regarding interconnected general pathophysiological pathways that link PM exposure with cardiopulmonary morbidity and mortality are fascinating results.
- These results have important scientific, medical, and public health implications that are much broader than debates over legally mandated air quality standards.

Conclusions II

- The U.S. EPA proposed new NAAQS around the time this critical review was being prepared for initial reviews.

- Polarized responses to the proposed NAAQS demonstrated that some lines of division that troubled Vedal in 1997 continue today--especially the problem of setting standards in the absence of clearly defined health effect thresholds.

Some reviewers of this critical review opined that

"the big question is: how valid is the EPA NAAQS proposal?"

↓

A critical review of the scientific literature can't provide a clear answer

But,

The literature provides evidence that continued reductions in $PM_{2.5}$ will likely result in improvements in cardiopulmonary health.

- Recommendations by EPA's CASAC were responsible standards given current knowledge. The WHO guidelines for PM_{10} and $PM_{2.5}$ provide reasonable goals for most urban environments.