Overview of PM$_{2.5}$-Related Mortality Studies

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Presented at: ARB Symposium
Methodology for Estimating Premature Deaths from PM$_{2.5}$ Exposure
Sacramento, CA
February 26, 2010
Blood
- Altered rheology
- Increased coagulability
- Translocated particles
- Peripheral thrombosis
- Reduced oxygen saturation

PM Inhalation

Heart
- Altered cardiac autonomic function
- Increased dysrhythmic susceptibility
- Altered cardiac repolarization
- Increased myocardial ischemia
- Heart failure exacerbation

Lungs
- Inflammation
- Oxidative stress
- Accelerated progression and exacerbation of COPD
- Increased respiratory symptoms
- Effected pulmonary reflexes
- Reduced lung function

Systemic Inflammation Oxidative Stress
- Increased CRP
- Proinflammatory mediators
- Leukocyte & platelet activation

Vasculature
- Atherosclerosis, accelerated progression of and destabilization of plaques
- Endothelial dysfunction
- Vasoconstriction and Hypertension

Brain
- Increased cerebrovascular ischemia

Vasculature
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.
Overall literature is now far too massive to review in a short presentation.

The objective of this presentation:

Focus on the most relevant studies to estimate overall mortality effects

--cohort studies of long-term exposure.
Summary of published cohort and related studies of long-term fine PM exposure. Percent increases in mortality and related risk (95% CIs) associated with 10 μg/m$^3$ PM$_{2.5}$ (or other as indicated).
An Association Between Air Pollution and Mortality in Six U.S. Cities

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

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Current Smoker, 25 Pack years</th>
<th>Most vs. Least Polluted City</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td><strong>2.00</strong></td>
<td><strong>1.26</strong></td>
</tr>
<tr>
<td></td>
<td>(1.51-2.65)</td>
<td>(1.08-1.47)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td><strong>8.00</strong></td>
<td><strong>1.37</strong></td>
</tr>
<tr>
<td></td>
<td>(2.97-21.6)</td>
<td>(0.81-2.31)</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td><strong>2.30</strong></td>
<td><strong>1.37</strong></td>
</tr>
<tr>
<td></td>
<td>(1.56-3.41)</td>
<td>(1.11-1.68)</td>
</tr>
<tr>
<td>All other</td>
<td><strong>1.46</strong></td>
<td><strong>1.01</strong></td>
</tr>
<tr>
<td></td>
<td>(0.89-2.39)</td>
<td>(0.79-1.30)</td>
</tr>
</tbody>
</table>
SPECIAL REPORT

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
Six-Cities: 
Extended analyses: Laden et al. AJRCCM 2006


**Figure 2.** The estimated concentration–response relation between PM$_{2.5}$ and the risk of death in the Six Cities Study, based on averaging the 32 possible models that were fit. Also shown are the pointwise 95\% CIs around that curve, based on jackknife estimates.

**Figure 4.** The model-averaged estimated effect of a 10-µg/m$^3$ increase in PM$_{2.5}$ on all-cause mortality at different lags (in years) between exposure and death. Each lag is estimated independently of the others. Also shown are the pointwise 95\% CIs for each lag, based on jackknife estimates.
Harvard six-cities studies:

- Dockery et al. NEJM 1993—Original report
- Krewski et al. HEI 2000—Reanalysis
- Laden et al. AJRCCM 2006—Extended analysis

Well-designed study that has undergone extensive peer review and reanalyses. Robust and reproducible results.
Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults


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 and the range of sulfates and fine particles

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Current Smoker</th>
<th>Sulfates</th>
<th>Fine Particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.07 (1.75-2.43)</td>
<td>1.15 (1.09-1.22)</td>
<td>1.17 (1.09-1.26)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>9.73 (5.96-15.9)</td>
<td>1.36 (1.11-1.66)</td>
<td>1.03 (0.80-1.33)</td>
</tr>
<tr>
<td>Cardio-Pulmonary</td>
<td>2.28 (1.79-2.91)</td>
<td>1.26 (1.16-1.37)</td>
<td>1.31 (1.17-1.46)</td>
</tr>
<tr>
<td>All other</td>
<td>1.54 (1.19-1.99)</td>
<td>1.01 (0.92-1.11)</td>
<td>1.07 (0.92-1.24)</td>
</tr>
</tbody>
</table>
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
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 air pollution and increased risk of various adverse health outcomes, including cardiopulmonary mortality. However, studies of health effects of long-term particulate air pollution have been less conclusive.

Objective  To assess the relationship between long-term exposure to fine particulate air pollution and all-cause, lung cancer, and cardiopulmonary mortality.

Design, Setting, and Participants  Vital status and cause of death data were collected by the American Cancer Society as part of the Cancer Prevention II Study, a prospective mortality study, which enrolled approximately 1.2 million adults.
Figure 2. Nonparametric Smoothed Exposure Response Relationship

A. All-Cause Mortality

B. Cardiopulmonary Mortality

C. Lung Cancer Mortality

D. All Other Cause Mortality

Log RR (95% CI)

PM$_{2.5}$, $\mu g/m^3$
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
Spatial analysis of air pollution and mortality in Los Angeles.
(Jerrett, Burnett, Ma, Pope, et al. Epidemiology 2005)
<table>
<thead>
<tr>
<th>Follow up 1982-2000 Cox Model Covariates</th>
<th>Cause of Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects: N=22,905</td>
<td>5,856</td>
<td>1,462</td>
</tr>
<tr>
<td>PM2.5 (LUR28pred) only</td>
<td>1.197 (1.082,1.325)</td>
<td>1.415 (1.154,1.735)</td>
</tr>
<tr>
<td>44 Individual Covariates</td>
<td>1.143 (1.033,1.266)</td>
<td>1.331 (1.084,1.634)</td>
</tr>
<tr>
<td>+ Air Conditioning</td>
<td>1.142 (1.031,1.263)</td>
<td>1.333 (1.083,1.658)</td>
</tr>
<tr>
<td>+ Percent of Black</td>
<td>1.145 (1.033,1.269)</td>
<td>1.347 (1.096,1.656)</td>
</tr>
<tr>
<td>+ Percent of White</td>
<td>1.151 (1.036,1.278)</td>
<td>1.362 (1.103,1.682)</td>
</tr>
<tr>
<td>+ Percent of Hispanic</td>
<td>1.132 (1.016,1.261)</td>
<td>1.322 (1.065,1.641)</td>
</tr>
<tr>
<td>+ Percent of Unemployed</td>
<td>1.127 (1.015,1.252)</td>
<td>1.328 (1.075,1.641)</td>
</tr>
<tr>
<td>+ Mean Income</td>
<td>1.146 (1.035,1.268)</td>
<td>1.332 (1.086,1.635)</td>
</tr>
<tr>
<td>+ Total population</td>
<td>1.141 (1.030,1.264)</td>
<td>1.322 (1.076,1.624)</td>
</tr>
<tr>
<td>+ Income inequality</td>
<td>1.110 (0.999,1.234)</td>
<td>1.254 (1.014,1.552)</td>
</tr>
<tr>
<td>+ Percent of GRD12</td>
<td>1.144 (1.033,1.266)</td>
<td>1.334 (1.087,1.637)</td>
</tr>
<tr>
<td>+ All social factors</td>
<td>1.142 (1.026,1.272)</td>
<td>1.322 (1.064,1.642)</td>
</tr>
<tr>
<td>+ AC, Income, GRD12, SF</td>
<td>1.115 (1.003,1.239)</td>
<td>1.263 (1.020,1.563)</td>
</tr>
<tr>
<td>+ Parsimonious con. Covs.</td>
<td>1.126 (1.014,1.251)</td>
<td>1.264 (1.022,1.563)</td>
</tr>
<tr>
<td>Copollutant control</td>
<td>1.191 (1.069,1.327)</td>
<td>1.455 (1.171,1.810)</td>
</tr>
<tr>
<td>44 Covs. + O3 (EPDC)</td>
<td>1.176 (1.057,1.307)</td>
<td>1.431 (1.155,1.772)</td>
</tr>
<tr>
<td>44 Covs. + O3 (Average)</td>
<td>1.170 (1.054,1.299)</td>
<td>1.393 (1.127,1.721)</td>
</tr>
<tr>
<td>Copollutant risk estimates</td>
<td>0.985(0.964,1.006)</td>
<td>0.973(0.932,1.015)</td>
</tr>
<tr>
<td>Ozone (EPDC)</td>
<td>0.993(0.977,1.010)</td>
<td>0.984(0.952,1.017)</td>
</tr>
<tr>
<td>Ozone (Average)</td>
<td>0.987(0.875,1.113)</td>
<td>0.898(0.706,1.143)</td>
</tr>
<tr>
<td>FreeWay within 500 m</td>
<td>0.974(0.894,1.062)</td>
<td>1.048(0.885,1.241)</td>
</tr>
<tr>
<td>FreeWay within 1000m</td>
<td>0.987(0.977,1.010)</td>
<td>0.984(0.952,1.017)</td>
</tr>
</tbody>
</table>
Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality

Daniel Krewski, Michael Jerrett, Richard T. Burnett, Renjun Ma, Edward Hughes, Yuanli Shi, Michelle C. Turner, C. Arden Pope III, George Thurston, Eugenia E. Calle, and Michael J. Thun

with Bernie Beckerman, Pat DeLuca, Norm Finkelstein, Kaz Ito, D.K. Moore, K. Bruce Newbold, Tim Ramsay, Zev Ross, Hwashin Shin, and Barbara Tempalski
ACS cohort studies:
• Pope et al. AJRCCM 1995—Original report
• Krewski et al. HEI 2000—Reanalysis
• Pope et al. JAMA 2002 and
• Pope et al. Circulation 2004—Extended analysis
• Jerrett et al. Epidemiology 2005—Intra-metro LA
• Krewski et al. HEI 2009—Extended analysis

Large well-designed study that has undergone extensive peer review, reanalyses, and extended analyses. Robust and reproducible results.
U.S. Medicare Cohort studies:
- Eftim et al. Epidemiology 2008
- Zegar et al. EHP 2008

Established cohorts of Medicare participants for 6 cities, cities of the ACS study, and the whole U.S. stratified by East, Central, and West regions and by age. Similar or somewhat larger excess risk estimate for 6-cities, ACS cities, and U.S. Significant excess risk not observed for West region or for oldest age group.
AHSMOG Studies:
• Chen et al. EHP 2005

Study of a cohort of California Adventists. Somewhat mixed results, but evidence of excess mortality risk.
VA hypertensive males study:
- Lipfert et al. Atmospheric Environ. 2006
- Lipfert et al. Inhal Toxicol. 2006

Excess risks were most strongly associated with indicators of traffic-source pollution (traffic density).
In single pollutant models, PM$_{2.5}$ was positively associated with mortality risk:
  - significant for the first follow-up (1989-1996),
  - not for a subsequent follow-up (1997-2001)
11 CA county, elderly study:
• Enstrom Inhal Toxicol. 2005
  - Cohort enrolled in 1959, ACS CPS I
  - Re-contacted in 1972
  - Initial follow-up 1973-1982
  - Subsequent follow-up 1983-2002

For the initial follow-up (and the time-period approximately concurrent with PM$_{2.5}$ monitoring) there was a significant PM$_{2.5}$ association. There was no significant association in the subsequent follow-up.
Women's Health Initiative study:
• Miller et al. NEJM 2007

Study focused on cardiovascular events (fatal and nonfatal) in postmenopausal women.
Large pollution effect on both fatal and nonfatal cardiovascular events.
Nurses’ Health Study:
• Puett et al. Am. J. Epidemiology 2008

Stronger association with CVD than with all cause.
Oslo, Norway, intra-metro study:
• Naess et al. Am. J. Epidemiology 2007

Estimates for men and women ages 51-70 and 71-90. Significant excess risks, but smaller for older age group.
Dutch, French, and German women studies:
• Beelen et al. EHP 2008
• Filleul et al. OEM 2005
• Gehring et al. Epidemiology 2006

Again, positive associations, generally stronger for cardiovascular disease.

Brunekreef (summary paper)
JESEE 2007
California Teachers study:
• Ostro et al. EHP 2010
  (online 26 Oct. 2009)


Exceptionally large, associations, generally stronger for cardiovascular disease.

Bart Ostro          Peggy Reynolds
Summary of published cohort and related studies of long-term fine PM exposure. Percent increases in mortality and related risk (95% CIs) associated with 10 μg/m³ PM$_{2.5}$ (or other as indicated).

**FIGURE 3.** Uncertainty distributions for the PM$_{2.5}$—mortality C–R coefficient for annual average PM$_{2.5}$ concentrations of 4–30 μg/m$^3$. Note: Box plots represent distributions as provided by the experts to the elicitation team. Experts in group 1 preferred to give conditional distributions and keep their probabilistic judgment about the likelihood of a causal or noncausal relationship separate. Experts in group 2 preferred to give distributions that incorporate their likelihood that the PM$_{2.5}$—mortality association may be noncausal. Therefore, the expert distributions from these two groups are not directly comparable.

Full disclosure:
Evidence a bit stronger now.

FIGURE 3. Uncertainty distributions for the PM$_{2.5}$—mortality $C$–$R$ coefficient for annual average PM$_{2.5}$ concentrations of 4–30 µg/m$^3$ Note: Box plots represent distributions as provided by the experts to the elicitation team. Experts in group 1 preferred to give conditional distributions and keep their probabilistic judgment about the likelihood of a causal or noncausal relationship separate. Experts in group 2 preferred to give distributions that incorporate their likelihood that the PM$_{2.5}$—mortality association may be noncausal. Therefore, the expert distributions from these two groups are not directly comparable.
So what do we learn from these studies?

1. The predominant statistical inference is that long-term exposure to elevated levels of PM$_{2.5}$ is associated with elevated risk of mortality.

2. Reasonable central effect estimates range from approximately 5-15% increased mortality risk per 10 $\mu$g/m$^3$ long-term elevated PM$_{2.5}$ exposure.

3. In general, PM$_{2.5}$ exposure is more strongly associated with cardiovascular-related mortality.

4. There is evidence that the PM$_{2.5}$-related excess relative risk is smaller for older populations and declines as cohorts age with longer follow-up.
Which studies are appropriate to use to estimate PM$_{2.5}$-Related Mortality in California?

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

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Sun et al. (JAMA 2005)

Representative Photomicrographs of Aortic Arch Sections

Normal Chow

- Clean Filtered Air
- PM Polluted Air

High-Fat Chow

- Clean Filtered Air
- PM Polluted Air

apoE⁻/⁻ mouse
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
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 μg/m³ of PM$_{2.5}$, stratified by various characteristics.
Corotid ultrasound to measure carotid intima-media thickness (CIMT).

Safe, non-invasive technique to evaluate the burden of subclinical vascular (atherosclerotic) disease.
Southern California Children’s Health Study

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

W. James Gauderman

John Peters

David Bates, Advisor
Gauderman et al. The effect of air pollution on lung development from 10 to 18 years of age. *New England Journal of Medicine* 2004
Figure: Percent-predicted lung function at age 18 years versus residential distance from a freeway. The horizontal line at 100% corresponds to the referent group, children living > 1500 m from a freeway.

Result emphasized by Enstrom et al. Low effect estimate is at least partially explained by relatively poor exposure assessment, and old/aging cohort.
Percent increase in mortality risk (95% CI)

All Cause

CPD

CVD

IHD

Published estimates using California-based data
So . . . ?

Are hyperlipidemic mice in California less susceptible than those in NY?
• Probably not.

Are Californian’s children’s lungs and adult cardiovascular systems less susceptible to fine particulate pollution than those elsewhere?
• Probably not.

Is pollution from California cars, trucks, and other sources less toxic to humans than elsewhere?
• Probably not.

Then which health studies are relevant to California?
• Some of the highest quality research on the health effects of air pollution has been conducted in California. The results are similar to studies from elsewhere.
• It is evident that well-conducted epidemiological, clinical and toxicology studies conducted both in California and elsewhere are relevant.
Figure A. Adjusted RRs of cardiovascular disease for different increments of cigarette smoking based on analyses from the ACS CPS-II cohort.
So why is there variability in risk estimates?

1. Simply random or stochastic variability across studies (different sample sizes, exposure variability, etc.).

2. Differences in quality of exposure assessment. For example, the Harvard 6-cities, WHI, ACS intra-metro LA studies have relatively high quality exposure assessment and tend to have larger effect estimates.

3. Differences in population age and length of follow-up. For example, the decline in pollution related risk with more aged or more aging with longer follow-up is observed in the Medicare cohort, the VA hypertensive male cohort, the 11 CA county cohort, and the Oslo cohort. Even with cigarette smoking, a similar phenomena is observed.

4. Different pollution sources and toxicity.