Health Effects of Particulate Matter Air Pollution

C. Arden Pope III
Mary Lou Fulton Professor of Economics

Presented at
EPA Wood Smoke Health Effects Webinar
July 28, 2011
What we breathe impacts our health

- **Pure Air** -- nitrogen (78%), oxygen (21%), argon, CO₂...

- **Various gaseous pollutants including:**
  - SO₂, NO₂, CO, O₃...

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

- **Other air toxics**
How small are fine particles?

Human Hair (60 µm diameter)

PM$_{10}$ (10 µm)

PM$_{2.5}$ (2.5 µm)
Magnified ambient particles  (www.nasa.gov/vision/earth/environment)
This presentation not organized chronologically, but methodologically

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

Studies of long-term exposure (years-decades)
- Population-based cross-sectional
- Cohort-based mortality
- Cohort- and panel-based morbidity
- Case-control studies

Intervention/natural experiment (months-years)

Controlled experimental human and animal
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Early “Killer smog” episodes demonstrated that air pollution at extreme levels can contribute to respiratory and cardiovascular disease and death.

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

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

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

Respiratory and cardiovascular disease and death
London Fog Episode, Dec. 1952

THE BIG SMOKE

From: Brimblecombe P. The Big Smoke, Methuen
Utah Valley, 1980s

- Winter inversions trap local pollution
- Natural test chamber

- Local Steel mill contributed ~50% PM$_{2.5}$
- Shut down July 1986-August 1987
- Natural Experiment
Large difference in air quality when inversions trap air pollution in valley

Utah Valley: Clean day

Utah Valley: Dirty day

$\text{PM}_{10} = 220 \, \mu\text{g/m}^3$
When the steel mill was open, total children’s hospital admissions for respiratory conditions **approx. doubled**.
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Health studies take advantage of highly variable air pollution levels that result from inversions.

$PM_{2.5}$ concentrations January 1, 1998-December 12, 2009. Black dots, 24-hr $PM_{2.5}$; Red line, 30-day moving average $PM_{2.5}$; Green line, 1-yr moving average $PM_{2.5}$. 
Daily changes in air pollution ➔ Daily death counts

Utah Valley

<table>
<thead>
<tr>
<th>Time (days)</th>
<th># of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500</td>
<td>2</td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
</tr>
<tr>
<td>1500</td>
<td>6</td>
</tr>
</tbody>
</table>

% Day PM10 (ug/m3)

Deaths/Day

---

The graph shows the relationship between daily changes in air pollution and daily death counts in Utah Valley. The data suggests a correlation between increased air pollution and increased daily death counts.
**Poisson Regression**

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

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

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

\[
\ln \lambda_t = \alpha + \beta(w_0P_t + w_1P_{t-1} + w_2P_{t-2} + \ldots) + s^1(t) + s^2(\text{temp}_t) + \ldots
\]

**Modeling controversies**

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

Also: How to combine or integrate information from multiple cities
**Daily time-series studies ***of over 200 cities***

### Estimates from meta analysis

- 29 cities (Levy et al. 2000)
- Publication bias adjusted (Anderson et al. 2005)
- Multicity studies (Levy et al. 2000)

### Estimates from Multicity studies

- 29 cities (Levy et al. 2000)
- Unadjusted (Anderson et al. 2005)

### Estimates from Multicity studies

- 6 U.S. cities (Klemm and Mason 2003)
- 8 Canadian cities (Burnett and Goldberg 2003)
- 9 Californian cities (Ostro et al. 2006)
- 10 U.S cities (Schwartz 2000, 2003)
- 14 U.S cities, case-crossover (Schwartz 2004)
- NMAPS, 20-100 U.S. cities (Dominici et al. 2003)
- APHEA-2, 15-29 European cities (Katsouyanni et al. 2003)
- 9 French cities (Le Tertre et al. 2002)
- 7 Korean cities (Lee et al. 2000)
- 13 Japanese cities (Omori et al. 2003)
- 18 Latin Am. studies (PAHO 2005)

### Asian Lit. incorporating PAPA studies

- 8 studies (HEI Report, Table TS2)

### 18 Latin Am. studies

(PAHO 2005)

### 13 Japanese cities

(Omori et al. 2003)

### 7 Korean cities

(Lee et al. 2000)

### APHEA-2, 15-29 European cities

(Katsouyanni et al. 2003)

### 9 French cities

(Le Tertre et al. 2002)

### 10 U.S cities

(Schwartz 2000, 2003)

### 14 U.S cities, case-crossover

(Schwartz 2004)

### 8 Canadian cities

(Burnett and Goldberg 2003)

### 9 Californian cities

(Ostro et al. 2006)

### 6 U.S. cities

(Klemm and Mason 2003)

### 29 cities

(Levy et al. 2000)

### Publication bias adjusted

(Anderson et al. 2005)

### Multicity studies

(Levy et al. 2000)

### GAM-based studies

(Stieb et al. 2002, 2003)

### Non-GAM-based studies

(Stieb et al. 2002, 2003)

### Meta analysis

(Levy et al. 2000)

### PM$_{10}$

10 µg/m$^3$ PM$_{2.5}$ or 20 µg/m$^3$ PM$_{10}$ $\rightarrow$ 0.4% to 1.5% increase in relative risk of mortality — Small but remarkably consistent across meta-analyses and multi-city studies.
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Intervention/natural experiment (months-years)
Controlled experimental human and animal
Panel studies of asthmatics and non-asthmatics
Fig. 1. Daily PM$_{10}$ levels, mean peak expiratory flow deviations (ΔPEF), percentage who reported cough, and number of participants for the symptomatic sample.
Summary of early Utah Valley epidemiological studies

**Health effects**

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

**Study References**


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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
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 μg/m³ of PM$_{2.5}$, or PM$_{10}$ for different lag structures.
Short-term PM exposures contributed to acute coronary events, especially among patients with underlying coronary artery disease.

Figure 2. Percent increase in risk (and 95% CI) of acute coronary events associated with $10 \mu g/m^3$ of $PM_{2.5}$, stratified by various characteristics.
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Any Questions?
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Age-, sex-, and race- adjusted population-based mortality rates in U.S. cities for 1980 plotted over various indices of particulate air pollution (From Pope 2000).
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An Association Between Air Pollution and Mortality in Six U.S. Cities

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.
Average Polluted cities
Highly Polluted cities
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 \( \beta \) which can vary in time.
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>2.00 (1.51-2.65)</td>
<td>1.26 (1.08-1.47)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>8.00 (2.97-21.6)</td>
<td>1.37 (0.81-2.31)</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td>2.30 (1.56-3.41)</td>
<td>1.37 (1.11-1.68)</td>
</tr>
<tr>
<td>All other</td>
<td>1.46 (0.89-2.39)</td>
<td>1.01 (0.79-1.30)</td>
</tr>
</tbody>
</table>
**Methods:** Linked and analyzed ambient air pollution data from 51-151 U.S. metro areas with risk factor data for over 500,000 adults enrolled in the ACS-CPSII cohort.
Adjusted mortality risk ratios (and 95% CIs) for cigarette smoking the range of sulfates and fine particles

<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 selected by the American Cancer Society as part of the Cancer Prevention II study going 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
Figure 1. Adjusted relative risk ratios for cardiovascular and respiratory mortality associated with a 10 mg/m$^3$ change in PM$_{2.5}$ for 1979-1983, 1999-2000, and the average of the two periods. (Relative size of the dots correspond to the relative number of deaths for each cause.)
Other cohort studies have shown associations between exposure to fine PM and increased risk of cardiovascular death.
Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

Kristin A. Miller, M.S., David S. Siscovick, M.D., M.P.H., Lianne Sheppard, Ph.D., Kristen Shepherd, M.S., Jeffrey H. Sullivan, M.D., M.H.S., Garnet L. Anderson, Ph.D., and Joel D. Kaufman, M.D., M.P.H.
Nurses’ Health Study:
• Puett et al. Am. J. Epidemiology 2008

Stronger association with CVD than with all cause.
**Netherlands, Germany, Norway studies:**
Beelen et al. EHP 2008
Gehring et al. Epidemiology 2006
Naess et al. Am. J. Epidemiology 2007

Again, positive associations, generally stronger for cardiovascular disease.

Brunekreef (summary paper)
JESEE 2007
U.S. Medicare Cohort Studies:

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

Cohorts of Medicare participants cities of the 6-cities and ACS study, plus all U.S.
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Intervention/natural experiment (months-years)

Controlled experimental human and animal
Southern California Children’s Health Study

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

W. James Gauderman

John Peters

David Bates, Advisor
Southern California Children’s Health Study, has shown that air pollution impacts lung development in children.

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

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

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

Evaluate changes in Life Expectancy with changes in PM$_{2.5}$ for the 2-decade period of approximately 1980-2000.
Covariates included in the regression models

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

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

Proxy cigarette smoking variables—available for all 211 counties

- COPD mortality rates
- Lung Cancer mortality rates

Survey-based metro-area estimates of smoking prevalence

- National Health Interview Survey (1978-1980)
- Matching data available for only 24 of 51 metro areas
Clustered standard errors (clustered by the 51 metro areas) were estimated for all models except for analysis that included only the 51 largest counties in each metro area.
A 10 µg/m³ decrease in PM$_{2.5}$ was associated with a 7.3 (± 2.4) month increase in life expectancy. This increase in life expectancy persisted even after controlling for socio-economic, demographic, or smoking variables.
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Cardiovascular disease as part of chronic and acute inflammatory processes.

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

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

Ridker PM. 2001;103:1813-1818.
Fine Particulate exposure

↓

Pulmonary and systemic inflammation and oxidative stress (along with blood lipids)

↓

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

• Acute airway injury and inflammation in rats and humans

• *In vitro* oxidative stress and release of proinflammatory mediators by cultured respiratory epithelial cells

• Differential toxicities of PM when the mill was operating versus when it was not (metals content and mixtures?)
A series of studies by van Eeden, Hogg, Suwa et al. (1997-2002) suggest:

PM exposure
↓
Pulmonary inflammation
↓
Systemic inflammatory responses (including release of inflammatory mediators, bone marrow stimulation and release of leukocytes and platelets)
↓
Progression and destabilization of atherosclerotic plaques

In rabbits naturally prone to develop atherosclerosis they found that:

PM exposure
↓↓
Accelerated progression of atherosclerotic plaques with greater vulnerability to plaque rupture
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
Many studies using various study designs and approaches with companion statistical modeling approaches and techniques have provided remarkably coherent evidence.

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**Common Statistical Model Approaches**

- Simple Comparative Stats, Graphs
- Poisson reg., (GAMs, smooths for time, weather etc.)
- Linear and Logistic Reg., (fixed effects, temporal autocorr., etc.)
- Cox Proportional Hazards models (random effect, spatial autocorr., etc.)
- Conditional Logistic Reg.
- Various regression modeling strategies (fixed effects, mixed models, etc.)
### Table 6. Overall Summary of Epidemiological Evidence of the Cardiovascular Effects of PM$_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure at Ambient Levels

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

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

<table>
<thead>
<tr>
<th>Animal Studies</th>
<th>Human Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>General “Intermediary” pathways whereby PM inhalation can instigate extrapulmonary effects on the cardiovascular system</td>
<td>├───────────┼───┤</td>
</tr>
<tr>
<td>Pathway 1: Instigation of systemic proinflammatory responses</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Pathway 2: Alterations in systemic ANS balance/activity</td>
<td>↑</td>
</tr>
<tr>
<td>Pathway 3: PM and/or associated constituents directly reaching the systemic circulation</td>
<td>↑</td>
</tr>
<tr>
<td>Specific biological mechanisms directly responsible for triggering cardiovascular events</td>
<td>│</td>
</tr>
<tr>
<td>Vascular dysfunction or vasoconstriction</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Enhanced thrombosis or coagulation potential</td>
<td>↑↑</td>
</tr>
<tr>
<td>Elevated arterial BP</td>
<td>↑↑</td>
</tr>
<tr>
<td>Enhanced atherosclerosis or plaque vulnerability</td>
<td>↑</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>↑</td>
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</tbody>
</table>
This presentation not organized chronologically, but methodologically

Studies of short-term exposure (hours-days)
- Episode
- Population-based daily time-series
- Panel-based acute exposure
- Case-crossover

Studies of long-term exposure (years-decades)
- Population-based cross-sectional
- Cohort-based mortality
- Cohort- and panel-based morbidity
- Case-control studies

Intervention/natural experiment (months-years)

Controlled experimental human and animal

Any Questions?
Adjusted Relative Risk

1.0

1.5

2.0

Estimated daily dose of PM2.5, mg

18-22 cigs/day

Pack-a-day smoker:
RR ~ 2
Daily inhaled dose ~ 240 mg

Live in polluted city or
With smoking spouse
RR ~ 1.15 – 1.35
Daily inhaled dose ~ 0.2–1.0 mg
Figure 1. Adjusted relative risks (and 95% CIs) of IHD (light gray), CVD (dark gray), and CPD (black) mortality plotted over estimated daily dose of PM$_{2.5}$ from different increments of current cigarette smoking. Diamonds represent comparable mortality risk estimates for PM$_{2.5}$ from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General’s report and from the INTERHEART study.
Exposure from

Second hand cigarette smoke:
Stars, from 2006 Surgeon General Report and INTERHEART study

And air pollution:
Hex, from Womens Health Initiative cohort
Diamonds, from ACS cohort
Triangles, Harvard Six Cities cohort

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