Global Health Impact of Air Pollution: Epidemiological Evidences and Biological Mechanisms

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Daytime in London, December 1952

Particle levels – 3,000 µg/m³

Source: National Archives
1952 London Fog Episode

Total Deaths

Pollution Concentration (mg/m³) vs Deaths per day

Smoke (mg/m³)
Sulfur Dioxide
Deaths/Day

December 1952

4000 extra deaths in the week
Effects of PM$_{10}$ on Daily Mortality

**Estimates from meta analysis**

- 29 cities (Levy et al. 2000)
- Unadjusted (Anderson et al. 2005)
- Publication bias adjusted (Anderson et al. 2005)
- 18 Latin Am. studies (PAHO 2005)

**Estimates from Multicity studies**

- 6 U.S. cities (Klemm and Mason 2003)
- 8 Canadian cities (Burnett and Goldberg 2003)
- 10 U.S. cities (Schwartz 2000, 2003)
- 10 U.S. cities, case-crossover (Schwartz 2004)
- NMMAPS, 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)
- 9 Californian cities (Ostro et al. 2006)
- 10 U.S. cities (Schwartz 2004)
- 14 U.S. cities, case-crossover (Schwartz 2004)
- 7 Korean cities (Kim et al. 2000)
- 13 Japanese cities (Ono et al. 2003)
- APHEA-2, 9-15 European cities (Katsouyanni et al. 2003)
- 9 French cities (Le Tertre et al. 2002)

**Estimates from review of Asian Lit**

- 8 studies (HEI Report, Table TS2)

**Estimates from PAPA studies**

- 4 studies (HEI Report, Table TS2)

**Estimates from Asian Lit incorporating PAPA studies**

- 8 studies (HEI Report, Table TS2)
% Change in daily emergency admissions for cardiovascular disease associated with a 10 µg/m³ increase in daily PM$_{10}$ concentration
Time Series Analyses

- Time-series studies assess the association of short-term variation in pollution and health outcomes within the same geographical area.

- Examines associations over time rather than space.

- Is the association causal?
Health Effects of Ambient Air Pollution:

Epidemiological Evidence from Intervention Studies

Effect of the coal sale ban in Dublin City on black smoke and SO$_2$
Effects of coal ban in Dublin on mortality rates

Clancy et al, Lancet 2002

-6% post-ban

-10% post-ban

-16% post-ban
Intervention Study in Hong Kong

Over a weekend in July 2000, all power plants and vehicles started to use fuel oil with < 0.5% sulfur
SO$_2$ and RSP sulfate in Kwai Tsing (solid line) and Southern districts (dotted line)

From Wong et al, 1998, JECH
Intervention Study in Hong Kong: some findings (Hedley et al 2002, Lancet)

• Within the 1st 24 months, the intervention led a significance decline in annual death rates: 2.1% from all causes, 3.9% from respiratory, and 2.0% from cardiovascular

• Average gain in life expectancy per year was 20 days (females) and 41 days (males)
Coal heating and cooking stove with chimney installed for winter.
Improved Stoves Brought to Xuanwei County in early 1980s

- The reduction in particle levels was ~a factor of three.
- Reduction in lung cancer was ~40% in men and ~45% in women.
- Reduction in COPD rates was also significant in both men and women.
Long Term Effects: Cross-sectional Studies

• Cross-sectional studies assess the association of long-term exposure in pollution and health outcomes across different communities.

• Examines associations over space and (over time if there is a longitudinal component).

• Is the association causal?
Harvard Six Cities Studies

- Watertown
- Portage
- St. Louis
- Topeka
- Steubenville
- Kingston
Increase in Lifetime Mortality Risk per 6.5 µg/m³ PM$_{2.5}$
Decreasing mortality rate ratios & decreasing pollution

Adjusted ORs and 95% CIs of symptoms and respiratory diseases in Swiss Surveillance Program of Childhood Allergy and Respiratory Symptoms with respect to air pollution and climate associated with a decline of 10 μg/m³ PM$_{10}$ levels (A). 1. Mean change in adjusted prevalence2 (1998-2001 to 1992-1993) versus mean change in regional annual averages of PM10 (1997-2000 to 1993) for chronic cough, across nine SCARPOL regions.
Biological Mechanisms of Air Pollution Health Effects
Potential pathways for the effects of PM on the respiratory system

PM Core and Soluble Components

- Irritant Receptors
- Altered Lung Function
- AHR and Airway Remodeling
- Allergic Asthma and Other Allergic Disorders
- Impaired Host Defense and Infections
- Progression of Pre-existing Lung Disease
- DNA Damage and Lung Cancer

ROS/RNS

Pulmonary Inflammation and Injury

Death or Hospitalization for Asthma, Pneumonia, COPD and Lung Cancer
Potential pathways for the effects of PM on the cardiovascular system

Brook et al, Circulation 109:2655-2671, 2004
Exploring Biological Mechanisms of Air Pollution Health Effects in Humans
Controlled Environmental Facility at EOHSI
Oxford Street, London, UK (Exposure Site)
Hyde Park, London (Control Site)
Subjects, accompanied by study staff, walking at control site
Personal Exposure Measurement Set-up
Respiratory Effects of Exposure to Diesel Traffic in Persons with Asthma

James McCreanor, M.R.C.P., Paul Cullinan, M.D., Mark J. Nieuwenhuijsen, Ph.D., James Stewart-Evans, M.Sc., Eleni Malliarou, M.Sc., Lars Jarup, Ph.D., Robert Harrington, M.S., Magnus Svertengren, M.D., In-Kyu Han, M.P.H., Pamela Ohman-Strickland, Ph.D., Kian Fan Chung, M.D., and Junfeng Zhang, Ph.D.
Findings -2

Hypothesis (2): The worsening of asthma is accompanied by increased oxidative stress and inflammation of the lungs.

Evidence found on neutrophilic inflammation, airway acidification, and oxidative stress with increases in

- Exhaled breath condensate pH
- Exhaled breath condensate 8-isoprostane
- Sputum myeloperoxidase (MPO)
- Sputum neutrophils

See figures to follow....
The Beijing HEART Study

Health Effects of Air Pollution Reduction Trial
Investigators

UMDNSJ: J Zhang, H Kipen, D Rich, S Diehl, S Lu, P Ohman-Strickland, J Tong, J Gong, K McNeil, etc.

Peking University: T Zhu, G Wang, P Zhu, W Huang, X Tang, M Hu, Y Wang, etc.

University of Southern California: D Thomas
Acknowledgement

- Study participants
- Lab and field technicians, nurses, graduate students

China Natural Science Foundation Committee

Funding Agencies

- Health Effects Institute: 4760-RPFA05-3
- NIEHS/NIH: 1 R01 ES015864
- China Natural Science Foundation: 20637020
- Beijing Environmental Protection Bureau
Study Subjects

- Young adults: 131 nonsmoking, healthy medical residents of Peking University 1st Hospital
- Panel study design
Peking University First Hospital
HEART Study Schedule

Pre-Olympics

V1
6/10 to 6/23

V2
6/24 to 7/7

During-Olympics

V3
8/4 to 8/15

V4
8/16 to 8/29

Post-Olympics

V5
10/6 to 10/17

V6
10/20 to 10/31

July 20, 2008

September 24, 2008
First Hospital
Air Monitoring Site
## On-campus Air Pollution Measurements

<table>
<thead>
<tr>
<th>Species</th>
<th>Sampling/Monitoring equipment</th>
<th>Time resolution</th>
<th>Principle/equipment of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$<em>{10}$ and PM$</em>{2.5}$ mass</td>
<td>MetOne/BAM 1020</td>
<td>continuous</td>
<td>$\beta$-radiation attenuation</td>
</tr>
<tr>
<td>PM$<em>{10}$ and PM$</em>{2.5}$ mass</td>
<td>Cyclone/quartz fiber filter/Teflon filter</td>
<td>24 hours</td>
<td>Gravimetric</td>
</tr>
<tr>
<td>PM number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 nm-800 nm</td>
<td>TDMPS</td>
<td>continuous</td>
<td>Twin Differential Mobility Particle Sizer</td>
</tr>
<tr>
<td>500 nm-10 $\mu$m</td>
<td>APS</td>
<td>continuous</td>
<td>Aerosol Particle Sizer</td>
</tr>
<tr>
<td>Black Carbon in PM$_{2.5}$</td>
<td>Cyclone/MAAP</td>
<td>0.5 hr (semi-continuous)</td>
<td>Multi-Angle-Absorption-Photometer Thermal optical reflectance (TOR) analyzer</td>
</tr>
<tr>
<td>EC/OC in PM$_{2.5}$</td>
<td>Cyclone/quartz fiber filter</td>
<td>24 hours</td>
<td>GC/MS</td>
</tr>
<tr>
<td>PAHs in PM$_{2.5}$</td>
<td>Cyclone/Teflon filter</td>
<td>24 hours</td>
<td>IC</td>
</tr>
<tr>
<td>Ions in PM$_{2.5}$</td>
<td>Cyclone/Teflon filter</td>
<td>24 hours</td>
<td>ICP/MS</td>
</tr>
<tr>
<td>Metals in PM$_{2.5}$</td>
<td>Cyclone/Teflon filter</td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O$_3$</td>
<td>Ecotech EC9810B</td>
<td>continuous</td>
<td>UV detector</td>
</tr>
<tr>
<td>SO$_2$</td>
<td>Ecotech EC9850B</td>
<td>continuous</td>
<td>Fluorescence detector</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>Ecotech EC9841B</td>
<td>continuous</td>
<td>Chemiluminescence detector</td>
</tr>
<tr>
<td>CO</td>
<td>Ecotech EC9830B</td>
<td>continuous</td>
<td>IR detector</td>
</tr>
</tbody>
</table>
# Measurements of Biomarkers in HEART

<table>
<thead>
<tr>
<th>Physiological function/pathway/domain</th>
<th>Specimen type</th>
<th>Collection/measurement duration</th>
<th>Biomarker</th>
<th>Principle/equipment of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary inflammation and oxidative stress</td>
<td>Exhaled breath condensate</td>
<td>20 min</td>
<td>pH</td>
<td>pH meter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8-Isoprostane</td>
<td>ELISA based assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nitrite + nitrate</td>
<td>HPLC-UV</td>
</tr>
<tr>
<td></td>
<td>Exhaled breath</td>
<td>5 min</td>
<td>Exhaled nitric oxide (eNO)</td>
<td>NO\textsubscript{x} chemiluminescence analyzer</td>
</tr>
<tr>
<td>Autonomic tone</td>
<td>N/A</td>
<td>30 min</td>
<td>Heart rate variability (HRV)</td>
<td>Holter Analysis Systems</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>Blood</td>
<td>~5 min</td>
<td>Vascular NO production – blood nitrite (+nitrate)</td>
<td>HPLC-UV</td>
</tr>
<tr>
<td>Endothelial derived procoagulation</td>
<td>Blood</td>
<td>~2 min</td>
<td>von Willebrand Factor</td>
<td>ELISA based assay</td>
</tr>
<tr>
<td>Platelet function</td>
<td>Blood</td>
<td>~2 min</td>
<td>Soluble CD62P</td>
<td>ELISA based assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sCD40L</td>
<td>ELISA based assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platelet aggregation</td>
<td>Photometric aggregometer</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Blood</td>
<td>~2 min</td>
<td>White blood cell (WBC)</td>
<td>Standard automated clinical methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma C-reactive protein</td>
<td>ELISA based assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma fibrinogen</td>
<td>Immunological based chemistry assay</td>
</tr>
<tr>
<td>Systemic oxidative stress</td>
<td>Urine</td>
<td>~1 min</td>
<td>8-Hydroxy-2'-deoxyguanosine (8-OHdG)</td>
<td>HPLC-UV-MS</td>
</tr>
</tbody>
</table>
**Air Pollutant Concentrations and Percent Changes**

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Pre-Olympic (Jun. 1 - Aug. 7)</th>
<th>During-Olympic (Aug. 8 - Sep. 17)</th>
<th>Post-Olympic (Sep. 18 - Oct. 31)</th>
<th>(dur-pre)/pre%</th>
<th>(post-dur)/dur%</th>
<th>(post-pre)/pre%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$($\mu$g/m$^3$)</td>
<td>98.2±42.1</td>
<td>64.1±30.0</td>
<td>72.4±49.8</td>
<td>-34.7</td>
<td>+12.9</td>
<td>-26.3</td>
</tr>
<tr>
<td>SO$_2$(ppb)</td>
<td>11.5±12.6</td>
<td>4.6±2.5</td>
<td>6.8±3.2</td>
<td>-60.0</td>
<td>+47.8</td>
<td>-19.0</td>
</tr>
<tr>
<td>NO$_2$(ppb)</td>
<td>21.2±7.2</td>
<td>20.2±8.6</td>
<td>37.8±16.1</td>
<td>-4.7</td>
<td>+87.1</td>
<td>+66.1</td>
</tr>
<tr>
<td>NO$_x$(ppb)</td>
<td>24.6±8.9</td>
<td>23.2±10.8</td>
<td>59.8±29.4</td>
<td>-5.7</td>
<td>+157.8</td>
<td>+140.6</td>
</tr>
<tr>
<td>CO(ppm)</td>
<td>1.0±0.4</td>
<td>0.6±0.2</td>
<td>0.7±0.6</td>
<td>-40.0</td>
<td>+16.7</td>
<td>-33.3</td>
</tr>
<tr>
<td>O$_3$(ppb)</td>
<td>36.0±15.6</td>
<td>35.9±14.4</td>
<td>15.8±6.2</td>
<td>-0.3</td>
<td>-56.0</td>
<td>-48.2</td>
</tr>
<tr>
<td>EC</td>
<td>3.2±1.0</td>
<td>1.8±0.7</td>
<td>4.8±2.3</td>
<td>-43.8</td>
<td>+166.7</td>
<td>+50.0</td>
</tr>
</tbody>
</table>
Exhaled Nitric Oxide (eNO): A Marker of Pulmonary Inflammation

![Graph showing eNO concentration (ppb) across Olympic periods: Pre-Olympic, During-Olympic, Post-Olympic.](image)
Date

Olympics Started
8/8/08

Paralympics ended
9/17/08

Pollution Controls
Started 7/21/08

PM2.5 (µg/m³)

6/1 6/16 7/1 7/16 7/31 8/15 8/30 9/14 9/29 10/14 10/29
## Biomarker-Pollutant Associations

<table>
<thead>
<tr>
<th>Physiological Function</th>
<th>Biomarker</th>
<th>PM$_{2.5}$</th>
<th>CO</th>
<th>NO$_{2}$</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Inflammation*</td>
<td>Fibrinogen</td>
<td>% Change (95% CI)</td>
<td>p value</td>
<td>% Change (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8 (-0.6, 2.3)</td>
<td>0.24</td>
<td>0.6 (-0.5, 1.6)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>vWF</td>
<td>3.8 (1.4, 6.2)</td>
<td>0.002</td>
<td>6.0 (4.3, 7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endothelial/Vascular Function*</td>
<td>SBP</td>
<td>1.2 (0.4, 2.0)</td>
<td>0.002</td>
<td>1.2 (0.6, 1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary Inflammation/Oxidative Stress**</td>
<td>EBC pH</td>
<td>-1.3 (-2.1, -0.6)</td>
<td>&lt;0.001</td>
<td>-0.5 (-0.9, 0.1)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>EBC Nitrite</td>
<td>9.5 (0.7, 19.1)</td>
<td>0.03</td>
<td>12.4 (5.0, 20.2)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>eNO</td>
<td>44.5 (34.1, 55.8)</td>
<td>&lt;0.001</td>
<td>42.1 (33.8, 50.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic Inflammation/Oxidative Stress***</td>
<td>CRP</td>
<td>Odds Ratio (95% CI)</td>
<td>p value</td>
<td>Odds Ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7 (0.5, 1.0)</td>
<td>0.03</td>
<td>1.1 (0.9, 1.5)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>8-OHdG</td>
<td>1.4 (1.0, 1.9)</td>
<td>0.06</td>
<td>1.3 (1.1, 1.6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Significance of the HEART Study

- Real world study expanding previous studies by: measuring a larger suite of PM components; measuring a larger suite of biomarkers of pathophysiologic response; and examining multiple gene polymorphism – biomarker combinations

- Provide mechanistic explanation of epidemiologic findings on associations between air pollution exposure and cardiopulmonary mortality and morbidity

- Cleaner air during the Beijing Olympics is directly translated to reduced body burden of oxidative stress and inflammation, improved vascular function, and cardioelectrical system, even in young healthy people.
Global Health Impact Of Air Pollution
Global ambient PM$_{2.5}$

Population-weighted geometric mean concentrations (µg/m$^3$)

- Global: 20
- North America: 10
- East Asia: 34

Outdoor air pollution

• Globally (2002), urban outdoor air pollution:
  ~ 800,000 deaths
  ~ 470,000 deaths in China

• Health impacts projected to increase: urbanization, epidemiologic and demographic transitions

<table>
<thead>
<tr>
<th>Table: Traditional, modern, and emerging environmental risk factors in China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Health Effects</strong></td>
</tr>
<tr>
<td><strong>Traditional</strong></td>
</tr>
<tr>
<td>Indoor air pollution from solid fuel combustion</td>
</tr>
<tr>
<td><strong>Modern</strong></td>
</tr>
<tr>
<td>Outdoor air pollution</td>
</tr>
</tbody>
</table>

Reductions in air pollution accounted for up to 15% of increased life expectancy (2.7 years).
Research Questions of Policy Relevance

- Are concentration-response relationships the same in developed and developing countries? (setting proper standards)

- Which pollutants (species or mixtures) are responsible for adverse health effects? (more targeted controls)

- How air pollution exposure interacts with social and behavioral factors in causing adverse health? (public awareness and risk communication)