Air Pollution and Stroke Risk in the WHI

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London Smog, 1952

- In central London the visibility remained below 500 meters continuously for 114 hours and below 50 meters continuously for 48 hours.
- At Heathrow airport visibility remained below 10 m for almost 48 hours from the morning of 6 December.
- Road, rail and air transport were brought to a standstill.
- Theatres had to be suspended when fog in the auditorium made conditions intolerable.
London Smog, 1952
Beijing, 2013
Air Pollution
Sources, Components, Products
Pollutants Regulated by the EPA

- NO$_2$
- Ozone
- CO
- SO$_2$
- Particulate Matter (PM)
- Lead
“…the overall evidence is consistent with a causal relationship between PM$_{2.5}$ exposure and cardiovascular morbidity and mortality.”

“…PM$_{2.5}$ exposure is deemed a modifiable factor that contributes to cardiovascular morbidity and mortality.”
Global Public Health Impact

• In 2010, globally,
  – 3.2 million excess deaths attributable to ambient particulate matter
  – 76.1 million (3.1%) DALYs attributable to ambient particulate matter

Global Public Health Impact


Disability-adjusted life-years (%)
• Stroke is the fourth leading cause of death in the US and a major cause of disability.
• Approximately 800,000 new or recurrent strokes occur annually.
• Direct medical costs of $22.8 billion (2009), with another ~$16 billion in lost productivity.

Go et al. Circulation. 2013
Stroke Types and Subtypes

- 5% subarachnoid haemorrhage
- 15% primary intracerebral haemorrhage
- 80% ischaemic stroke

- Cardiac source of embolism: 20%
- Intracranial small-vessel disease: 25%
- Atherothromboembolism: 50%
- Rare causes: 5%
Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

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Table 3. Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 μg per Cubic Meter in the Level of Fine Particulate Matter (PM$_{2.5}$).※

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>First cardiovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular event†</td>
<td>1816</td>
<td>1.24 (1.09–1.41)</td>
</tr>
<tr>
<td>Coronary heart disease‡</td>
<td>1268</td>
<td>1.21 (1.04–1.42)</td>
</tr>
<tr>
<td>Cerebrovascular disease§</td>
<td>600</td>
<td>1.35 (1.08–1.68)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>584</td>
<td>1.06 (0.85–1.34)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>949</td>
<td>1.20 (1.00–1.43)</td>
</tr>
<tr>
<td>Stroke</td>
<td>554</td>
<td>1.28 (1.02–1.61)</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any death from cardiovascular cause</td>
<td>261</td>
<td>1.76 (1.25–2.47)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>80</td>
<td>2.21 (1.17–4.16)</td>
</tr>
<tr>
<td>Possible diagnosis</td>
<td>59</td>
<td>1.26 (0.62–2.56)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>122</td>
<td>1.83 (1.11–3.00)</td>
</tr>
</tbody>
</table>

Miller et al. NEJM 2007
HR (95% CI) associated with an interquartile range (4 μg/m$^3$) difference in average predicted PM$_{2.5}$ levels.

<table>
<thead>
<tr>
<th></th>
<th>Fatal CHD (746 cases)</th>
<th>Ischemic Stroke (230 cases)</th>
<th>Hemorrhagic Stroke (n=70 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Model</td>
<td>0.97 (0.83, 1.13)</td>
<td>0.74 (0.56, 0.96)</td>
<td>1.33 (0.86, 2.06)</td>
</tr>
<tr>
<td>Full Model</td>
<td>0.97 (0.83, 1.13)</td>
<td>0.76 (0.58, 0.99)</td>
<td>1.35 (0.87, 2.09)</td>
</tr>
</tbody>
</table>
Limitations of Prior Studies of Air Pollution and Stroke

- Long-term exposure
  - Few conducted in US
  - Few consider stroke type or etiology
  - Different exposure models across studies
  - Most focused on a small geographic area
  - Few have identified potentially susceptible subgroups
  - Few have considered pollution sources or mixtures
Prior Studies of Daily PM$_{2.5}$ and Stroke

Cerebrovascular Mortality

Ischemic Stroke Hospitalization

- Faustini et al. (2012), All age
- Franklin et al. (2007), All age
- Kettunen et al. (2007), 65+
- Kettunen et al. (2007), 65+
- Yorifuji et al. (2011), All age
- Zanobetti, A. and J. Schwartz (2009), All age

Relative Risk (95% CI)

- Mechtouff et al. (2012), All age
- Chan et al. (2006), 50+
- Lisabeth et al. (2008), 45+
- O’Donnell et al. (2011), All age
- Villeneuve et al. (2006), 65+
- Wellenius et al. (2012), 21+

Relative Risk (95% CI)
Limitations of Prior Studies

• Short-term exposures
  – Most relied on administrative data
  – Most based on date of hospitalization
  – Few consider stroke type or etiology
  – Most focused on a small geographic area
  – Few have identified potentially susceptible subgroups
  – Few have considered pollution sources or mixtures
Funded Study

- Evaluate the association between ambient air pollution and stroke risk
  - WHI CT and OS + HPFS
  - Long-term and short-term exposures
  - National context
  - Same exposure prediction models in both cohorts
  - Broad suite of pollutants considered
  - Consider cerebrovascular disease vs ischemic stroke vs hemorrhagic stroke
  - Consider ischemic stroke etiology
  - Identify susceptible subgroups
Study Population

- WHI
  - OS and CT components
  - Postmenopausal women recruited 1993-1998 from 40 clinical centers in 24 states and DC
  - ~160,000 women free of CVD at recruitment
  - Cerebrovascular events are centrally adjudicated by medical record review and classified as ischemic or hemorrhagic
  - Ischemic strokes are further classified by TOAST criteria
Study Population

• HPFS
  – National prospective cohort study of 51,529 male health professionals aged 40-75 upon recruitment in 1986
  – Cerebrovascular events are adjudicated through medical record review and classified as ischemic, hemorrhagic, or undetermined
  – Ischemic strokes are further classified as thrombotic or embolic
  – Analyses restricted to 45,358 participants alive and without history of stroke in 1993
Estimating Yearly Pollutant Levels

Bergen et al. *EHP* 20013
# Power for Detecting Effects of Long-Term Exposure

## Table 1: Minimum detectable differences (MDD) per 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MDD 80% power</th>
<th>MDD 90% power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cerebrovascular events</td>
<td>6580</td>
<td>1.10</td>
<td>1.11</td>
</tr>
<tr>
<td>Stroke hospitalizations</td>
<td>5486</td>
<td>1.11</td>
<td>1.13</td>
</tr>
<tr>
<td>Ischemic Strokes</td>
<td>4115</td>
<td>1.13</td>
<td>1.15</td>
</tr>
<tr>
<td>Hemorrhagic Strokes</td>
<td>823</td>
<td>1.30</td>
<td>1.36</td>
</tr>
<tr>
<td>Cerebrovascular deaths</td>
<td>1094</td>
<td>1.26</td>
<td>1.30</td>
</tr>
<tr>
<td><strong>HPFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cerebrovascular events</td>
<td>2117</td>
<td>1.18</td>
<td>1.21</td>
</tr>
<tr>
<td>Stroke hospitalizations</td>
<td>1632</td>
<td>1.21</td>
<td>1.24</td>
</tr>
<tr>
<td>Ischemic Strokes</td>
<td>1089</td>
<td>1.26</td>
<td>1.30</td>
</tr>
<tr>
<td>Hemorrhagic Strokes</td>
<td>159</td>
<td>1.82</td>
<td>2.00</td>
</tr>
<tr>
<td>Cerebrovascular deaths</td>
<td>485</td>
<td>1.41</td>
<td>1.49</td>
</tr>
</tbody>
</table>
Estimating Daily Pollutant Levels
WHI Contextual Data Available

- Residential proximity to major roadways
- Neighborhood SES
- National Land Cover Dataset (tree, vegetation, water, development, wetland)
- Emerald Ash Borer infestation
- Estimates of local population density
- Meteorologic data
WHI Contextual Data Available
Proximity to Major Roadway and Incident HTN in WHI CT
Study Team

- Brown
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  - Duanping Liao
  - Jeff Yanosky
- FHCRC
  - Lesley Tinker
Size Fractions of Ambient Particles

Brook et al. *Circulation* 2004
Figure 2: Relation between OR and the PAF for each studies trigger
PAFs were calculated and reported with their 95% CI (error bars). Not significant triggers show 95% CIs that are lower than 0%. X-axis is log scale, and ORs are given as anti-logs. OR=odds ratio. PAF=population attributable fraction.