Cardiovascular Effects of Household Air Pollution
Evidence and Gaps

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Objectives

• Brief epidemiology overview cardiovascular risk
• Review evidence for association b/w chronic exposure to HAP and CVD with focus on LMIC
• Review evidence for the acute effect of exposure on CVD and risk
• Discuss known mechanisms by which acute exposure to HAP, specifically PM contributes to increased cardiovascular risk?
• Highlight gaps and opportunities
Epidemiology Linking PM Exposure to Mortality

- The impact of elevated levels of air pollution particles on human health has been repeatedly demonstrated.
  - Meuse Valley, Belgium in 1930
  - Donora, Pennsylvania in 1948
- Levels were $>1000 \mu g/m^3$
- Large increases in human mortality
- Clean Air Act resulted in 1970.
Epidemiology linking PM exposure to mortality

- Large cohort studies in mid 1990’s
- Long-term health effects of PM
  - Pope CA, et al. *JAMA* 2002; 287: 1132
- Short term health effects of PM
Harvard Six Cities Study

• A cohort of 8111 adults from six US cities
• 14 to 16 years of follow-up

• Results
  – Correlation between PM levels and mortality
  – Residents of the most polluted city had a 26% increased risk of premature mortality compared to those of the least polluted city

## Harvard Six Cities Study

<table>
<thead>
<tr>
<th></th>
<th>Portage WI</th>
<th>Topeka KS</th>
<th>Watertwon MA</th>
<th>Harriman TN</th>
<th>St. Louis MO</th>
<th>Steubenville OH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalable Particles (µg/m³)</strong></td>
<td>18.2</td>
<td>26.4</td>
<td>24.2</td>
<td>32.5</td>
<td>31.4</td>
<td>46.5</td>
</tr>
<tr>
<td><strong>Fine Particles (µg/m³)</strong></td>
<td>11</td>
<td>12.5</td>
<td>14.9</td>
<td>20.8</td>
<td>19</td>
<td>29.6</td>
</tr>
</tbody>
</table>
Six cities study: probability of survival

The Lancet 2012;380:2197–223
## Six cities study: cause of death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage of Total</th>
<th>Current Smokers†</th>
<th>Former Smokers‡</th>
<th>Most vs. Least Polluted City</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100</td>
<td>2.00 (1.51–2.65)</td>
<td>1.39 (1.10–1.75)</td>
<td>1.26 (1.08–1.47)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>8.4</td>
<td>8.00 (2.97–21.6)</td>
<td>2.54 (0.90–7.18)</td>
<td>1.37 (0.81–2.31)</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>53.1</td>
<td>2.30 (1.56–3.41)</td>
<td>1.52 (1.10–2.10)</td>
<td>1.37 (1.11–1.68)</td>
</tr>
<tr>
<td>All others</td>
<td>38.5</td>
<td>1.46 (0.89–2.39)</td>
<td>1.17 (0.80–1.73)</td>
<td>1.01 (0.79–1.30)</td>
</tr>
</tbody>
</table>

*The city with the highest level of air pollution (indicated by the level of fine particles) was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. CI denotes confidence interval. Rates have been adjusted for age, sex, smoking, education, and body-mass index.

†The risk of death for a current smoker with approximately the average number of pack-years of smoking at enrollment (25 pack-years), as compared with that for a nonsmoker.

‡The risk of death for a former smoker with approximately the average number of pack-years of smoking at enrollment (20 pack-years), as compared with that for a nonsmoker.
Global Burden of Cardiovascular Disease

- CVD is the leading cause of mortality globally
- Over 80% of CVD mortality occur in LMIC
- 32% of female and 27% of male deaths/ yr are related to CVD
- 16% of YLL are associated with CVD
- Trend will worsen with projected increase in NCD
- Diet, HAP, tobacco smoking and HTN are top risk factors for CVD

Biomass users are prone to HTN and CHD

- 480 Pre-menopausal Indian women who live 5K from any ambient pollution source recruited
  - 244 Biomass; 236 LPG; Use for at least 5 yrs.
- PM2.5 and PM10 levels measured
- BP measured and laboratory studies performed
  - Oxidized LDL (oxLDL)
  - Platelet aggregation determined
  - Anti-cardiolipin antibodies (IgG and IgM)

PM2.5 Levels significantly higher in Biomass homes

Oxidized LDL Levels (oxLDL) higher in Biomass users

HTN is more common in Biomass Users

<table>
<thead>
<tr>
<th>Arterial blood pressure</th>
<th>LPG user ( n = 236 )</th>
<th>Biomass user ( n = 244 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (SBP &lt;120 and DBP &lt;80 mmHg)</td>
<td>69.9</td>
<td>31.1*</td>
</tr>
<tr>
<td>Pre-hypertension (SBP 120–139 and DBP 80–89 mmHg)</td>
<td>19.1</td>
<td>39.3*</td>
</tr>
<tr>
<td>Hypertension (SBP ≥140 and/or DBP ≥90 mmHg)</td>
<td>11.0</td>
<td>29.5*</td>
</tr>
<tr>
<td>Systolic (SBP ≥140 and DBP &lt;90 mmHg)</td>
<td>5.9</td>
<td>9.8*</td>
</tr>
<tr>
<td>Diastolic (DBP ≥90 and SBP &lt;140 mmHg)</td>
<td>0.9</td>
<td>3.7*</td>
</tr>
<tr>
<td>Systolic + diastolic (SBP ≥140 and DBP ≥90 mmHg)</td>
<td>4.2</td>
<td>16.0*</td>
</tr>
</tbody>
</table>

Results are expressed as percentage of subjects in each group; \(*P < 0.05\) compared with LPG users in Chi-square test. DBP, diastolic blood pressures; LPG, liquefied petroleum gas; SBP, systolic blood pressure.
HTN risk is higher in Biomass users

<table>
<thead>
<tr>
<th>Variables</th>
<th>PM$_{10}$ OR (95% CI)*</th>
<th>PM$_{2.5}$ OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.35 (1.14–1.95)</td>
<td>1.41 (1.22–2.08)</td>
</tr>
<tr>
<td>Increase in the number of P-selectin-expressing platelets in circulation</td>
<td>2.63 (1.73–3.58)</td>
<td>2.89 (2.15–4.11)</td>
</tr>
<tr>
<td>Increase in platelet aggregation</td>
<td>1.91 (1.33–2.69)</td>
<td>2.04 (1.68–2.35)</td>
</tr>
<tr>
<td>Rise in of oxidized low-density lipoprotein level in plasma</td>
<td>2.24 (1.86–3.89)</td>
<td>2.66 (1.98–4.13)</td>
</tr>
<tr>
<td>Depletion of erythrocyte SOD</td>
<td>1.19 (1.04–1.37)</td>
<td>1.25 (1.08–1.46)</td>
</tr>
<tr>
<td>Up-regulation of ROS generation in leukocytes</td>
<td>1.51 (1.24–2.21)</td>
<td>1.72 (1.34–2.62)</td>
</tr>
<tr>
<td>Rise in serum anticardiolipin IgG</td>
<td>1.33 (1.12–1.57)</td>
<td>1.58 (1.19–1.84)</td>
</tr>
<tr>
<td>Rise in serum anticardiolipin IgM</td>
<td>1.19 (1.06–1.31)</td>
<td>1.22 (1.10–1.44)</td>
</tr>
</tbody>
</table>

Platelet aggregation is heightened by Biomass exposure

Biomass fuel use increases CVD Risk

• Cross sectional study in Puno, Peru
  • 112 Clean fuel users, 156 Biomass fuel users
  • 24h indoor personal PM2.5 measurement in random 84
  • PM2.5 280 vs. 14µg/m³; p<0.001

• Blood pressure
  – SBP 111 vs. 118; p<0.001. DBP 71 vs. 77
  – Mean SBP difference=9.2 mmHg, 95% CI 5.4 to 13.0; p<0.001).

• Carotid ultrasound
  • Carotid intima thickness
  • Carotid atherosclerotic plaques

Painschab et al: Heart 2013: 99; 984-91
Biomass fuel use compromises carotid lumen

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted values, mean (SD) or %</th>
<th></th>
<th></th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=266)</td>
<td>Clean fuel (n=112)</td>
<td>Biomass fuel (n=154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CIMT</td>
<td>0.63 (0.13)</td>
<td>0.60 (0.12)</td>
<td>0.66 (0.13)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Max CIMT</td>
<td>0.74 (0.14)</td>
<td>0.71 (0.14)</td>
<td>0.76 (0.14)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Prevalence of plaques</td>
<td>21.1</td>
<td>14.3</td>
<td>26.1</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>
Stove Intervention reduced indoor PM levels

Alexander DA et al; Air Quality, Atmosphere and Health 2014; 7;2;
Decrease in 24 hr. PM correlated with SBP reduction

Alexander DA et al; Air Quality, Atmosphere and Health 2014; 7;2;
Why does Exposure to PM pose such a huge CVD Risk?
HUMAN HAIR
50-70 µm (microns) in diameter

PM2.5
Combustion particles, organic compounds, metals, etc.
< 2.5 µm (microns) in diameter

PM10
Dust, pollen, mold, etc.
< 10 µm (microns) in diameter

90 µm (microns) in diameter
FINE BEACH SAND

Image courtesy of the U.S. EPA
Transition Metals in Bangladesh Biomass Smoke

- Fe: 49%
- Mn: 2%
- Ni: 9%
- Other: 3%
- Al: 36%
- Pb: 1%
- Sb: 2%
- Cr: 0%
- Co: 0%
- Cd: 1%
- As: 0%

Courtesy Faruque Pravez, Columbia University
## Trace Metals in Bangladesh Biomass Smoke

<table>
<thead>
<tr>
<th>Element</th>
<th>Avg. conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>12,713</td>
</tr>
<tr>
<td>As</td>
<td>83</td>
</tr>
<tr>
<td>Cd</td>
<td>275</td>
</tr>
<tr>
<td>Co</td>
<td>57</td>
</tr>
<tr>
<td>Cr</td>
<td>37</td>
</tr>
<tr>
<td>Fe</td>
<td>17,257</td>
</tr>
<tr>
<td>Mn</td>
<td>848</td>
</tr>
<tr>
<td>Ni</td>
<td>3,019</td>
</tr>
<tr>
<td>Pb</td>
<td>190</td>
</tr>
<tr>
<td>Sb</td>
<td>873</td>
</tr>
<tr>
<td>Se</td>
<td>13</td>
</tr>
<tr>
<td>Ve</td>
<td>43</td>
</tr>
</tbody>
</table>
## Characteristics of PM

<table>
<thead>
<tr>
<th></th>
<th>Düsseldorf PM</th>
<th>Washington DC PM</th>
<th>ROFA</th>
<th>Mt St Helen’s dust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>19.7</td>
<td>17.7</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ash</td>
<td>63.2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cobalt</td>
<td>103</td>
<td>16.4</td>
<td>44</td>
<td>10</td>
</tr>
<tr>
<td>Copper</td>
<td>48</td>
<td>223</td>
<td>107</td>
<td>164</td>
</tr>
<tr>
<td>Chromium</td>
<td>104</td>
<td>211</td>
<td>53</td>
<td>N/A</td>
</tr>
<tr>
<td>Iron</td>
<td>14,521</td>
<td>2,980</td>
<td>1,254</td>
<td>376</td>
</tr>
<tr>
<td>Manganese</td>
<td>21</td>
<td>237</td>
<td>26</td>
<td>7600</td>
</tr>
<tr>
<td>Nickel</td>
<td>1519</td>
<td>166</td>
<td>2261</td>
<td>N/A</td>
</tr>
<tr>
<td>Titanium</td>
<td>131</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vanadium</td>
<td>2767</td>
<td>345</td>
<td>2611</td>
<td>1.2</td>
</tr>
</tbody>
</table>
HAP/Ambient PM

- Pulmonary Reflexes
- Autonomic Nervous System
  - Automaticity
  - Conduction
  - Repolarization
  - Heart Rate
  - Rhythm
- Pulmonary Inflammation
  - Oxidative Stress
  - Endothelial Dysfunction
  - Atherosclerosis Progression And Plaque Instability
  - Plaque Rupture
- Leukocyte/Platelet Activation
  - Acute Phase Response/Activation of Coagulation
  - Thrombosis

Myocardial Infarction

Direct effect on the Heart

Adapted from Brooks et al. Circulation. 2010; 121: 2331-2378
Exposure to PM causes a prothrombotic state

PM causes intravascular thrombin generation

PM accelerates arterial thrombosis

Pre-FeCl₃

Post-FeCl₃

PM accelerates arterial thrombosis

IL-6 and its association with ischemic heart disease

- IL-6 and ischemic heart disease
  - IL-6 levels correlate with risk factors for CAD
  - IL-6 induces acute phase reactants including CRP, which is a surrogate marker of IL-6
  - Both IL-6 and CRP are independently associated with increased relative risk for mortality from CV disease
IL-6 and its association with hemostasis

• IL-6 and coagulation cascade
  – Plays a important role in hemostasis and can induce a thrombophilic state
  – IL-6 may increase risk of both arterial and venous thrombosis
  – Similar association has not been shown with other cytokines (IL-1, IL-2, TNFα)
IL-6 and its association with hemostatic factors

- Fibrinogen
  - Antithrombin
    - Thrombin
    - Factor Xa
    - Prothrombin
  - Tissue factor
    - Factor X
    - Factor VIII
      - Protein S
      - vWF
    - IL-6
Exposure to PM increases BAL fluid IL-6 levels

IL-6 is required for prothrombotic state induced by PM
Exposure to PM alters blood coagulation in humans

- Individuals in areas with higher PM concentrations have lower prothrombin times than carefully matched controls.
- The levels of ambient PM and the distance to major roadways increases the risk of venous thromboembolism.
- PM exposure was associated with increased markers of inflammation (CRP) and abnormalities in blood coagulation in normal individuals and men with coronary artery disease.
Ambient PM

Pulmonary Reflexes

Autonomic Nervous System

Automaticity
Conduction
Repolarization

Heart Rate
Rhythm

Pulmonary Inflammation

Oxidant Stress
Endothelial Dysfunction

Leukocyte/
Platelet Activation

Atherosclerosis
Progression
And Plaque Instability

Plaque Rupture

Acute Phase
Response/Activation of Coagulation

Thrombosis

Myocardial Infarction

Direct effect on the Heart

Adapted from Brooks et al. Circulation. 2010; 121: 2331-2378
Exposure to PM elevates catecholamines

β-adrenergic blockade prevents the prothrombotic effect of PM
Loss of $\beta_2$-adrenergic receptor prevents prothrombotic effects of PM

- **BALF IL-6 (pg/ml)**
  - $\beta_1^{+/+}\beta_2^{+/+}$ controls show higher levels compared to $\beta_1^{-/-}\beta_2^{+/-}$.
  - $\beta_1^{+/-}\beta_2^{+/+}$ and $\beta_1^{+/-}\beta_2^{-/-}$ show intermediate levels.

- **Plasma TAT (ng/ml)**
  - $\beta_1^{+/-}\beta_2^{+/+}$ controls show lower levels compared to $\beta_1^{-/-}\beta_2^{+/-}$.
  - $\beta_1^{+/-}\beta_2^{-/-}$ shows higher levels.

- **Carotid blood flow (%)**
  - $\beta_1^{+/-}\beta_2^{+/+}$ shows a decrease in blood flow over time compared to controls.
  - $\beta_1^{-/-}\beta_2^{-/-}$ shows a more pronounced decrease in blood flow.
Conclusion

• Chronic exposure to PM from HAP is a major risk factor for CVD
• Acute exposure to PM promotes thrombogenesis and compromises vascular flow
• IL-6, CRP, oxLDL are useful biomarkers for HAP-mediated cardiovascular risk
• Beta blockage might prevent PM-related prothrombotic state
• Larger studies are needed to better define the role of biomarkers in risk assessment
Strategies for the Future

• Defining level of improvement in indoor air quality that will mitigate CVD risk
• Developing biomarkers for early screening and risk stratification
• Defining how effective the available stoves need to be in meeting the challenges of reducing CVD risk
• How important are the transition metals in CVD and inflammation
• Is there a role for augmenting anti-oxidant defense as a strategy?
• 20 men with prior MI, exposed to diesel particulate matter (300 µg/m³) and filtered air for 1 hour.
• Post-exposure stress test and assessment of t-PA
Exposure to diesel exhaust results in myocardial ischemia in men with stable CAD

Cause of NCD Deaths in LMIC

- Neoplasms (cancer) 19%
- Cardiovascular and circulatory disease 46%
- Chronic respiratory disease 13%
- Cirrhosis of the liver
- Digestive diseases (except cirrhosis)
- Neurological disorders
- Mental and behavioral disorders
- Diabetes, urogenital, blood, and endocrine diseases
- Musculoskeletal disorders
- Other noncommunicable diseases

Institute for Health Metrics, GBD 2013
Particulate Matter
Summary of Cohort Studies

Particle exposure is estimated to account for:
- 4,000,000 premature deaths per year worldwide.
- 40,000-60,000 excess deaths per year in the US.
- In the developed world, PM levels have declined in the last four decades but levels in the developing world remain high.
- Mortality associated with ambient PM is largely due to increased ischemic/thrombotic cardiovascular events.