PM and CVD Morbidity: Clinical Effects, Subclinical Effects, Biomarkers

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Outline

• Particulate matter (PM) – what is it?
• How is it regulated?
• Global burden of disease
• Integrated exposure-response
• PM and cardiovascular effects
• Biological mechanisms
Particulate Matter (PM)

- PM is a mixture, including particles of differing origin (combustion, crustal, biological) and varying size.

- Multiple sources
  - Ultrafines ($\text{PM}_{<0.1}$): Fossil fuel combustion
  - $\text{PM}_{2.5}$: Fossil fuel combustion
  - $\text{PM}_{10-2.5}$: Road dust and crustal material
Particle Size

Human Hair
(60 µm diameter)

Hair cross section (60 µm)

PM10
(10 µm)

PM0.1
(0.1 µm)

PM2.5
(2.5 µm)
Particle deposition

Figure 4: Compartmental deposition of particulate matter
Diesel Exhaust

- Mixture of oxidant gases and particulate matter (PM)
- PM has a carbon core with surfaces characterized by complex chemistry and physical structure
- Diesel exhaust contains oxidizing agents that can injure cells and lead to inflammation
Diesel Exhaust – What is It?

- Particulate phase (DEP)
  - Mostly elemental carbon (soot)
  - About 20% to 40% adsorbed organic compounds
  - Also sulfate, nitrate, metals, other trace elements
  - The most toxicologically relevant adsorbed compounds (less than 1% of PM by mass):
    - PAHs
    - Nitro-PAHs
    - Oxidized PAH derivatives
  - 92% of mass is in particles smaller than 1 micron
Diesel Emissions

• Nationwide, diesel emissions at ~ 4% of PM$_{2.5}$ inventory (~10% excluding natural and misc. sources)
• In some western cities DEP estimated to be 10% to 20% of total PM$_{2.5}$
• Over decades, off-road diesel has overtaken on-road diesel emissions.
• Recent diesel emissions trends have been relatively stagnant.
Toxic Pollutants in Biomass Fuel Smoke from Simple (poor) Combustion

Similar to tobacco smoke

- PM, CO, NOx
- Free radicals
- Toxic organic compounds: formaldehyde, acrolein, benzene, 1-3 butadiene, PAHs

Naehler et al. J Inhal Tox, 2007
Air Quality Regulation in the U.S.

- Clean Air Act (1963)
- U.S. EPA (1970)
- National Ambient Air Quality Standards
What is a “criteria” pollutant?

• A pollutant for which there is sufficient scientific evidence of health effects to regulate ambient levels.
• The EPA then promulgates a National Ambient Air Quality Standard (NAAQS) for that pollutant.
• A NAAQS must have an adequate margin of safety to protect the most susceptible groups (e.g., children, the elderly, those with pre-existing disease).
What scientific evidence is used?

- Epidemiologic studies
- Controlled human exposure studies
- Animal toxicological studies
Current PM NAAQS

- Particulate Matter (PM$_{10}$)
  - 150 µg/m$^3$ 24-hour

- Particulate Matter (PM$_{2.5}$)
  - 12 µg/m$^3$ annual
  - 35 µg/m$^3$ 24-hour
PM-associated Mortality

• Multiple time-series studies have shown cardiopulmonary mortality to be associated with levels of PM.

• Several longitudinal studies have also linked chronic PM exposure and mortality.
An Association between Air Pollution and Mortality in Six U.S. Cities

Fine-Particulate Air Pollution and Life Expectancy in the United States

Heart Disease and Combustion Particle Doses

From “Mind the Gap,” Smith/Peel, 2010 and Pope et al., 2009
Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013

Lancet 2015;386:2287-2323
Expert position paper on air pollution and cardiovascular disease

David E. Newby¹, Pier M. Mannucci², Grethe S. Tell³, Andrea A. Baccarelli⁴, et al.

European Heart Journal 2015;36:83-93
AIR POLLUTION

Oxidative stress & inflammation

Atheroma
- Plaque progression
  - Plaque rupture

Endothelium
- Endothelial dysfunction
  - Vasoconstriction

Platelets
- Impaired fibrinolysis
  - Thrombosis
- Platelet hyperreactivity
  - Arrhythmia

Heart rhythm
- Arrhythmogenesis?

Myocardial ischaemia and infarction

Cardiovascular death

Population-based studies in many locations have shown cardiac mortality rate to be elevated on the day following high levels of PM.

High levels of PM have also been associated with increased hospital admissions for acute coronary syndrome and/or acute MI.

A case-crossover study linked high levels of PM in the Greater Boston area with an increased risk of MI.

Circulation 2004;109:2655-2671
Epidemiological time series studies of PM$_{2.5}$ and daily mortality and hospital admissions: a systematic review and meta-analysis

R W Atkinson,$^1$ S Kang,$^1$ H R Anderson,$^{1,2}$ I C Mills,$^3$ H A Walton$^{2,4}$

Thorax 2014;69(7):660-5.
PM and Stroke

- Short-term exposure was associated with risk of ischemic stroke in the Greater Boston area.
- Onset of stroke was most strongly associated with traffic-related PM exposures 12-14 hrs before the event.

Wellenius et al. Arch Intern Med 2012;172(3):229-234
### Table 3. HRs (95% CIs) in the full cohort for an increase of 10 μg/m³ in PM$_{2.5}$ (satellite-derived estimates) by cause of death and model specification.

<table>
<thead>
<tr>
<th>Cause of death/model</th>
<th>n$^0$</th>
<th>PM$_{2.5}$ only</th>
<th>PM$_{2.5}$ covariates</th>
<th>PM$_{2.5}$ covariates + ecological covariates</th>
<th>PM$_{2.5}$ covariates + urban/rural indicator</th>
<th>PM$_{2.5}$ covariates + ecological covariates + urban/rural indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonaccidental</td>
<td>192,300</td>
<td>1.07 (1.06, 1.08)</td>
<td>1.12 (1.12, 1.14)</td>
<td>1.11 (1.10, 1.12)</td>
<td>1.14 (1.12, 1.16)</td>
<td>1.15 (1.13, 1.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.06 (1.01, 1.11)</td>
<td>1.12 (1.07, 1.17)</td>
<td>1.06 (1.01, 1.10)</td>
<td>1.12 (1.07, 1.18)</td>
<td>1.10 (1.05, 1.15)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>72,600</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.10 (1.08, 1.12)</td>
<td>1.09 (1.07, 1.11)</td>
<td>1.16 (1.13, 1.18)</td>
<td>1.16 (1.13, 1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.05 (0.99, 1.12)</td>
<td>1.11 (1.03, 1.18)</td>
<td>1.07 (1.00, 1.15)</td>
<td>1.17 (1.09, 1.26)</td>
<td>1.15 (1.07, 1.24)</td>
</tr>
<tr>
<td>Circulatory</td>
<td>74,700</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.10 (1.08, 1.12)</td>
<td>1.09 (1.07, 1.11)</td>
<td>1.15 (1.13, 1.18)</td>
<td>1.16 (1.13, 1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.04 (0.98, 1.11)</td>
<td>1.10 (1.03, 1.17)</td>
<td>1.06 (0.99, 1.14)</td>
<td>1.16 (1.08, 1.25)</td>
<td>1.14 (1.06, 1.22)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>43,400</td>
<td>1.14 (1.12, 1.17)</td>
<td>1.21 (1.19, 1.24)</td>
<td>1.22 (1.19, 1.25)</td>
<td>1.31 (1.27, 1.34)</td>
<td>1.31 (1.27, 1.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.16 (1.06, 1.27)</td>
<td>1.22 (1.11, 1.33)</td>
<td>1.18 (1.08, 1.29)</td>
<td>1.32 (1.20, 1.45)</td>
<td>1.30 (1.18, 1.43)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>13,300</td>
<td>0.94 (0.90, 0.99)</td>
<td>0.99 (0.95, 1.03)</td>
<td>0.97 (0.93, 1.02)</td>
<td>1.05 (0.99, 1.10)</td>
<td>1.04 (0.99, 1.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95 (0.87, 1.04)</td>
<td>1.01 (0.91, 1.13)</td>
<td>0.96 (0.87, 1.07)</td>
<td>1.08 (0.96, 1.21)</td>
<td>1.04 (0.93, 1.16)</td>
</tr>
</tbody>
</table>

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**Risk of Nonaccidental and Cardiovascular Mortality in Relation to Long-term Exposure to Low Concentrations of Fine Particulate Matter: A Canadian National-Level Cohort Study**

Dan L. Crouse,¹ Paul A. Peters,² Aaron van Donkelaar,³ Mark S. Goldberg,⁴ Paul J. Villeneuve,⁵ Orly Brion,¹ Saeeda Khan,² Dominic Odwa Atari,⁷ Michael Jerrett,⁶ C. Arden Pope III,⁷ Michael Brauer,⁷ Jeffrey R. Brook,⁵,⁸ Randall V. Martin,³,¹⁰ David Stieb,¹ and Richard T. Burnett¹

Crouse et al. Environ Health Perspect 2012;120:708-714
PM$_{2.5}$ concentration decreased 27% from the pre-Olympic period to the during the Olympics.

P-selectin decreased by 34% and von Willebrand factor by 13% from the pre-Olympic period to during the Olympics.
Higher levels of residential PM$_{2.5}$ during the follow-up period were associated with greater IMT progressions.
Figure 1. Associations between retinal arteriolar diameter (CRAE) and modeled long-term PM2.5 concentrations after control for covariates.

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000372
PM and Metabolic Syndrome

• Associations between PM$_{2.5}$ exposures and the prevalence of diabetes and diabetes mortality have been observed in the US and Canada
• Several studies in the US and Canada have also found that exposure to PM$_{2.5}$ was associated with an increased risk of incident hypertension
• Several studies have also shown associations between traffic-related air pollution and obesity
Jerrett et al., Prev Med 2010
Risk of Incident Diabetes in Relation to Long-term Exposure to Fine Particulate Matter in Ontario, Canada

Hong Chen, Richard T. Burnett, Jeffrey C. Kwong, Paul J. Villeneuve, Mark S. Goldberg, Robert D. Brook, Aaron van Donkelaar, Michael Jerrett, Randall V. Martin, Jeffrey R. Brook, and Ray Copes

Table 2. HRs (95% CIs) for the association between incident diabetes and a 10-μg/m³ increase in PM$_{2.5}$.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusting for sex and stratified by age, survey year, and region</td>
<td>1.08 (0.99, 1.17)</td>
</tr>
<tr>
<td>+ All individual-level covariates$^a$</td>
<td>1.11 (1.02, 1.21)</td>
</tr>
<tr>
<td>+ All neighborhood-level covariates$^b$</td>
<td>1.11 (1.02, 1.21)</td>
</tr>
<tr>
<td>+ All other comorbidities$^c$</td>
<td>1.11 (1.02, 1.21)</td>
</tr>
</tbody>
</table>

$^a$Adjusted for sex, marital status, education, household income adequacy, BMI, physical activity, smoking, alcohol consumption, diet, race, hypertension, and urban residency. 
$^b$Also adjusted for neighborhood-level unemployment rate, education, and household income. 
$^c$Also adjusted for COPD, asthma, congestive heart failure, and acute myocardial infarction.
Potential Mechanism

- Air pollution can induce oxidative stress and systemic inflammation
- Persistent autonomic imbalance, inflammation within insulin-sensitive tissues (e.g., adipose and hepatic), altered adipokine expression, and endoplasmic reticulum stress have all been implicated
- PM$_{2.5}$ induced adipose tissue inflammation and insulin resistance in a mouse model of diet-induced obesity
  
  (Sun et al. Circulation 2009)
Hypothetical pathways through which particulate matter might induce cardiovascular effects

Oxidative Stress

• Ozone, nitrogen dioxide, and PM are capable of generating reactive oxygen species (ROS) when inhaled into the airways and alveoli of the lungs.
PM and IHD – Early Experimental Evidence

- Rabbits regularly exposed to PM showed increased coronary atherosclerosis, plaque size, and lipid-laden plaques more prone to rupture compared to controls


**A**

![Bar chart showing volume fraction of atherosclerotic lesions in coronary arteries.](chart1.png)

- **PM10** (n=10) mean volume fraction: 33.3 ± 1.9%
- Control (n=6) mean volume fraction: 19.5 ± 1.5%

**B**

![Scatter plot showing correlation between alveolar macrophages that phagocytosed particles and volume fraction of atherosclerotic lesions in LMCA and RCA.](chart2.png)

- Equation: Y = 11.0 + 0.29X, p<0.05, r = 0.53
- Data points: PM10 (n=10) and Control (n=6)
A small interquartile range increase in long-term PM$_{2.5}$ levels (2 mcg/m$^3$) was associated with decreased flow-mediated dilation of the brachial artery

Am J Cardiol 2014;113:2057e 2063
Figure 1. Traffic related exposure variables and oxidized-LDL.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0016200
PM exposure was associated with a pro-thrombotic change in platelet function.

The magnitude of the change was about two-thirds (in the opposite direction) of the average effect of antiplatelet medication.

Diabetic patients showed evidence of a pro-inflammatory response to both recent and chronic exposure to PM air pollution.
Myocardial Ischemia during 15-min of Exercise-Induced Stress and Exposure to 300 μg/m³ Diesel Exhaust or Filtered Air in 20 Subjects

PM and Heart Rate Variability

• A large body of literature supports that PM is capable of disturbing cardiac autonomic balance
• A meta-analysis of 29 epidemiologic studies involving 18,667 subjects demonstrated that a 10-μg/m³ increase in PM$_{2.5}$ was associated with significant reductions in metrics of heart rate variability (HRV)
• Decreased HRV is associated with increased risk of adverse cardiovascular events, including arrhythmias
Conclusions

• Epidemiological evidence that ambient PM contributes to CVD continues to grow
• Mechanistic understanding of PM-CVD association involves three pathways
  – “spillover” of inflammation and oxidative stress from the lungs into the systemic circulation
  – autonomic nervous system imbalance, characterized by sympathetic predominance
  – penetration of particles or components directly into cardiovascular tissues
• Reductions of ambient PM can improve public health through reduced risk of CVD
Prevention

Brook et al., Curr Probl Cardiol 2015;40:207-238
Thank you
Guatemala Stove Intervention Blood Pressure Data

### Table 2. Electrocardiogram measures for between-groups comparisons during the trial period and before-and-after comparisons among the control group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Between-groups</th>
<th>Before-and-after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (open fire)</td>
<td>Intervention (chimney)</td>
</tr>
<tr>
<td>Subjects</td>
<td>70</td>
<td>49</td>
</tr>
<tr>
<td>20-hr sessions</td>
<td>110</td>
<td>112</td>
</tr>
<tr>
<td>30-min measures</td>
<td>4,256</td>
<td>4,333</td>
</tr>
<tr>
<td>ST value [mm (mean ± SD)]</td>
<td>−0.04 ± 0.62</td>
<td>0.06 ± 0.54</td>
</tr>
<tr>
<td>ST depression events (n^a)</td>
<td>272</td>
<td>105</td>
</tr>
<tr>
<td>ST depression rate (n/)</td>
<td>3.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>