From car to coronary: The cardiovascular effects of nanoparticles in vehicle exhaust

Dr Mark R. Miller, Centre for Cardiovascular Science
John Evelyn (1620-1706)
Air pollution and mortality (death)

World-wide air pollution is responsible for 3 - 7 million premature deaths every single year.

Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015


Outdoor air pollution
Air pollution globally

- More than 90% of the world's population live in areas of air pollution about WHO recommended levels
- Air pollution is on the rise in many developing countries
- No ‘safe’ level of air pollution
Systemic effects of air pollution

- Neurodegenerative Diseases
- Impaired cognition
- Altered behaviour
- Depression
- Stem cell alterations
- Liver toxicity
- Renal Disease
- Metabolic syndrome & Diabetes
- Decreased Fertility
- Autoimmune rheumatic diseases
- Peripheral artery disease
- Stroke
- Problems with smell
- Cardiovascular disease
- Asthma
- COPD
- Respiratory infection
- Lung cancer
- Pre-eclampsia
- Premature birth
- Low birth weights
- Epigenetic changes
- Detrimental health effects in offspring
Air pollution and mortality (death)

World-wide air pollution is responsible for 3 - 7 million early deaths every single year.

Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015

Cardiovascular disease

Air pollution and cardiovascular disease

- **Long-term** exposure to air pollution:
  
  Living in areas of high air pollution means you are likely to develop vascular disease

- **Short-term** exposure to air pollution:
  
  You are 3 times more likely to have a heart attack if in traffic beforehand

- **Underlying cause for link unknown.**
  
  - How does pollution cause cardiovascular effects?
  - Which air pollutants are responsible?

- Associations strongest for **particles** in air pollution
PM₁₀ is measured as the mass of particles with an aerodynamic diameter of 10 µm or less.

“Coarse” (PM₁₀): <10.0

“Fine” (PM₂.₅): <2.5

PM₀.₁ (nanoparticles, <100 nm): <0.1

Vehicle exhaust rich in nanoparticles
Controlled exposure to dilute diesel exhaust
Dilute diesel exhaust and blood vessels

- 1 hour in the exposure chamber
- Measuring blood vessel relaxation in the forearm

- Substantial loss of blood vessel vascular function
- Rapid effect: within 2 hours
- Long-lasting impairment: > 24-h

Mills et al. Circulation 2005
Other effects on the cardiovascular system

**Blood**
- Blood is more likely to clot
- Body cannot get rid of clots as it should

**Heart**
- Change in the rhythm of the heart
- Heart more susceptible to damage from lack of oxygen

**Blood vessels**
- Blood vessels can relax in a healthy way
- Increased blood pressure
- Increased stiffness of arteries
Diesel exhaust (DE): Short-term vs long-term

Short-term effects of DE  →  Cardiovascular disease  →  Cardiovascular event

Could exposure to diesel exhaust promote the development of cardiovascular disease?
Vascular Disease: Atherosclerosis

Cerebral
Ischemic stroke
Transient ischemic attack

Cardiac
Myocardial infarction
Angina pectoris (stable, unstable)

Peripheral Arterial Disease
Critical limb ischemia, claudication
Diesel exhaust particles (DEP) and atherosclerosis

8 weeks high fat diet

DEP to lung

saline to lung

Blood vessel wall
Atherosclerotic plaque

Size of plaque (%)

saline  DEP  saline  DEP

healthy mice  atherosclerotic mice

Miller et al. 2012 Particle & Fibre Toxicology
From car to carotid

Air pollution — lungs — Heart, blood vessels — blood
Lung-blood barrier

- Lung tissue
- Blood vessels
- Air spaces
Investigating particle translocation: difficulties

- Small size of particles
- Low levels of particles
- Large volume of blood
- Uptake by organs
- Hard to track carbon particles
Why use gold?
- Size similar to particles in vehicle exhaust
- Safe to use
- Techniques to measure very low levels
- Low levels of gold in the body normally
• 16 healthy volunteers
• 2-hour inhalation of gold nanoparticles
• Measure gold in blood after the exposure

Miller & Raftis et al. (2017). ACS Nano
Do translocated particles reach areas of vascular disease?

• Only very low amounts of nanoparticles will translocate
• But where do translocated nanoparticles go to?

Miller & Raftis et al. (2017). ACS Nano
Gold nanoparticles reach areas of vascular disease

- Do diesel exhaust particles behave in the same way?
- What would happen if they did?
DEP can harm cells in many ways:

- Direct toxicity
- Membrane damage
- DNA mutation
- Inflammation pathways
- Oxidative stress

Particles can lead to necrosis (cell death) and apoptosis (regulated cell death).
Diesel exhaust particles generate superoxide free radicals

Free radical generation

Blood vessel relaxation

Oxygen

Diesel exhaust particle

Arterial wall

DEP

Blood vessel relaxation

constriction

relaxation

Blank

Diesel exhaust particles

Free radicals

Magnetic wavelength

3330 3340 3350 3360 3370 3380

Miller et al. 2009 Environmental Health Perspective
That was the bad news, how about the good news?
Are we reducing the right pollutants?

Policies aiming to tackle air pollution rely on metrics of particle mass.

Increases in vehicles likely to be associated by an ‘unseen’ increase in numbers of nanoparticles.
Therefore, still a need for alternative strategies to tackle vehicle emissions

Use of 'particle traps' on exhausts of modern cars decreases particulate emissions

Retrofit exhaust particle traps

But...

- Limited lifespan?
- Need to reach specific temperature before trap works efficiently
- May increase co-pollutants or change in reactivity of remaining particles

- Therefore, still a need for alternative strategies to tackle vehicle emissions

Lucking et al. 2011, Circulation
Fuel additives

- Addition of additives to fuel to make combustion more efficient
  - e.g. cerium oxide nanoparticles added to diesel exhaust

- ApoE ko mice fed Western diet for 4 weeks
- 4 weeks daily via inhalation to diesel exhaust
- Fuel either Ce-spiked or non-spiked diesel
- Size of atherosclerotic plaque measured

Harmful?
Components of diesel exhaust

- elemental carbon core
- secondary sulphates and nitrates
- organic carbon species
- adsorbed soluble and vaporous hydrocarbons
- hydrated sulphates and nitrates
- redox-active metals
Organic constituents of diesel exhaust particles
‘Cleaning DEP’ with aqueous washes

Direct addition of particulate to isolated rat aorta

- ‘whole’ DEP
- Aqueous wash
- ‘aqueous-washed DEP’

Pulmonary administration of particulate to ApoE^{-/-} mice

- Atherosclerotic burden

Miller et al., unpublished data
Efficiency of facemasks

Could facemasks be used to protect susceptible individuals from the cardiovascular effects of air pollution?
BHF Beijing air Pollution Study

在研究人员的陪同下在市区内步行两小时
Walk for 2 hours in the city with researcher

病人可以自由活动
Free to do own activities

十八点返回医院
18:00 - Reattend the Fuwai Hospital

病人在八点到达阜外医院
08:00 - Attend the Fuwai Hospital

扯掉监控装置
Monitors removed

此次数据采集过程结束
Study complete

下一次数据采集过程将在奥林匹克运动会之后进行
One more visit with alternative intervention

- 24 hours randomised to face mask or no mask

安上心率血压测试仪器
Heart rate and blood pressure monitors applied

开启空气污染监测仪
Air pollution monitors applied and switched on
Blood pressure and heart rate variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Mask</th>
<th>Mask</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data validity, %</td>
<td>99.2 (96.24-100)</td>
<td>98.9 (96.75-100)</td>
<td>n/a</td>
</tr>
<tr>
<td>LF-power, ms²</td>
<td>136 (52-227)</td>
<td>133 (68-97)</td>
<td>0.98</td>
</tr>
<tr>
<td>HF-power, ms²</td>
<td>40 (20-69)</td>
<td>54 (27-108)</td>
<td>0.005</td>
</tr>
<tr>
<td>LFn, ms</td>
<td>62.9 (51.1-75.5)</td>
<td>58.4 (45.6-69.1)</td>
<td>0.008</td>
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<td>HFn, ms</td>
<td>20.5 (13.5-27.9)</td>
<td>23.5 (18.0-32.4)</td>
<td>0.0006</td>
</tr>
<tr>
<td>HF/LF Ratio</td>
<td>0.33 (0.21-0.57)</td>
<td>0.42 (0.26-0.71)</td>
<td>0.004</td>
</tr>
<tr>
<td>Average NN interval, ms</td>
<td>742 (685-804)</td>
<td>747 (689-788)</td>
<td>0.84</td>
</tr>
<tr>
<td>Average heart rate, bpm</td>
<td>81 (75-88)</td>
<td>81 (76-88)</td>
<td>0.75</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>0.7 (0.0-2.3)</td>
<td>1.2 (0.2-2.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>14.8 (10.9-19.6)</td>
<td>16.7 (13.2-22.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>60.1 (41.0-79.3)</td>
<td>59.8 (46.4-79.1)</td>
<td>0.53</td>
</tr>
<tr>
<td>Triangular index</td>
<td>8.5 (6.7-10.6)</td>
<td>8.9 (7.3-11.5)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Beneficial HRV parameters if wearing mask

Small reduction in BP if wearing mask

**Parameter**

- **Distance travelled, km**: 6.40 ± 1.51 (No Mask), 6.37 ± 1.44 (Mask)
- **Average moving speed, km/h**: 4.27 ± 1.01 (No Mask), 4.25 ± 0.96 (Mask)
- **Energy expenditure, Kcal**: 347 ± 93 (No Mask), 345 ± 87 (Mask)
- **Energy expenditure, METS**: 2.33 ± 0.55 (No Mask), 2.32 ± 0.52 (Mask)
- **Systolic blood pressure, mmHg**: 128 ± 16.5 (No Mask), 127 ± 15.9 (Mask)
- **Diastolic blood pressure, mmHg**: 79 ± 9 (No Mask), 78 ± 9 (Mask)
- **Mean arterial pressure, mmHg**: 96 ± 10 (No Mask), 93 ± 10 (Mask)
- **Pulse pressure, mmHg**: 49 ± 13 (No Mask), 49 ± 13 (Mask)
- **Heart rate, bpm**: 76 ± 12 (No Mask), 77 ± 11 (Mask)

**Table**: Data validity, %

- **Data validity, %**: 99.2 (96.24-100) (No Mask), 98.9 (96.75-100) (Mask)
- **P**: n/a

**Table**: LF-power, ms²

- **LF-power, ms²**: 136 (52-227) (No Mask), 133 (68-97) (Mask)
- **P**: 0.98

**Table**: HF-power, ms²

- **HF-power, ms²**: 40 (20-69) (No Mask), 54 (27-108) (Mask)
- **P**: 0.005

**Table**: LFn, ms

- **LFn, ms**: 62.9 (51.1-75.5) (No Mask), 58.4 (45.6-69.1) (Mask)
- **P**: 0.008

**Table**: HFn, ms

- **HFn, ms**: 20.5 (13.5-27.9) (No Mask), 23.5 (18.0-32.4) (Mask)
- **P**: 0.0006

**Table**: HF/LF Ratio

- **HF/LF Ratio**: 0.33 (0.21-0.57) (No Mask), 0.42 (0.26-0.71) (Mask)
- **P**: 0.004

**Table**: Average NN interval, ms

- **Average NN interval, ms**: 742 (685-804) (No Mask), 747 (689-788) (Mask)
- **P**: 0.84

**Table**: Average heart rate, bpm

- **Average heart rate, bpm**: 81 (75-88) (No Mask), 81 (76-88) (Mask)
- **P**: 0.75

**Table**: pNN50, %

- **pNN50, %**: 0.7 (0.0-2.3) (No Mask), 1.2 (0.2-2.8) (Mask)
- **P**: 0.15

**Table**: RMSSD, ms

- **RMSSD, ms**: 14.8 (10.9-19.6) (No Mask), 16.7 (13.2-22.5) (Mask)
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**Table**: SDNN, ms

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**Table**: Triangular index

- **Triangular index**: 8.5 (6.7-10.6) (No Mask), 8.9 (7.3-11.5) (Mask)
- **P**: 0.25

**Langrish et al. 2012, Environ Health Perspect**
Conclusions

- Diesel exhaust particles have many harmful effects on cardiovascular health
- Inhaled nanoparticles can cross into the blood and accumulate at areas of vascular disease
- If nanoparticles in diesel exhaust behave the same way it is highly likely that they would promote disease
- Interventions that reduce particles can limit the cardiovascular effects of vehicle emissions
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