Air Pollution as a Cardiovascular Risk Factor

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PI SAPALDIA Cohort
Air pollution – largest single environmental health risk

- 3.7 million deaths <60 years attributed to outdoor air pollution
- 80% the result of cardiovascular and cerebrovascular disease
  [www.who.int/mediacentre/factsheets/fs313/en/](http://www.who.int/mediacentre/factsheets/fs313/en/)

remains a problem

- no «safe limit»
- stagnant weather patterns
- rapid global expansion
- >95% of the urban population in major cities is exposed to pollution levels exceeding WHO air quality guidelines
Air pollution – a complex mixture

Motor vehicles – the dominant source of urban air pollution:
- Nitrogen oxides
- Carbon dioxide
- Sulphur dioxide
- Carbon monoxide
- Hydrocarbons
- Metals......
- **Particulate matter**
  
  *evidence for health effects most consistent*  

Figure 2 | Size categorization of airborne pollutants. The particulate matter that contributes to airborne pollution is categorized according to the mean aerodynamic diameter of the particles. The broadest category (PM$_{10}$) includes all particles <10 μm diameter. This category is subdivided into coarse, fine, and ultrafine particles. Fine particles <2.5 μm diameter are also known as PM$_{2.5}$. Biological entities representative of this range of sizes are also shown.

*Source: Cosselman et al Nature Rev Cardiology 2015*
Air pollution – effects of short-term exposure

short-term increases (ie, over hours to days) in ambient particulate matter are associated with higher risk of cardiovascular morbidity (e.g. hospitalizations) and mortality

• triggering of myocardial infarction, arrhythmias, heart failure exacerbations, and stroke (ischaemic stroke?; total anterior circulation infarcts?)

in the US and EU, all-cause mortality is estimated to rise 0.7-1.7% with each 10 µg/m3 increase in the level of PM2.5 in the preceding days

Cosselman et al Nature Rev Cardiology 2015
Longterm PM$_{2.5}$ exposure - natural-cause mortality

*Beelen et al. Lancet 2014*

<table>
<thead>
<tr>
<th>PM$_{2.5}$ Concentration (µg/m$^3$)</th>
<th>Number of cohorts</th>
<th>Number of observations</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>68 527</td>
<td>1.02 (0.87–1.19)</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>241 293</td>
<td>1.04 (0.98–1.11)</td>
</tr>
<tr>
<td>20</td>
<td>17</td>
<td>304 759</td>
<td>1.07 (1.01–1.13)</td>
</tr>
<tr>
<td>25</td>
<td>17</td>
<td>309 310</td>
<td>1.06 (1.00–1.12)</td>
</tr>
<tr>
<td>No threshold</td>
<td>19 (all)</td>
<td>322 159</td>
<td>1.07 (1.02–1.13)</td>
</tr>
</tbody>
</table>
Air pollution – CVD effects of longterm exposure

Heart failure (HF) and Ischemic Heart Disease (IHD)

the risk of death from IHD has been estimated to increase by 10-30% per 10 µg/m3 rise in residential levels of PM2.5

Stroke & MI recurrence/heart failure exacerbation

strong heterogeneity of effects on stroke incidence

Sudden cardiac death

Cosselman et al Nature Rev Cardiology 2015
Road way proximity and risk of sudden cardiac death in women

Table 2. HRs (95% CIs) for the Association of Risk of SCD (1986–2012) With Residential Proximity to A1 to A3 Roads Among Participants (n=107 130)

<table>
<thead>
<tr>
<th>Distance, m</th>
<th>Cases, n</th>
<th>Person-Years</th>
<th>Basic*</th>
<th>Multivariable†</th>
<th>Multivariable‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–49</td>
<td>103</td>
<td>354 901</td>
<td>1.56 (1.18–2.05)</td>
<td>1.40 (1.06–1.85)</td>
<td>1.38 (1.04–1.82)</td>
</tr>
<tr>
<td>50–199</td>
<td>150</td>
<td>661 072</td>
<td>1.27 (0.98–1.63)</td>
<td>1.19 (0.92–1.53)</td>
<td>1.17 (0.91–1.51)</td>
</tr>
<tr>
<td>200–499</td>
<td>169</td>
<td>770 257</td>
<td>1.26 (0.98–1.61)</td>
<td>1.20 (0.94–1.54)</td>
<td>1.20 (0.93–1.53)</td>
</tr>
<tr>
<td>≥500</td>
<td>101</td>
<td>594 129</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Linear (per 100 m closer)§</td>
<td>523</td>
<td>2 380 358</td>
<td>1.08 (1.03–1.14)</td>
<td>1.06 (1.01–1.12)</td>
<td>1.06 (1.01–1.11)</td>
</tr>
</tbody>
</table>

Note that n, person-years, and number of cases apply for all models. CI indicates confidence interval; HR, hazard ratio; NHS, Nurses' Health Study; and SCD, sudden cardiac death.

*Models adjusted for age, race, and calendar time.
†Models additionally adjusted for smoking status; secondhand smoke exposure during childhood, at home, and at work; body mass index; menopausal status and postmenopausal hormone use; the Alternative Healthy Eating Index; alcohol consumption; physical activity; family history of myocardial infarction; aspirin, multivitamin, and vitamin E use; region of residence; Census tract median home value and median income; and incidence of diabetes mellitus or cancer.
‡Models additionally adjusted for comorbidities: incidence of high cholesterol, high blood pressure, stroke, or coronary heart disease.
§Linear models for distances of 0 to 499 m compared with addresses ≥500 m away.
Subclinical effects of air pollution on obesity and diabetes

Ambient levels of air pollutants have been associated with BMI, prevalent and incident diabetes, and cardiometabolic measures such as insulin resistance and levels of serum leptin.
Air pollution and obesity

Prenatal air pollution exposure of mice induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner

*Jarrett M et al. Environmental Health 2014*

Traffic pollution & BMI growth in childhood


Traffic pollution and weight gain in adult women

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**Table 3. Mean Weight Change Over 16 Years (1997–2011) per IQR Increase in Pollutants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low: IQR ≤ 0.3</th>
<th>Moderate: 0.3 &lt; IQR ≤ 0.5</th>
<th>High: IQR &gt; 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$, μg/m$^3$ (IQR=2.9 μg/m$^3$)</td>
<td>0.07 (−0.19, 0.34)</td>
<td>0.48 (−0.05, 1.01)</td>
<td>−1.04 (−2.59, 0.51)</td>
</tr>
<tr>
<td>Cities, n</td>
<td>32</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>O$_3$, ppb (IQR=6.7 ppb)</td>
<td>0.38 (−0.01, 0.78)</td>
<td>0.01 (−0.43, 0.45)</td>
<td>−0.37 (−1.34, 0.60)</td>
</tr>
<tr>
<td>Cities, n</td>
<td>23</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>NO$_2$, ppb (IQR=9.7 ppb)</td>
<td>−0.28 (−0.75, 0.19)</td>
<td>−0.78 (−1.41, −0.16)</td>
<td>−1.39 (−2.88, 0.10)</td>
</tr>
<tr>
<td>Cities, n</td>
<td>15</td>
<td>23</td>
<td>18</td>
</tr>
</tbody>
</table>
Air pollution and systemic inflammation (hs-crp)
Lanki T et al. Environmental Health Perspectives 2015
Ambient air pollution exaggerates adipose inflammation and insulin resistance

Mouse Model of Diet-Induced Obesity

Sun et al. Circulation 2009

Alterations of macrophages and adipocytes in relation to inflammation

McNelis & Olefsky. Immunity 2014
Long-term exposure to air pollution and serum leptin in older adults

the SAPALDIA cohort

**Long-term air pollution and diabetes prevalence**

*Eze I et al Environ Int 2014*

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**Fig. A2** Correlation between adjusted diabetes prevalence and mean PM$_{10}$ by area.
the SAPALDIA cohort
Air pollution and metabolic syndrome

![Graph showing odds of metabolic syndrome with 95% CI for active and inactive groups, with p-values 0.025, 0.082, and 0.874 for MetS-W, MetS-I, and MetS-A respectively.](image)
# Association of PM10 with diabetes, by quartiles of diabetes gene risk score

*Eze et al. Environ Int 2016*

<table>
<thead>
<tr>
<th>Quartile</th>
<th>N</th>
<th>Increase in odds of diabetes per 10 μg/m³ increase in PM$_{10}$\textsuperscript{b} OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q$_1$</td>
<td>385</td>
<td>0.82 (0.41, 1.65)</td>
</tr>
<tr>
<td>Q$_2$</td>
<td>378</td>
<td>0.92 (0.55, 1.54)</td>
</tr>
<tr>
<td>Q$_3$</td>
<td>381</td>
<td>1.54 (0.95, 2.49)</td>
</tr>
<tr>
<td>Q$_4$</td>
<td>380</td>
<td>1.97 (1.00, 3.87)</td>
</tr>
<tr>
<td>Q$_4$ vs. Q$_1$</td>
<td>765</td>
<td>2.06 (0.69, 6.19)</td>
</tr>
</tbody>
</table>

[Graph showing odds ratio for diabetes (95% CI) per 10 μg/m³ exposure to PM$_{10}$ & per T2D risk allele across different genetic risk scores.]
The Vehicular Traffic and Obesity/Metabolic Syndrome Pathway

- **Vehicular Traffic**
  - Exposure (Diesel Exhaust; PM, SOx, NOx, Ozone, etc)
  - Active Travel
  - Perceived Safety
  - Noise
  - Vibration

- **Systemic Inflammation**
  - e.g. Bisphenol A, Diethylstilbestrol, Phthalates, Organotins, Perfluorooctanoic acid (PFOA)...

- **Cardio-respiratory disease**
  - Endocrine Disruption:
    - Hypothalamic Pituitary
    - Adrenal Axis
    - Metabolic Sensors NRs
    - Sex steroid dysregulation
      --Insulin resistance

- **Physical Activity**
  - Appetite, hyperplasia, hypertrophy, metabolic set-point, basal metabolic rate

- **Obesity/Metabolic Syndrome**
  - Cortisol Dysregulation
  - Caloric Intake
  - Sleep Disruption

- **Diabetes, Hypertension, Cardio-respiratory disease, Cancer, Depression, etc..**

Figure 1

Jarrett M et al. Environmental Health 2014
## Association of residential long-term air pollution and satellite-derived greenness with insulin-resistance in adolescents

*Thiering E et al. Environ Health Perspectives 2016*

Table 4. Associations of air pollution exposure (annual average concentrations) and NDVI (based on data from 2003) with HOMA-IR. Results of generalized additive models fitted separately for each exposure.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Basic model$^b$</th>
<th>Further adjusted model$^c$</th>
<th>Plus adjustment for NO$_2$</th>
<th>Plus adjustment for NDVI (1000m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDVI (500m)$^a$</td>
<td></td>
<td>5.5 (-11.3, 0.8)</td>
<td>-0.7 (-7.6, 6.8)</td>
<td>5.9 (-8.6, 22.8)</td>
</tr>
<tr>
<td>NDVI (1000m)$^a$</td>
<td></td>
<td>-7.4 (-13.3, -1.1)</td>
<td>-2.7 (-9.9, 5.1)</td>
<td>4.8 (2.2, 18.4)</td>
</tr>
<tr>
<td>NO$_2$$^a$</td>
<td>10.6 (3.8, 18.0)</td>
<td>11.4 (4.4, 18.9)</td>
<td>9.8 (1.8, 18.5)</td>
<td>3.1 (1.8, 4.4)</td>
</tr>
<tr>
<td>PM$_{10}$$^a$</td>
<td>11.2 (0.3, 23.3)</td>
<td>11.4 (0.4, 23.7)</td>
<td>7.0 (-4.7, 20.2)</td>
<td>2.1 (1.7, 2.5)</td>
</tr>
<tr>
<td>PM$_{2.5}$$^a$</td>
<td>13.2 (-3.4, 32.7)</td>
<td>14.6 (-2.5, 34.6)</td>
<td>9.1 (-7.8, 29.2)</td>
<td>2.5 (1.7, 3.3)</td>
</tr>
<tr>
<td>PM$_{2.5}$ abs.$^a$</td>
<td>3.9 (-4.8, 13.4)</td>
<td>4.7 (-4.2, 14.3)</td>
<td>1.4 (-7.7, 11.2)</td>
<td>0.4 (-1.3, 2.1)</td>
</tr>
</tbody>
</table>

$^a$ estimates per 2SD increase in the exposure variables: 0.2 NDVI units NDVI (500m) and (1000m) 0.2 NDVI units, 8.9 µg/m$^3$ NO$_2$, 6.7 µg/m$^3$ PM$_{10}$, 4.4 µg/m$^3$ PM$_{2.5}$, and 0.5 10-5/m PM$_{2.5}$ abs.

$^b$ adjusted for: study area, cohort, sex, age, BMI

$^c$ adjusted for: study area, cohort, sex, age, BMI, smoking by the adolescent, maternal and paternal education levels, second hand smoke at home, physical activity, income, pubertal scale
Subclinical effects of air pollution atherosclerosis

Air pollutant are related to lipid peroxidation and HDL dysfunction and contribute to multiple phases of atherosclerotic disease

(etiology and stability of atherosclerotic plaques)
Longterm air pollution and longitudinal change in coronary artery calcification


Figure 3: Long-term average air pollutant concentrations and coronary artery calcium progression

coronary calcium average increase 24 Agatston units/year

5 µg/m3 increase in PM2.5: additional 4.1 Agatston units/year
Ultrafine particles and CIMT
the SAPALDIA Cohort
Aguilera I et al. EHP 2016

% difference in CIMT
Subclinical effects of air pollution
blood pressure and vascular function

positive association between longterm air pollution
and blood pressure or hypertension
(incl. pre-eclampsia and other pregnancy complications)

anti-hypertensive medications mitigate PM-related BP
increase suggesting PM influence established
pathways to hypertension
(e.g. endothelial dysfunction)

Cosselman et al Nature Rev Cardiology 2015
Subclinical effects of air pollution
cardiac function & structure

- cardiac electric instability
- alterations in heart rate (variability)
- irregularities in myocardial and ventricular repolarization

*but*

*association thought to be limited to highly susceptible individuals, as controlled-inhalation studies have shown no short-term risk of arrhythmia in healthy adults*

- cardiac dysfunction and remodelling

*Cosselman et al Nature Rev Cardiology 2015*
Traffic-related air pollution and right ventricle (mass; end-diastolic volume)

Leary PJ et al. AJRCCM 2014

MESA participants had a 1.0 g (5%) increase in RV mass

RV hypertrophy in MESA participants associated with a three-fold increased risk of heart failure or cardiovascular death

Effect size comparable to smoking and diabetes
Population-level effects and interventions
Population-level effects of improved air quality

The US Environmental Protection Agency estimates that the Clean Air Act prevented

• over 160’000 deaths and 130’00 cases of MI in 2010

Benefits from decrease in both, longterm and acute exposure:

• longterm follow-up of large cohorts estimated a 27-31% decrease in total and CVD mortality for a 10 µg/m3 PM2.5 decrease

• short-term effects of air pollution control during Beijing Olympics (e.g. thrombosis decrease)
Air pollution in perspective

Health risks of air pollution expressed in equivalent of passively smoked cigarettes

van der Zee SC et al. Environ Res 2016

<table>
<thead>
<tr>
<th>Health benefit</th>
<th>NO$_2$</th>
<th>BC</th>
<th>Overall estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta 11.7 \mu g/m^3$</td>
<td>$\Delta 1.4 \mu g/m^3$</td>
<td></td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>1.5 (0.8)</td>
<td>4.4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Percentage lung function decrement in children (FEV1)</td>
<td>4.3 (2.3)</td>
<td>11.7 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4.2 (1.0)</td>
<td>4.3 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.0 (0.7)</td>
<td>2.0 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Arithmetic mean</td>
<td>3.0 (0.7)</td>
<td>5.6 (1.6)</td>
<td>4.3 (0.9)</td>
</tr>
</tbody>
</table>

$^a$ standard error in parentheses.
Air pollution and longevity
a nationwide analysis of the US
Baccarelli et al. EHP 2016

A 85-94-year-olds

\[
P_{\text{E6-94}} \quad \text{PM}_{2.5} \quad \text{PM}_{1.3}
\]

\[
\text{Difference in } P_{\text{E6-94}} \\
\text{vs PM}_{2.5} \quad \text{vs PM}_{1.3}
\]

\[
\text{Percent of Daily Smokers}
\]

\[
\text{EDF=2.0} \\
\text{EDF=3.6}
\]

B Smoking and 85-94-year-olds

\[
\text{Difference in } P_{\text{E6-94}} \\
\text{vs PM}_{2.5} \\
\text{vs PM}_{1.3}
\]

\[
\text{Percent of Daily Smokers}
\]

\[
\text{EDF=2.0} \\
\text{EDF=2.3}
\]

C PM2.5 and 100-104-year-olds

\[
\text{Difference in } P_{\text{E6-94}} \\
\text{vs PM}_{2.5}
\]

\[
\text{Percent of Daily Smokers}
\]

\[
\text{EDF=2.0}
\]

D Smoking and 100-104-year-olds

\[
\text{Difference in } P_{\text{E6-94}} \\
\text{vs PM}_{2.5}
\]

\[
\text{Percent of Daily Smokers}
\]

\[
\text{EDF=2.3}
\]
SAPALDIA - MAKING USE OF 25 YEARS OF DATA towards understanding healthy aging

> 25 Mio. CHF since 1991
7.6 Mio. CHF for 2014-2018