Epidemiology and biomarkers – Aerosol relevant properties for linkage with health effects

Steffen Loft
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Department of Public Health
University of Copenhagen, Denmark

Health effects of ambient air pollution

Progression and mortality of cardiovascular and cerebrovascular disease and diabetes particularly among elderly
Progression (cause of ?) and mortality of chronic obstructive lung disease particularly among elderly
Cognitive dysfunction, aging, autoimmune diseases and ?
Precipitation of asthma attacks in children and adults, progression, cause ?, sensibilisation/adjuvant effects
Lung and possibly other cancers
Reduced fetal growth, low IQ
Mortality
Reduced lung growth
IQ

Long and short-term
Long and short-term
Long-term
Long and short-term
Long-term
Aerosol properties, size, shape, composition etc. are related to sources and probably to health effects

**Epidemiology to assess aerosol properties and health effects**

**Short term effects (acute)**
- **time-series or panel**
  - One or more urban areas
  - Daily change in air pollutants (stations)
  - Daily change in:
    - Mortality including causes
    - Admissions, including causes
    - Symptoms in panel
    - Medicine consumption in panel/population

**Long term effects (chronic)**
- Many urban areas with large cohort(s)
  - Populations of 8000-500,000
  - With known risk factors (life style, education)
  - Exposure (stations or model based on sources)
  - 10-20 years observation
Asthma among school children
Wheezing among infants
Lung disease among elderly (>65 yr)
Heart disease among elderly (>65 yr)
Cardiac arrest
Stroke

Mild ischaemic strokes without atrial fibrillation (n = 1698) are mechanistically similar to myocardial infarction
Associations (per IQR) with pollutants (lag0−4 mean) adjusted for temperature, relative humidity and wind speed.

<table>
<thead>
<tr>
<th>Air Pollutant (unit)</th>
<th>One-pollutant model</th>
<th>Two-pollutant models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Particle numbers (#/cm³)</td>
<td>1.21 (1.04-1.41)</td>
<td>1.18 (1.06-1.42)</td>
</tr>
<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt; (µg/m³)</td>
<td>1.08 (0.98-1.19)</td>
<td>1.04 (0.93-1.16)</td>
</tr>
<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt; (ppb)</td>
<td>1.11 (0.95-1.30)</td>
<td>-</td>
</tr>
<tr>
<td>CO (ppm)*</td>
<td>1.10 (0.92-1.32)</td>
<td>-</td>
</tr>
</tbody>
</table>

Effect of Ultrafine particles vs. Stroke Severity Score
Associations in multipollutant models:

<table>
<thead>
<tr>
<th>Model</th>
<th>PM$_{10}$ mass</th>
<th>PM$_{10}$ daily component</th>
<th>PM$_{2.5}$ mass</th>
<th>Particle count</th>
<th>NO$_2$</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular admission (&gt;65 yr)</td>
<td>++ crustal</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>+</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>-</td>
<td></td>
<td>-</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic likely thrombotic stroke</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory admissions (65 yr)</td>
<td>++ biomass</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asthma admissions (0-18 yr)</td>
<td>++ vehicle</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wheezing (0-1 yr) d.o. (0-3 yr)</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
</tr>
</tbody>
</table>


Size-Segregated Particle Number Concentrations and Respiratory Emergency Room Visits in Beijing, China

Arne Marian Leitte,1 Uwe Schlink,1 Off Herbarth,2 Alfred Wiedensohler,3 Xiao-Chuan Pan,4 Min Hu,5 Matthias Richter,1 Birgit Wehner,7 Thomas Tuch,2 Zhijun Wu,6 Minjuan Yang,6 Liquan Liu,4,6 Susanne Breitner,6 Josef Cyrys,5,7 Annette Peters,6 H.-Erich Wichmann,6,7 and Ulrich Franck1

Table 4. Overview of RRs (95% CIs) between respiratory ERV and an IQR increment of air pollutant while controlling for NO$_2$ or PM$_{10}$.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Time delay (days)</th>
<th>IQR</th>
<th>While controlling for NO$_2$</th>
<th>While controlling for PM$_{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$</td>
<td>3</td>
<td>40</td>
<td>1.07 (1.01–1.13)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>40</td>
<td>1.07 (1.01–1.14)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>40</td>
<td>1.08 (1.01–1.15)*</td>
<td></td>
</tr>
<tr>
<td>PNC$_{100-100}$</td>
<td>2</td>
<td>3,600</td>
<td>1.06 (0.99–1.14)</td>
<td>1.07 (1.00–1.15)*</td>
</tr>
<tr>
<td>PNC$_{100-300}$</td>
<td>3</td>
<td>3,600</td>
<td>1.06 (0.98–1.16)</td>
<td>1.08 (1.01–1.17)*</td>
</tr>
<tr>
<td>PSC$_{100-100}$</td>
<td>2</td>
<td>60</td>
<td>1.06 (0.99–1.14)</td>
<td>1.07 (1.01–1.15)*</td>
</tr>
<tr>
<td>PSC$_{100-300}$</td>
<td>3</td>
<td>60</td>
<td>1.07 (0.98–1.16)</td>
<td>1.09 (1.01–1.17)*</td>
</tr>
</tbody>
</table>

*For a complete table, see Supplemental Material, Table 3 (doi:10.1289/ehp.1002263). Estimates were calculated using cumulative effects models representing time-delayed effects with moving averages up to 6 days (mean of the same day and 5 previous days) and including both pollutants with the same lag, for example, same-day total particle number concentration and same-day NO$_2$ concentration. 4Units for IQR: NO$_2$ (µg/m$^3$); PNC, (1/cm$^3$); PSC, (µm$^3$/cm$^3$). *p < 0.05 (p-values for the null hypothesis that the corresponding parameter is zero).
The Effects of Particulate Matter Sources on Daily Mortality: A Case-Crossover Study of Barcelona, Spain

Bart Ostro,1 Aurelio Tobias,2 Xavier Querol,2 Andrés Alastuey,2 Fulvio Amato,2 Jorge Pey,2 Noemi Pérez,2 and Jordi Sunyer1

Figure 2. All-cause mortality excess risks (95% CIs) associated with IQR increases in sources of PM2.5 (lag 2): single-source models (A), multsource models (B), multisource models with traffic (C), and PM mass models (D); PM2.5, mass from periodic sampling; PM2.5dp, mass from daily sampling.

Environmental Health Perspectives • VOLUME 119 | NUMBER 12 | December 2011

Figure 3. Percent excess mortality risk in the warm season in Seattle.

Cold season

Detroit

Seattle

Figure 4. Percent excess mortality risk in the cold season in Seattle.

Time-Series Analysis of Mortality Effects of Fine Particulate Matter Components in Detroit and Seattle

Jian Zhou, Kazueko Ro, Ramaa Loi, Markos Lippmann, and George Thurston

Environmental Health Perspectives • VOLUME 119 | ISSUE 4 | April 2011
Black Carbon as an Additional Indicator of the Adverse Health Effects of Airborne Particles Compared with PM$_{10}$ and PM$_{2.5}$

Steffen Loft
Pope, Inhalation Toxicol 2007

Black Smoke
NLCS-AIR cohort
Beelen et al. EHP 2008
Brunekreef et al. HEI 2009

Short and long term studies of PM-related mortality with time as axis and fixed exposure


*Cities included in the pooled estimate: *Eggen et al. (2001); *Katsouyanni et al. (2003).
Steffen Loft

Relative risks per IQR similar for PM$_{2.5}$ and EC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort</th>
<th>Correlation (r)</th>
<th>HR (95% CI)</th>
<th>PM$_{2.5}$</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkel et al. 2009</td>
<td>14,264 adults; age 25–59 years</td>
<td>0.07</td>
<td>1.06 (1.03, 1.09)</td>
<td>1.01 (1.04, 1.01)</td>
<td>1.06 (1.03, 1.09)</td>
</tr>
<tr>
<td>Lipsett et al. 2006</td>
<td>70,000 male U.S. veterans</td>
<td>0.54</td>
<td>1.18 (1.05, 1.33)</td>
<td>1.01 (1.02, 1.03)</td>
<td>1.18 (1.05, 1.33)</td>
</tr>
<tr>
<td>Bokel et al. 2009</td>
<td>120,052 adults; age 55–69 years</td>
<td>0.02</td>
<td>1.05 (1.00, 1.10)</td>
<td>1.00 (1.00, 1.03)</td>
<td>1.05 (1.00, 1.10)</td>
</tr>
<tr>
<td>Smith et al. 2009</td>
<td>500,000 adults; age 20–47 years</td>
<td>NA</td>
<td>1.10 (1.03, 1.19)</td>
<td>1.02 (1.00, 1.10)</td>
<td>1.10 (1.03, 1.19)</td>
</tr>
</tbody>
</table>

*Coefficient of the correlation (r) between PM and BC.* HR for EC in European studies estimated from BS as 10 µg/m$^3$ = 1.14 µg/m$^3$. HR for PM$_{2.5}$ estimated from TSP as PM$_{2.5}$ = 8.1 $+$ TSP (Vorkahl et al. 2006). Van der Zee et al. 1996. *Numbers available for 10 sites (microsomal). International Classification of Diseases, 9th Revision (World Health Organization 1979), codes < 800. *Pooled effects when using 10 µg/m$^3$ = 1.81 µg/m$^3$. 1.05 (95% CI 1.02, 1.07) when using 10 µg/m$^3$ = 0.5 µg/m$^3$. 1.11 (95% CI 1.06, 1.16).

Long-Term Exposure to Constituents of Fine Particulate Air Pollution and Mortality: Results from the California Teachers Study

Bart Ostro, Michael Lipsett, Peggy Reynolds, Debbie Goldberg, Andrew Hertz, Cynthia Garcia, Katherine D. Henderson, and Leslie Bernstein

Figure 1. Association of cardiopulmonary mortality with PM$_{2.5}$ and its constituents using alternative exposure metrics: HR and 95% CI for 8-km buffer and cohort follow-up from June 2003 through July 2007.

9,208/52,226 female Californian teachers from 10 counties within 8/30 km of monitor followed for 6 yr
The AIRGIS model for assessment of exposure in terms of NOx and NO\textsubscript{2} at residences from 1971 onwards at follow up of 57,053 participants in the Danish Diet, Cancer and Health cohort from baseline in 1993–1997 through 2009.

Environmental Sciences, Aarhus Universitet: Ole Hertel, Sten S. Jensen, Martin Hvidberg, Matthias Kettzel

**Danish Diet, Cancer and Health Cohort study of air pollution lung effects**

57,053 participants (aged 50-65 years) mainly from Copenhagen were recruited 1993-1997. Follow-up through 2006 for diagnoses of lung cancer or first admission for asthma or COPD. Exposure assessment in terms of NO\textsubscript{x} or NO\textsubscript{2} modelled at all addresses from 1971 to censoring of all subjects (>200,000 addresses).

<table>
<thead>
<tr>
<th>Hazard ratio*</th>
<th>all</th>
<th>current smokers</th>
<th>never smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer (592 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 100 µg/m\textsuperscript{3} NOx</td>
<td>1.09 (0.79-1.55)</td>
<td>1.02 (0.71-1.46)</td>
<td>1.51 (0.72-3.16)</td>
</tr>
<tr>
<td>Asthma (997 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per IQR in NO\textsubscript{2}</td>
<td>1.13 (1.04-1.22)</td>
<td>1.15 (0.95-1.35)</td>
<td>1.03 (0.88-1.18)</td>
</tr>
<tr>
<td>COPD (1797 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per IQR NO\textsubscript{2}</td>
<td>1.08 (1.02-1.14)</td>
<td>1.07 (1.00-1.14)</td>
<td>1.08 (0.85-1.30)</td>
</tr>
</tbody>
</table>

*Adjusted for Smoking Status, Smoking Duration, Smoking Intensity, environmental tobacco smoke, body mass index, education, occupational exposure, and fruit consumption.

Association between exposure to NO\textsubscript{2} levels (log transformed) at residence and incident diabetes defined by strict definition (n = 2877) (log relative hazard with 95% confidence interval) for 51 818 DCH cohort members, adjusted for gender, BMI, waist-to-hip ratio, smoking status (never, previous, current), smoking intensity, smoking duration, environmental tobacco smoke, physical activity, alcohol intake, fat intake, and educational level.

Andersen et al. Diabetes Care 35: 92-8, 2012

### Air pollution from traffic and diabetes incidence in a cohort study

<table>
<thead>
<tr>
<th></th>
<th>Diabetes Original</th>
<th>Diabetes Strict</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 4,040</td>
<td>n = 2,877</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full adjusted(^†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ hypertension,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypercholesterolemia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted(^†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ hypertension,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypercholesterolemia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Air pollution from traffic and diabetes incidence in a cohort study

<table>
<thead>
<tr>
<th>NO\textsubscript{2} (µg/m\textsuperscript{3})</th>
<th>1971 follow-up</th>
<th>1.06 (1.03-1.09)</th>
<th>1.00 (0.97-1.03)</th>
<th>1.00 (0.97-1.04)</th>
<th>1.11 (1.07-1.15)</th>
<th>1.04 (1.00-1.08)</th>
<th>1.04 (1.00-1.08)</th>
</tr>
</thead>
</table>

### Stroke and Long-Term Exposure to Outdoor Air Pollution From Nitrogen Dioxide: A Cohort Study

Zorana J. Andersen, Lise C. Kristiansen, Klaus K. Andersen, Tom S. Olsen, Martin Hvidberg, Steen S. Jensen, Matthias Ketzel, Steffen Loft, Mette Sorensen, Anne Tjonneland, Kim Overvad and Ole Raaschou-Nielsen

Stroke 2012, 43:320-325

Figure. Exposure–response relationship between NO\textsubscript{2} and incident (left total; n = 1984; right ischemic; n = 629) and fatal (left total n = 142; right ischemic, n = 23) stroke among 52,215 participants in the Diet, Cancer, and Health cohort members. NO\textsubscript{2} indicates nitrogen dioxide.
Respiratory Effects of Exposure to Diesel Traffic in Persons with Asthma

60 adults with either mild or moderate asthma to participate in a randomized, crossover study. Each participant walked for 2 hours along Oxford Street in London and, on a separate occasion, through Hyde Park.

Changes in lung function and inflammatory markers were associated most consistently with exposures to ultrafine particles and elemental carbon.

Figure 3. Point Estimates and 95% CIs of the Percent Change in Health End Points per Incremental Change in Pollutant Components. Changes in the health end points volume (A, n-6-C14:0, 18:2n-6, 18:3n-3), nasal vital capacity (PVn), and the fraction of nasal exhaled volume (FNO) are shown according to incremental changes in the levels of ultrafine particles (panel A), fine particles (panel B), elemental carbon (panel C), and aromatic hydrocarbons (panel D).
**Cellular responses in blood to air way exposure**

Inflammation

ROS - oxidative stress

DNA repair

Expression • Genes • microRNA

Mutation

▼

Cell death/
Cancer

Telomeres/aging

Shape/size
Charge
Constituents

Blood vessel function

Vasodilation by NO

Cell / platelet adhesion

Lipid oxidation

8-oxodG

But systemic oxidative stress in DNA from peripheral blood monoclear cells

Exposure to ambient concentrations of particulate air pollution does not influence vascular function or inflammatory pathways in young healthy individuals

Elvira V. Brauner,1 Lykke Forchhammer,1 Peter Møller,1 Jacob Simonsen,1 Marianne Glasius,2∗ Peter Wählö,2 Ole Raaschou-Nielsen,2∗ and Steffen Loft1

KVR—100 channel ventilator 230 m³/h
Continuous exchange ± HEPA filter
Chamber volume – 30 m³

Effects of Ambient Air Particulate Exposure on Blood Gas Bars and Lung Function

Endothelial function & inflammatory markers

Lung function & alveoli integrity

No effects of exposure to ambient levels of traffic generated ultrafine particles in 30 healthy volunteers ± exercise in 2 × 2 cross over design on
Diesel exhaust PM mass µg/m³ 348
PNC 1 x 10⁶
NO2 ppb 200

Filtered air

Similar:
Filtered diesel exhaust PM mass µg/m³ 6 70
PNC 2 x 10³ 4 x 10⁶
NO2 ppb 200 0

Filtered air

6-8 h after exposure for 2 h with exercise in 16 healthy subjects
Endothelial function measured as peripheral artery tone in index finger after forearm ischemia

Intervention study with 21 married elderly (>60 yr) couples living in apartments at busy streets in Copenhagen. Air filtered for all particles or not and monitored for 2 x 48 hours. Effect related to volume (PM$_{2.5}$) and potassium (biomass).

Endopat score increased by intervention: 8% (1%-16%; 95% CI; p=0.03)

No inflammation signs

Am J Resp Crit Care Med 2008

Indoor Particles Affect Vascular Function in the Aged
An Air Filtration-based Intervention Study

An Air Filter Intervention Study of Endothelial Function
Among Healthy Adults in a Woodsmoke-Impacted Community

Ryan W. Allen$^{1,}$, Chris Carlsten$^{2,3}$, Barb Karlen$^{3}$, Sara Leckie$^{3}$, Stephan van Eeden$^{4}$, Sverre Vedal$^{5}$, Imelda Wone$^{3}$, and Michael Brauer$^{3}$

AJRCCM Articles in Press, Published on January 21, 2011 as doi:10.1164/rcmm.201010-1572OC
Wood smoke randomized double-blinded cross over design

20 atopic participants were exposed to three different scenarios 2 weeks apart
• Wood smoke ~400 µg/m\(^3\) (high)
• Wood smoke ~200 µg/m\(^3\) (low)
• Clean air (control exposure)

The participants were exposed at rest for 3½h in the exposure chamber

Results DNA damage

No observed effect on SB, EndoIII or FPG sensitive sites
Neither on HO-1 or OGG1
(Forchhammer et al. Particle Fibre Toxicol 2012)
Results: microvascular effect

No observed effect on the microvascular function
(Forchhammer et al. Particle Fibre Toxicol 2012)

Vascular Function and Short-Term Exposure to Fine Particulate Air Pollution

Panels of 6-7 young adults exposed 3 h to 180 µg/m3 PM from combustion of wood or coal morning or afternoon. EndoPat results related to ambient PM$_{2.5}$

Table 2. Regression coefficients from models that regressed MVRi on subject-specific fixed effects indicator variables and various combinations of a variable indicating exposure in the chamber, average local ambient PM$_{2.5}$ concentrations for the previous 2 days, and a diurnal trend variable.

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>All Observations (n = 136)</th>
<th>Female (n = 84)</th>
<th>Male (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure chamber</td>
<td>-0.012 (0.098)</td>
<td>0.012 (0.048)</td>
<td>-0.046 (0.061)</td>
</tr>
<tr>
<td></td>
<td>Previous 2-day ambient PM$_{2.5}$</td>
<td>-0.136 (0.074) (P = 0.067)</td>
<td>-0.270 (0.094) (P = 0.008)</td>
<td>0.006 (0.114)</td>
</tr>
<tr>
<td>2</td>
<td>Diurnal trend</td>
<td>0.080 (0.023) (P &lt; 0.001)</td>
<td>0.053 (0.028) (P = 0.067)</td>
<td>0.115 (0.039) (P = 0.003)</td>
</tr>
<tr>
<td></td>
<td>Exposure chamber</td>
<td>0.048 (0.037)</td>
<td>0.051 (0.047)</td>
<td>0.045 (0.058)</td>
</tr>
<tr>
<td>3</td>
<td>Previous 2-day ambient PM$_{2.5}$</td>
<td>-0.136 (0.077) (P = 0.080)</td>
<td>-0.270 (0.096) (P = 0.007)</td>
<td>0.006 (0.122)</td>
</tr>
<tr>
<td>4</td>
<td>Diurnal trend</td>
<td>0.077 (0.029) (P = 0.001)</td>
<td>0.056 (0.025) (P = 0.009)</td>
<td>0.103 (0.031) (P = 0.002)</td>
</tr>
</tbody>
</table>

Notes: Data presented as regression coefficients with standard errors and P values when <0.10 in parentheses.
**Conclusions and summary**

Health effects of aerosols have so far mainly been related to particle mass on aggregate area level, with limited address of individual exposure and properties beyond mass: small size, surface area and reactivity, charge, chemical composition of especially elemental carbon, PAH and transition metals, biopersistance, ROS generation capacity and source specific characteristics.

Time series and case-crossover designed epidemiological studies suggest that increased ambient levels of ultrafine particles, elemental or black carbon, traffic exposure proxies and further chemical/elemental composition with source apportionment could be more closely associated with pulmonary and vascular outcomes than total PM mass and add important information although data are not fully consistent.

Long-term cohort studies of health effects also point at important information from elemental or black carbon including modelling by land use regression or traffic related exposure proxies as NOx or more simple indices. This consistently points to traffic as the most important source for virtually all relevant health outcomes in Western urban surroundings.

A large variety of biomarker related to health effect have been applied in relation to aerosols. Transition metals in PM$_{2.5}$, ultrafine and soot mode numbers, elemental carbon, black carbon, exhaust particles and indirect traffic indicators have been particularly associated with systemic oxidative stress and asthma aggravation, whereas diesel exhaust particles appear to have specific properties in inducing vascular dysfunction. Wood smoke particulates in contrast appear less potent on relation to these biomarkers.
Thanks for your attention!