Health Consequences of Ultrafine Particles
an exposome perspective

Prof. Dr. Nicole Probst-Hensch
Head Chronic Disease Epidemiology
PI SAPALDIA Cohort & Biobank
Chronic PM10/2.5 exposure and cardiovascular mortality

Brook Circulation 2010
Biological pathways: ambient particles to CVD
Brook Circulation 2010

**Blood**
- PM or constituents in the circulation
  - UFP, soluble metals
  - Organic compounds
- Vasoconstriction
- Endothelial dysfunction
- PM-mediated ROS
- BP
- Atherosclerosis
- Platelet aggregation

**Vasculature**
- Endothelial cell dysfunction/vasoconstriction, ROS
- Atherosclerosis progression/plaque vulnerability
- Thrombogenicity (e.g. tissue factor)

**Metabolism**
- Insulin resistance, dyslipidemia, impaired HDL function

**Blood**
- Coagulation, thrombosis; fibrinolysis (e.g. PAI-1)

**ANS**
- SNS / PSNS imbalance
- Vasocostriction
- Endothelial dysfunction
- Neural-mediated ROS
- BP
- Platelet aggregation

**Heart**
- HRV
- Heart rate
- Arrhythmia potential

**Systemic Oxidative Stress and Inflammation**
- Cellular inflammatory response (activated WBCs, platelets, MPO)
- Cytokine expression/levels (IL-1β, IL-6, TNF-α)
- ET, histamine, cell microparticles, oxidized lipids, anti-oxidants

**Acute**
- Activation of lung ANS reflex arcs

**Chronic**
- PM and/or constituents transmitted into blood
- "Systemic spill-over"

**Sub-acute & Chronic**
- Bronchioles/Alveoli
- Pulmonary oxidative stress & inflammation

**30.6.2015**
Normalized Particle Size Distributions of Roadway Aerosol

HEI Perspective 3 2013
Why are ultrafine particles potentially of specific concern?
Concerns related to UFP health effects
Araujo et al. Particle Fibre Toxicol 2009

• larger number of particles – larger surface – different composition – largely traffic-related
• larger redox activity
• pattern of lung deposition – reach alveoli
• lower clearance from the lung
• enter cells more easily – escape phagocytosis
• translocation across lung – reach distant organs (e.g. brain; translocation in humans not substantial)
Health effects of coarse PM air pollution from rural location randomized double-blind crossover study

Brook RD et al. EHP 2015
Inhaled UFP impact on cardio-respiratory system and brain: hypothesized pathways

*HEI Perspective 3 2013*

**Ambient UFP**
— Deposition in the respiratory tract

- Sensory Nerves, Ganglia
- Autonomic Nervous System

**Effects on:**
- Epithelial Cells
- Endothelial Cells
- Macrophages
  - Increased ROS
  - Inflammation

**Extrapulmonary Tissues**
- Heart
- Brain
- Liver
- Bone marrow, etc.

**Respiratory Tract Effects**
- Respiratory Dysfunction
- Acute Phase Response
- Blood Coagulability

**Platelet Activation**

**Translocation through circulation**

**Brain Effects**

**Nose**

Translocation via olfactory nerve to olfactory bulb
What is the evidence for (stronger/specific) health effects of ultrafine particles?
Mouse model of atherosclerosis: PM2.5 vs. UFP
Health Effects Institute 2013

Understanding the health effects of ambient ultrafine particles

**Experimental & epidemiological evidence on short-term effects**

Mortality (strongest for CVD)

Cardiorespiratory acute morbidity

- Hospital admissions
- Respiratory symptoms
- Pulmonary function
- Allergy & atopy
- Heart rate variability; arrhythmia
- Ischemia (ST-segment changes)
- Vascular reactivity/thrombogenic/endothelial function
- Blood pressure
- Soluble markers/brain inflammation

- Similar to fine particles
- Limited consistency
- Some evidence for CVD effects in absence of lung inflammation
- Susceptible subgroups
Epidemiological evidence on long-term effects

- no long-term cohort studies – limited UFP monitoring
Understanding the health effects of ambient ultrafine particles

Methodological challenges in assigning UFP specific effects

Co-pollutant confounding
- correlations between exposure metrics (long-term observational studies; correlation of temporal variability of exposure metrics)

Exposure measurement error
- large small-scale spatial variation
- non-consideration of indoor sources
- UFP exposure metrics (particle number vs. mass concentration; source; composition)
need for new metric to capture intradurnal variability and peaks
Relevant post-HEI report evidence for (stronger/specific) short-term health effects of ultrafine particles?
Short-term UFP (PNC) and mortality
Meta-Analysis of the published evidence

<table>
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<tr>
<th>RMID</th>
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<th>Year</th>
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Cardiovascular

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Respiratory

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little evidence for association - lack of adjustment for co-pollutants

30/06/2015
Short-term UFP and respiratory mortality/morbidity

UFIREG Project 2014

Figure 7. Seasonal variation of particle number concentration (10-100 nm) in UFIREG cities from May 2012 to April 2014 (Chernivtsi: January 2013 – April 2014).

Figure 15. Percent change in respiratory mortality associated with each 1,000 particles/cm³ increase in daily UFP (lag 5).

Figure 20. Percent change in respiratory hospital admissions associated with each 1,000 particles/cm³ increase in daily UFP (6-day average; lag 0-5).

effects on acute cardiovascular morbidity were heterogenous
Registry-based myocardial infarction and short-term exposure to PM10 and UFP

Wolf K et al. Int J Hygiene and Environ Health 2015
Personal exposure PNC induced immediate changes in HRV persons with impaired glucose tolerance /diabetes

*Peters Particles Fibre Toxicol 2015*
Table 4 Percent change in SDNN per IQR increases in proceeding 4-hour moving average exposures to ambient pollutants estimated in single-, and two-pollutant mixed-effects models

<table>
<thead>
<tr>
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<th>Single-pollutant</th>
<th>Two-pollutant</th>
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<td>Adj. for BC</td>
<td>Adj. for NO₂</td>
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<td>BC</td>
<td>-6.14 (-8.12,-4.11)</td>
<td>1.09 (-1.72,3.98)</td>
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<td>NO₂</td>
<td>-8.98 (-10.72,-7.18)</td>
<td>-9.56 (-11.85,-7.2)</td>
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<tr>
<td>CO</td>
<td>-7.33 (-8.91,-5.73)</td>
<td>-7.37 (-9.43,-5.25)</td>
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<tr>
<td>SO₂</td>
<td>-4.36 (-5.85,-2.86)</td>
<td>-2.91 (-4.66,-1.13)</td>
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<td>O₃</td>
<td>1.55 (-0.13,3.27)</td>
<td>0.51 (-1.22,2.27)</td>
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<td><strong>PNC₅–₅₆₀</strong></td>
<td>-7.89 (-9.69,6.07)</td>
<td>-6.82 (-8.87,4.72)</td>
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<tr>
<td><strong>PNC₅₀–₁₀₀</strong></td>
<td>-7.0 (-8.88,5.08)</td>
<td>-7.05 (-8.92,5.14)</td>
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<td><strong>PNC₁₀₀–₂₀₀</strong></td>
<td>-6.57 (-8.07,5.04)</td>
<td>-5.77 (-7.34,4.17)</td>
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<tr>
<td><strong>PNC₂₀₀–₅₆₀</strong></td>
<td>-5.37 (-7.34,3.35)</td>
<td>-2.76 (-5.29,0.16)</td>
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<td><strong>PNC₅₀₀–₁₀₀₀</strong></td>
<td>-2.98 (-4.63,1.3)</td>
<td>2.53 (-0.29,5.42)</td>
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<td><strong>PNC₁₀₀₀–₂₀₀₀</strong></td>
<td>-0.45 (-2.43,1.56)</td>
<td>5.15 (2.53,7.84)</td>
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</table>
Stronger UFP effects in obese persons

*Sun et al. Particle Fibre Toxicol 2015*
UFP LDSA & traffic noise
HRV
short-term exposure of highway maintenance workers
Meier R EHP 2014
UFP LDSA & traffic noise: **blood pressure**
short-term exposure of highway maintenance workers

*Meier R EHP 2014*

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**UFP LDSA**

![Graph showing the effect of UFP LDSA on blood pressure](image)

Percent change (95% CI) with a 10-μm²/cm³ increase in UFP LDSA (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)

---

**PM2.5Mass**

![Graph showing the effect of PM2.5Mass on blood pressure](image)

Percent change (95% CI) with a 10-μg/m³ increase in PM2.5Mass (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)

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30.6.2015
## Particle exposure and blood markers

**highway maintenance workers**  
*Meier et al. EHP 2014*

### Table 3. Associations of particle exposures during work and proinflammatory and prothrombotic markers in the blood [percent differences (95% CI)].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PM$_{2.5}$Realtime</th>
<th>PM$_{2.5}$Mass</th>
<th>LDSA</th>
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<tr>
<td>IL-6</td>
<td>-1.18 (-2.60, 0.26)</td>
<td>-1.52 (-3.98, 1.00)</td>
<td>-0.65 (-1.98, 0.70)</td>
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<td>TNF$\alpha$</td>
<td>-0.25 (-0.58, 0.08)</td>
<td>-0.60 (-1.15, -0.04)</td>
<td>0.02 (-0.31, 0.35)</td>
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<td>CRP</td>
<td>1.97 (-0.62, 4.62)</td>
<td>5.56 (1.05, 10.27)</td>
<td>1.38 (-0.88, 3.70)</td>
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<td>SAA</td>
<td>1.23 (-0.79, 3.29)</td>
<td>3.56 (0.04, 7.21)</td>
<td>1.00 (-0.88, 2.91)</td>
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<td>vWF</td>
<td>0.30 (-0.55, 1.15)</td>
<td>0.41 (-1.06, 1.88)</td>
<td>0.17 (-0.66, 0.99)</td>
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<td>Tissue factor</td>
<td>-0.96 (-2.24, 0.32)</td>
<td>-0.56 (-2.80, 1.69)</td>
<td>-0.84 (-2.05, 0.37)</td>
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5-day average exposure to air pollutants and inflammatory blood markers in panel of genetically susceptible

Rückerl
Environ International 2014
Particles & systemic biomarkers in single blind cross-overs study

UFP and urinary 8-OHdG

Liu et al. EHP 2015

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Table 3. Mean changes in urinary biomarker concentrations (95% CI) per 100-μg/m³ increase in CAP mass concentration in single- and two-pollutant models.

<table>
<thead>
<tr>
<th>Biomarker/model</th>
<th>Coarse CAP</th>
<th>Fine CAP</th>
<th>Ultrafine CAP</th>
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<tr>
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<td>1 hr postexposure</td>
<td>21 hr postexposure</td>
<td>1 hr postexposure</td>
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<td>8-OHdG (ng/mg creatinine)</td>
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<td>CAP alone</td>
<td>0.24 (0.02, 0.50)*</td>
<td>0.01 (0.26, 0.27)</td>
<td>-0.19 (0.55, 0.17)</td>
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<tr>
<td>+ SO₂</td>
<td>0.29 (0.02, 0.56)**</td>
<td>0.06 (0.22, 0.35)</td>
<td>-0.20 (0.58, 0.18)</td>
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<tr>
<td>+ O₃</td>
<td>0.22 (-0.07, 0.51)</td>
<td>-0.03 (-0.32, 0.27)</td>
<td>-0.23 (-0.60, 0.15)</td>
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<tr>
<td>+ NO₂</td>
<td>0.27 (-0.03, 0.57)*</td>
<td>-0.05 (-0.38, 0.27)</td>
<td>-0.20 (-0.62, 0.21)</td>
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<tr>
<td>+ CO</td>
<td>0.30 (0.04, 0.57)**</td>
<td>0.02 (-0.26, 0.30)</td>
<td>-0.12 (-0.50, 0.26)</td>
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Association of particle air pollution
4-week moving average
with gene-specific methylation
*Bind M-A EHP 2015*

**Particle Number and DNA methylation**

30.6.2015
Relevant post-HEI report evidence for (stronger/specific) **long-term** health effects of ultrafine particles?
Long-Term Effect of Fine and Ultrafine Particles
Ischemic Heart Disease Mortality in California Teachers
Ostro et al. EHP 2015

Association of $\text{PM}_{0.1}$ Constituents with IHD Mortality
(Hazard Ratios and 95% CI Using IQR)

Two-pollutant model $1.19 (1.08-1.31)$

association with IHD, but not overall/pulmonary mortality

UFP provided slightly better fit than PM2.5
Acute effect studies – myocardial infarction
*Nawrot et al meta-analysis, Lancet*

2% increase per 10µg/m³ PM2.5

Long-term effect studies – coronary events in ESCAPE
*Cesaroni et al, BMJ 2014*

26% increase per 10µg/m³ PM2.5
Systolic blood pressure and traffic load on major roads within 100 m – ESCAPE Study

*Fuks EHP 2015*

In persons without blood pressure lowering medication
Atherosclerosis - main underlying pathology of CVD - association with longterm PM2.5 exposure

Nawrot
PLoS One 2015
SAPALDIA
PM monitoring sites for long-term spatial modelling
SAP3 Monitoring Methods

\( \text{NO}_2 \)
- Passive Passam tubes
- 2-week sampling periods

Gravimetric \( \text{PM}_{2.5} / \text{PM}_{10} \)
- \( \text{PM}_{2.5} \) & \( \text{PM}_{10} \) w/ Harvard Impactors (@ 4 L/min)
- 37mm Teflon filter (23±2 °C, 35±5% RH)
- 2-week sampling periods

Particle Number & Size
- miniDiSC (1-sec resolution)
- 2 week monitoring period
- \( D_p > 15 \) nm
# SAPALDIA

**CIMT association with home-outdoor pollutants**

4 sites; 1500 subjects age >50

*Aguilera et al – in preparation*

<table>
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<th>Exposure, P90-P10 increase</th>
<th>Main Model</th>
<th>Two-Pollutant Model</th>
<th>PNC estimate in two-pollutant model</th>
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<td>PM10 last year (5.5 µg/m³)</td>
<td>1.58</td>
<td>-0.05</td>
<td>2.13</td>
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<td>PM2.5 last year (4.2 µg/m³)</td>
<td><strong>2.10</strong></td>
<td>1.73</td>
<td>0.63</td>
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<td>Vehicular source of PM2.5</td>
<td>1.67</td>
<td>1.27</td>
<td>0.87</td>
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<td>Crustal course of PM2.5</td>
<td>-0.58</td>
<td>-1.53</td>
<td>3.35</td>
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<td>LDSA (30.5 µg/m³)</td>
<td><strong>2.32</strong></td>
<td>3.41</td>
<td>-1.11</td>
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<td>PNC (12’639 particles/m³)</td>
<td><strong>2.06</strong></td>
<td>n.a.</td>
<td>n.a.</td>
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Pearson PNC with LDSA, PM10, PM2.5, Vehicular PM2.5: >.085
## SAPALDIA
### CIMT association with home-outdoor pollutants modification by anti-inflammatory, CIMT-related SNP

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<thead>
<tr>
<th>Genotype</th>
<th>% change</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>4.764</td>
<td>-1.419</td>
<td>10.985</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>19.132</td>
<td>5.128</td>
<td>33.332</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>33.707</td>
<td>6.120</td>
<td>62.050</td>
</tr>
</tbody>
</table>

#### PM 2.5 biannual mean (10 µg/m3 increase)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% change</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>0.914</td>
<td>-0.201</td>
<td>2.029</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>3.325</td>
<td>0.766</td>
<td>5.891</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>5.743</td>
<td>0.721</td>
<td>10.790</td>
</tr>
</tbody>
</table>

#### LDSA (10µm2/m3 increase)
## Longterm exposure to traffic PM & Incident Diabetes

*Weinmayer EHP 2015*

<table>
<thead>
<tr>
<th></th>
<th>Increase in PM equivalent to the IQR</th>
<th>Increase of 1 μg/m³ PM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IQR</td>
<td>Crude model</td>
</tr>
<tr>
<td><strong>Total PM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM&lt;sub&gt;10&lt;/sub&gt;ALL</td>
<td>3.78</td>
<td>1.08 (0.96;1.21)</td>
</tr>
<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;ALL</td>
<td>2.29</td>
<td>1.03 (0.92;1.15)</td>
</tr>
<tr>
<td><strong>Traffic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM&lt;sub&gt;10&lt;/sub&gt;TRA</td>
<td>0.33</td>
<td>1.15 (1.05;1.27)</td>
</tr>
<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;TRA</td>
<td>0.32</td>
<td>1.15 (1.04;1.26)</td>
</tr>
<tr>
<td><strong>Distance to major road (&gt;200 m reference) (N = 3186)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 100 (N = 180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100-200 (N = 339)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> main model adjusted for age, gender, lifestyle variables, BMI, individual and neighbourhood SES, and city

30.6.2015
Longterm exposure to traffic air pollution modification of association with diabetes and HRV modified by IL6 gene variants

Adam M PLoOne 2014; Eze in preparation

<table>
<thead>
<tr>
<th>HRV parameters</th>
<th>IL6-174 G/C</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p_{TPM10} (by genotype)</th>
<th>p_{Interaction} (genetic model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>GG</td>
<td>-1.77</td>
<td>-3.51</td>
<td>0.01</td>
<td>0.051</td>
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<tr>
<td></td>
<td>GC</td>
<td>1.06</td>
<td>-0.47</td>
<td>2.62</td>
<td>0.177</td>
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<tr>
<td></td>
<td>CC</td>
<td>0.73</td>
<td>-1.62</td>
<td>3.14</td>
<td>0.545</td>
</tr>
</tbody>
</table>

P(additive)=0.031
P(recessive)=0.058
P(dominant)=0.078

P(additive)=0.042
P(recessive)=0.041
P(dominant)=0.530

Air pollutant-genotype interaction (µg/m^3)
Longterm PM10 and diabetes: modification by diabetes gene scores

\[ \text{Eze / Probst-Hensch, unpublished} \]
Traffic Air Pollution in Schools and Cognitive Development in School Children

Air pollution and cognitive function in women: modification by apoE gene variants

Schikowski T Environ Res 2015

Effect on z-score of figure drawing

-1.2 -0.8 -0.4 0 0.4 0.8 1

Traffic load (P=0.0059) NO₂ (P=0.5097) PM₁₀ (P=0.1932) PM₂.₅ (P=0.4884) PM₂.₅ abs (P=0.0380) NOₓ (P=0.9951)

APOE=1 APOE=0
UFP – role in gastrointestinal disorders?

Beamish
J Crohns & Colitis 2011
UFP effects on lipid metabolism and inflammation in mouse digestive system

Li R EHP 2015

- arachidonic acid
- shortening of villi in small intestines
- increased number of macrophages in small intestines
Can exposome approaches improve understanding of health effects of ultrafine particles?
Air pollution exposome & phenome

Air Pollution Components

Air Pollution Components

Air Pollution Components

? intermediate «multi-omics» profiles of effect - pointing to specific networks ?

Lung Function

COPD

Asthma

Respiratory Sympt.

Heart Rate Variability

Blood Pressure

CVD

Diabetes

Markers of Aging

Mortality
SAPALDIA in Exposomics
EU 7th Framework Project, PI P. Vineis

SAPALDIA
archived blood
historical health & pollution data

SAPALDIA subgroup
personalized air pollution measurements
blood for -omics

- omics biomarkers of health phenotypes
- omics biomarkers of specific air pollutants

overlap
mechanisms

10. Mai 2015
SAPALDIA Acknowledgement

Study directorate
N Probst-Hensch (PI, e/g), T Rochat (p), C Schindler (s), N Kuenzli (e), JM Gaspoz (c)

Scientific team
JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), C Brombach (n), PO Bridevaux (p), L Burdet (p), D Felber Dietrich (e), M Frey (p), U Frey (pd), MW Gerbase (p), D Gold (e), E de Groot (c), W Karrer (p), F Kronenberg (g), B Martin (pa), D Miedinger (o), M Pons (p), F Roche (c), T Rothe (p), P Schmid-Grendelmeyer (a), A Schmidt-Trucksäss (pa), JM Tschopp (p), A Turk (p), J Schwartz (e), A von Eckardstein (cc), E Zemp Stutz (e).

“Scientific team at coordinating centers:”
M Adam (e), I Aguilera (exp), D Carballo (c), S Caviezel (pa), I Curjuric (e), J Dratva (e), R Ducret (s), E Dupuis Lozeron (s), M Eeftens (exp), I Eze (e), E Fischer (g), M Foraster (e), M Germond (s), L Grize (s), S Hansen (e), A Hensel (s), M Imboden (g), A Ineichen (exp), D Keidel (s), A Kumar (g), N Maire (s), A Mehta (e), R Meier (exp), E Schaffner (s), T Schikowski (e), M Tsai (exp)

(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics