Ultrafine particles and health – the urban exposome perspective

Prof. Dr. Nicole Probst-Hensch

Head Department of Epidemiology and Public Health, Swiss TPH
Principle Investigator, SAPALDIA Cohort
Evidence on health effects of UFP
Particulate Matter Air Pollution and Health

• Increases all-cause mortality

• Impacts particularly on respiratory, cardiometabolic and cognitive health, and early childhood development

  Thurston ERJ 2017

• Considered the most important environmental risk factor for mortality worldwide

  Cohen Lancet 2017; Forouzanfar Lancet 2016

• Estimated to reduce life expectancy in EU by ~1 year

  European Environmental Agency 2017 https://doi.org/10.2800/358908
Ultrafine Particles (UFP)

- aerodynamic size $< 100$ nm
- urban areas: mostly originate from motorized vehicles (& air ports)
- peak concentrations at the curbside - up to 10fold higher than background - reaching background concentrations within 150 m of the road

*Karner Environ Sci Technol 2010*

- inhaled deeply into the lungs - penetrate biological membranes - pass into the systemic circulation - overcome the placental barrier - diffuse into all organ systems including the brain & nervous system
- Toxicology: higher toxicity per mass unit than larger particles

*HEI 2013. Understanding the health effects of ambient ultrafine particles. HEI perspectives 3.*
Short-term UFP Effects – evidence 2011-2017
Ohlwein Int J Publ Health 2019

Suggestive evidence for independent short-term health effects on inflammation, autonomic tone and blood pressure

- majority of 11 studies indicate an association with increased arterial blood pressure
- likely short-term exposure to UFP/quasi-UFP changes autonomic tone and therefore adversely influences arterial blood pressure
- potentially contributing pathway to an increased cardiovascular disease risk: elicitation of pulmonary and systemic inflammation

Insufficient evidence on effects on mortality or ER/hospital admissions:
- Effects may be larger in warm season
*Ohlwein Int J Publ Health 2019*

- ten studies on long-term UFP effects & various health outcomes
- mostly modeled UFP concentrations: limited external validation of the model output
- mostly elevated point estimates for associations of UFP with adverse health outcomes - still unclear to what extent these associations overlap with other pollutants

- **insufficient evidence to draw firm conclusions on long-term effects of UFP**
  
i.e. associations with natural, cardiovascular, respiratory, neurological, or birth outcome-related morbidity and mortality
Cohort Approaches to Long-term UFP Effects

*Ostro et al. EHP 2015* suggested an association between UFP mass and ischemic heart disease mortality:

UFP was calculated via chemical transport models over a 4-km² spatial scale that would not have captured small-scale variation, which has been found to be important for UFP.

*Van Nunen E Environ Sci Technol 2017* in Exposomics:

- harmonized short-term and mobile monitoring campaign contemporaneously in six European study areas
- robust cross-area UFP LUR models on short-term monitoring explaining around 50% of spatial variance in longer-term measurements
- providing the opportunity to better investigate the role of long-term UFP exposure
### Long-term UFP exposure & cardiovascular disease incidence

*Downward GS et al. EHP 2019*

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>All cardiovascular disease (4,304 events)</th>
<th>Coronary heart disease (2,399 events)</th>
<th>Myocardial infarctions (797 events)</th>
<th>Heart failure (369 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Single-pollutant models</td>
<td></td>
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</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>0.98 (0.75, 1.28)</td>
<td>0.80 (0.55, 1.15)</td>
<td>0.83 (0.44, 1.57)</td>
<td>0.44 (0.16, 1.20)</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>1.20 (0.96, 1.50)</td>
<td>1.14 (0.85, 1.53)</td>
<td>1.34 (1.06, 1.79)</td>
<td>1.76 (1.17, 2.66)</td>
</tr>
<tr>
<td>UFP</td>
<td>1.18 (1.03, 1.34)</td>
<td>1.12 (0.94, 1.33)</td>
<td>1.12 (0.80, 1.56)</td>
<td>1.16 (0.70, 1.90)</td>
</tr>
<tr>
<td>PM$_{2.5}$ absorbance</td>
<td>1.07 (0.92, 1.23)</td>
<td>0.97 (0.80, 1.18)</td>
<td>1.10 (0.97, 1.25)</td>
<td>1.13 (0.93, 1.37)</td>
</tr>
<tr>
<td>NO$_x$</td>
<td>1.03 (0.98, 1.09)</td>
<td>1.02 (0.95, 1.10)</td>
<td>1.12 (0.99, 1.26)</td>
<td>1.22 (1.01, 1.48)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>1.04 (0.98, 1.10)</td>
<td>1.04 (0.97, 1.12)</td>
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<tr>
<td>Two-pollutant models</td>
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<tr>
<td>UFP + PM$_{2.5}$</td>
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</tr>
<tr>
<td>PM$<em>{2.5}$ + PM$</em>{10}$</td>
<td>1.28 (1.09, 1.49)</td>
<td>1.27 (1.04, 1.57)</td>
<td>1.59 (1.13, 2.24)</td>
<td>3.10 (1.89, 5.10)</td>
</tr>
<tr>
<td>PM$_{2.5}$ + UFP</td>
<td>0.74 (0.54, 1.02)</td>
<td>0.61 (0.40, 0.94)</td>
<td>0.51 (0.24, 1.05)</td>
<td>0.11 (0.03, 0.36)</td>
</tr>
<tr>
<td>PM$<em>{10}$ + PM$</em>{coarse}$</td>
<td></td>
<td></td>
<td></td>
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<td>PM$_{10}$ + UFP</td>
<td>1.14 (0.95, 1.37)</td>
<td>0.99 (0.77, 1.27)</td>
<td>1.16 (0.76, 1.77)</td>
<td>1.84 (1.04, 3.26)</td>
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<td>PM$_{coarse}$</td>
<td>1.06 (0.83, 1.37)</td>
<td>1.27 (0.91, 1.78)</td>
<td>1.30 (0.74, 2.28)</td>
<td>0.90 (0.37, 2.19)</td>
</tr>
<tr>
<td>UFP + PM$_{10}$</td>
<td>1.25 (1.01, 1.56)</td>
<td>1.16 (0.86, 1.57)</td>
<td>1.67 (1.01, 2.75)</td>
<td>1.94 (0.96, 3.92)</td>
</tr>
<tr>
<td>UFP + PM$_{2.5sabs}$</td>
<td>0.88 (0.60, 1.28)</td>
<td>0.93 (0.56, 1.55)</td>
<td>0.63 (0.26, 1.50)</td>
<td>0.80 (0.22, 2.92)</td>
</tr>
<tr>
<td>PM$_{2.5sabs}$</td>
<td>1.42 (1.13, 1.77)</td>
<td>1.49 (1.10, 2.01)</td>
<td>1.87 (1.12, 3.10)</td>
<td>3.98 (1.97, 8.04)</td>
</tr>
<tr>
<td>UFP + NO$_x$</td>
<td>0.78 (0.60, 1.00)</td>
<td>0.68 (0.48, 0.95)</td>
<td>0.63 (0.35, 1.13)</td>
<td>0.30 (0.13, 0.73)</td>
</tr>
<tr>
<td>NO$_x$</td>
<td>1.26 (1.04, 1.51)</td>
<td>1.17 (0.91, 1.51)</td>
<td>1.31 (0.85, 2.03)</td>
<td>2.10 (1.17, 3.79)</td>
</tr>
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<td>UFP + NO$_2$</td>
<td>0.96 (0.89, 1.04)</td>
<td>0.97 (0.87, 1.09)</td>
<td>1.01 (0.83, 1.22)</td>
<td>0.86 (0.67, 1.18)</td>
</tr>
<tr>
<td>UFP</td>
<td>1.28 (1.04, 1.59)</td>
<td>1.09 (0.82, 1.47)</td>
<td>1.22 (0.74, 2.02)</td>
<td>1.75 (0.89, 3.45)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>0.96 (0.86, 1.05)</td>
<td>1.01 (0.90, 1.14)</td>
<td>1.05 (0.85, 1.28)</td>
<td>1.00 (0.74, 1.37)</td>
</tr>
</tbody>
</table>
### Long-term UFP exposure & cerebrovascular disease incidence

*Downward GS et al. EHP 2019*

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>All incident cerebrovascular disease (1,283 events)</th>
<th>Incident ischemic CVA (846 events)</th>
<th>Incident hemorrhagic CVA (241 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-pollutant models</td>
<td></td>
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</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>1.13 (0.69, 1.83)</td>
<td>0.90 (0.49, 1.66)</td>
<td>1.88 (0.66, 5.39)</td>
</tr>
<tr>
<td>PM$_{coarse}$</td>
<td>1.14 (0.80, 1.61)</td>
<td>1.22 (0.79, 1.86)</td>
<td>1.91 (0.90, 4.04)</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>1.10 (0.73, 1.68)</td>
<td>1.13 (0.67, 1.89)</td>
<td>1.79 (0.71, 4.52)</td>
</tr>
<tr>
<td>UFP</td>
<td>1.11 (0.88, 1.41)</td>
<td>1.07 (0.80, 1.44)</td>
<td>1.48 (0.88, 2.51)</td>
</tr>
<tr>
<td>PM$_{2.5}$ absorbance</td>
<td>1.07 (0.82, 1.40)</td>
<td>1.01 (0.72, 1.41)</td>
<td>1.47 (0.81, 2.66)</td>
</tr>
<tr>
<td>NO$_{x}$</td>
<td>1.03 (0.92, 1.14)</td>
<td>1.04 (0.92, 1.18)</td>
<td>1.15 (0.91, 1.44)</td>
</tr>
<tr>
<td>NO$_{2}$</td>
<td>1.00 (0.90, 1.11)</td>
<td>1.05 (0.92, 1.19)</td>
<td>1.09 (0.86, 1.37)</td>
</tr>
</tbody>
</table>

| Two-pollutant models |                                                   |                                    |                                       |
|----------------------|---------------------------------------------------|------------------------------------|                                       |
| UFP + PM$_{2.5}$     |                                                   |                                    |                                       |
| UFP                  | 1.11 (0.83, 1.48)                                 | 1.16 (0.81, 1.66)                   | 1.38 (0.72, 2.64)                     |
| PM$_{2.5}$           | 1.00 (0.55, 1.80)                                 | 0.76 (0.36, 1.59)                   | 1.29 (0.35, 4.74)                     |
| UFP + PM$_{coarse}$  |                                                   |                                    |                                       |
| UFP                  | 1.09 (0.79, 1.52)                                 | 0.96 (0.64, 1.43)                   | 1.18 (0.57, 2.44)                     |
| PM$_{coarse}$        | 1.04 (0.64, 1.68)                                 | 1.27 (0.71, 2.29)                   | 1.63 (0.57, 4.63)                     |
| UFP + PM$_{10}$      |                                                   |                                    |                                       |
| UFP                  | 1.19 (0.79, 1.78)                                 | 1.03 (0.63, 1.71)                   | 1.44 (0.60, 3.48)                     |
| PM$_{10}$            | 0.87 (0.42, 1.77)                                 | 1.08 (0.45, 2.59)                   | 1.07 (0.22, 5.17)                     |
| UFP + PM$_{2.5abs}$  |                                                   |                                    |                                       |
| UFP                  | 1.19 (0.79, 1.79)                                 | 1.19 (0.72, 1.99)                   | 1.42 (0.57, 3.52)                     |
| PM$_{2.5abs}$        | 0.91 (0.57, 1.46)                                 | 0.86 (0.48, 1.53)                   | 1.07 (0.38, 3.01)                     |
| UFP + NO$_{x}$       |                                                   |                                    |                                       |
| UFP                  | 1.14 (0.81, 1.59)                                 | 1.01 (0.67, 1.52)                   | 1.41 (0.68, 2.93)                     |
| NO$_{x}$             | 0.99 (0.85, 1.14)                                 | 1.04 (0.87, 1.24)                   | 1.03 (0.75, 1.43)                     |
| UFP + NO$_{2}$       |                                                   |                                    |                                       |
| UFP                  | 1.34 (0.91, 1.98)                                 | 0.96 (0.59, 1.57)                   | 1.95 (0.84, 4.53)                     |
| NO$_{2}$             | 0.90 (0.76, 1.07)                                 | 1.06 (0.86, 1.31)                   | 0.86 (0.59, 1.25)                     |
Challenges in studying UFP health effects
Ohlwein Int J Publ Health 2019

High spatial and temporal variability of UFP necessitate different exposure assessment designs than the “classical” air pollutants with more homogeneous spatial distribution

Probability of systematic bias toward the null in single- and multi-pollutant studies due possibly larger exposure estimation error for UFP

Unclear confounding by other environmental factors (transportation noise; green space) and socio-economic status
Insights offered by exposome approaches
The exposome concept: an opportunity in environmental research

Siroux V Eur Resp Rev 2016
External Exposome: Personalized ultrafine particle measurements

PEM MiniDisc, Subject 304, Low Traffic Site, Season B

- Home
- Kitchen
- Bicycle
- Shopping
- Walking
- Urban
- Work
- Indoor Concert
- Restaurant
- Personal UFP
- Home Outdoor UFP
Personal exposure monitoring: regression calibration
• Regression calibration to derive de-attenuated dose-response relationship to estimate relative risks and disease burden
• Example: PM2.5 regression calibration applied to ESCAPE estimates

<table>
<thead>
<tr>
<th></th>
<th>Not Calibrated</th>
<th>Calibrated, high end</th>
<th>Calibrated, low end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.07</td>
<td>1.19</td>
<td>1.13</td>
</tr>
<tr>
<td>Ischemic heart disease incidence</td>
<td>1.13</td>
<td>1.38</td>
<td>1.24</td>
</tr>
<tr>
<td>Asthma incidence</td>
<td>1.04</td>
<td>1.11</td>
<td>1.07</td>
</tr>
</tbody>
</table>

• higher disease burden – but wider confidence intervals

• BUT:
  • Are 3*24h personal monitoring more valid than long-term LUR models?
  • Is personal monitoring the gold standard – particularly for peaky UFP exposures?
Internal Exposome: Molecular fingerprints mediating UFP effects

_Vineis Environmental Molecular Mutagenesis 2013_

Prospective Biosampling in Longitudinal Cohorts
Acute changes in DNA methylation in relation to 24 h personal air pollution exposure measurements: A panel study in four European countries Mostavafi N Env Int 2018

PM2.5 & DNA methylation
short-term > long-term
personal > ambient

UFP:
- no single signals
- 16 DMR (personal)
- 15 DMR (outdoor)
Association between immune markers and personal (A) and ambient (B) air pollution in two Exposomics study populations

Mostavafi N Env Int 2018

time lag?
UFP summary measure?
short- vs. long-term effects?
Oxidative stress and inflammation mediate the effect of air pollution on cardio- and cerebro-vascular disease

Fiorito G Environ Mol Mutagenesis 2018

Pathway enrichment for inflammation related to:
- Cytokine signaling
- ROS/Glutathione/Cytotoxic granules
Perturbation of Metabolic Pathways Mediates the Association of Air Pollutants with Asthma and CVDs

Jeong A et al. Environ Int 2018

Linoleate metabolism found to mediate association of long-term UFP exposure with asthma, but not with CVD
Towards systems epidemiology approaches
Systems epidemiology in the era of precision health from exposome * genome to phenome
Life and health in urban space

Urban exposome
- Physical activity
- Obesity
- Noise, greenspace, air pollution, chemicals
- Psycho-social stressors

Mechanisms
- Respiratory diseases
- Cardiovascular diseases
- Diabetes
- Alzheimer’s Parkinson’s

Urban phenome
- Hypothalamus-pituitary-adrenal axis
- Systemic inflammation
- Insulin resistance
Towards global systems epidemiology - UFP & infections
Life and health in urban space in epidemiological transition

- **Urban exposome**
  - Physical activity
  - Obesity
  - Noise, greenspace, air pollution, chemicals...
  - Psycho-social Stressors, Social capital

- **Mechanisms**
  - Systemic inflammation
    - Insulin resistance
    - Hypothalamus-pituitary-adrenal axis

- **Urban phenome**
  - Changes in infection & microbiome profile
    - Respiratory diseases
    - Cardiovascular diseases
    - Diabetes
    - Alzheimer’s, Parkinson’s
In utero UFP exposure causes offspring pulmonary immunosuppression
*Rychlik KA PNAS 2019*

Mouse model representing a period of immune maturation: exposed to UFP representing urban composition & concentration

In utero UFP exposure at a level close to the WHO recommended PM guideline suppresses an early immune response to HDM allergen, likely predisposing neonates to respiratory infection and altering long-term pulmonary health
Acknowledgement

SAPALDIA Team - SNF funded

Exposomics Team – EU funded
Recommended Readings