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Ultrafine particles and health – the urban exposome perspective

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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

Long-term UFP Effects – evidence 2011-2017

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-km 2 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

Pollutants	All cardiovascular disease 4,304 events	Coronary heart disease 2,399 events	Myocardial infarctions 797 events	Heart failure 369 events
Single-pollutant models	—	—	—	—
$PM_{2.5}$	0.98 (0.75, 1.28)	0.80 (0.55, 1.15)	0.83 (0.44, 1.57)	0.44 (0.16, 1.20)
PM_{coarse}	1.21 (1.01, 1.45)	1.26 (0.99, 1.60)	1.50 (1.01, 2.21)	1.70 (0.90, 3.21)
PM_{10}	1.20 (0.96, 1.50)	1.14 (0.85, 1.53)	1.27 (0.77, 2.09)	2.09 (0.99, 4.40)
UFP	1.18 (1.03, 1.34)	1.12 (0.94, 1.33)	1.34 (1.00, 1.79)	1.76 (1.17, 2.66)
$PM_{2.5}$ absorbance	1.07 (0.92, 1.23)	0.97 (0.80, 1.18)	1.12 (0.80, 1.56)	1.16 (0.70, 1.90)
NO_x	1.03 (0.98, 1.09)	1.02 (0.95, 1.10)	1.10 (0.97, 1.25)	1.13 (0.93, 1.37)
NO_2	1.04 (0.98, 1.10)	1.04 (0.97, 1.12)	1.12 (0.99, 1.26)	1.22 (1.01, 1.48)
Two-pollutant models	—	—	—	—
UFP + $PM_{2.5}$	—	—	—	—
UFP	1.28 (1.09,1.49)	1.27 (1.04, 1.57)	1.59 (1.13, 2.24)	3.10 (1.89, 5.10)
$PM_{2.5}$	0.74 (0.54, 1.02)	0.61 (0.40, 0.94)	0.51 (0.24, 1.05)	0.11 (0.03, 0.36)
UFP + PM_{coarse}	—	—	—	—
UFP	1.14 (0.95, 1.37)	0.99 (0.77, 1.27)	1.16 (0.76, 1.77)	1.84 (1.04, 3.26)
PM_{coarse}	1.06 (0.83, 1.37)	1.27 (0.91, 1.78)	1.30 (0.74, 2.28)	0.90 (0.37, 2.19)
UFP + PM_{10}	—	—	—	—
UFP	1.25 (1.01, 1.56)	1.16 (0.86, 1.57)	1.67 (1.01, 2.75)	1.94 (0.96, 3.92)
PM_{10}	0.88 (060, 1.28)	0.93 (0.56, 1.55)	0.63 (0.26, 1.50)	0.80 (0.22, 2.92)
UFP + $PM_{2.5abs}$	—	—	—	—
UFP	1.42 (1.13, 1.77)	1.49 (1.10, 2.01)	1.87 (1.12, 3.10)	3.98 (1.97, 8.04)
$PM_{2.5abs}$	0.78 (0.60, 1.00)	0.68 (0.48, 0.95)	0.63 (0.35, 1.13)	0.30 (0.13, 0.73)
UFP + NO_x	—	—	—	—
UFP	1.26 (1.04, 1.51)	1.17 (0.91, 1.51)	1.31 (0.85, 2.03)	2.10 (1.17, 3.79)
NO_x	0.96 (0.89, 1.04)	0.97 (0.87, 1.09)	1.01 (0.83, 1.22)	0.86 (0.67, 1.18)
UFP + NO_2	—	—	—	—
UFP	1.28 (1.04, 1.59)	1.09 (0.82, 1.47)	1.22 (0.74, 2.02)	1.75 (0.89, 3.45)
NO_2	0.96 (0.86, 1.05)	1.01 (0.90, 1.14)	1.05 (0.85, 1.28)	1.00 (0.74, 1.37)

Long-term UFP exposure & cerebrovascular disease incidence

Downward GS et al. EHP 2019

Pollutants	All incident cerebrovascular disease 1,283 events	Incident ischemic CVA 846 events	Incident hemorrhagic CVA 241 events
Single-pollutant models	—	—	—
$PM_{2.5}$	1.13 (0.69, 1.83)	0.90 (0.49, 1.66)	1.88 (0.66, 5.39)
PM_{coarse}	1.14 (0.80, 1.61)	1.22 (0.79, 1.86)	1.91 (0.90, 4.04)
PM_{10}	1.10 (0.73, 1.68)	1.13 (0.67, 1.89)	1.79 (0.71, 4.52)
UFP	1.11 (0.88, 1.41)	1.07 (0.80, 1.44)	1.48 (0.88, 2.51)
$PM_{2.5}$ absorbance	1.07 (0.82, 1.40)	1.01 (0.72, 1.41)	1.47 (0.81, 2.66)
NO_x	1.03 (0.92, 1.14)	1.04 (0.92, 1.18)	1.15 (0.91, 1.44)
NO_2	1.00 (0.90, 1.11)	1.05 (0.92, 1.19)	1.09 (0.86, 1.37)
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

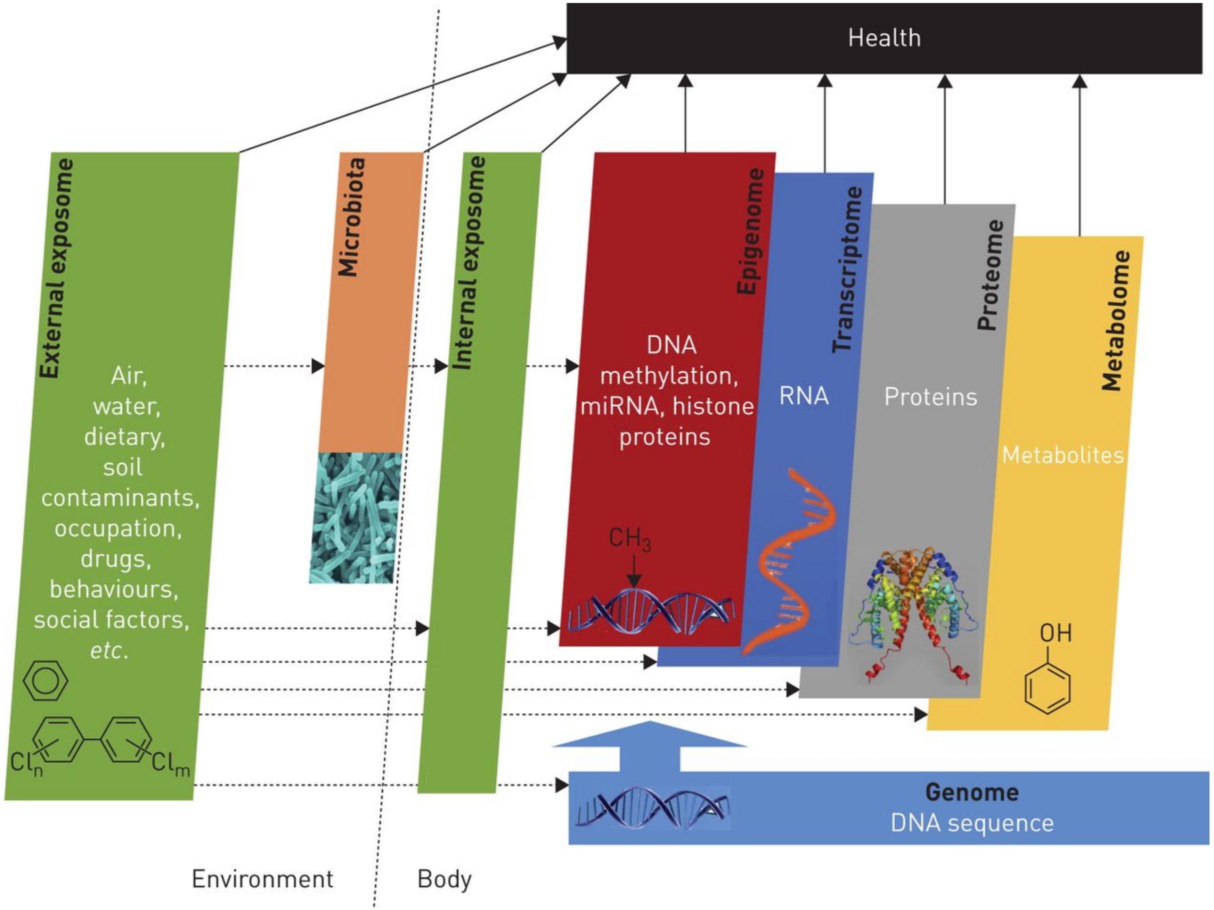
Probability of systematic bias toward the null in single- and multi-pollutant studies due possibily larger exposure estimation error for UFP

Unclear confounding by other environmental factors (transportation noise; green space) and socio-economic status

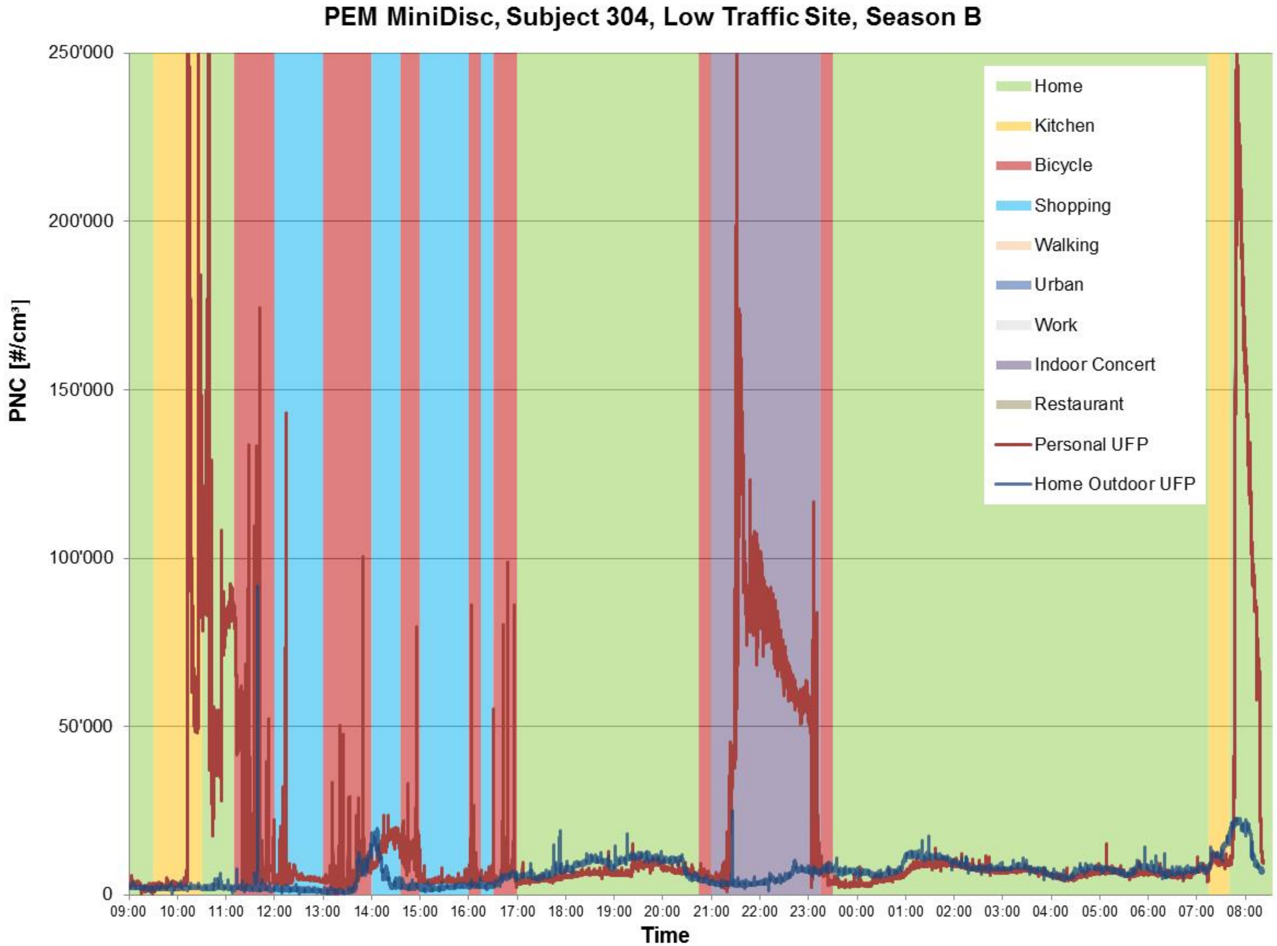
Insights offered by exposome approaches

The exposome concept: an opportunity in environmental research

Siroux V Eur Resp Rev 2016



External Exposome:
Personalized ultrafine particle measurements



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

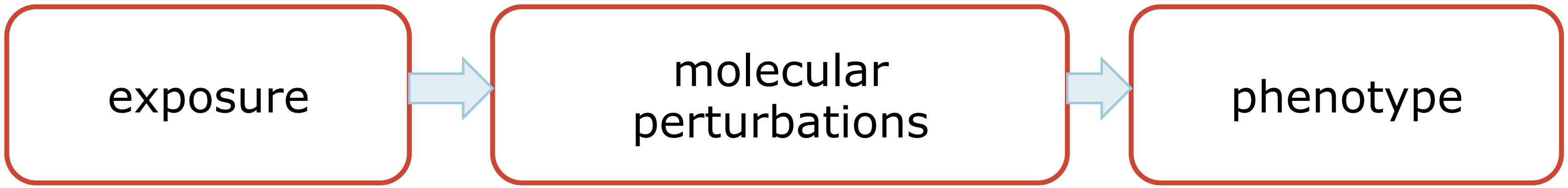
	Not Calibrated	Calibrated, high end	Calibrated, low end
Mortality	1.07	1.19	1.13
Ischemic heart disease incidence	1.13	1.38	1.24
Asthma incidence	1.04	1.11	1.07

  - 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

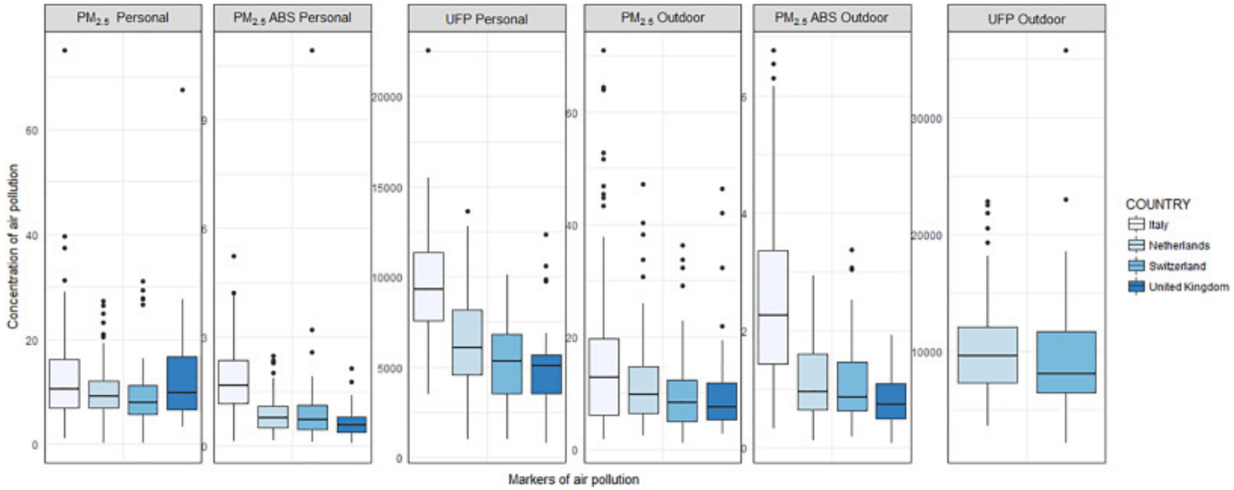
Vineis Environmental Molecular Mutagenesis 2013

Prospective Biosampling in Longitudinal Cohorts

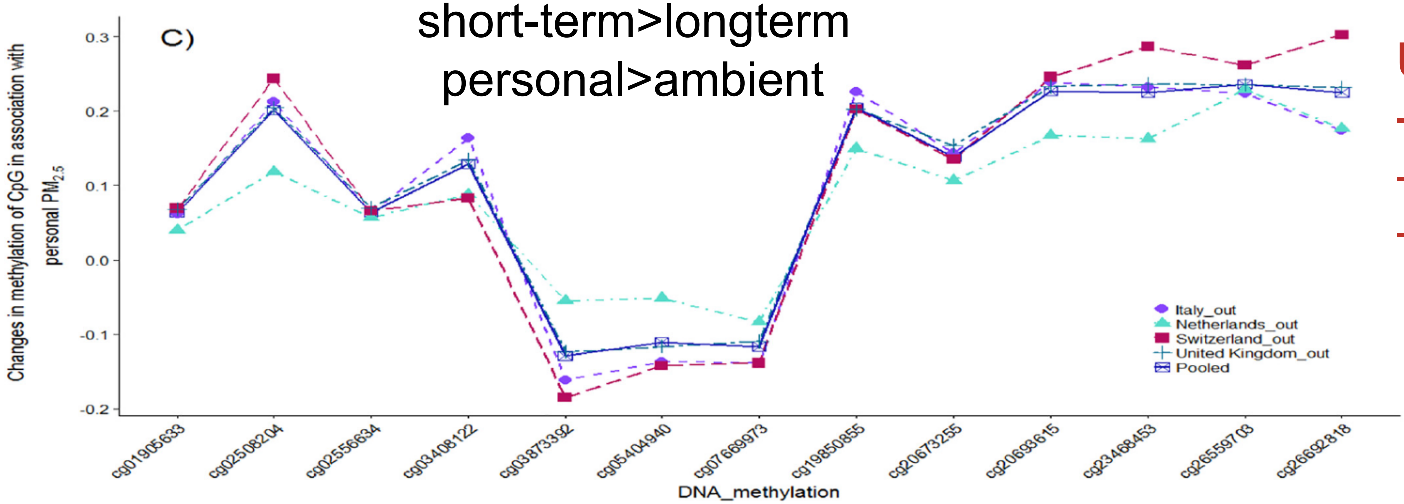


Acute changes in DNA methylation in relation to 24 h personal air pollution exposure measurements:

A panel study in four European countries *Mostavafi N Env Int 2018*



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

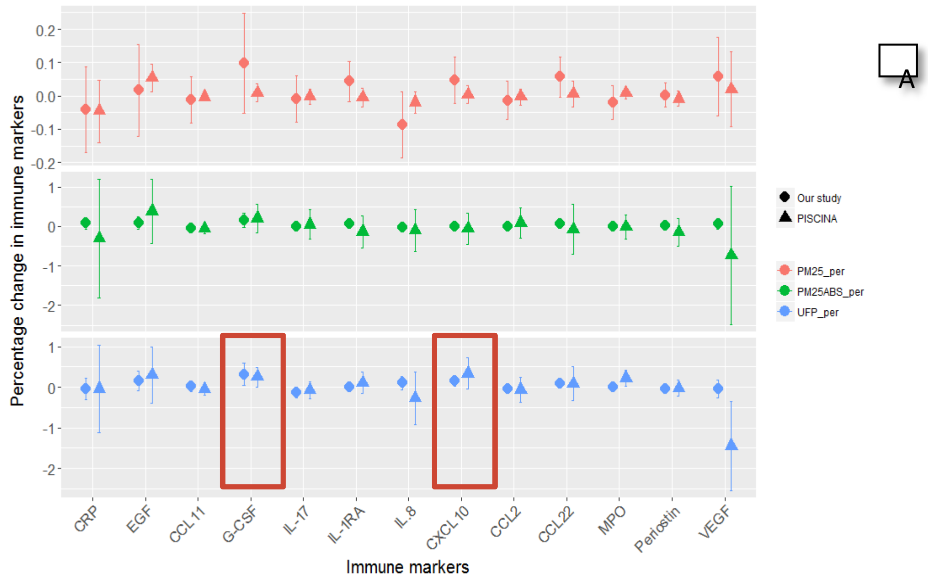


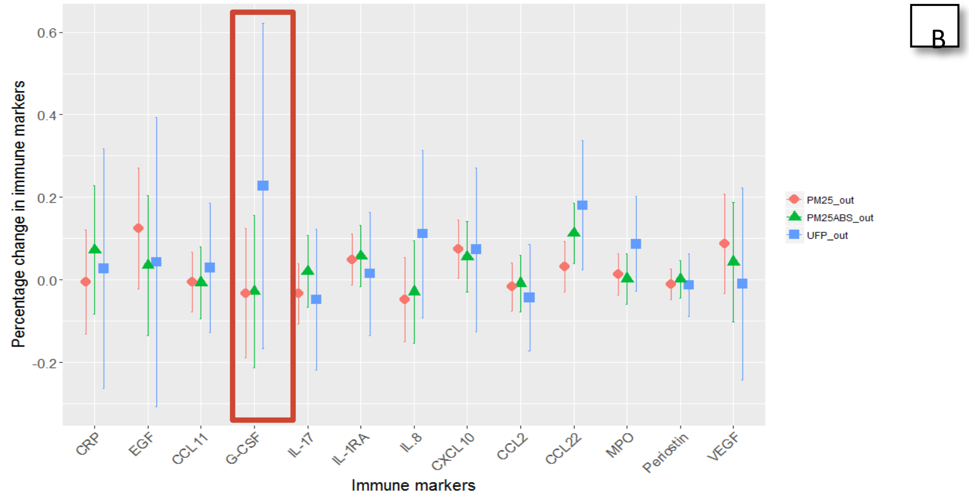
UFP:
- no single signals
- 16 DMR (personal)
- 15 DMR (outdoor)

Association between immune markers and personal (A) and ambient (B) air pollution in two Exposomics study populations

Mostavafi N Env Int 2018

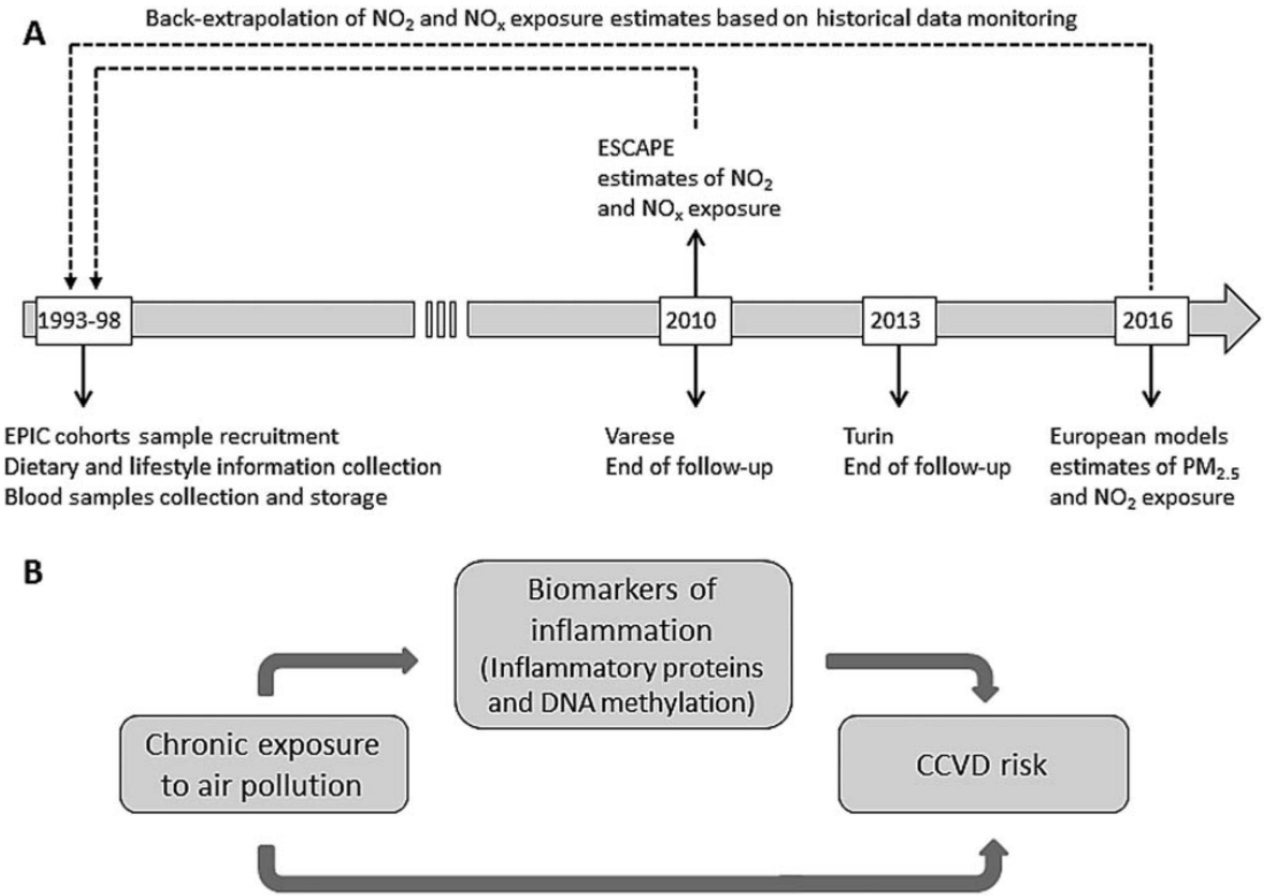
time lag ?
UFP summary measure?
short- vs. long-term effects?





Oxidative stress and inflammation mediate the effect of air pollution on cardio- and cerebro-vascular disease

Fiorito G Environ Mol Mutagenesis 2018

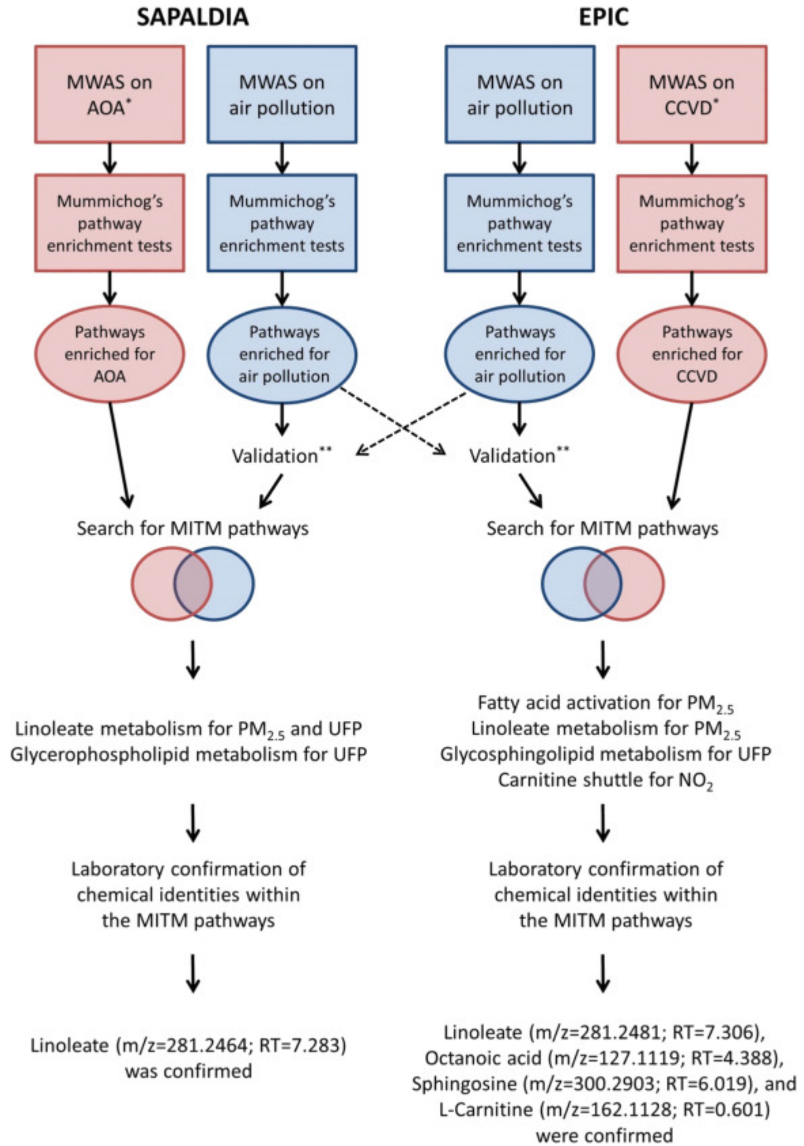


Pathway enrichment for inflammation related to:

- **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

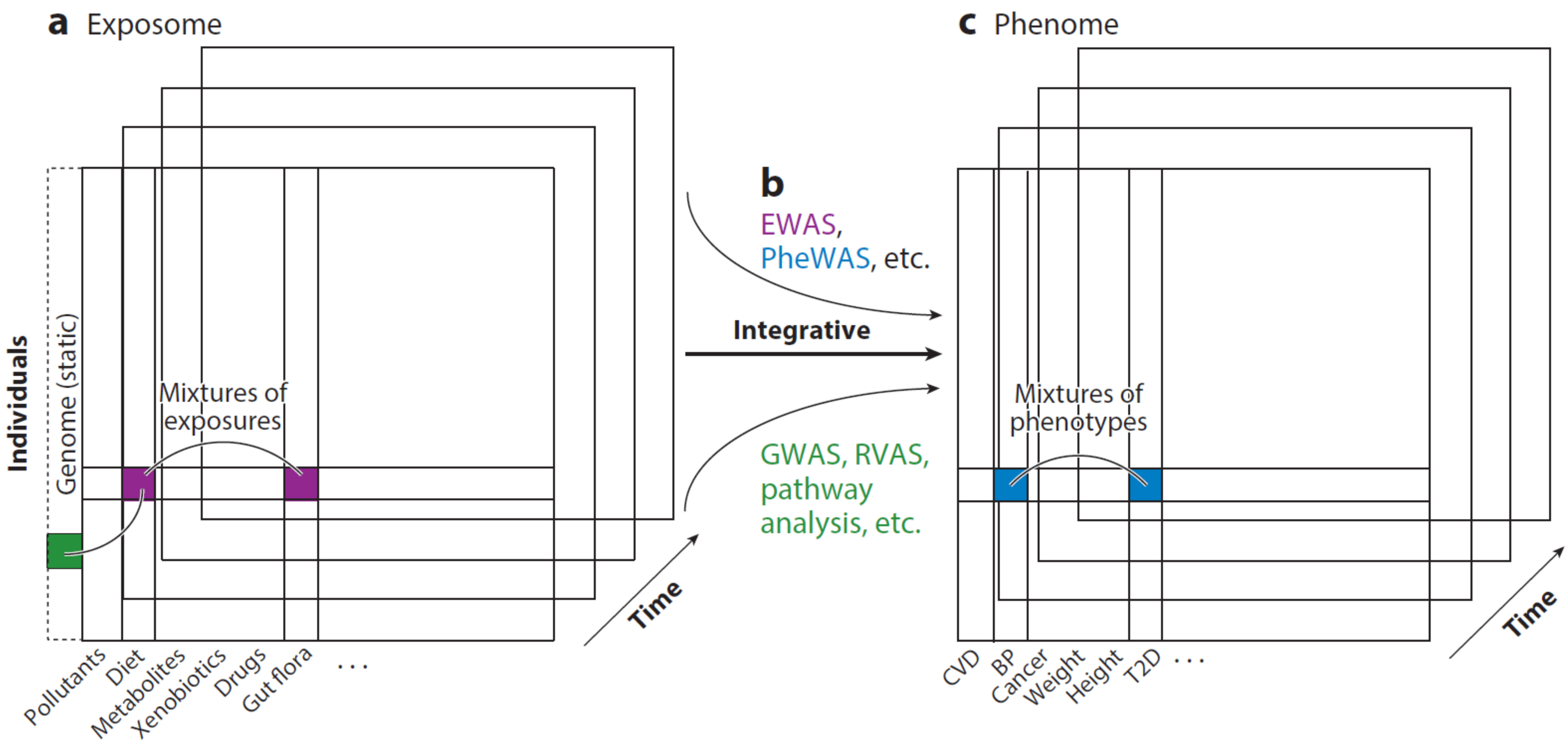
found to mediate association of long-term UFP exposure with asthma, but not with CVD

Towards systems epidemiology approaches

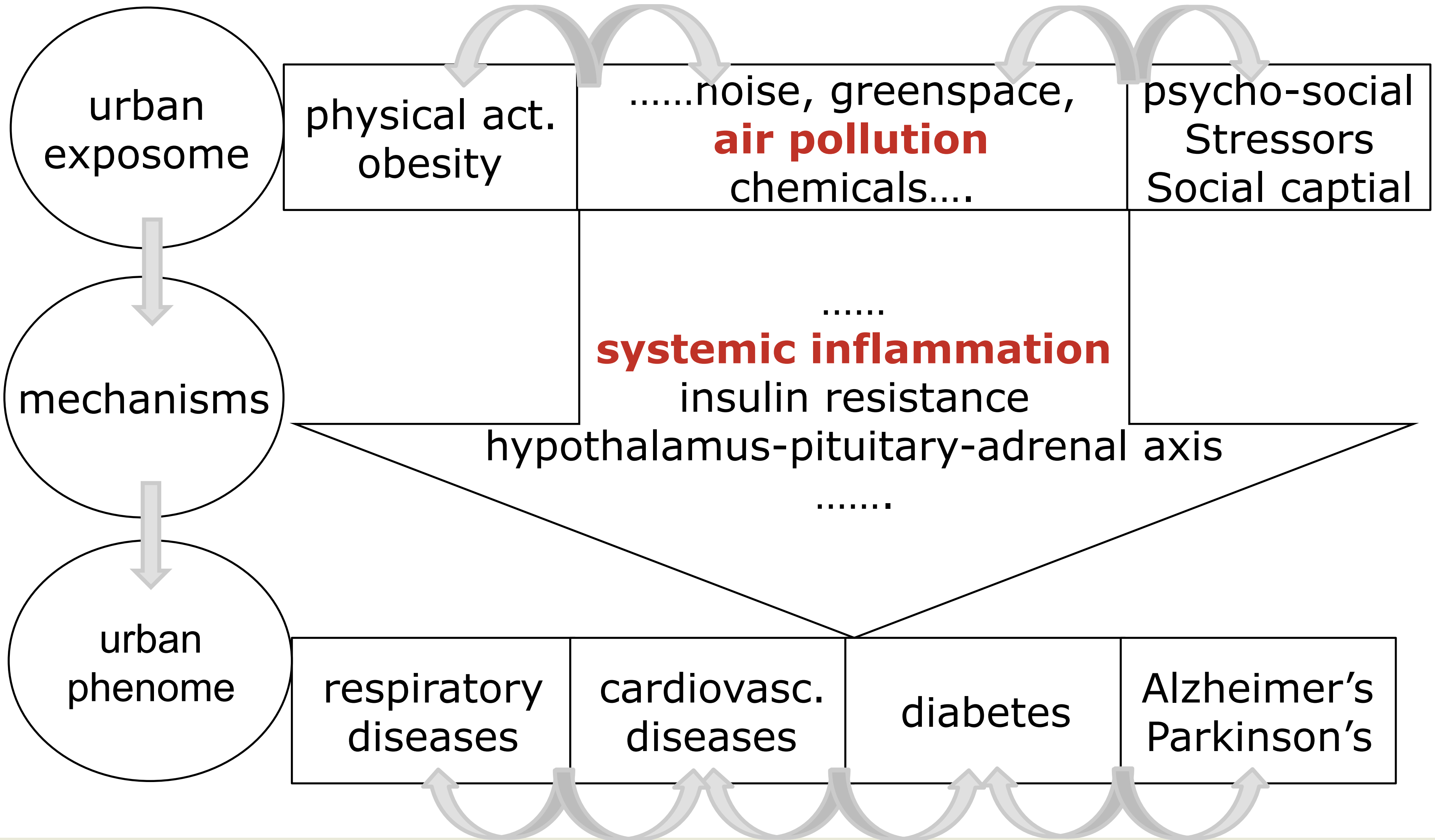
Systems epidemiology in the era of precision health

from exposome * genome to phenome

Manrai AK et al. Annu. Rev. Public Health 2017. 38:279–94

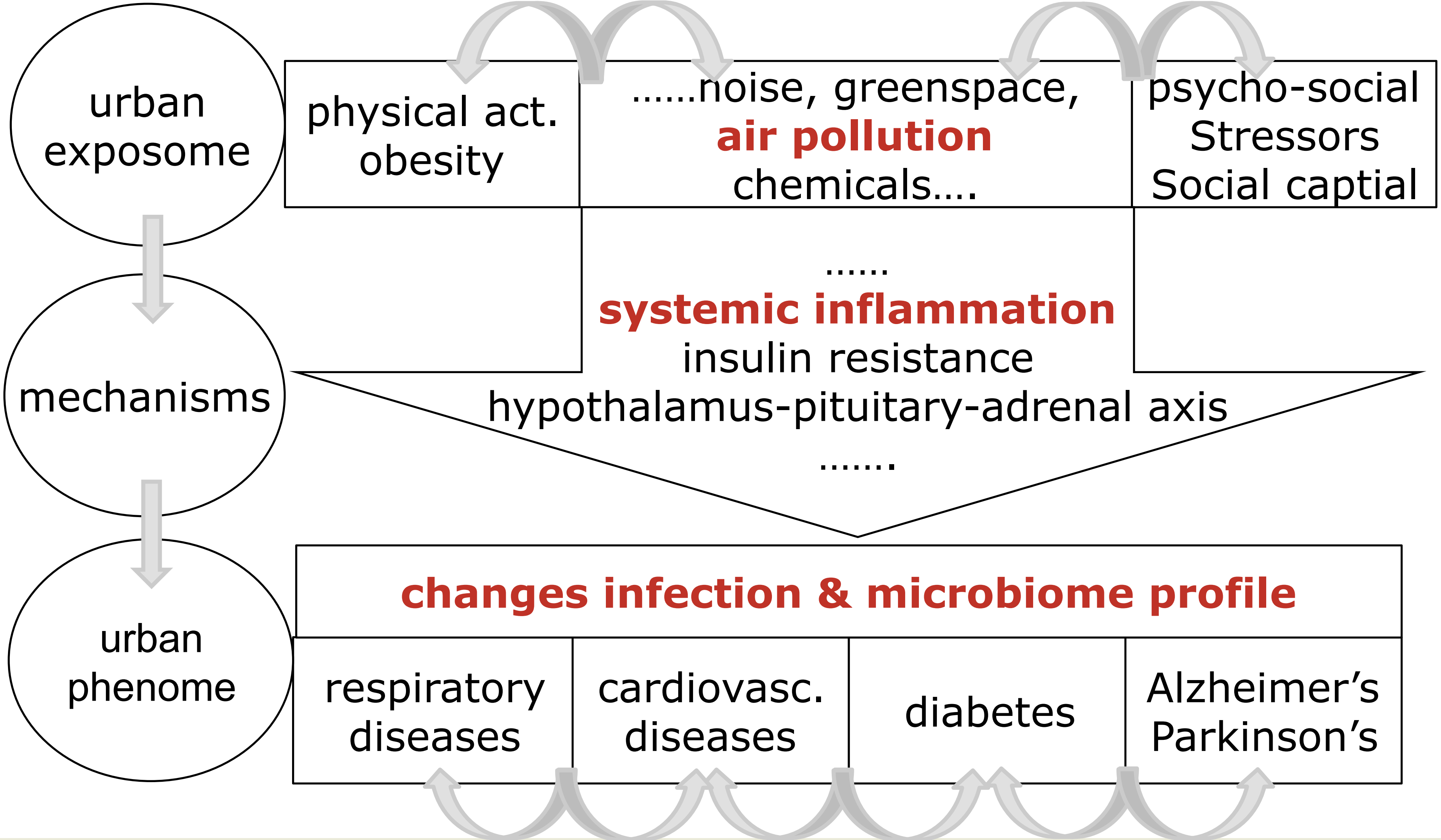


Life and health in urban space



Towards global systems epidemiology - UFP & infections

Life and health in urban space in epidemiological transition



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

Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of the epidemiological evidence. Int J Public Health 2019;64(4):547-559