New approaches to Epidemiological Risk Assessment of Low Level Exposures to Air Pollution

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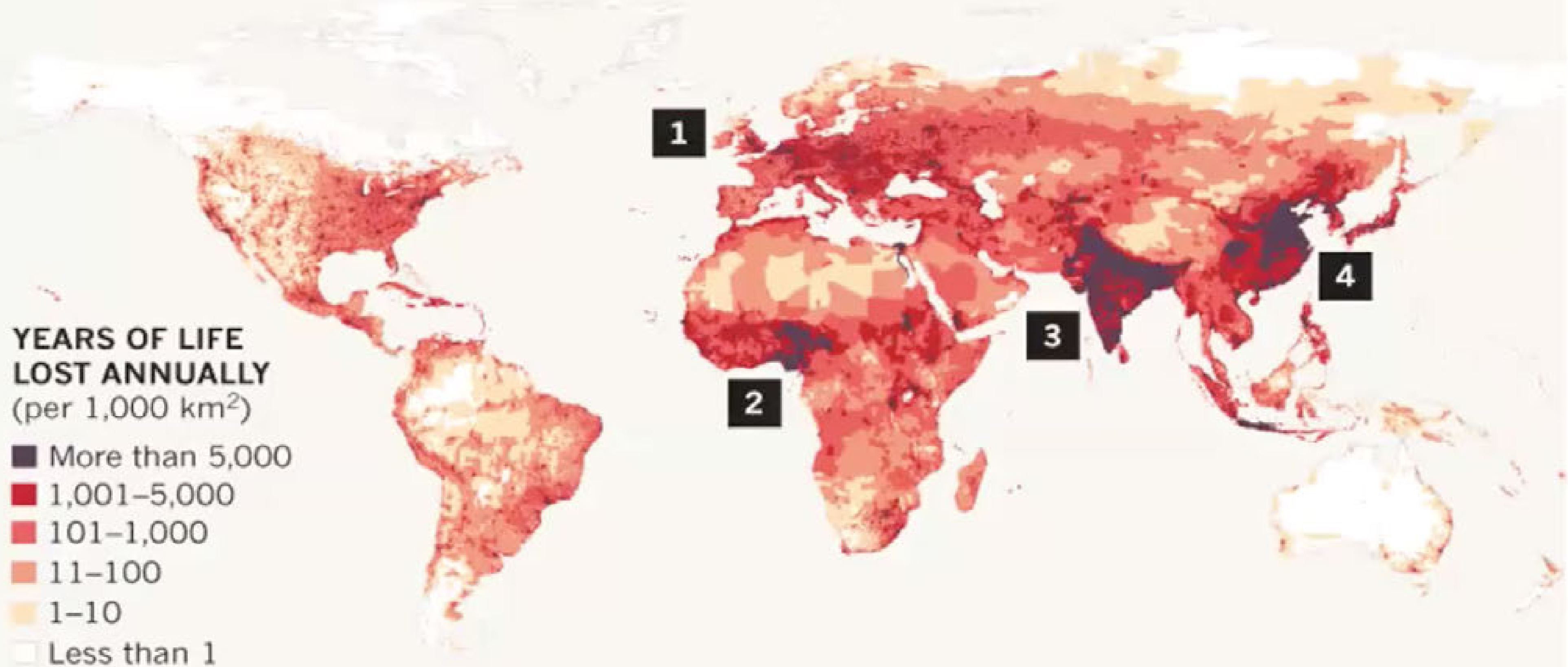
- I have no conflicts of interest to declare

LOST YEARS

Air pollution around the world leads to around 4.5 million deaths and 120 million years of life lost each year.



1 Since 1970, the **UK** death rate from air pollution has reduced by 30% through EU legislation.

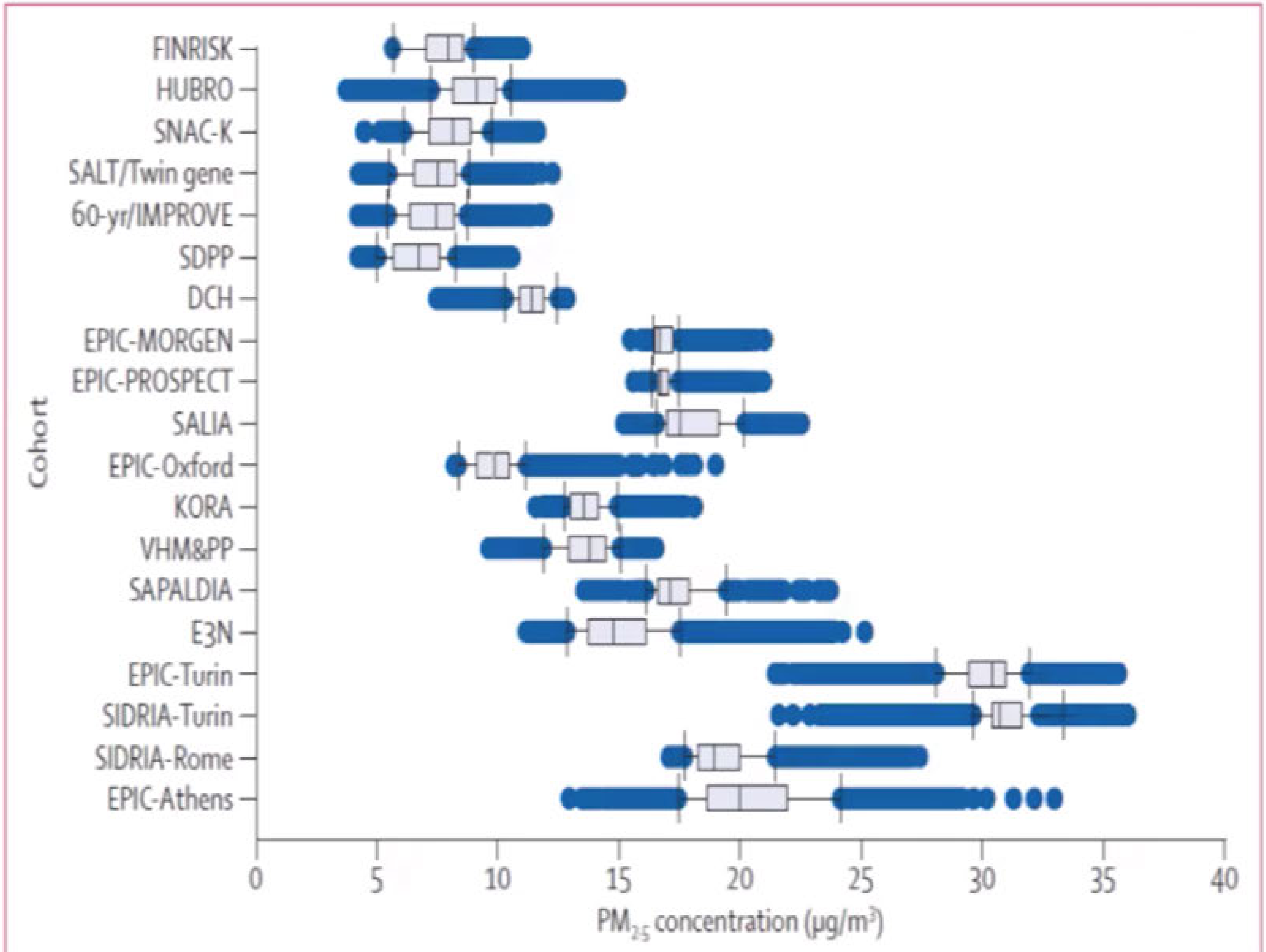
2 In **West Africa**, desert dust adds to air pollution.

3 **India's** air quality has worsened fastest in the past decade.

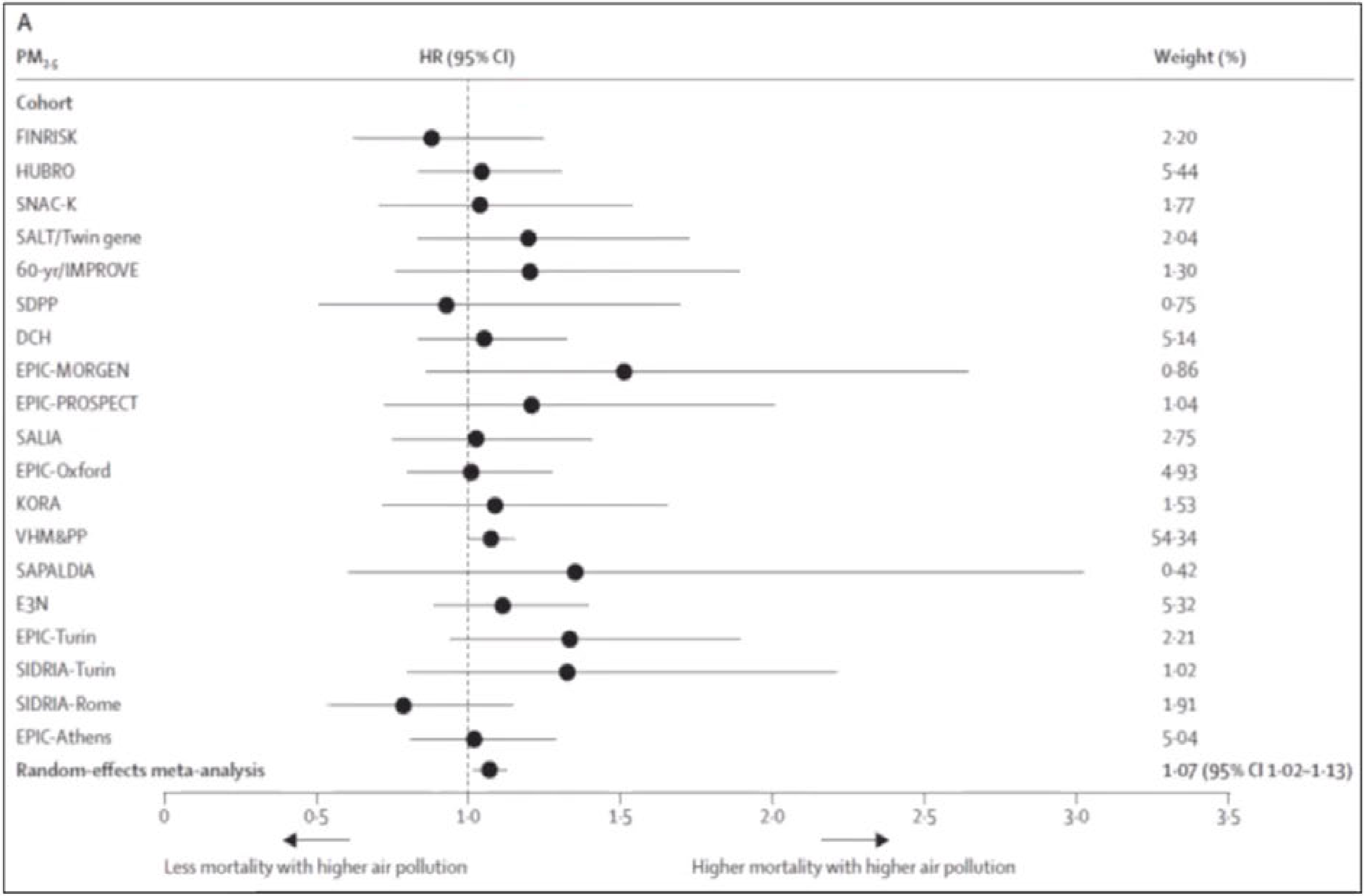
4 **China's** air quality started improving in 2010.

Areas with population data are shown; an average is assumed for countries without detailed data.

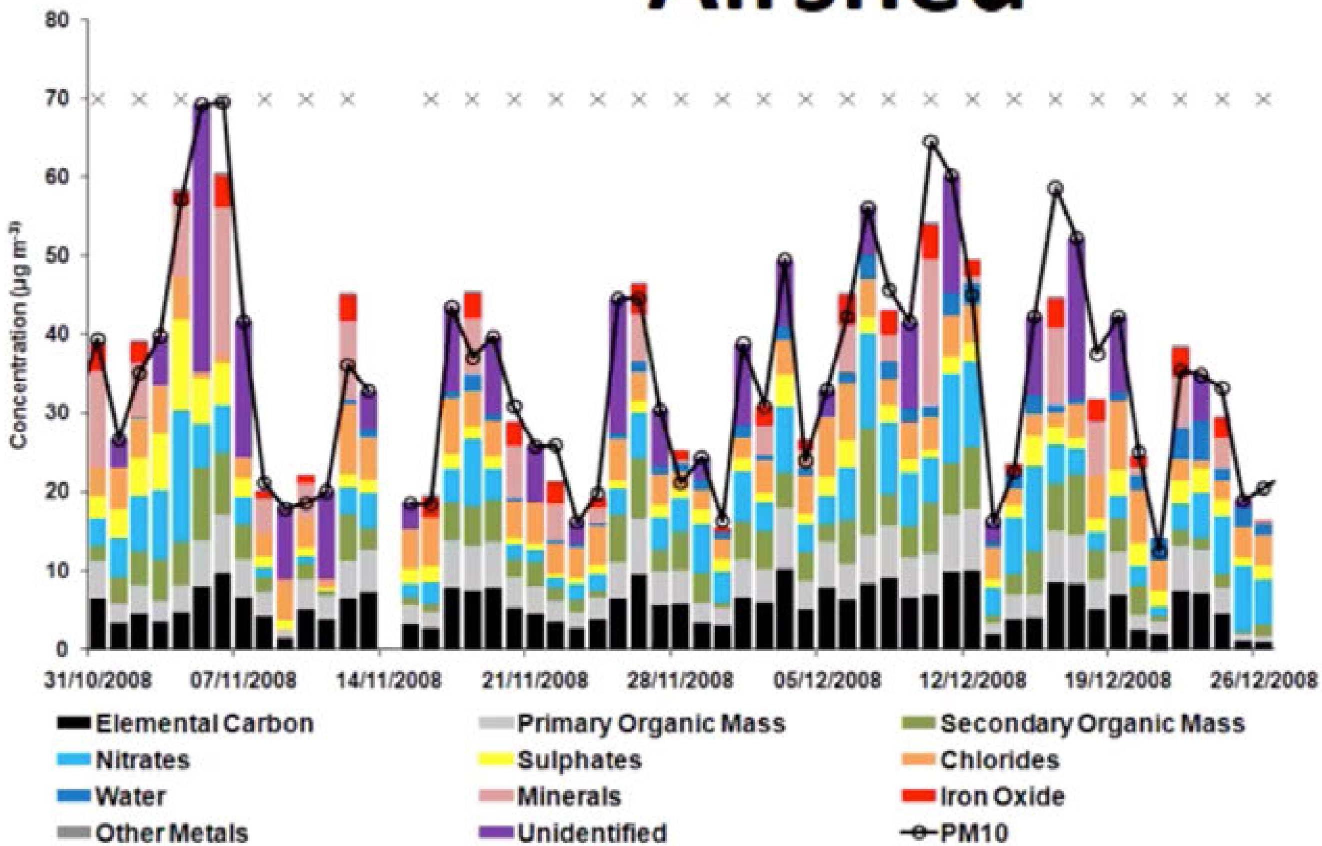
Heterogeneity of exposure in European cities: PM2.5 in the ESCAPE project.



Total mortality in relation to PM2.5 (Beelen R et al 2014, Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet. 2014 Mar 1;383(9919):785-95)



Traffic contributions to the London Airshed



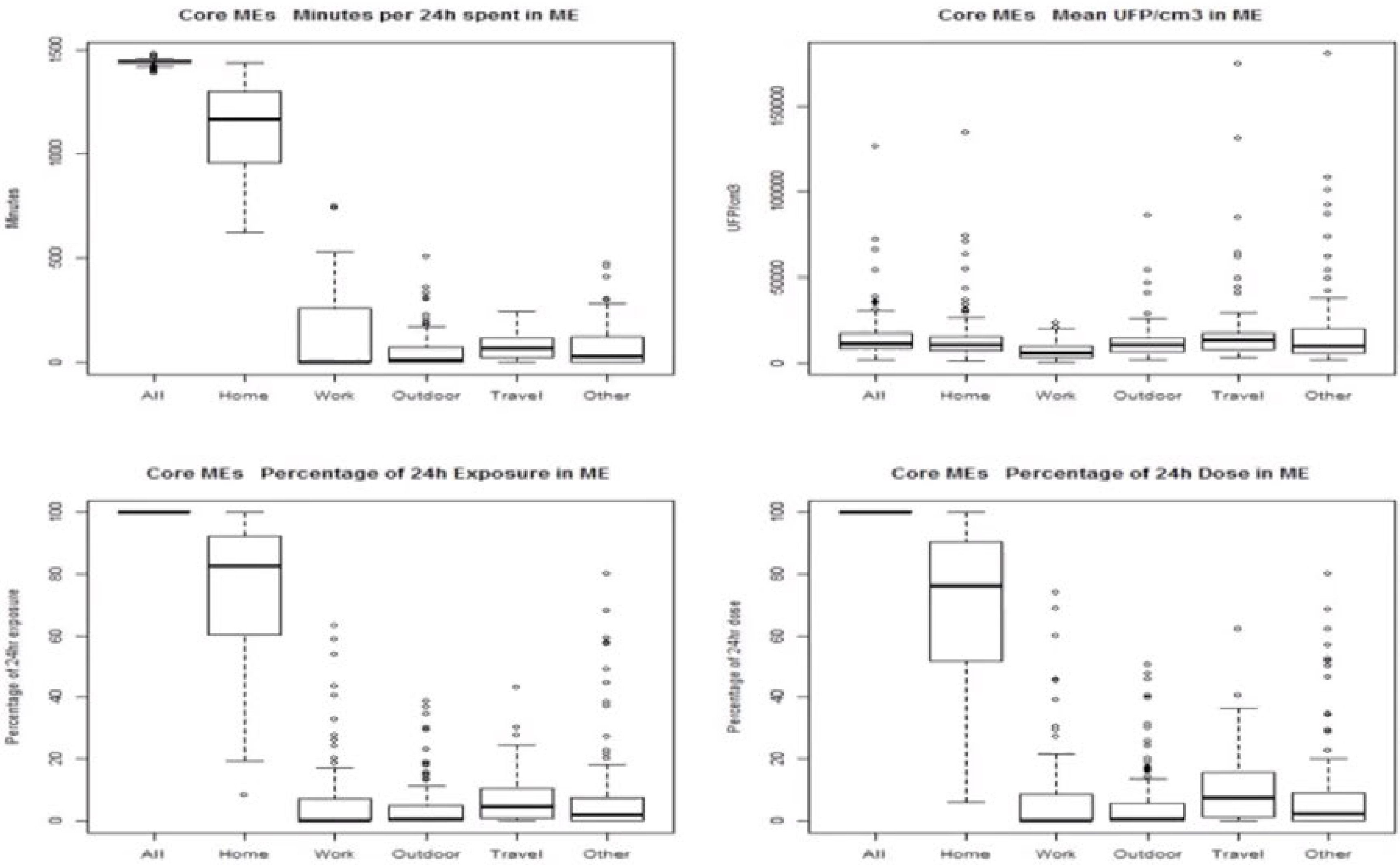
NOx background: Cars (21.6%), LGVs (7.1%), HGVs (8.8%), buses (10.6%). Total traffic contribution: 48.6%.

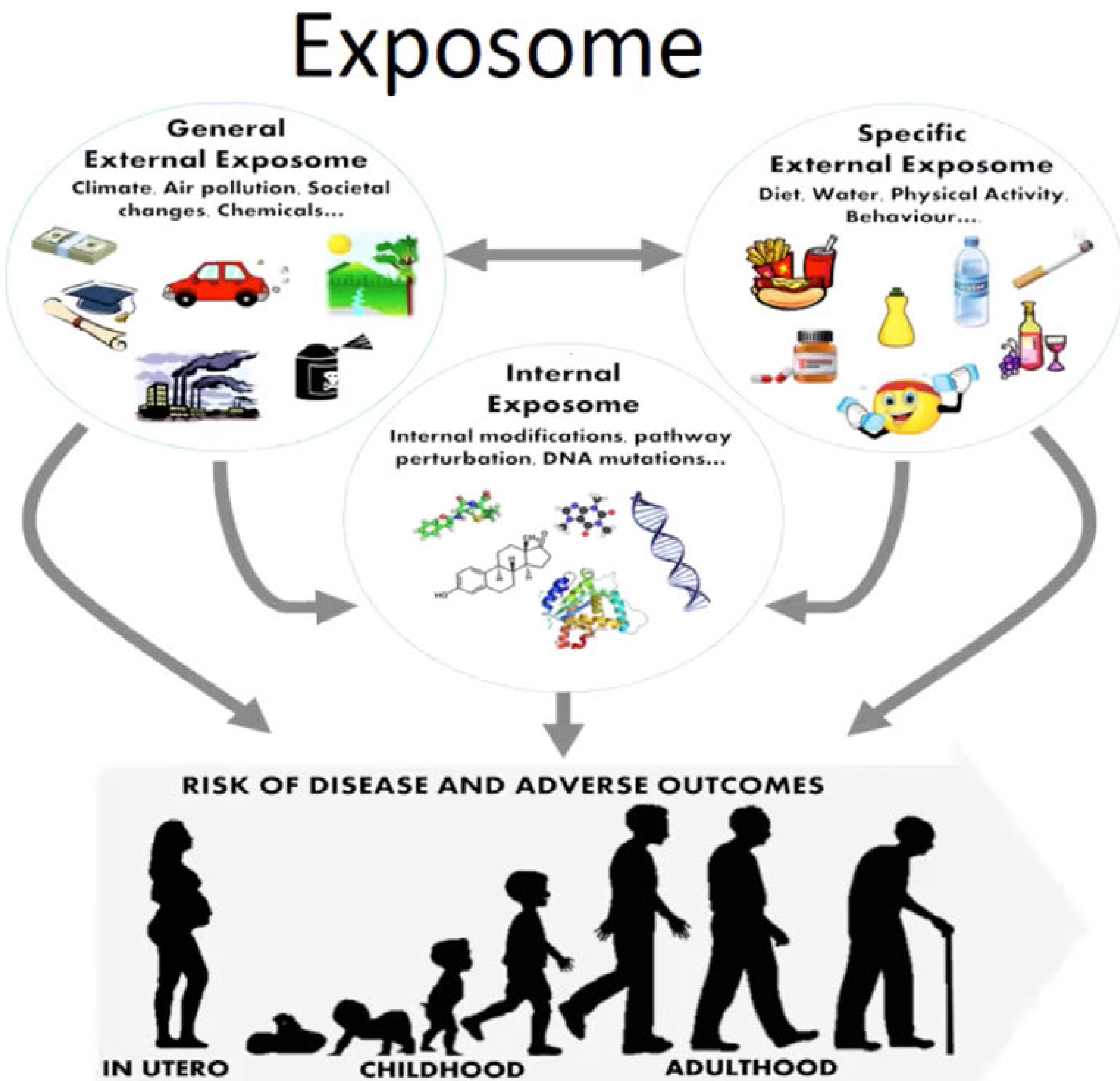
NOx roadside: Cars (28.3%), LGVs (11.1%), HGVs (10.1%), buses (30.6%). *Total traffic contribution: 80.1%.*

$PM_{2.5}$ background: Cars (2.9%), LGVs (1.1%), HGVs (0.9%), buses (0.3%), vehicle non-exhaust (5.8%). Total traffic contribution: 11.0%.

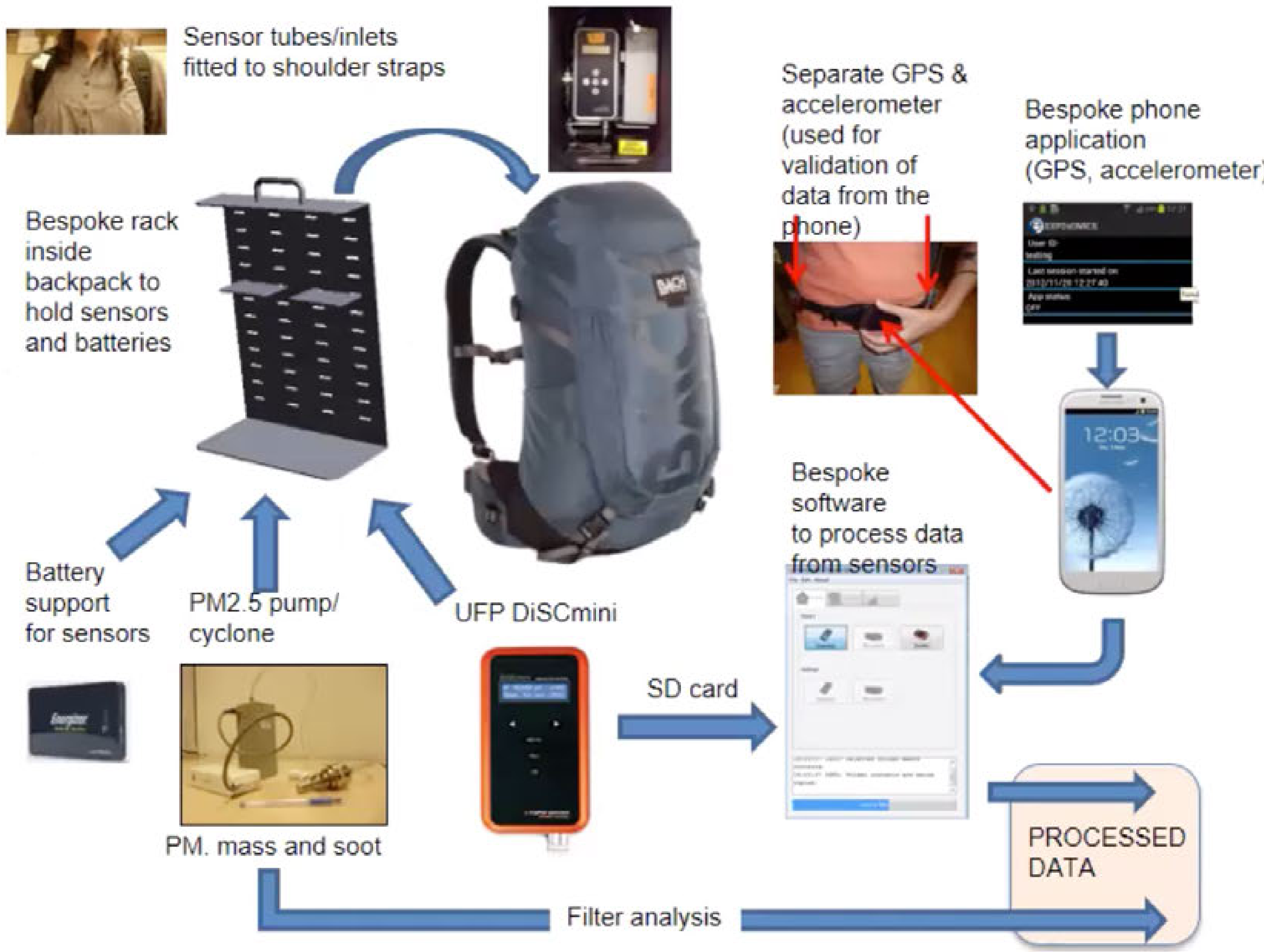
$PM_{2.5}$ roadside: Cars (7.0%), LGVs (2.9%), HGVs (2.3%), buses (2.2%), vehicle non-exhaust (14.7%). Total traffic contribution: 29.1%.

Contribution of microenvironment to UFP exposure in The Netherlands



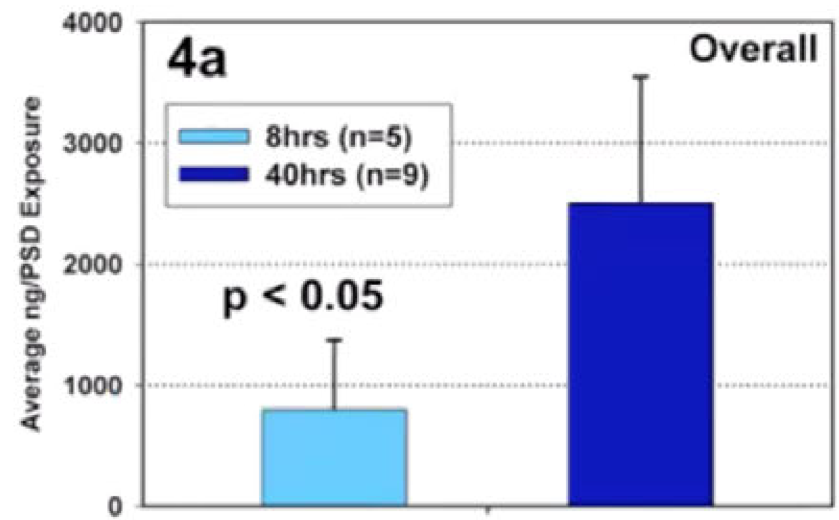


Exposome
General External Exposome
Climate, Air pollution, Societal changes, Chemicals...
Specific External Exposome
Diet, Water, Physical Activity, Behaviour...
Internal Exposome
Internal modifications, pathway perturbation, DNA mutations...
RISK OF DISEASE AND ADVERSE OUTCOMES
IN UTERO
CHILDHOOD
ADULTHOOD



Sensor tubes/inlets fitted to shoulder straps
Separate GPS & accelerometer (used for validation of data from the phone)
Bespoke phone application (GPS, accelerometer)
Bespoke rack inside backpack to hold sensors and batteries
12:03
Bespoke software to process data from sensors
Battery support for sensors
PM2.5 pump/ cyclone
UFP DiSCmini
SD card
PM. mass and soot
PROCESSED DATA
Filter analysis

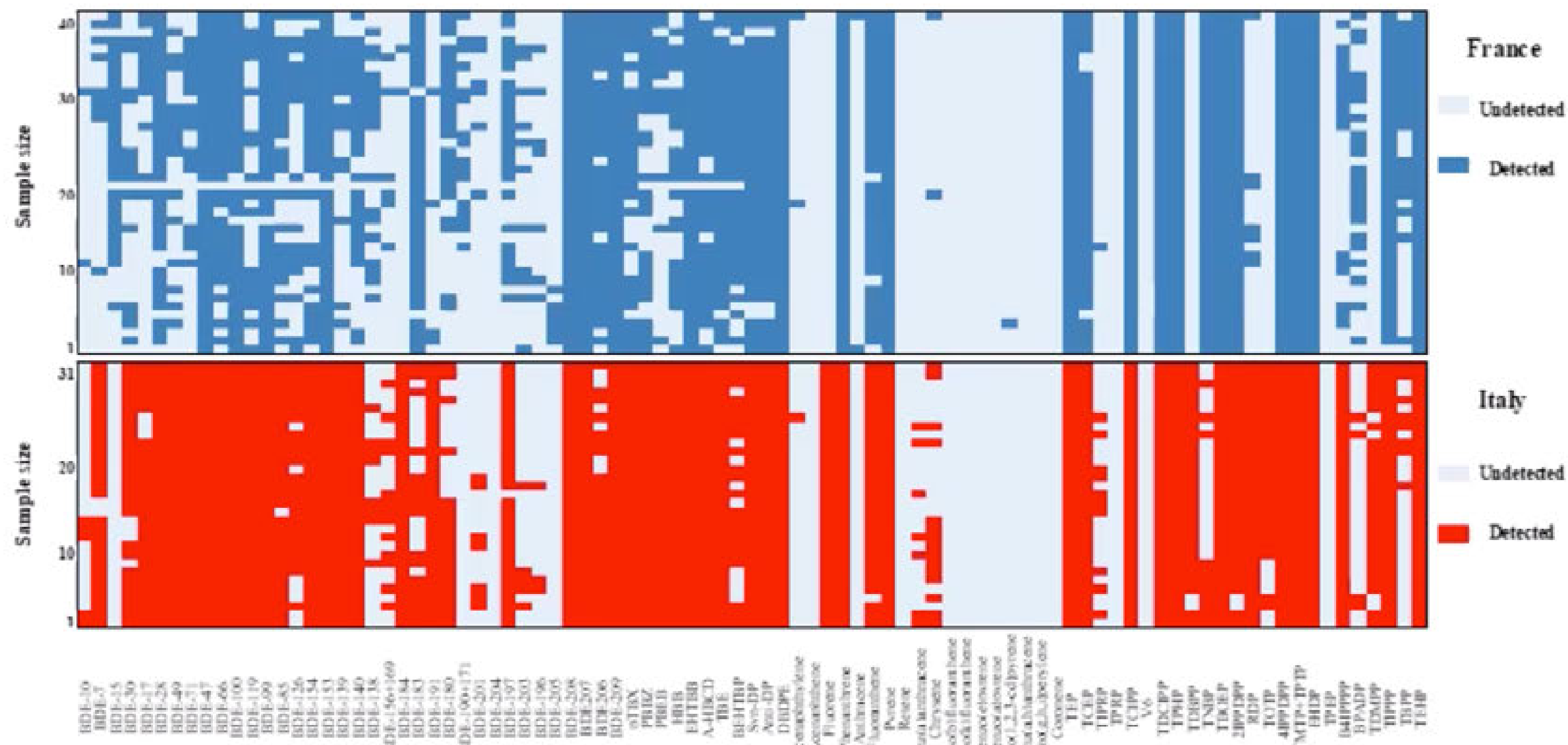
Silicone wristbands

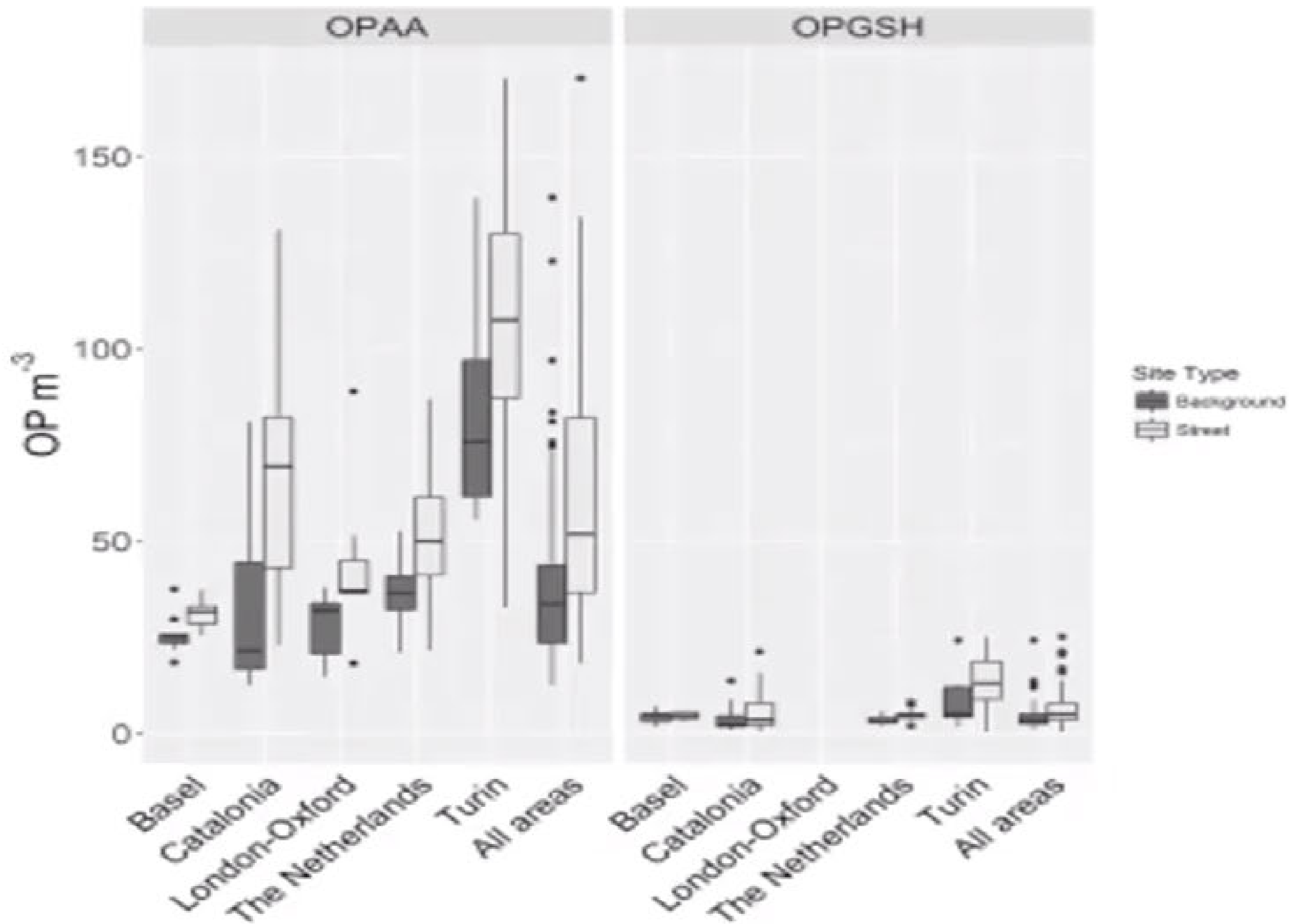


PAHS measured with wristbands

O'Connell et al., 2014, Silicone Wristbands as Personal Passive Samplers, ES&T, 48 : 3327-3335

Detection map of all 92 SVOCs (including 39 PBDEs (Polybrominated diphenyl ethers), 10 nBFRs, (brominated flame retardants) 25 OPE (Organophosphate esters)), and 18 PAHs) tested in the wristbands collected from France (n = 40) and Italy (n = 31). Wang et al, in press

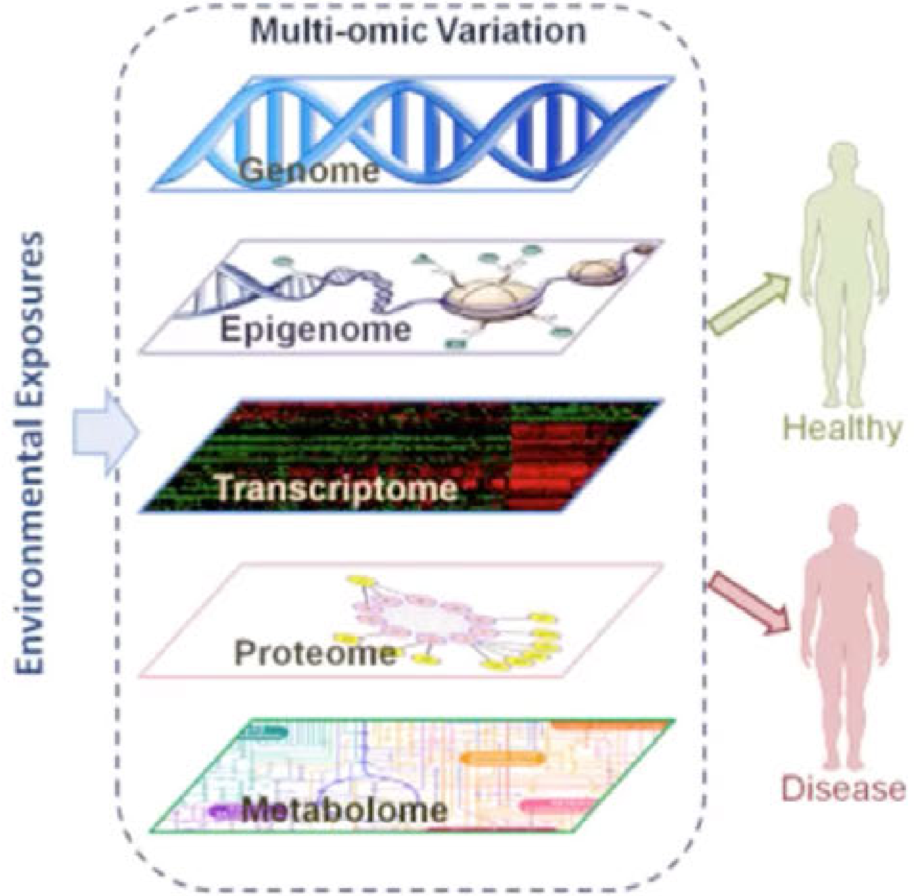




OXIDATIVE POTENTIAL OF AIR POLLUTION

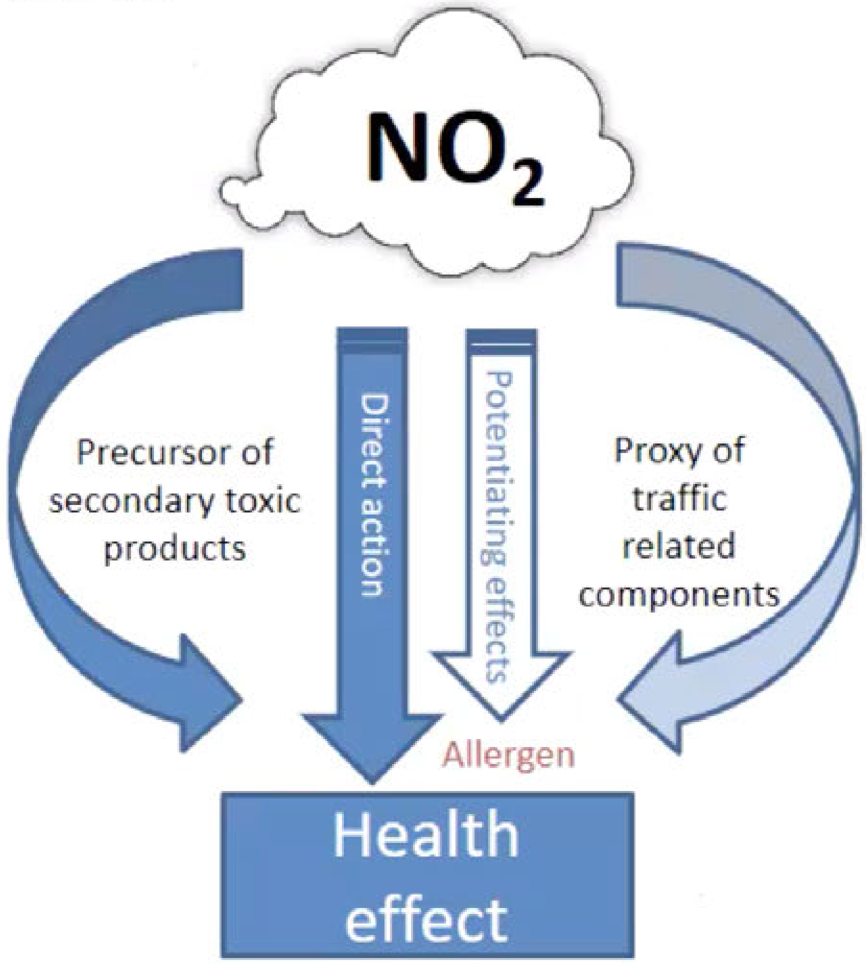
Gulliver et al, Environ Res 2017. Boxplots of measured annual average concentration (% consumption) of OP^{AA} and OP^{GSH} by study are

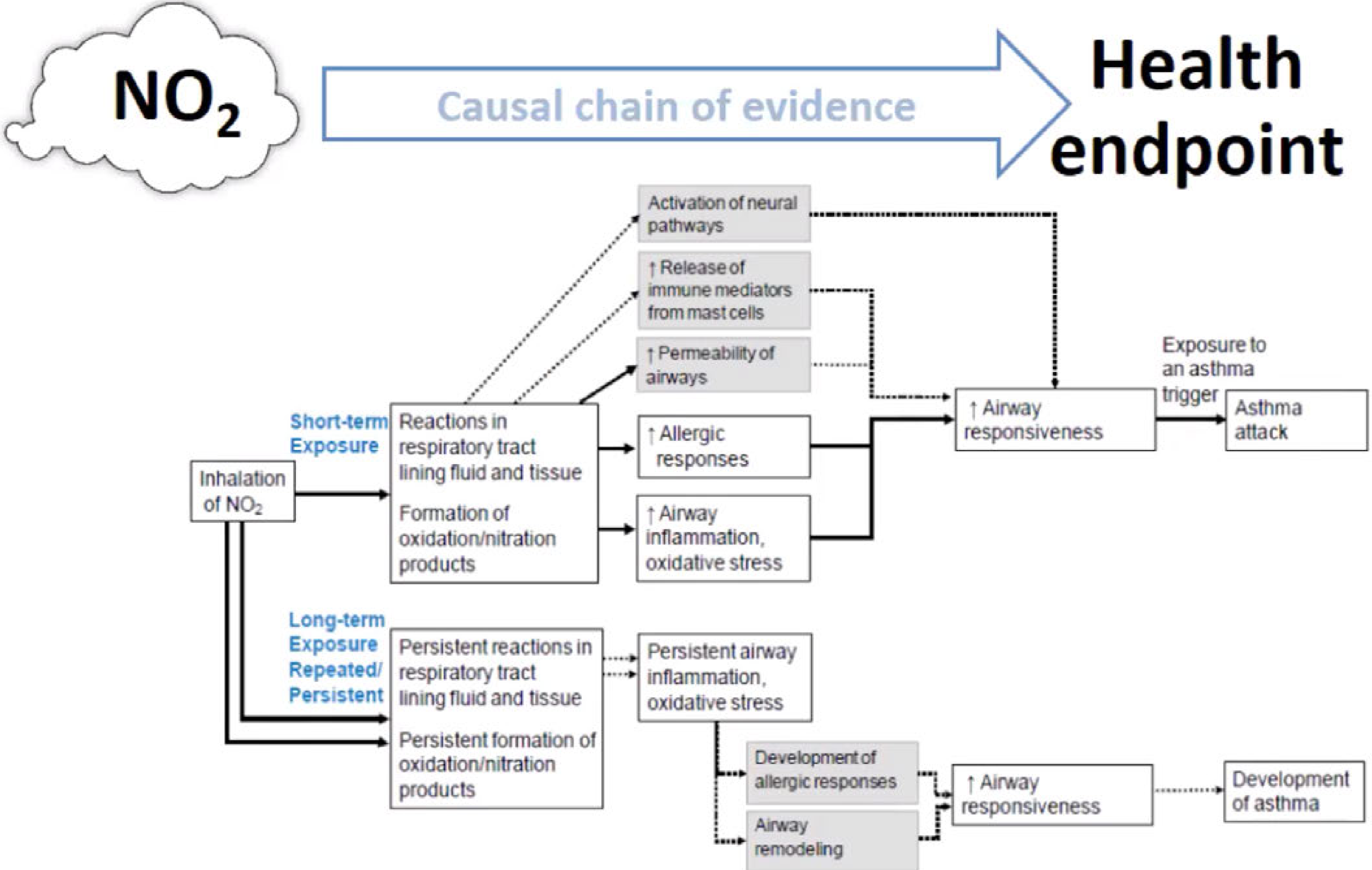
Internal exposome : “OMICS”



An example of questions: NO_2 - a surrogate for traffic pollutants?

- **<u>Still no robust basis</u>** for setting a value for NO_2 through any direct toxic effect.
- Does NO_2 at ambient levels have any detectable toxicity on the human lung?
- Which aspects/components of combustion mixtures are responsible for the adverse health effects observed in epidemiological studies?
- Is NO_2 able to synergise with other pollutants e.g. PM/allergen (role as an effect modifier)?

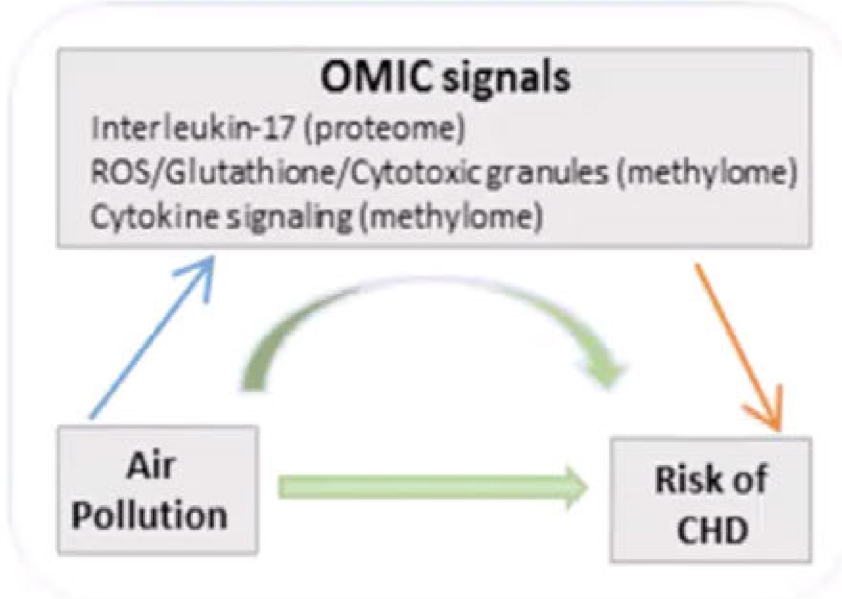



NO2
Causal chain of evidence
Health endpoint
Activation of neural pathways
↑ Release of immune mediators from mast cells
↑ Permeability of airways
Short-term Exposure
Reactions in respiratory tract lining fluid and tissue
Formation of oxidation/nitration products
Inhalation of NO2
↑ Allergic responses
↑ Airway inflammation, oxidative stress
↑ Airway responsiveness
Exposure to an asthma trigger
Asthma attack
Long-term Exposure Repeated/ Persistent
Persistent reactions in respiratory tract lining fluid and tissue
Persistent formation of oxidation/nitration products
Persistent airway inflammation, oxidative stress
Development of allergic responses
Airway remodeling
↑ Airway responsiveness
Development of asthma

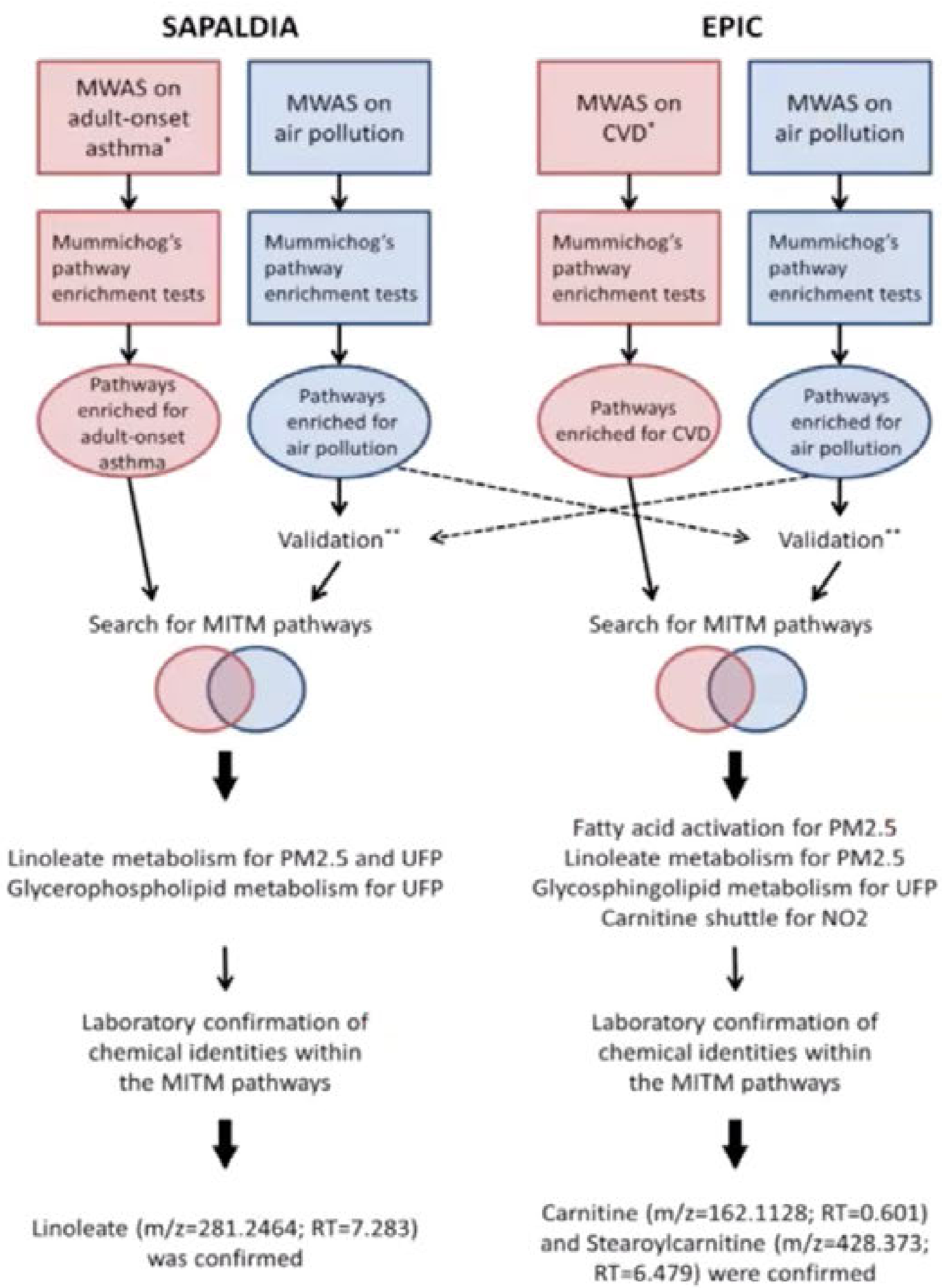
Meet-in-the-middle

CVD: One inflammatory protein (Interleukin-17), and two DNA methylation inflammatory pathways ('ROS/Glutathione/Cytotoxic granules' and 'Cytokine signaling') were significantly associated with both exposure to air pollution and the risk of CHD, fulfilling the 'meet-in-the-middle' hypothesis.

Fiorito et al, Environmental Molecular Mutagenesis, 2017

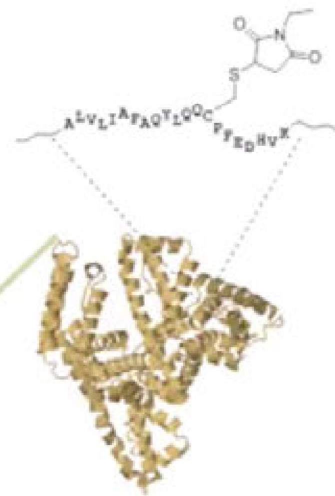


Results from molecular mediation are consistent with air pollution impacting on both asthma and CVD via pro-inflammatory and oxidative stress pathways, albeit different molecules may be involved in the two groups of diseases.



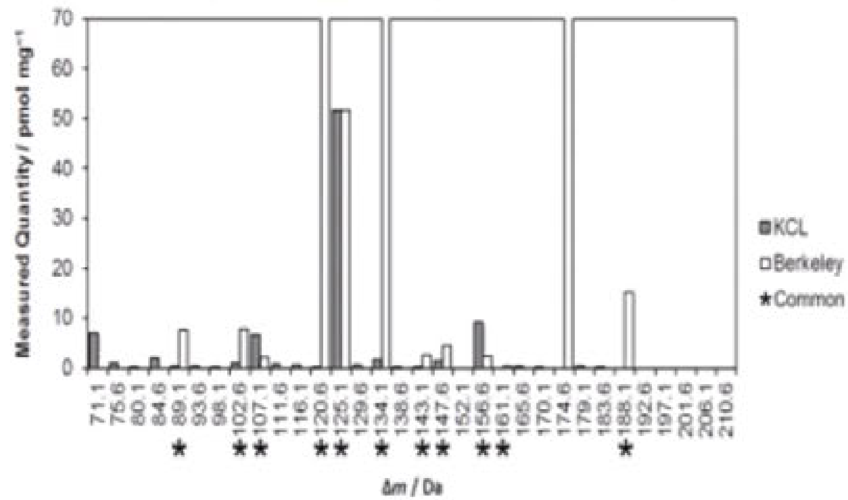
SAPALDIA
EPIC
MWAS on adult-onset asthma*
MWAS on air pollution
MWAS on CVD*
MWAS on air pollution
Mummichog's pathway enrichment tests
Mummichog's pathway enrichment tests
Mummichog's pathway enrichment tests
Mummichog's pathway enrichment tests
Pathways enriched for adult-onset asthma
Pathways enriched for air pollution
Pathways enriched for CVD
Pathways enriched for air pollution
Validation**
Validation**
Search for MITM pathways
Search for MITM pathways
Linoleate metabolism for PM2.5 and UFP
Glycerophospholipid metabolism for UFP
Fatty acid activation for PM2.5
Linoleate metabolism for PM2.5
Glycosphingolipid metabolism for UFP
Carnitine shuttle for NO2
Laboratory confirmation of chemical identities within the MITM pathways
Laboratory confirmation of chemical identities within the MITM pathways
Linoleate (m/z=281.2464; RT=7.283) was confirmed
Carnitine (m/z=162.1128; RT=0.601) and Stearoylcarnitine (m/z=428.373; RT=6.479) were confirmed

Fingerprints of exposure: Adductomics



New technologies may serve the purpose of increasing sensitivity and specificity in identifying relevant chemicals in mixtures, low-dose effects and dose-response : adductomics

- Pilot study of smokers and non-smokers (n=40)
- PISCINA 2 – before and after swimming in a chlorinated pool (n=120)
- PEM study – air pollution exposure measured by personal monitors (n=584)
- Oxford Street 2 – before and after 2 hours spent in a highly polluted street (n=354)
- Lung cancer study – nested case-control of EPIC cohort (n=400)

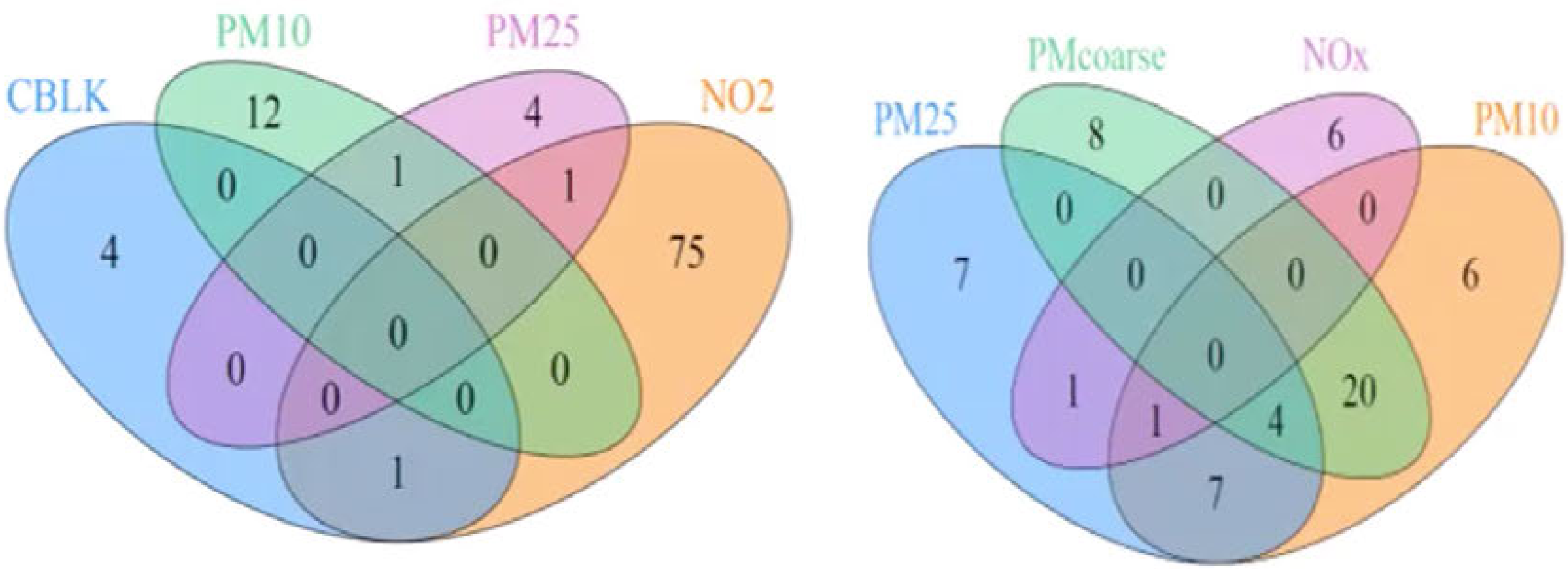


Courtesy G Preston and Steve Rappaport

- Untargeted methodology. Data from two different (complementary) MS-based platforms. Semi-synthetic control adduct detected by both groups

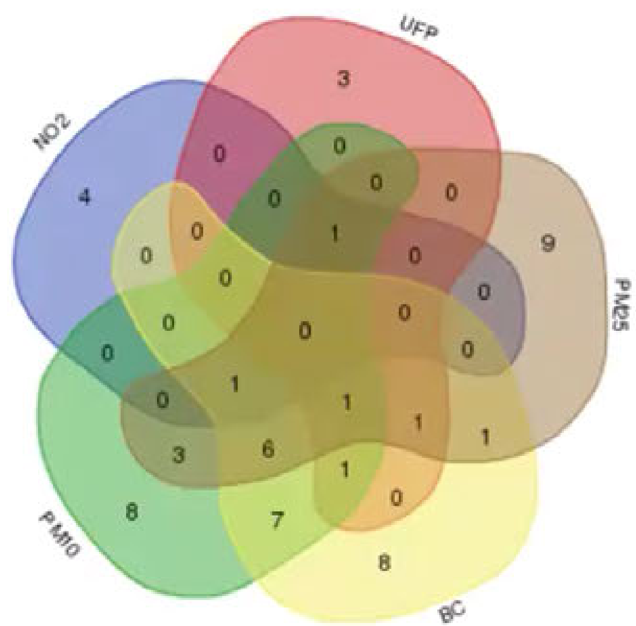
Effects of components in a mixture

Metabolomic signatures of different components of air pollution (Oxford Street study, left, and TAPAS, right) (Bonferroni significance)



Mixtures: Transcriptomics

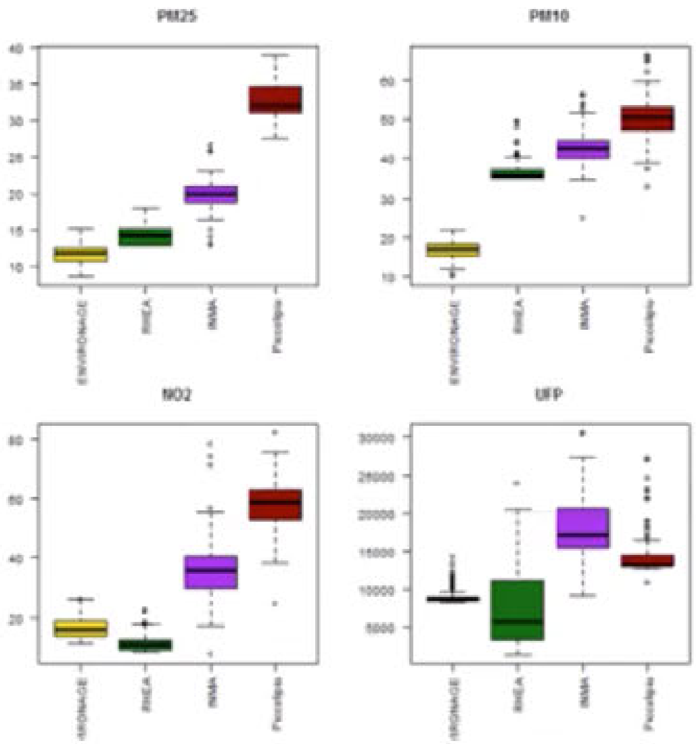
miRNA work in relation to air pollution shows that air pollutants impact several pathways via miRNA activation that in turn are relevant to the multi-organ toxicity of air pollution

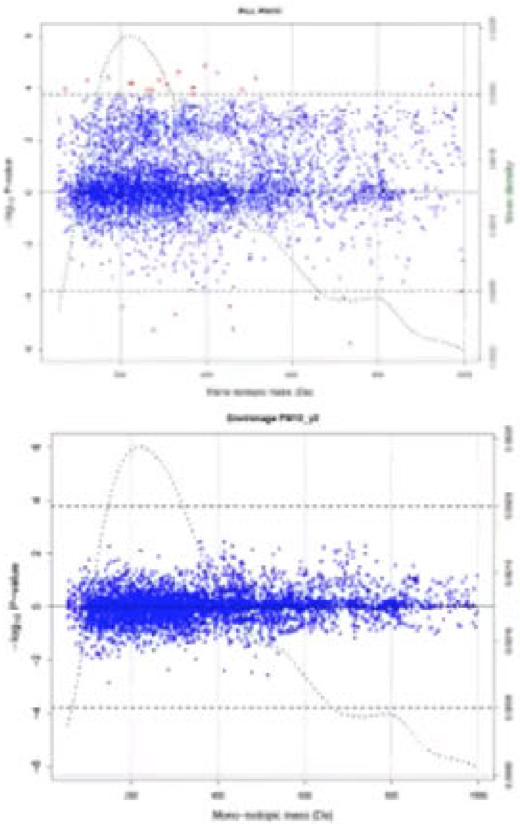


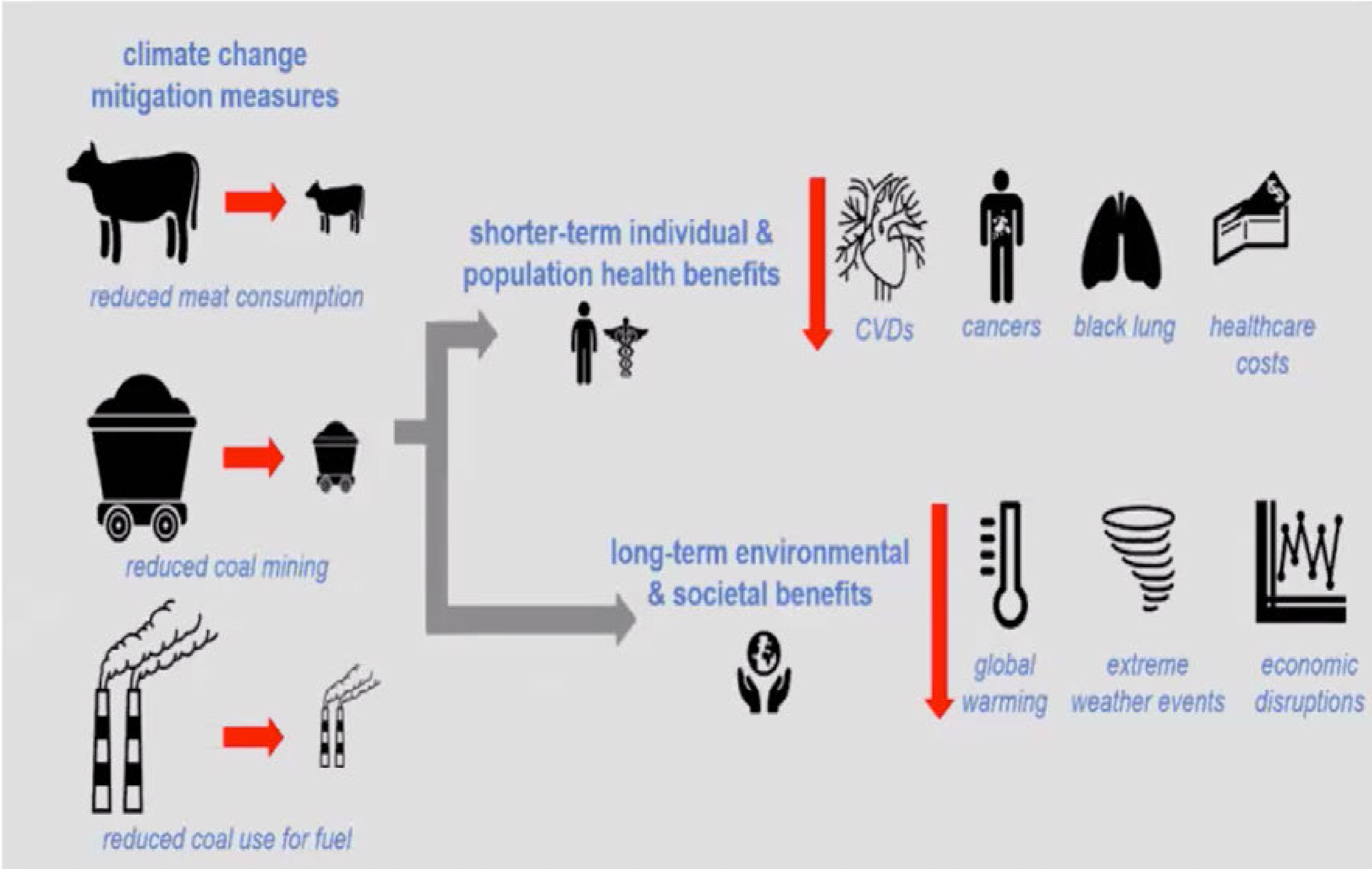
Pollutant-specific cmiRNAs associated with TRAP exposure. The figure shows the overlap as well as the specificity of the pollutant-specific cmiRNAs associated with exposure to NO2, UFP, PM2.5, BC and PM10 of the included subjects in Hyde Park and Oxford Street. **Julian Krauskopf et al, 2018**

Low levels of exposure in EXPOsOMICS

PM 10 by cohort (left) and metabolomic signals (right) in Piccoli+ (very high exposure levels) and in Environage (low exposure levels) Bonferroni threshold - $p = 1.63 \times 10^{-4}$







Philosophy of co-benefits

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