Imperial College London

The Science and Technology Facilities Council Air Quality Network to stimulate Multidisciplinary approaches to Unmet Air Pollution Challenges - Toxicology

Ian Mudway

Imperial College London

MRC Centre for Environment & Health

UKRI Medical Research Council

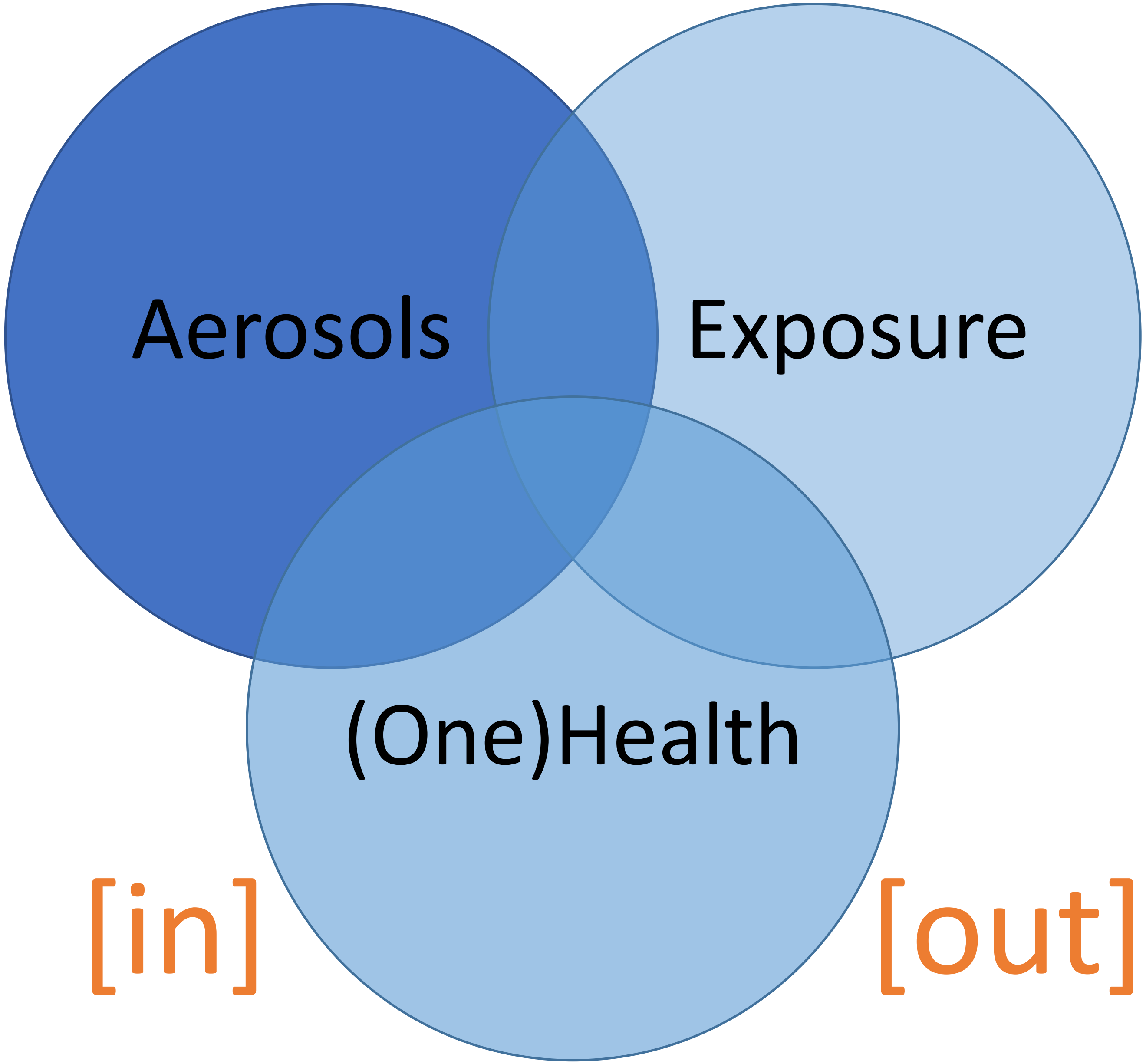
Imperial College London

NIHR | Health Protection Research Unit in Chemical and Radiation Threats and Hazards at Imperial College London

NIHR | Health Protection Research Unit in Environmental Exposures and Health at Imperial College London

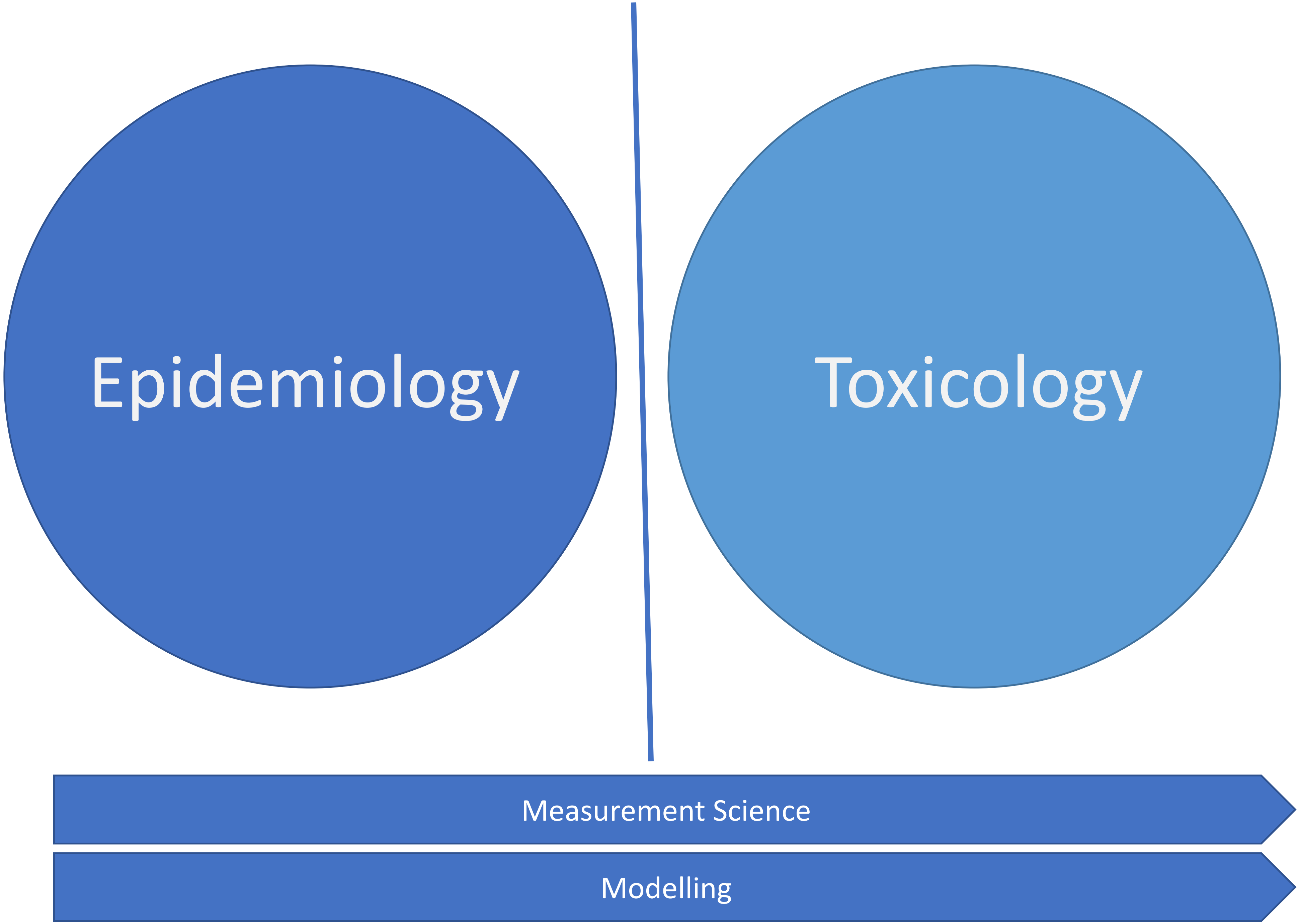
Imperial College London

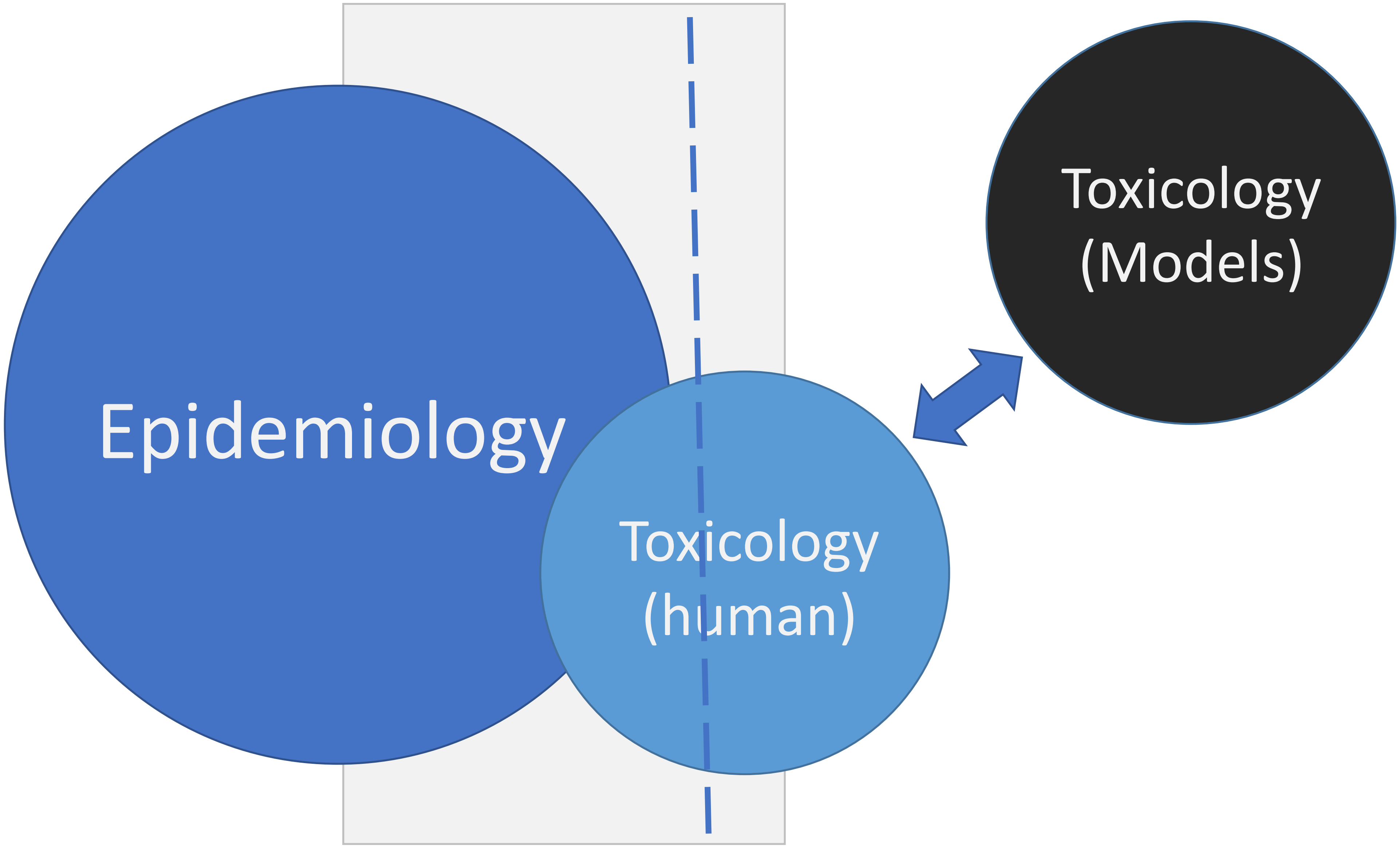
- Measurement / Modelling
- Exposomics / Epidemiology/ Biomarkers
- Toxicology / AOPS
- Synthesis



Philosophical questions

- What is an individuals 'true' exposure and how best should this be estimated?
- Not all components of air pollution are equally harmful – or are they, and if so how?
- What is the fate of inhaled xenobiotics in the body?
- Do observations of statistical associations at the population level need to be supported by mechanistic work to support causation, and if so how do you integrate and weight different types of evidence?
- Do currently available experimental models adequately reflect *in vivo* reality and vulnerability in the population?
- How do we study the mechanisms underpinning chronic effects to match long term impacts on the population?
- Do policy measures work, or are their risks of taking an overly generalised approach?


Epidemiology
Toxicology
Measurement Science
Modelling



Association vs. causation

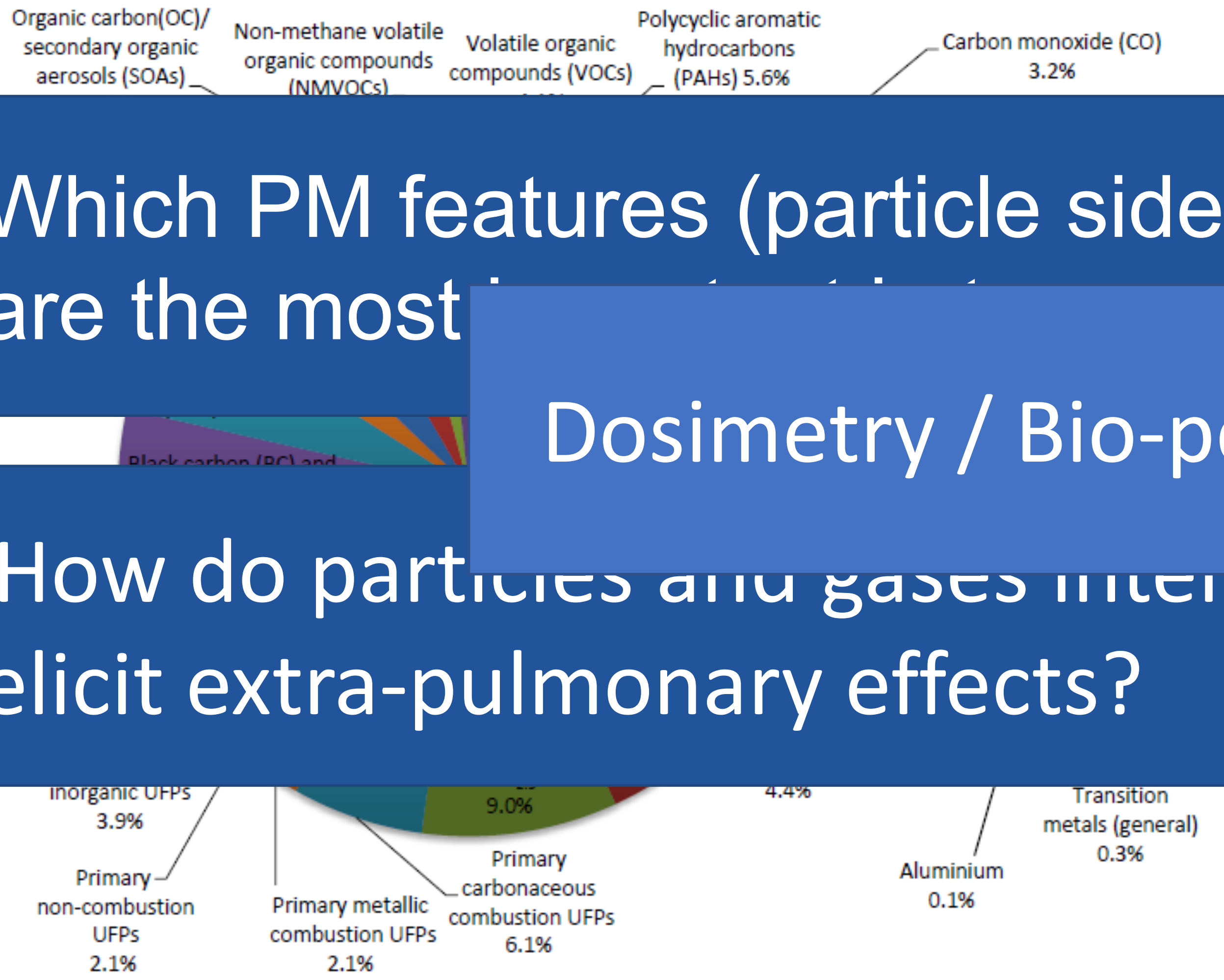
Acute response vs chronic endpoint

Biomarkers

Adverse Outcome Pathways - MIEs

Mixtures

What are the harmful components of PM2.5?



Ultrafines

Which PM features (particle side, number) or components are the most ... ity?

Dosimetry / Bio-persistence

How do partic... lung and elicit extra-pulmonary effects?

The Exposome

Editorial

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

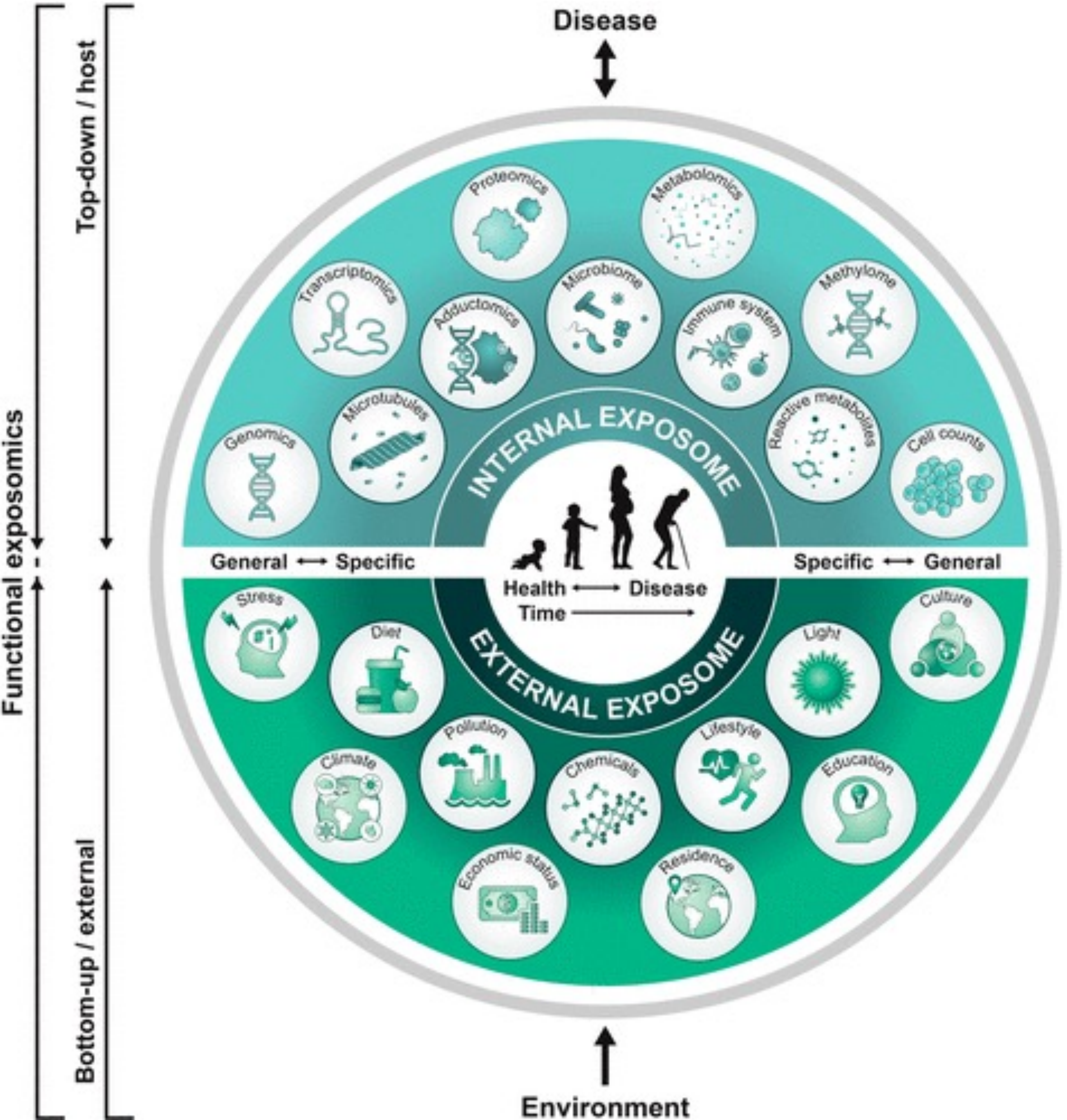
Christopher Paul Wild

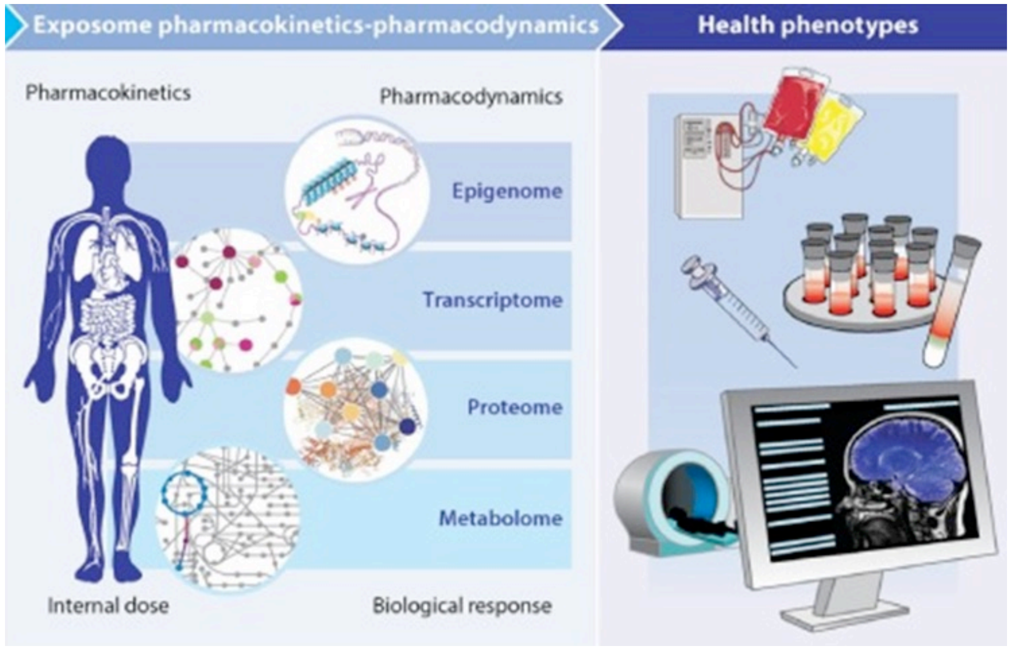
Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

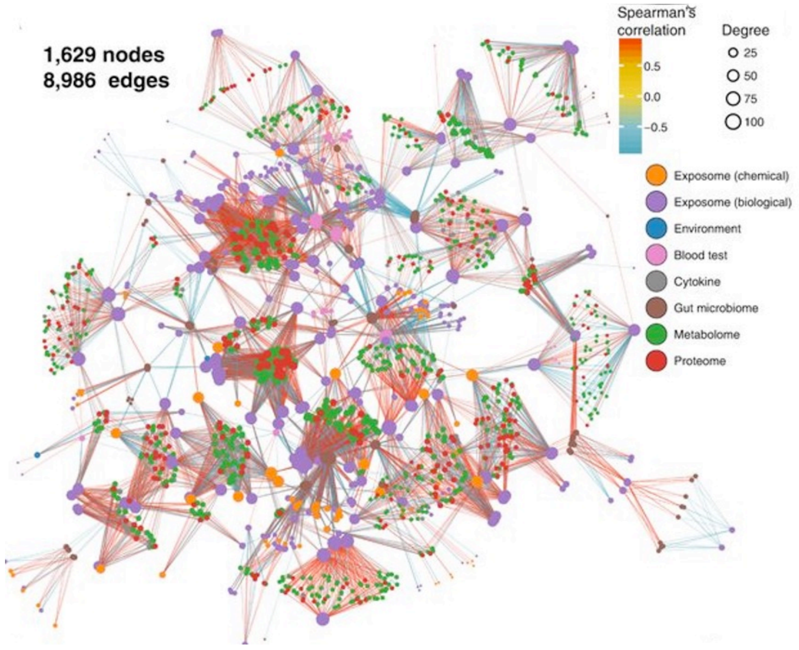
The sequencing and mapping of the human genome provides a foundation for the elucidation of gene expression and protein function, and the identification of the biochemical pathways implicated in the natural history of chronic diseases, including cancer, diabetes, and vascular and neurodegenerative diseases. This knowledge may consequently offer opportunities for a more effective treatment and improved patient management. Genetic research of this kind captures the public imagination in a positive manner and attracts political attention. For example, the 2003 UK Government White Paper on genetics (1), entitled "Our inheritance, our future: realising the potential of genetics in the National Health Service," highlighted the opportunities for tailored drug treatments and gene therapy flowing from the sequencing and mapping of the

UK Biobank will recruit half a million people at a cost of around £60 million ($110 million) in the initial phase. The proposal to establish a "Last Cohort" of 1 million people in the United States (7) or a similar-sized Asian cohort (8) would presumably exceed this sum. In each case, the high cost is heavily influenced by the collection and banking of biological material. This expense is predicated on the assumption that biochemical and molecular measures on this material will resolve the etiologic questions alluded to above. It is self-evident that unraveling of complex environmental and genetic aetiologies demands that both environmental exposures and genetic variation are reliably measured. Advances in statistical methods and in bioinformatics in relation to large data sets are also of critical importance.

Cancer Epidemiol Biomarkers Prev 2005;14(8).

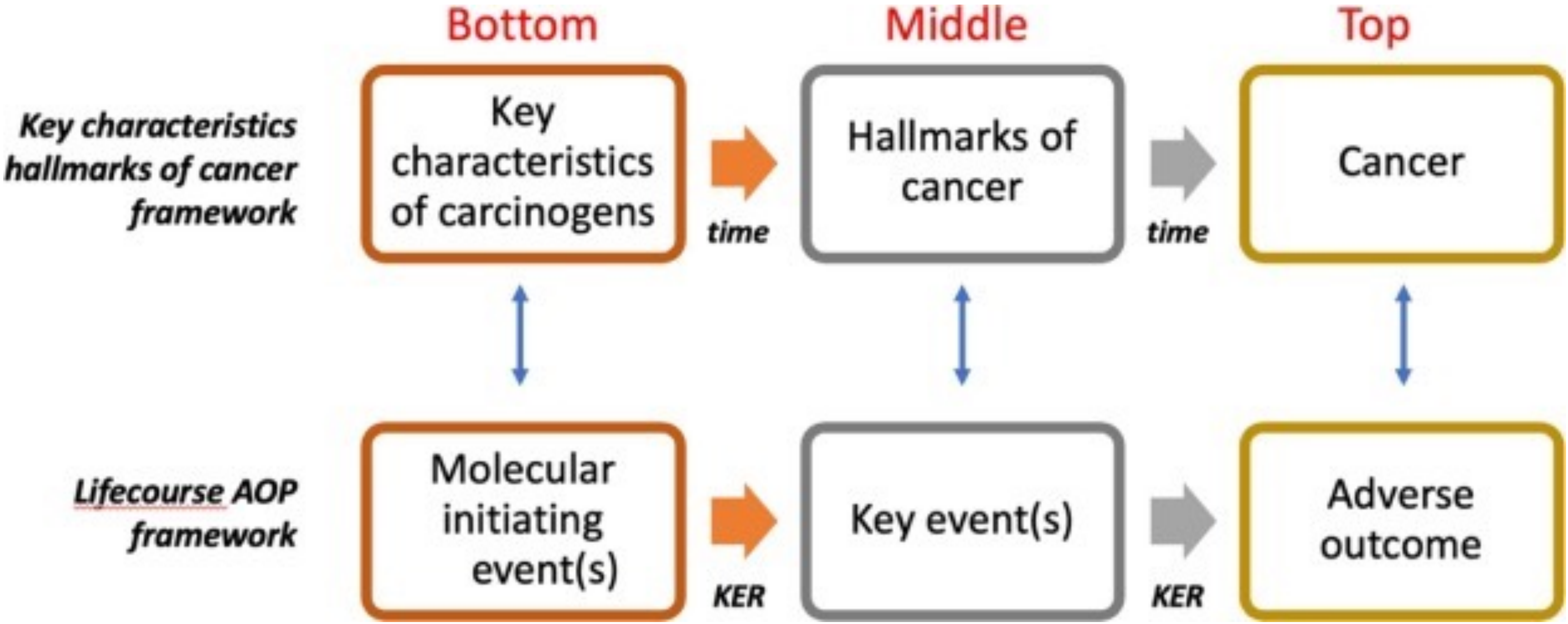






Environ. Sci. Technol. Lett. 2021, 8, 10, 839–852

Combining key characteristics and hallmarks of cancer into life course Adverse Outcome Pathways.



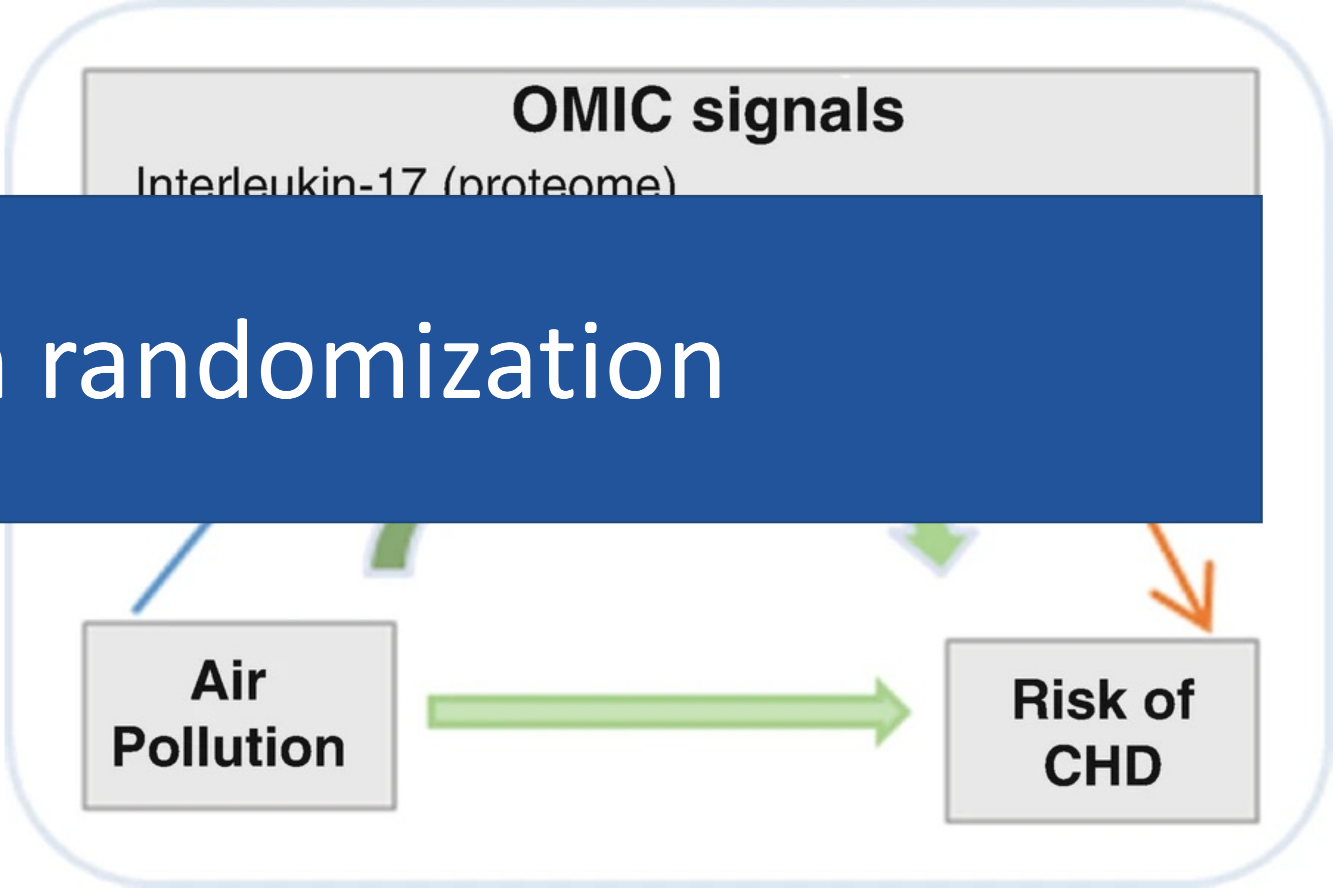
Douglas Hanahan D and Weinberg RA. Cell. 2011;144(5):646-74.

Meet-in-the-Middle: The Example of Air Pollution and Coronary Heart Disease

Case-control study on CVD nested in a cohort of 18,982 individuals from the EPIC-Italy study

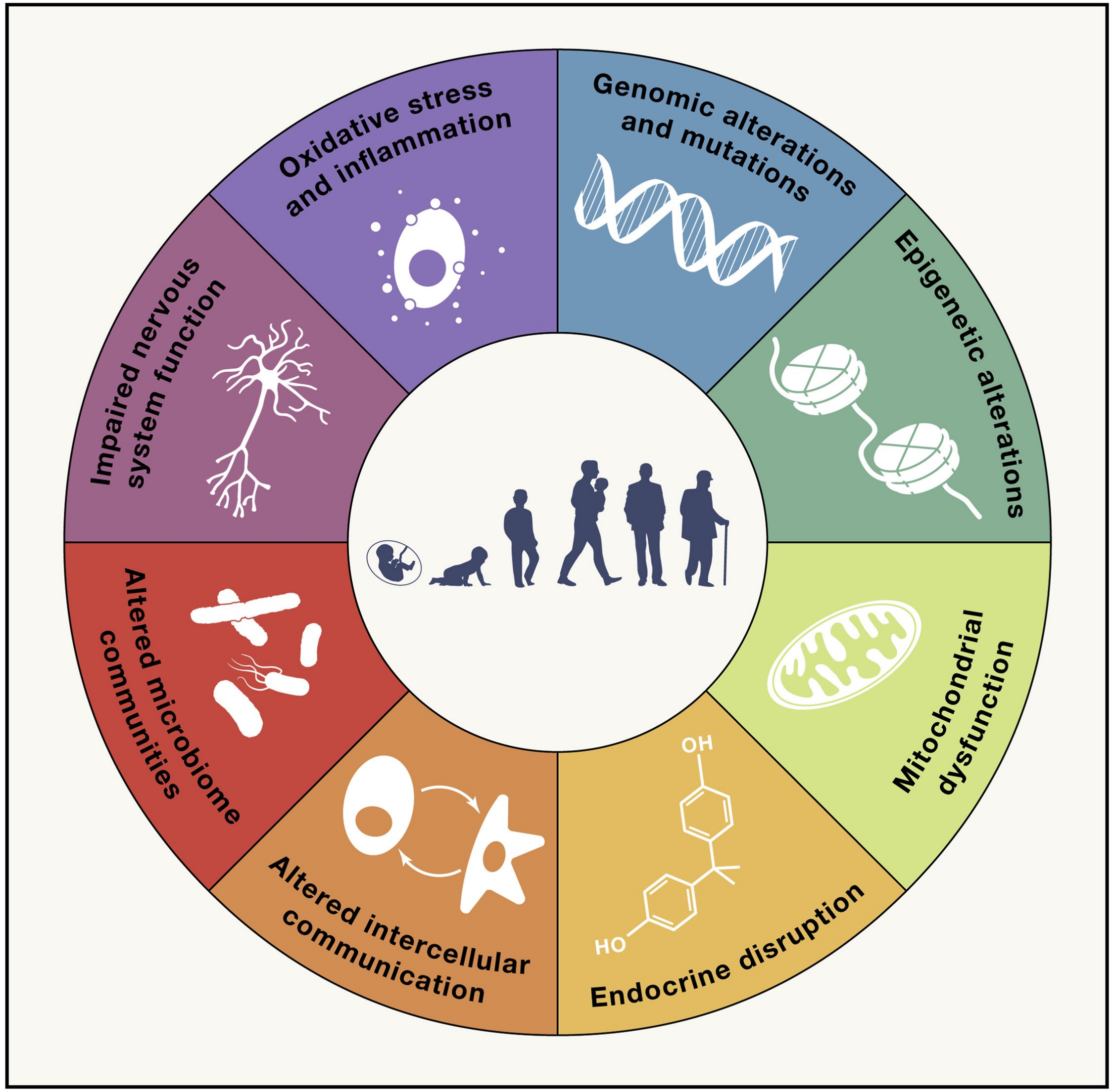
Mendelian randomization

Findings indicated that chronic exposure to air pollution lead to oxidative stress, which in turn activates a cascade of inflammatory responses mainly involving the “Cytokine signalling” pathway, leading to increased risk of CCVD – NO_2, $PM_{2.5}$, PM_{10}



Fiorito G et al., Environ Mol Mutagen 2017, 59(3):234–246.

Hallmarks of environmental insults



1. Oxidative stress and inflammation
2. Genomic alterations and mutations
3. Epigenetic alterations
4. Mitochondrial dysfunction
5. Endocrine disruption
6. Altered cell communication
7. Altered microbiome communities
8. Impaired nervous system function

X: Accelerated biological ageing

Peters A et al. Cell. 2021 Mar 18;184(6):1455-1468

Feeding Toxicologically ‘Informative’ Information into Epidemiological Studies: Oxidative Potential

- DNA strand breaks
- Biomolecule (surrogate) oxidation
- EPR based free radical generation
- Fluorescence-based techniques

Cell free

Cellular

Extracted PM

Real time

Daily time series / models

Toxicology (health) challenge

Imaging – particle/chemical tracking to full digital histopathology

- Policy relevant particles generation

Improved air pollution and health sensor technology – across scales, individual to global

Data management and high performance computing

- ADME principles

Better dosimetry models / predictive in silico toxicology / population impact simulations