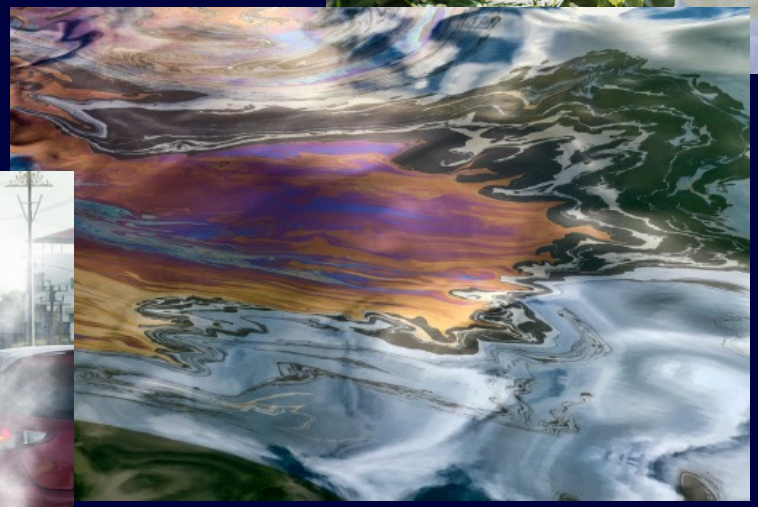
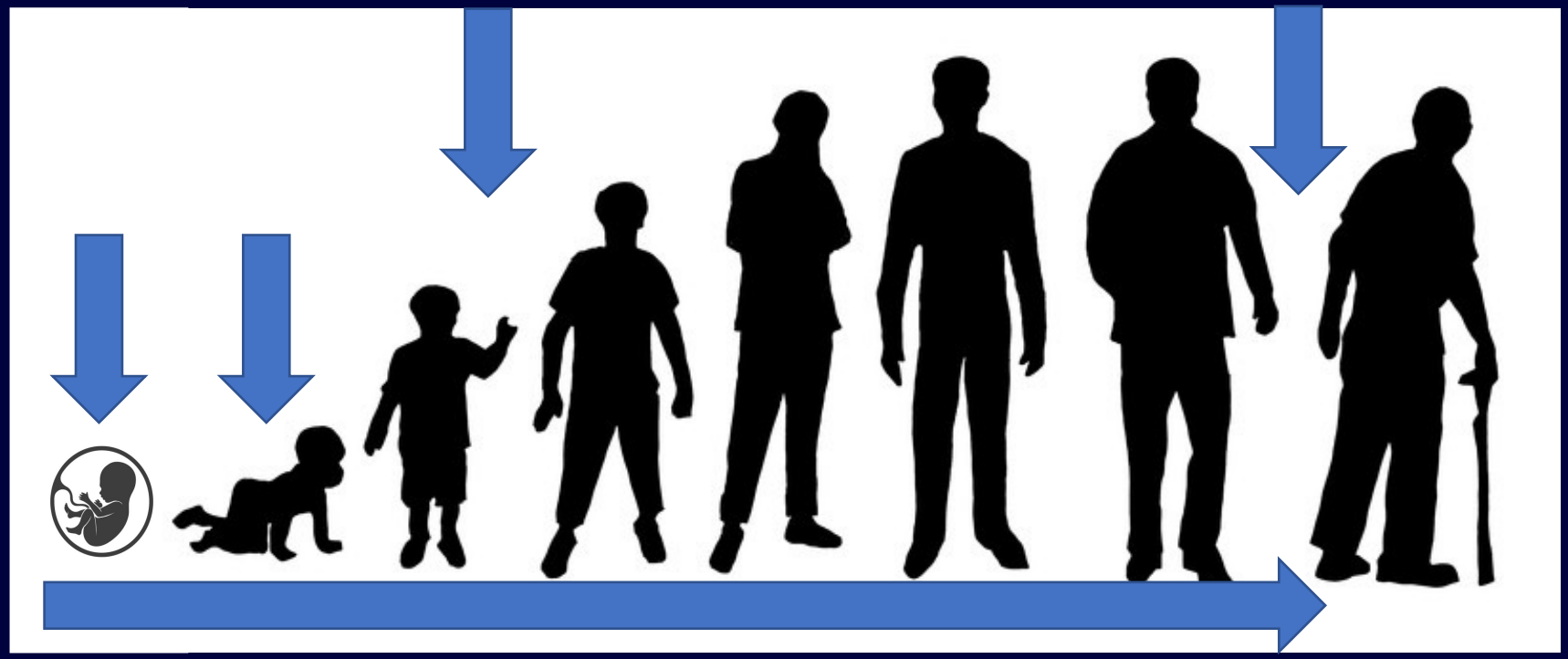
What Is the Exposome & Why Does It Matter to Your Health?



Dr Ian Mudway

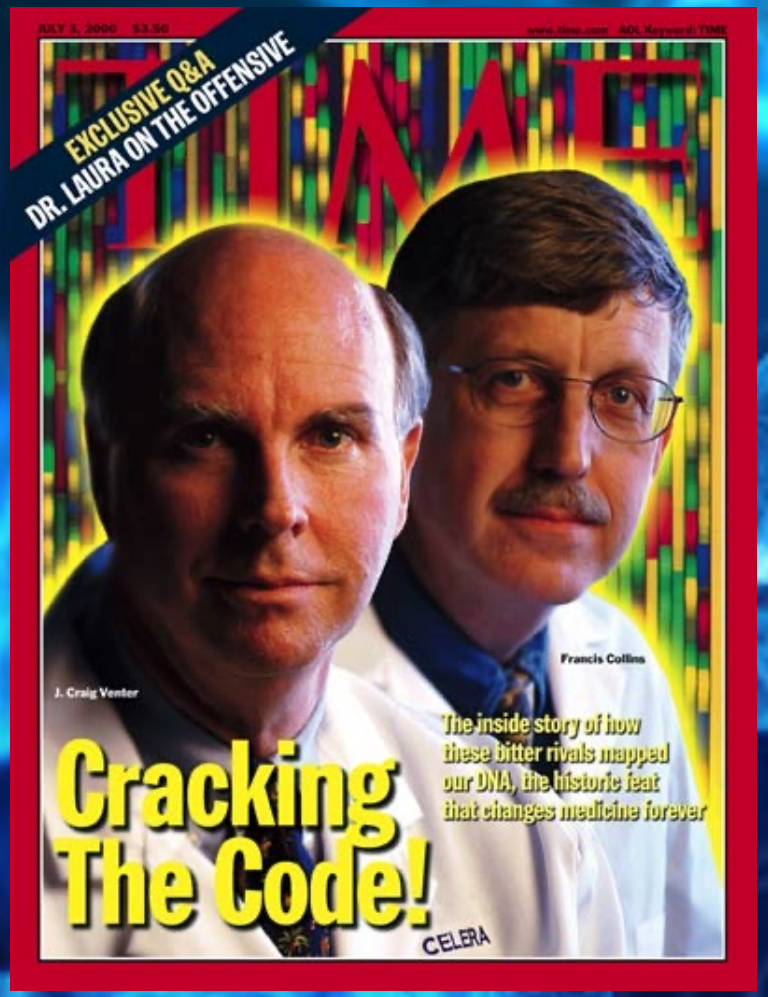
EST. 1597
GRESHAM COLLEGE

"A potential measure of the effects of life course exposures on health. It comprises the totality of exposures to which an individual is subjected from conception to death including environmental agents, socioeconomic conditions, lifestyle, diet and endogenous process."

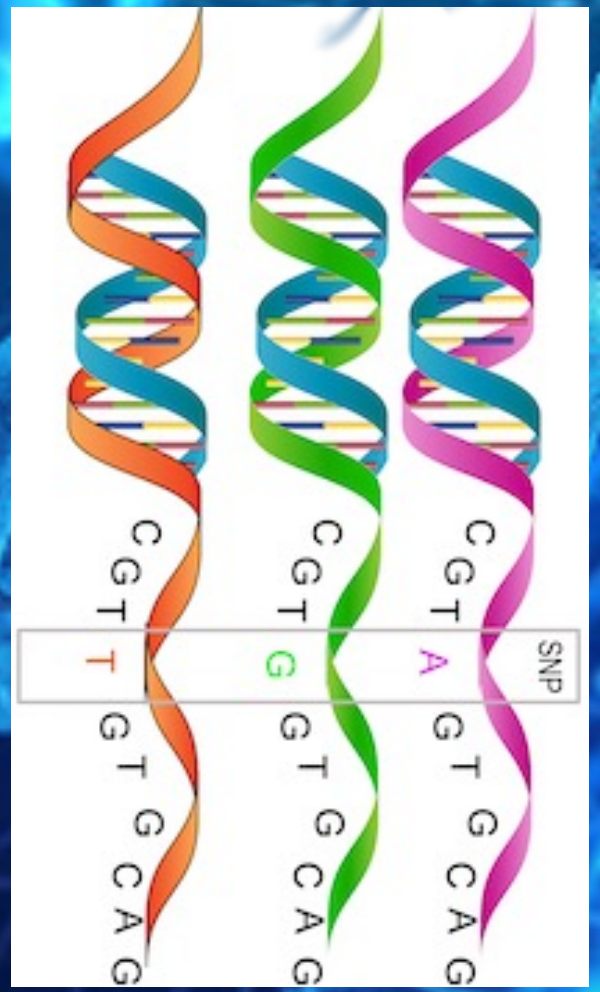


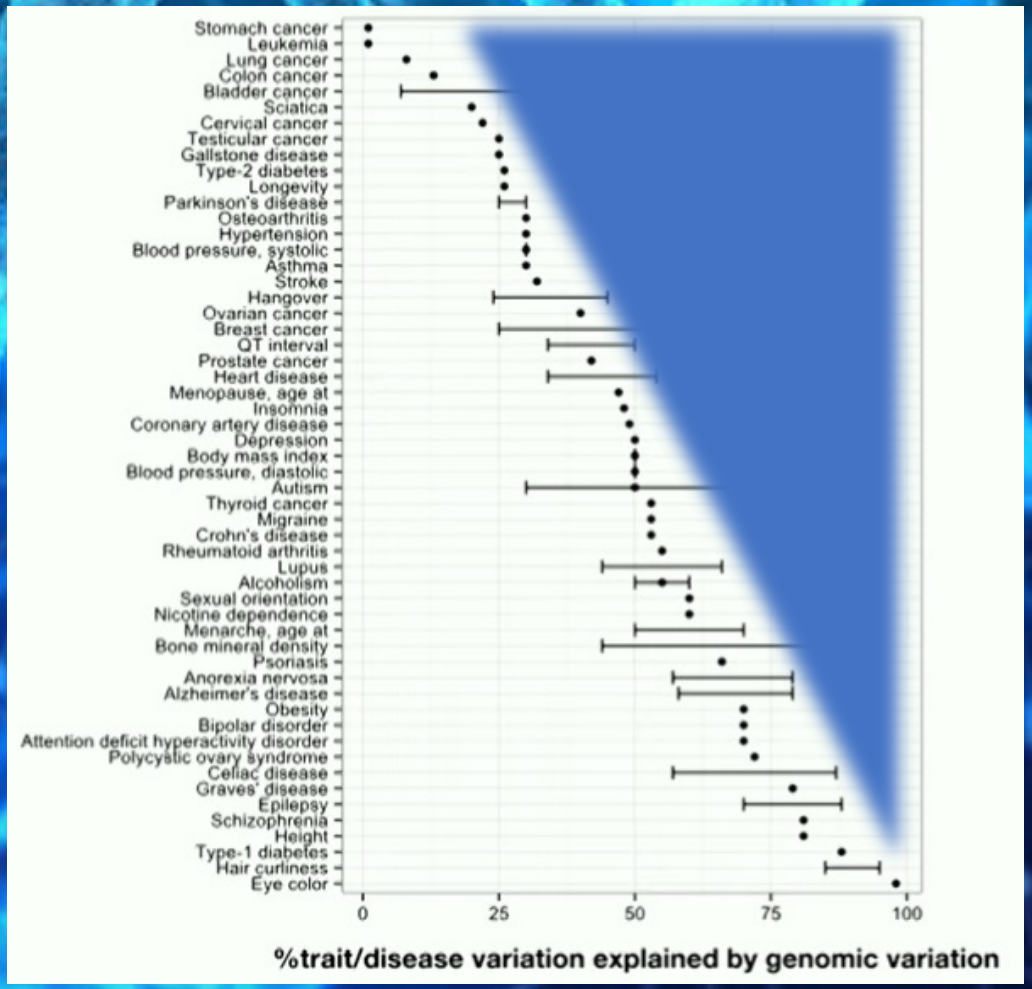
6th edition of the dictionary of epidemiology, 2014

Exposome

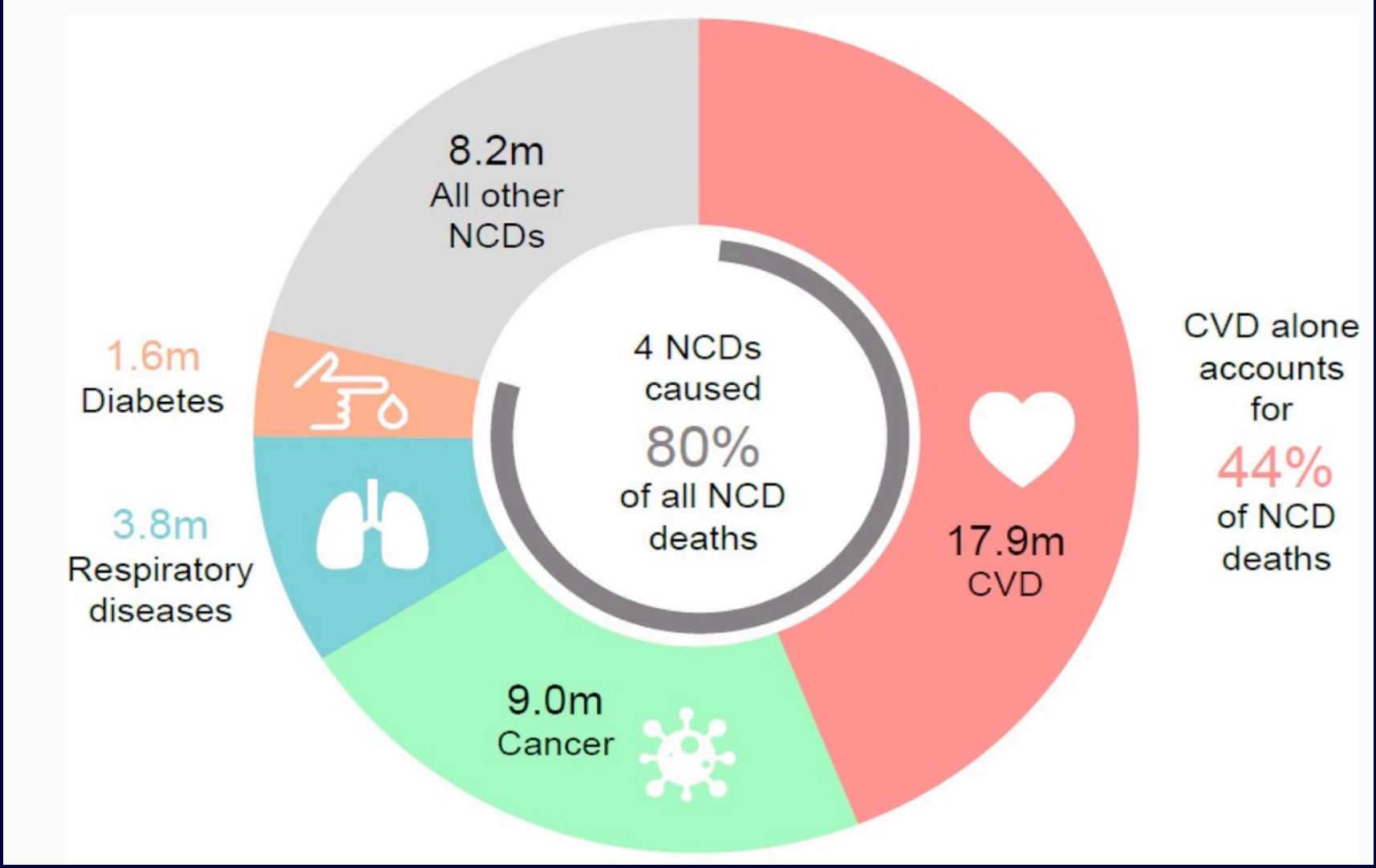

JULY 3, 2000 $3.50
www.time.com AOL Keyword: TIME
TIME
EXCLUSIVE Q&A
DR. LAURA ON THE OFFENSIVE
J. Craig Venter
Francis Collins
Cracking The Code!
The inside story of how these bitter rivals mapped our DNA, the historic feat that changes medicine forever
CELERA

July 3, 2000


C G T T G T G C A G
C G T G G T G C A G
C G T A G T G C A G
SNP

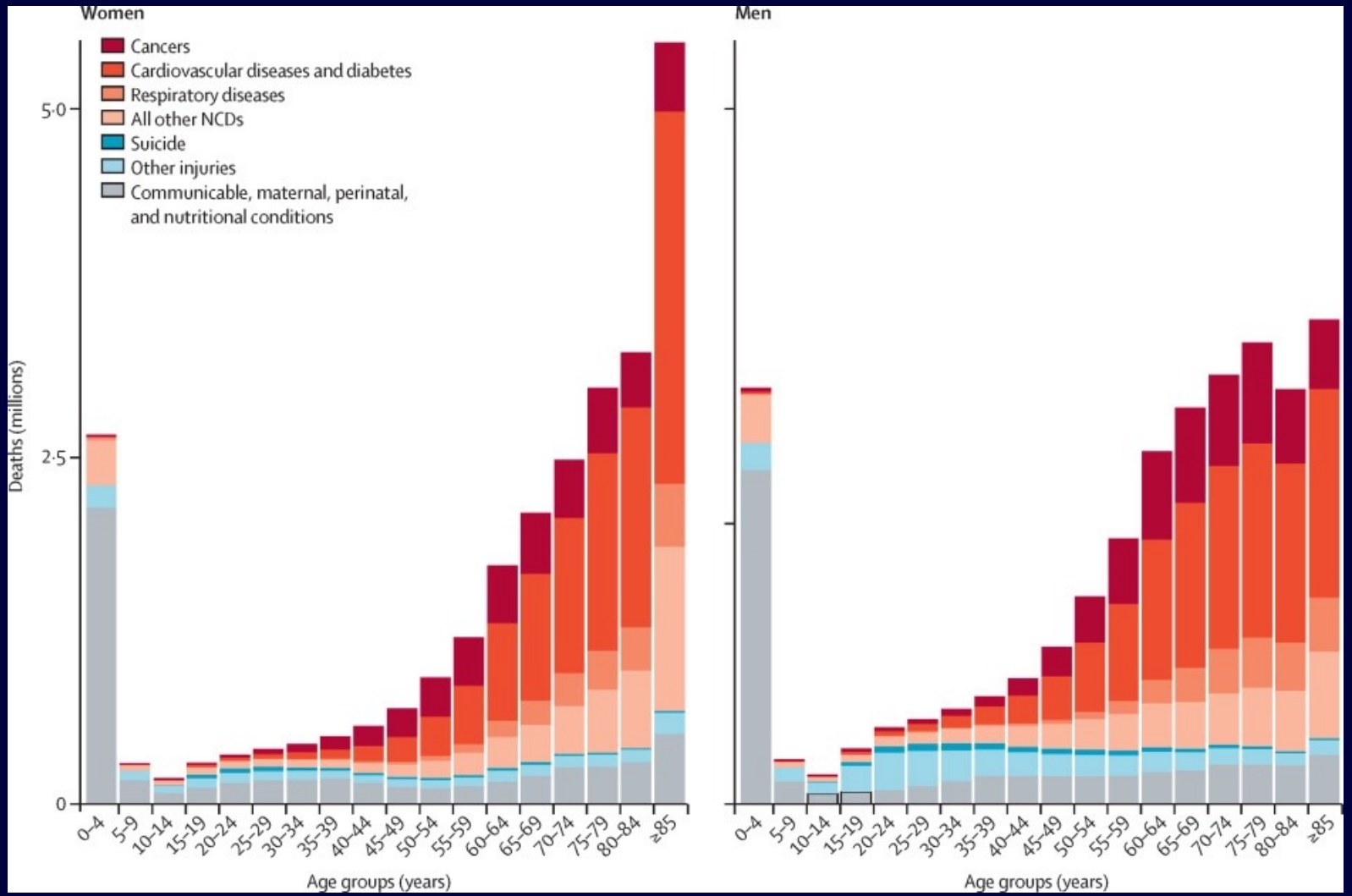

Stomach cancer
Leukemia
Lung cancer
Colon cancer
Bladder cancer
Sciatica
Cervical cancer
Testicular cancer
Gallstone disease
Type-2 diabetes
Longevity
Parkinson's disease
Osteoarthritis
Hypertension
Blood pressure, systolic
Asthma
Stroke
Hangover
Ovarian cancer
Breast cancer
QT interval
Prostate cancer
Heart disease
Menopause, age at
Insomnia
Coronary artery disease
Depression
Body mass index
Blood pressure, diastolic
Autism
Thyroid cancer
Migraine
Crohn's disease
Rheumatoid arthritis
Lupus
Alcoholism
Sexual orientation
Nicotine dependence
Menarche, age at
Bone mineral density
Psoriasis
Anorexia nervosa
Alzheimer's disease
Obesity
Bipolar disorder
Attention deficit hyperactivity disorder
Polycystic ovary syndrome
Celiac disease
Graves' disease
Epilepsy
Schizophrenia
Height
Type-1 diabetes
Hair curliness
Eye color
0
25
50
75
100
%trait/disease variation explained by genomic variation

Noncommunicable diseases



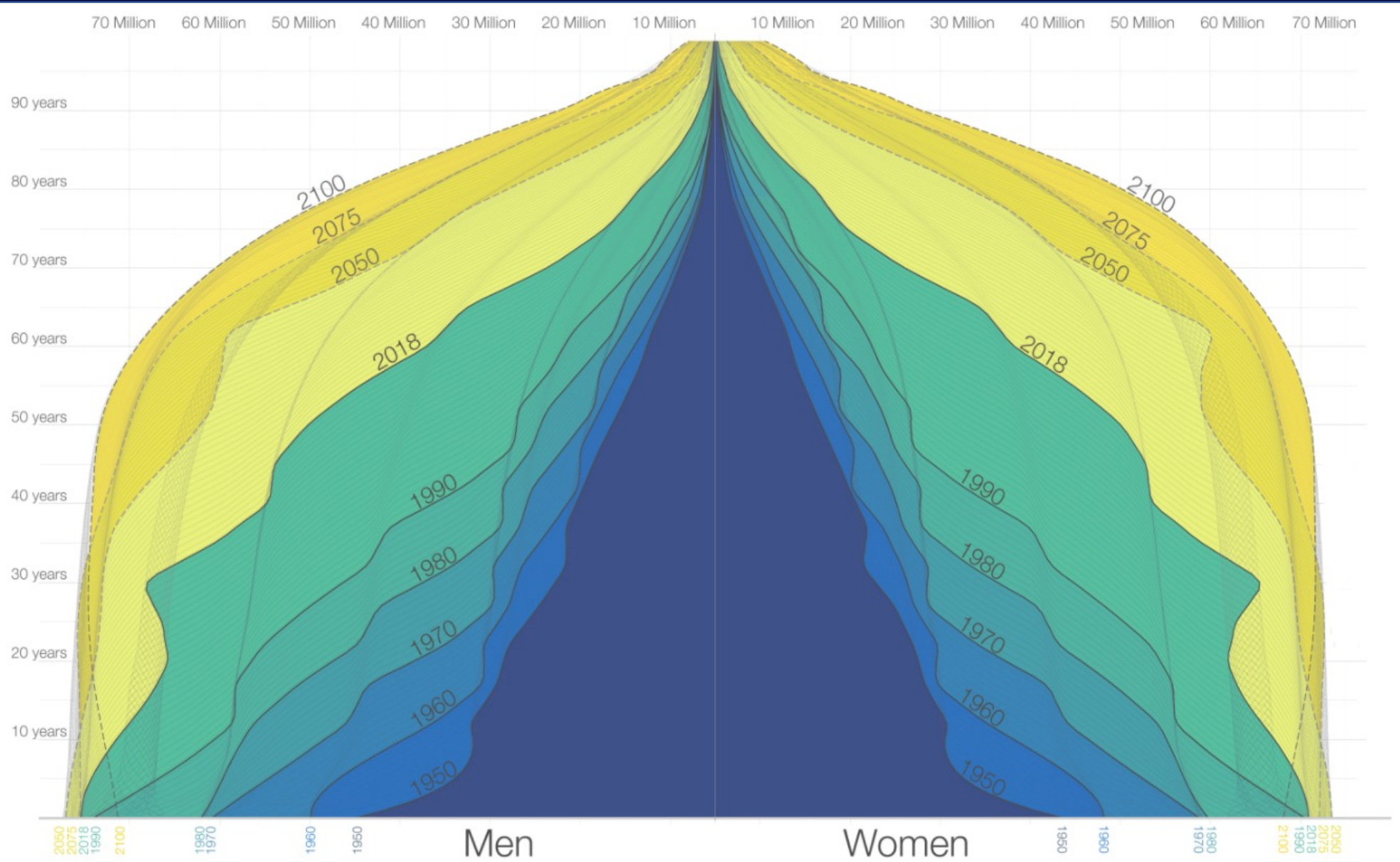
Zou KH et al. Health Services and Outcomes Research Methodology volume 21, 8–20 (2021)

Number of deaths in 2016 from non-communicable diseases

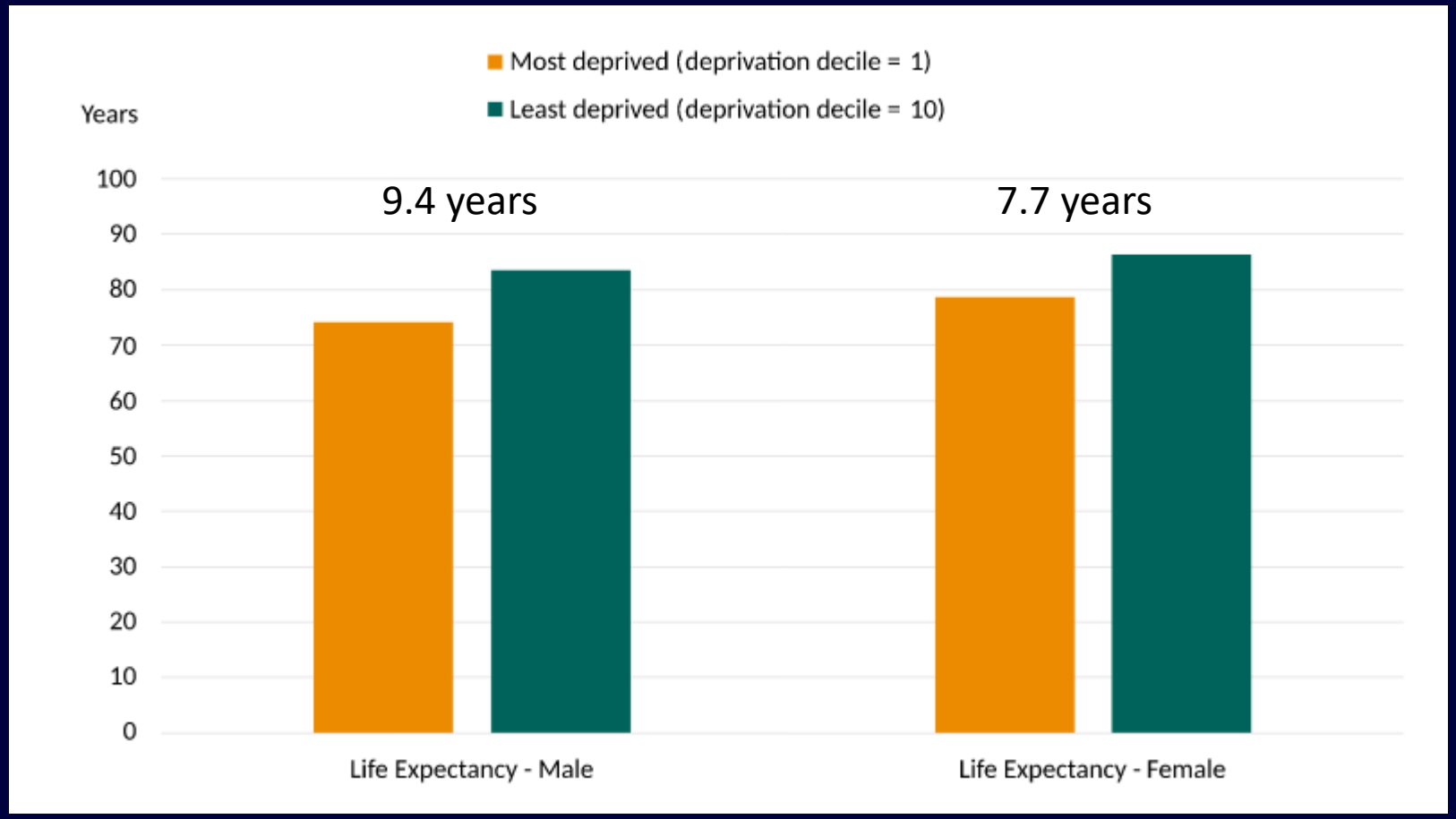


NCD Countdown 2030 collaborators. Lancet. 2018 Sep 22;392(10152):1072-1088.

The Demography of the World population from 1950 to 2100



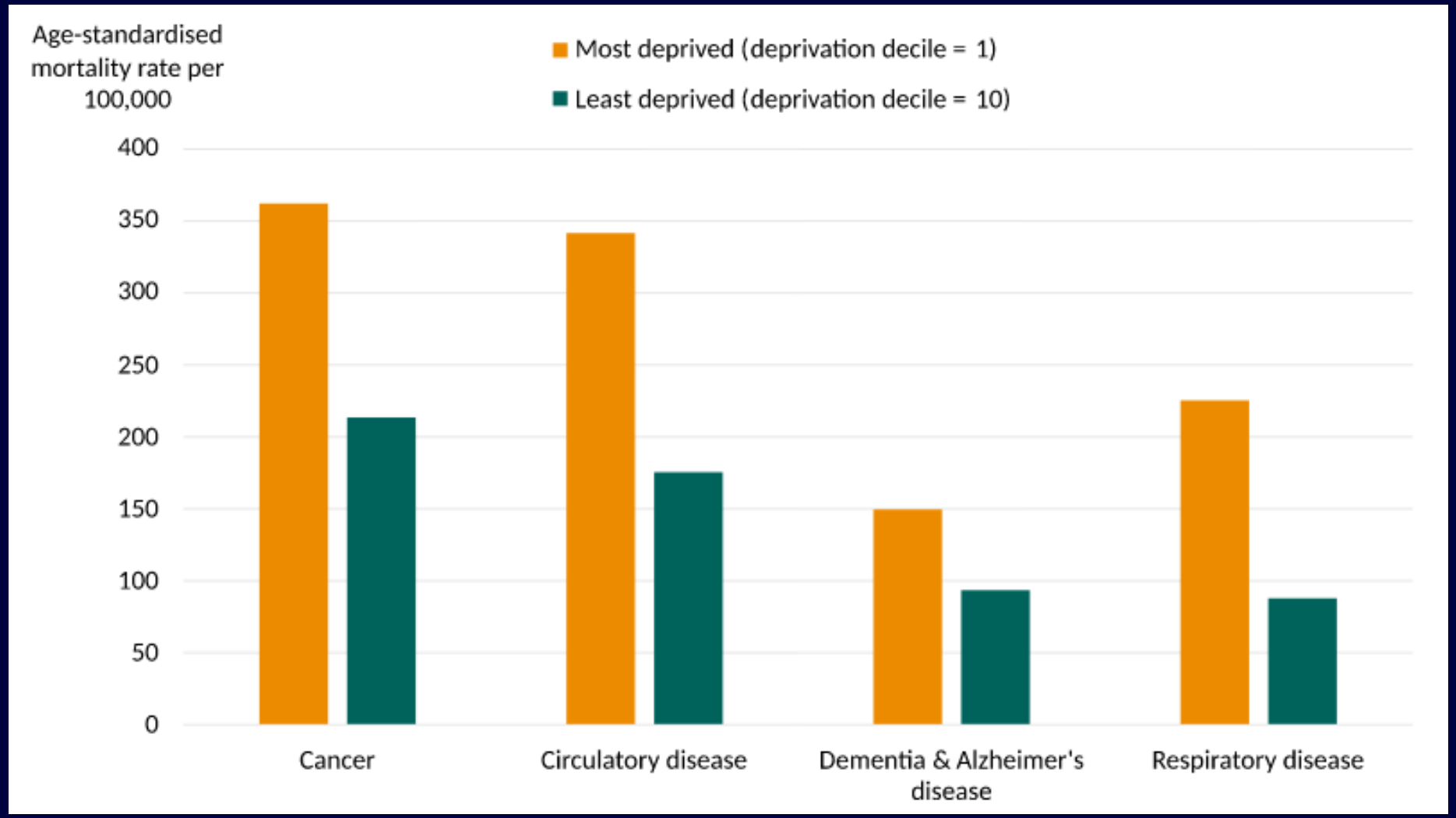
Life expectancy, England, 2017 to 2019

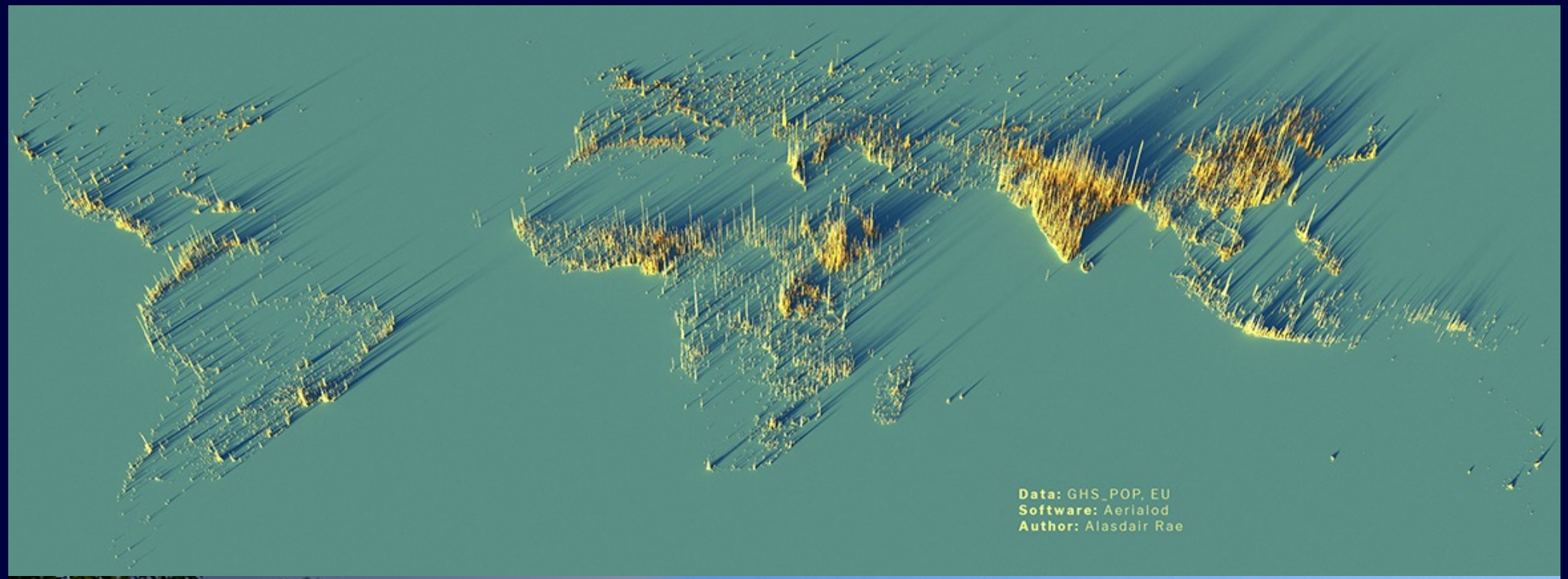


If we focus instead on years of good health, disability free years then for the period 2018-2020 for women the difference between the least and most deprived areas was 19.3 years, and for males 18.6 years

Source: Office for National Statistics (ONS)

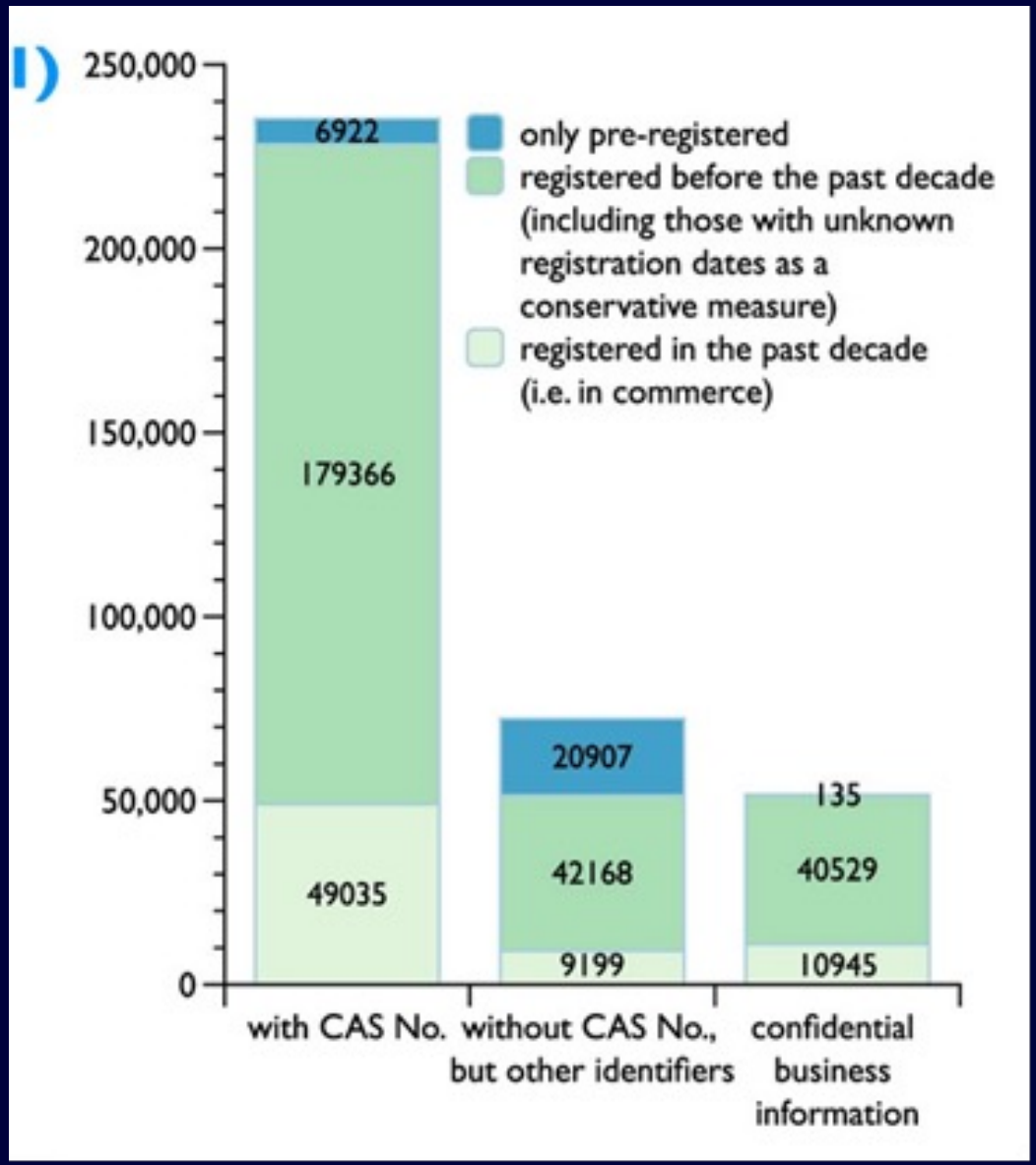
Mortality rates from leading causes in most- and least- deprived areas, England, 2015 to 2019




Data: GHS_POP, EU
Software: Aerialod
Author: Alasdair Rae

Chemical Complexities

- 201 million chemicals reported in the literature since early 1800s (CAS registry, as of today's date)
- Global inventory of chemicals licenced for manufacture and sale: 359,206 https://doi.org/10.1021/acs.est.9b06379, About 100,000 used in the EU https://echa.europa.eu/information-on-chemicals/ec-inventory
- REACH has 26,642 substances https://echa.europa.eu/information-on-chemicals/registered-substances



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).

EPIDEMIOLOGY

Environment and Disease Risks

Stephen M. Rappaport and Martyn T. Smith

A new paradigm is needed to assess how a lifetime of exposure to environmental factors affects the risk of developing chronic diseases.

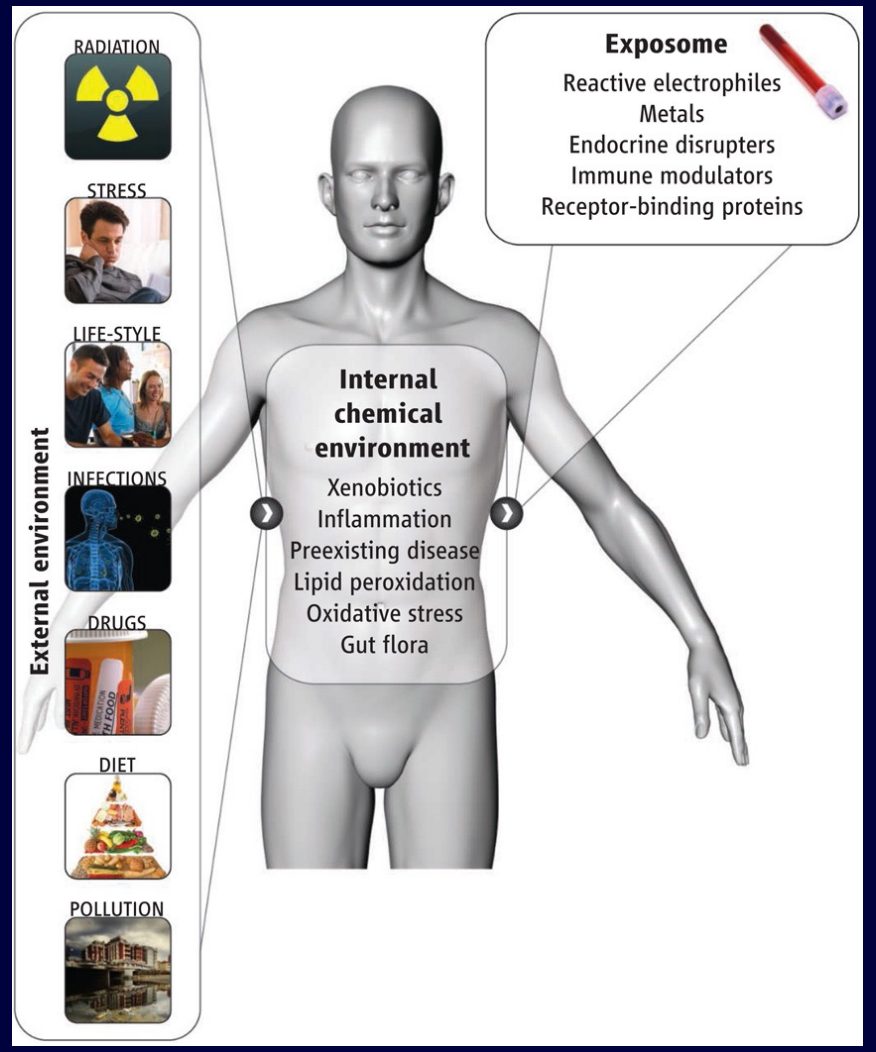
Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, 70 to 90% of disease risks are probably due to differences in environments (*1*–*3*). Yet, epidemiologists increasingly use genome-wide association studies (GWAS) to investigate diseases, while relying on questionnaires to characterize "environmental exposures." This is because GWAS represent the only approach for exploring the totality of any risk factor (genes, in this case) associated with disease prevalence. Moreover, the value of costly genetic information is diminished when inaccurate and imprecise environmental data lead to biased inferences regarding gene-environment interactions (*4*). A more comprehensive and quantitative view of environmental exposure is needed if epidemiologists are to discover the major causes of chronic diseases.

An obstacle to identifying the most important environmental exposures is the fragmentation of epidemiological research along lines defined by different factors. When epidemiologists investigate environmental risks, they tend to concentrate on a particular category of exposures involving air and water pollution, occupation, diet and obesity, stress and behavior, or types of infection. This slicing of the disease pie along parochial lines leads to scientific separation and confuses the definition of "environmental exposures." In fact, all of these exposure categories can contribute to chronic diseases and should be investigated collectively rather than separately.

To develop a more cohesive view of environmental exposure, it is important to recognize that toxic effects are mediated through chemicals that alter critical molecules, cells, and physiological processes inside the body. Thus, it would be reasonable to consider the "environment" as the body's internal chemical environment and "exposures" as the amounts of biologically active chemicals in this internal environment. Under this view, exposures are not restricted to chemicals (toxicants) entering the body from air, water, or food, for example, but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural processes (*5*, *6*) (see the figure). This internal chemical environment continually fluctuates during life due to changes in external and internal sources, aging, infections, life-style, stress, psychosocial factors, and preexisting diseases.

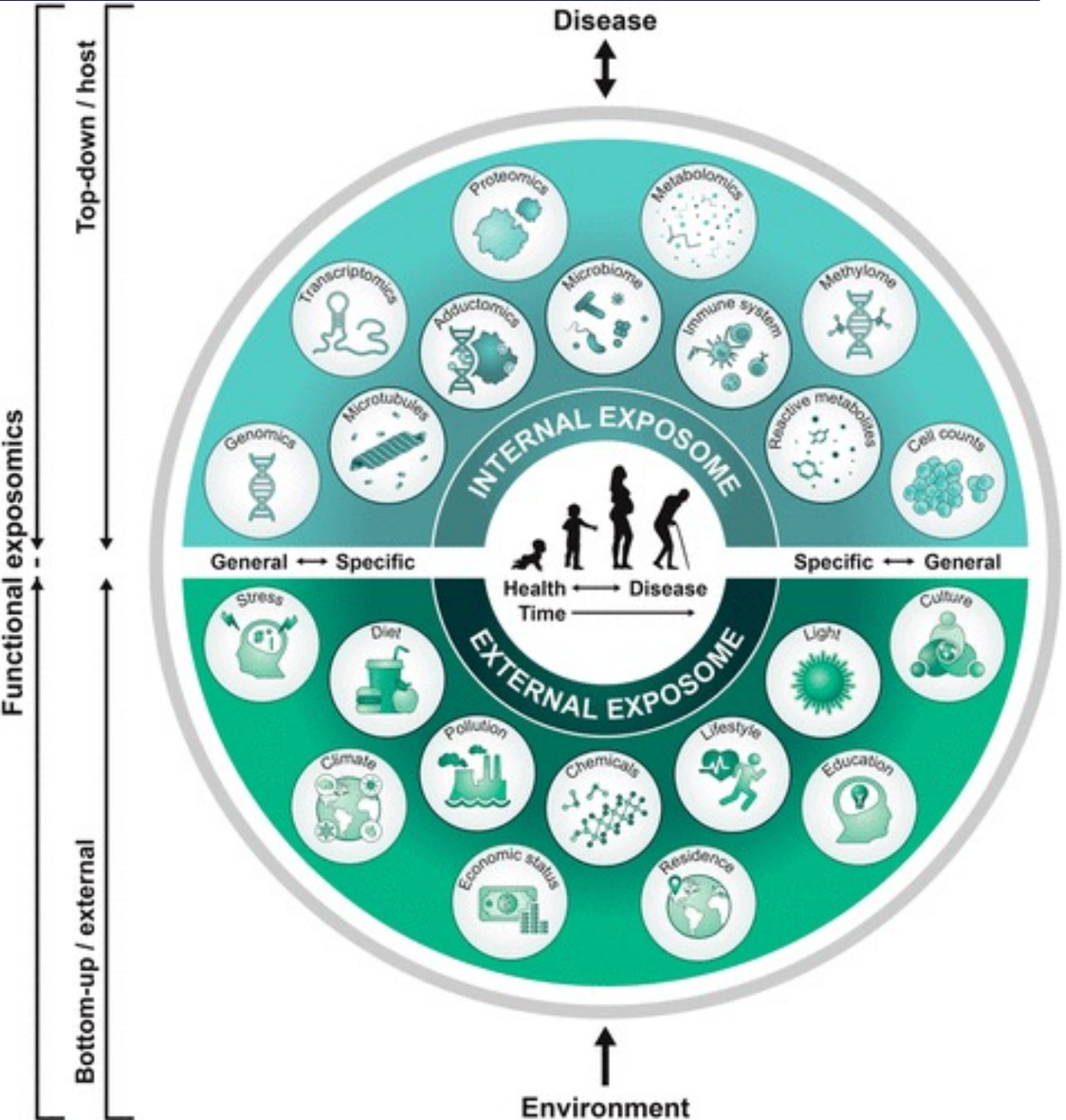
The term "exposome" refers to the totality of environmental exposures from conception onwards, and has been proposed to be a

School of Public Health, University of California, Berkeley, CA 94720–7356, USA. E-mail: srappaport@berkeley.edu

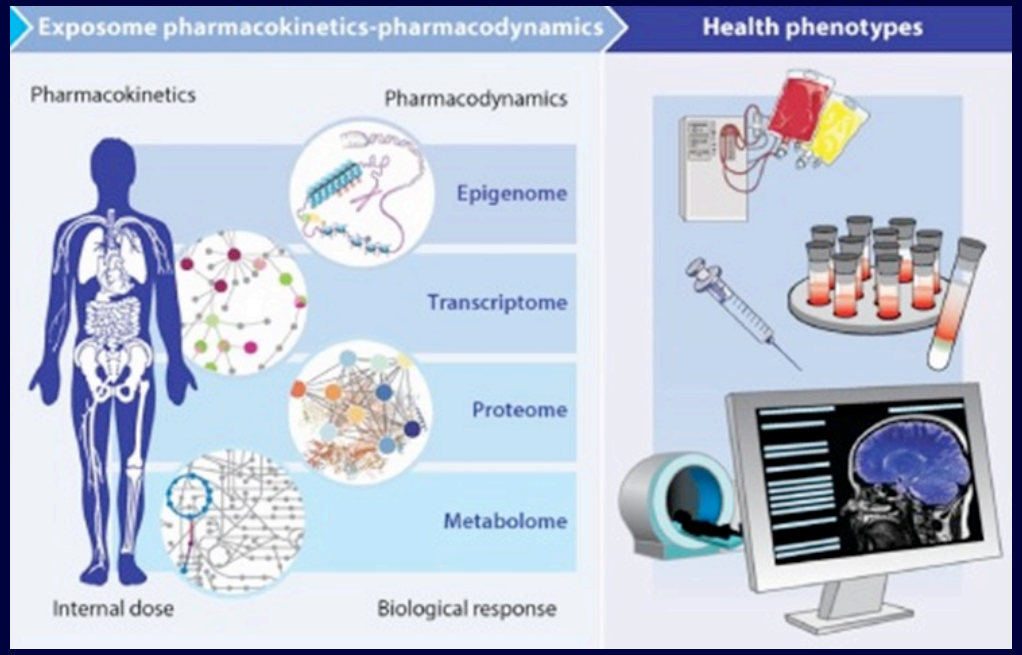


"*Bottom-up*" & "*top down*"

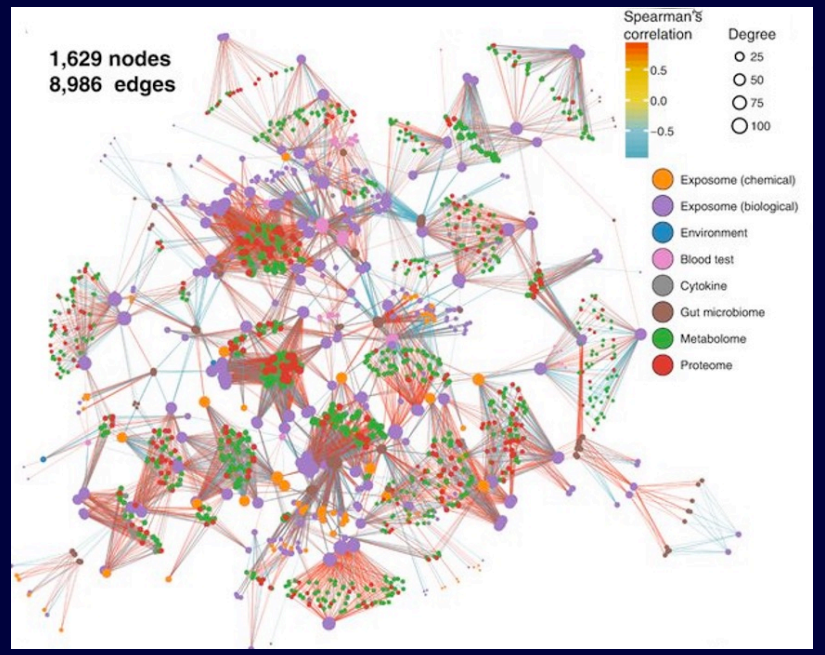
Science. 2010;330(6003):460-1.



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

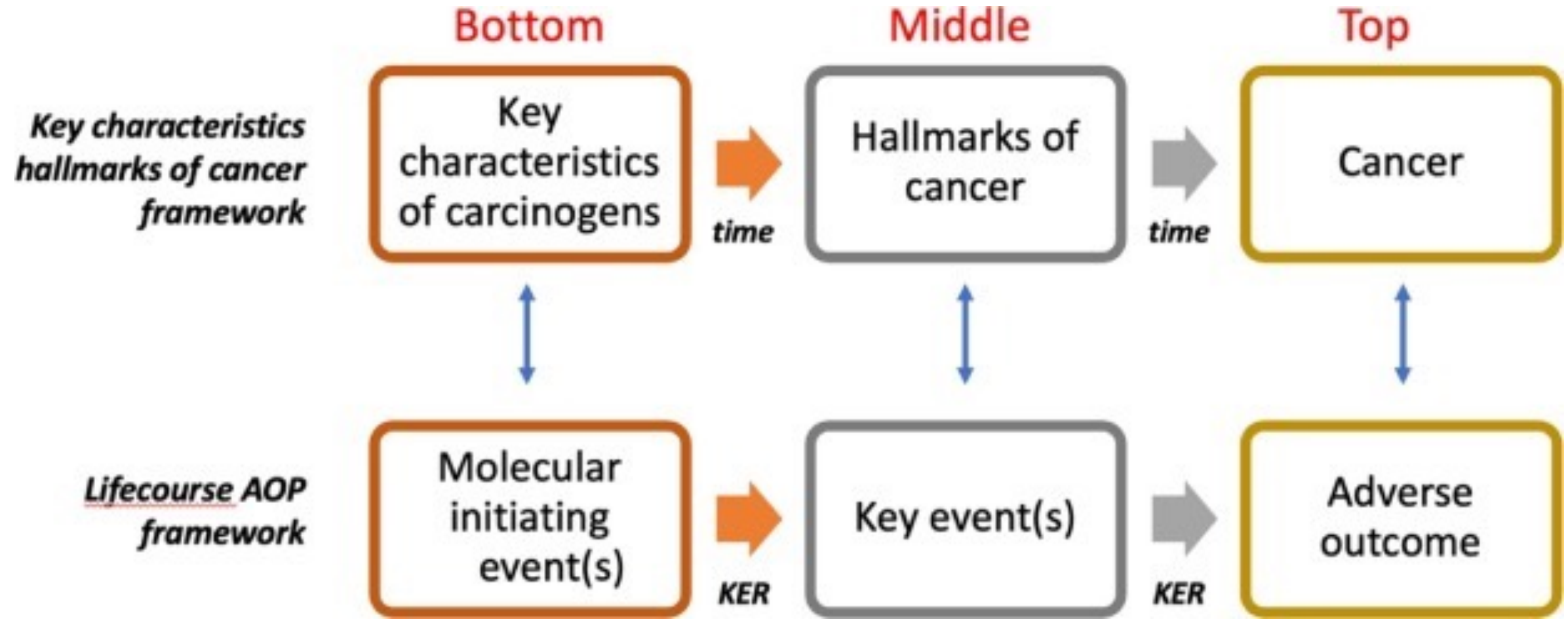


Niedzwiecki MM et al. Annu. Rev. Pharmacol. Toxicol., 59 (1) (2019), 107-127



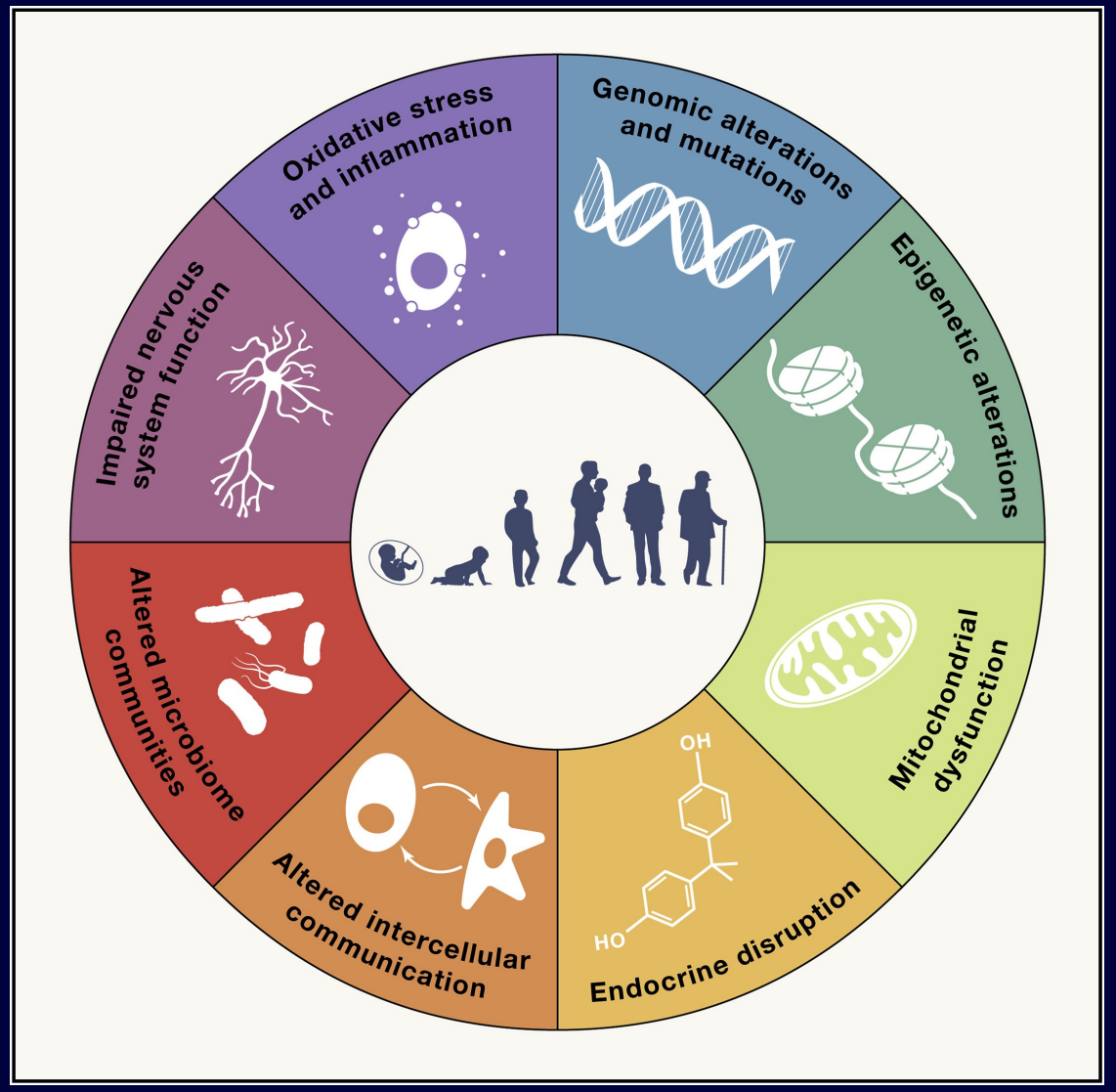
Gao P et al. Genome Res. 2022 Jun;32(6):1199-1214.

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.

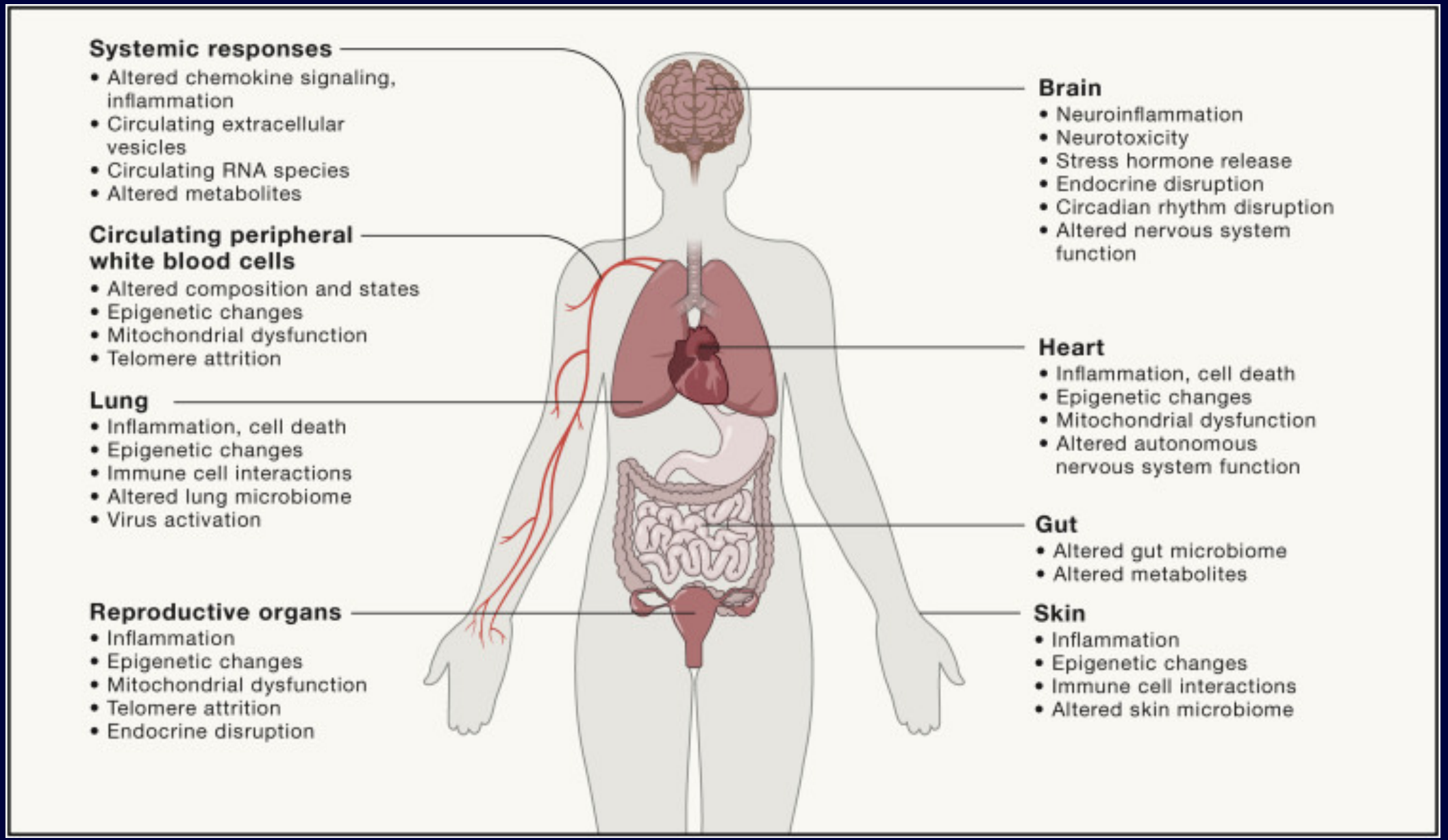
Hallmarks of environmental insults



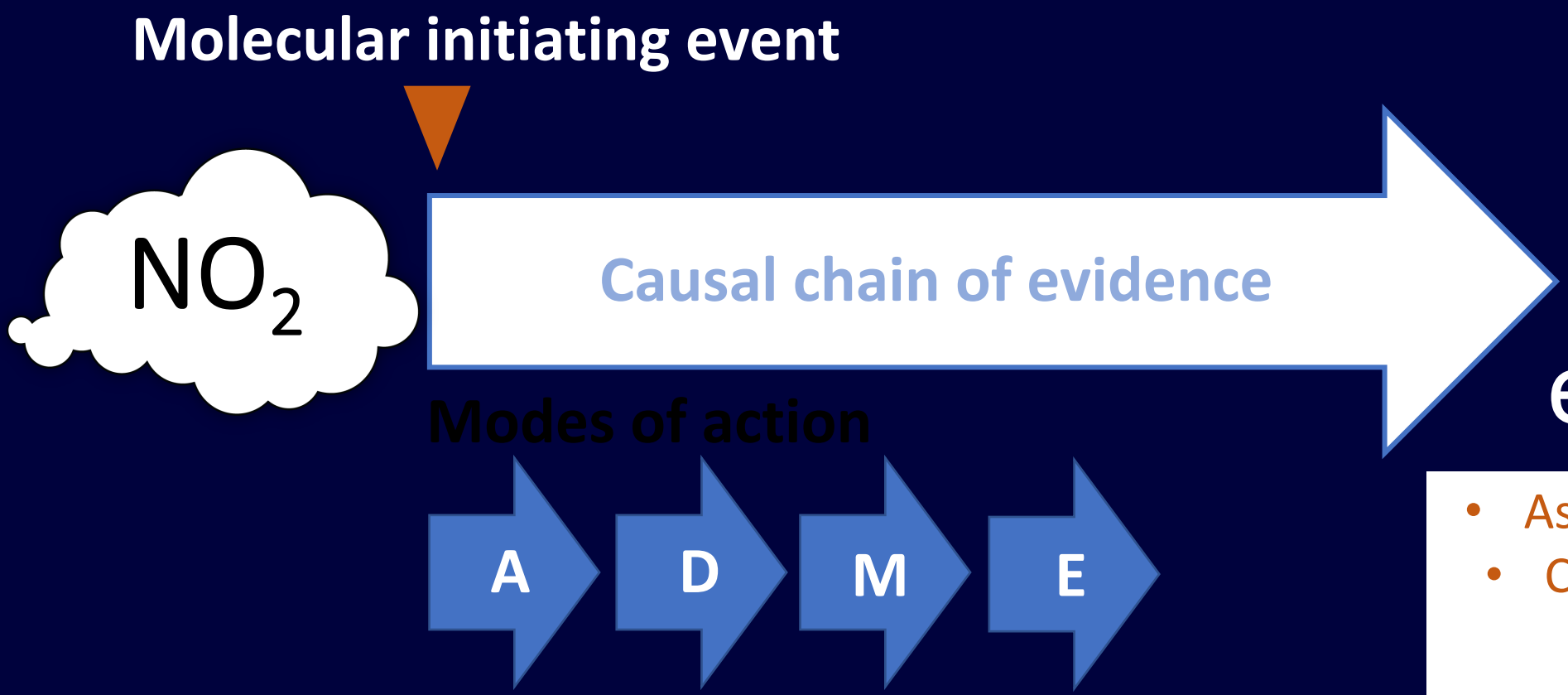
1. Oxidative stress and inflammation
2. Genomic alterations and mutations
3. Epigenetic alterations
4. Mitochondrial dysfunction
5. Endocrine disruption
6. Altered cell communication
7. Altered microbiome communities
8. Impaired nervous system function

X: Accelerated biological ageing

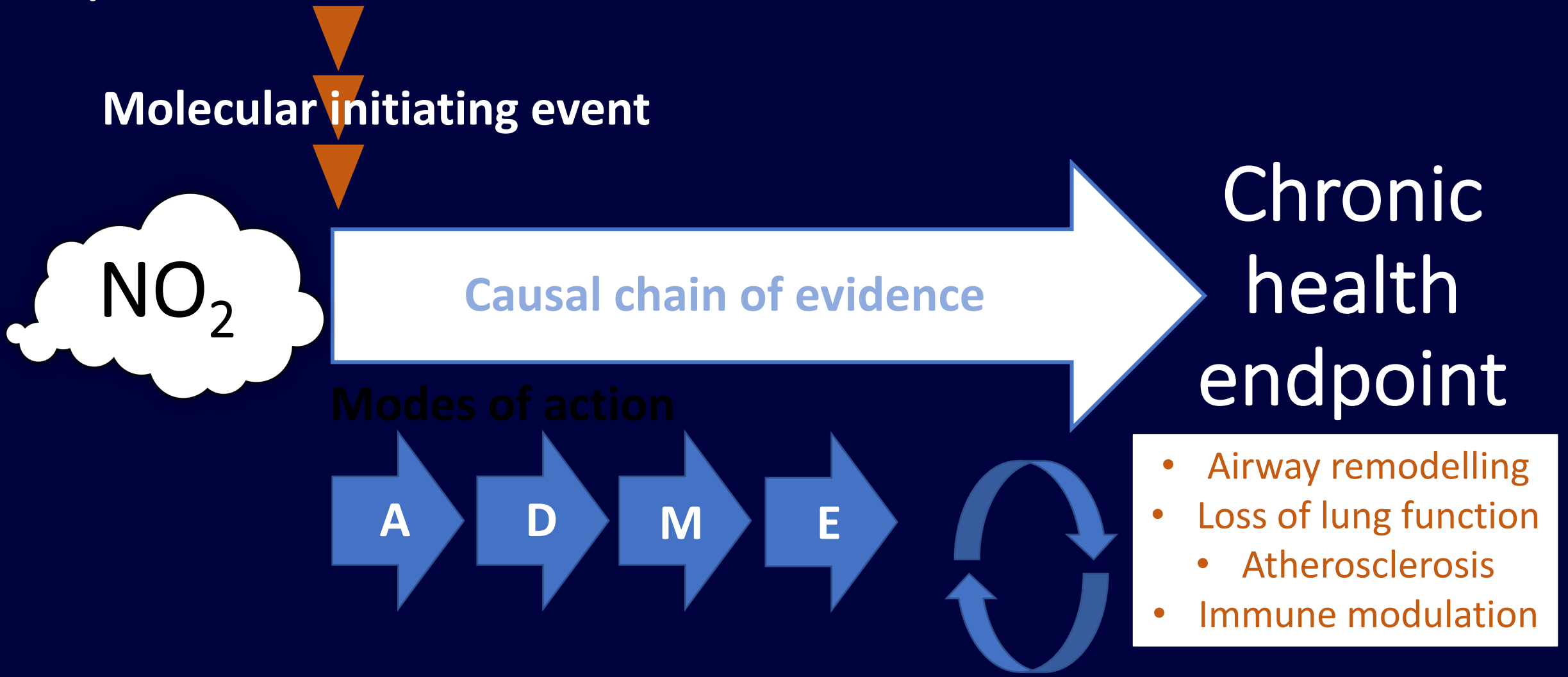
Peters A et al. Cell. 2021 Mar 18;184(6):1455-1468


Systemic responses
• Altered chemokine signaling, inflammation
• Circulating extracellular vesicles
• Circulating RNA species
• Altered metabolites
Circulating peripheral white blood cells
• Altered composition and states
• Epigenetic changes
• Mitochondrial dysfunction
• Telomere attrition
Lung
• Inflammation, cell death
• Epigenetic changes
• Immune cell interactions
• Altered lung microbiome
• Virus activation
Reproductive organs
• Inflammation
• Epigenetic changes
• Mitochondrial dysfunction
• Telomere attrition
• Endocrine disruption
Brain
• Neuroinflammation
• Neurotoxicity
• Stress hormone release
• Endocrine disruption
• Circadian rhythm disruption
• Altered nervous system function
Heart
• Inflammation, cell death
• Epigenetic changes
• Mitochondrial dysfunction
• Altered autonomous nervous system function
Gut
• Altered gut microbiome
• Altered metabolites
Skin
• Inflammation
• Epigenetic changes
• Immune cell interactions
• Altered skin microbiome

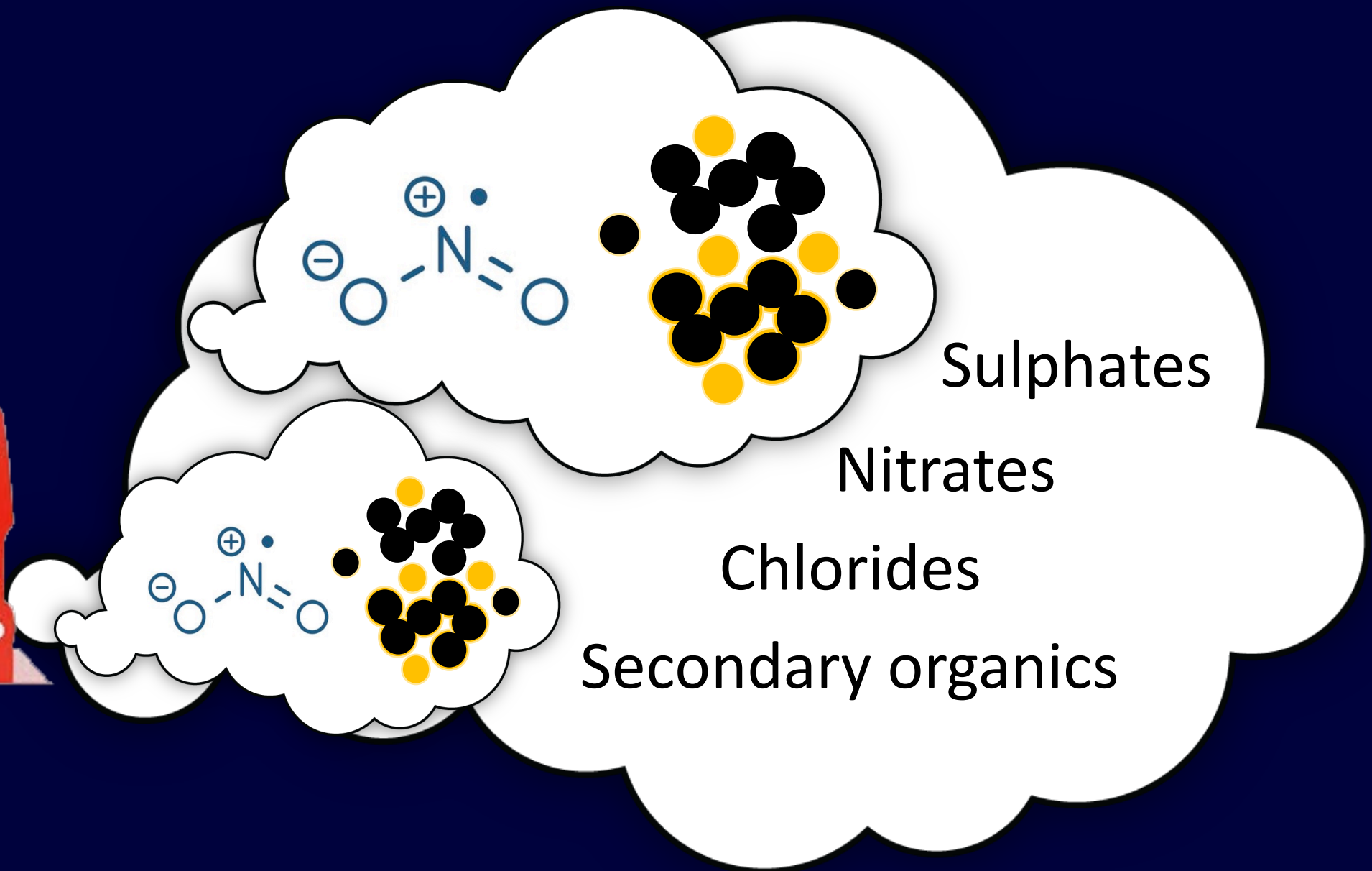
Adverse Outcome Pathway – relevance to the exposome



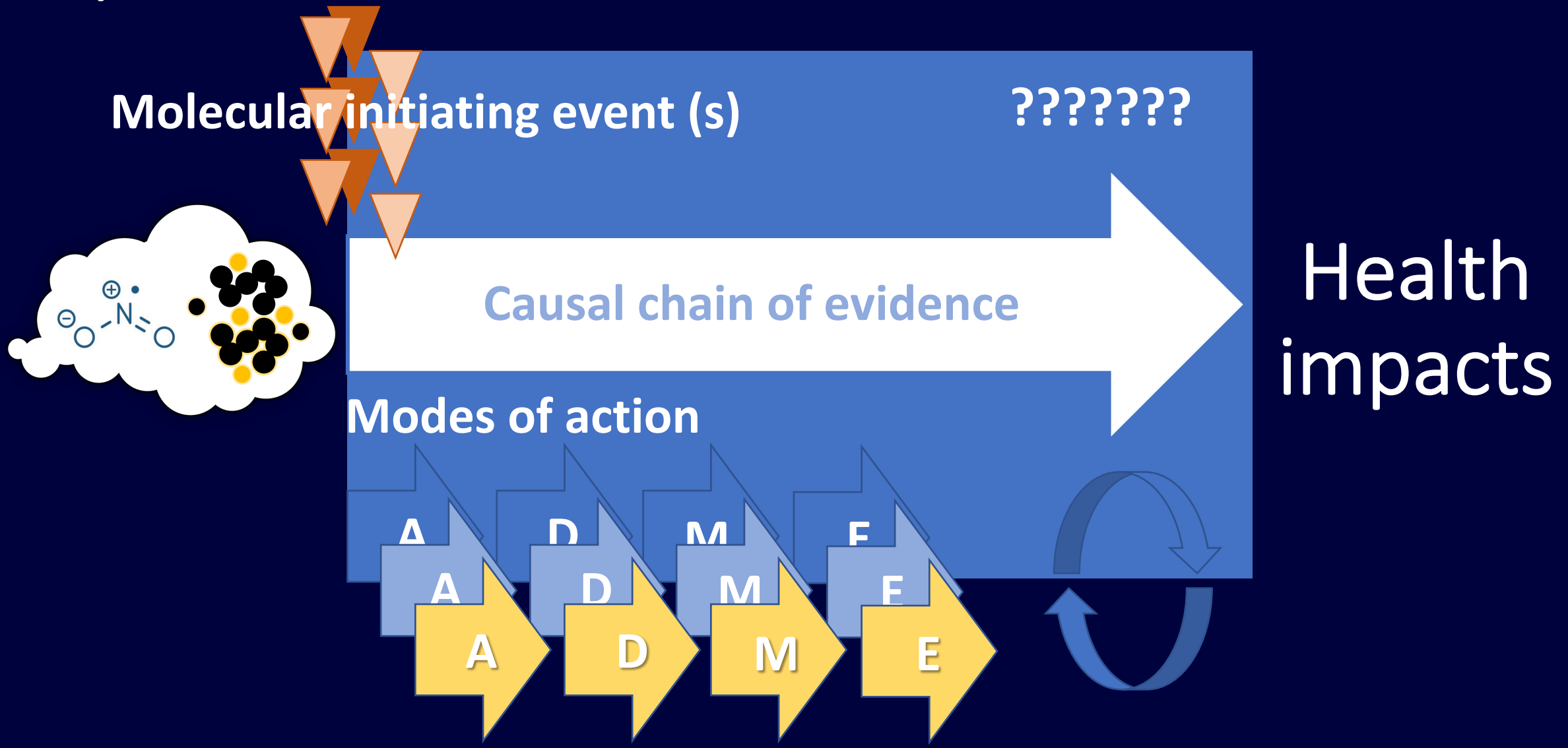
Adverse Outcome Pathway – relevance to the exposome



NO_2 controlling for $PM_{2.5}$



Adverse Outcome Pathway – relevance to the exposome

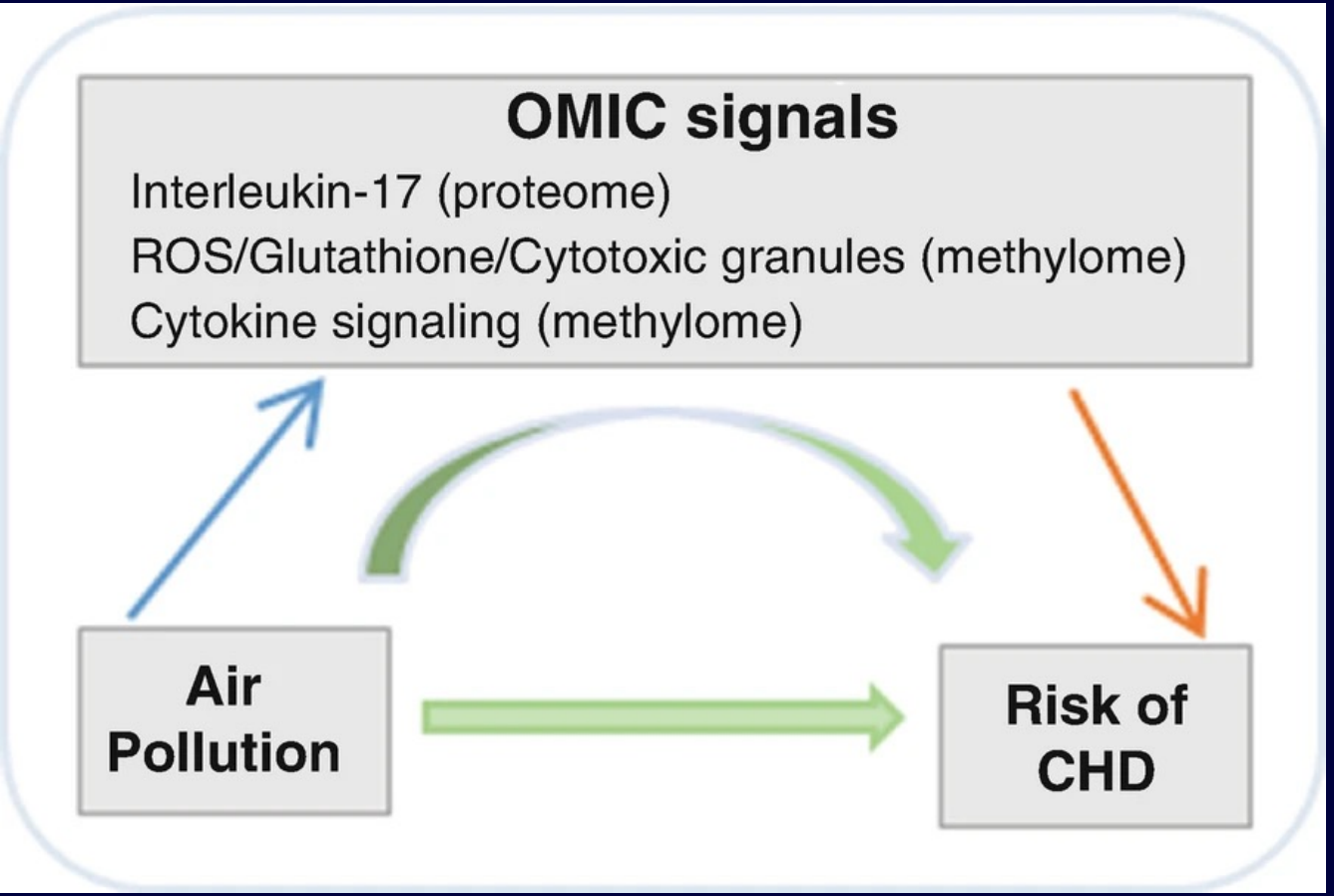


Meet-in-the-Middle: The Example of Air Pollution and Coronary Heart Disease

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

We measured air pollution, inflammatory biomarkers, and whole-genome DNA methylation in blood collected up to 17 years before the diagnosis.

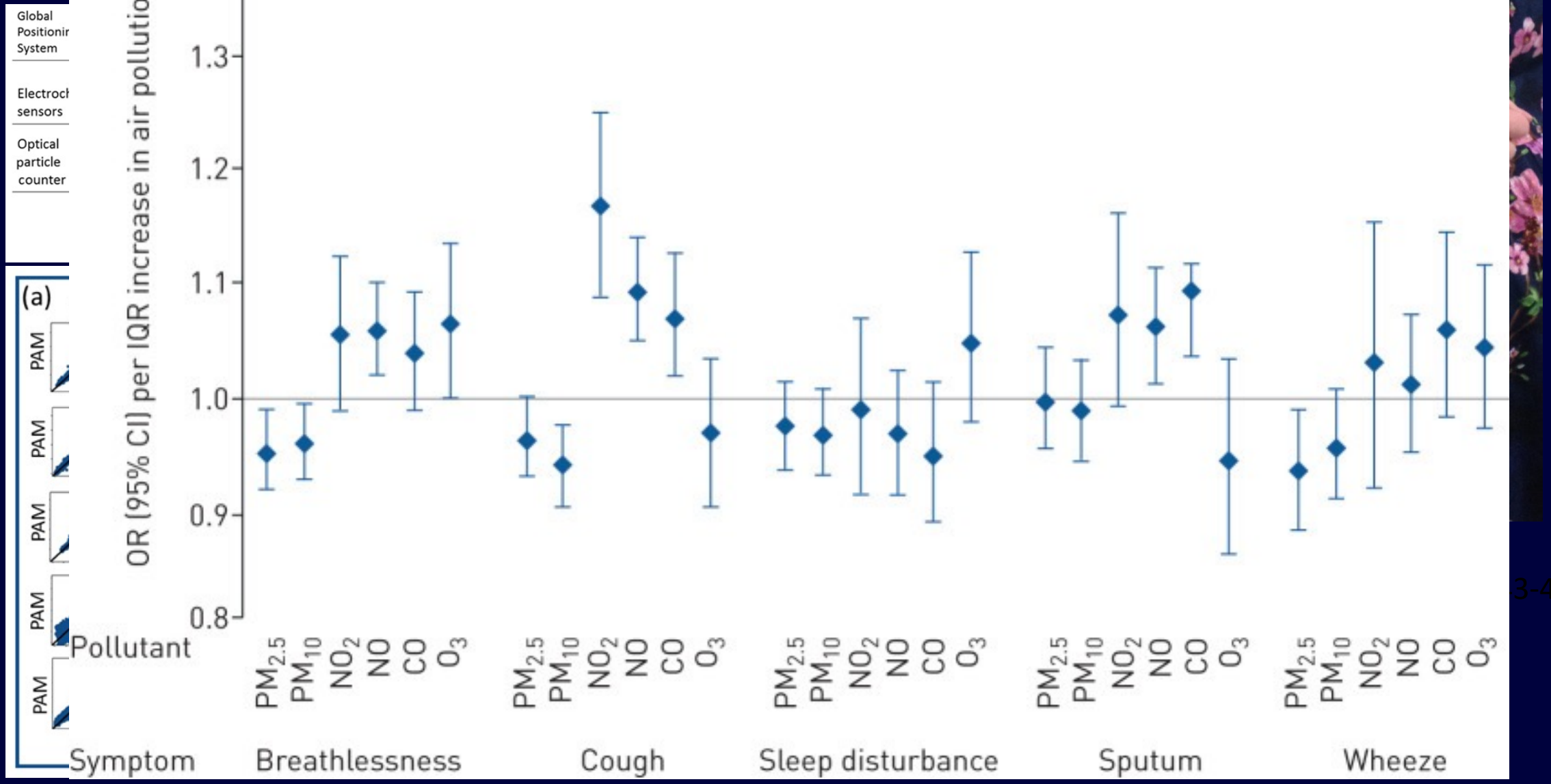
Our findings indicate that chronic exposure to air pollution can lead to oxidative stress, which in turn activates a cascade of inflammatory responses mainly involving the "Cytokine signalling" pathway, leading to increased risk of CCVD – NO_2, $PM_{2.5}$, PM_{10}



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

External exposome developments

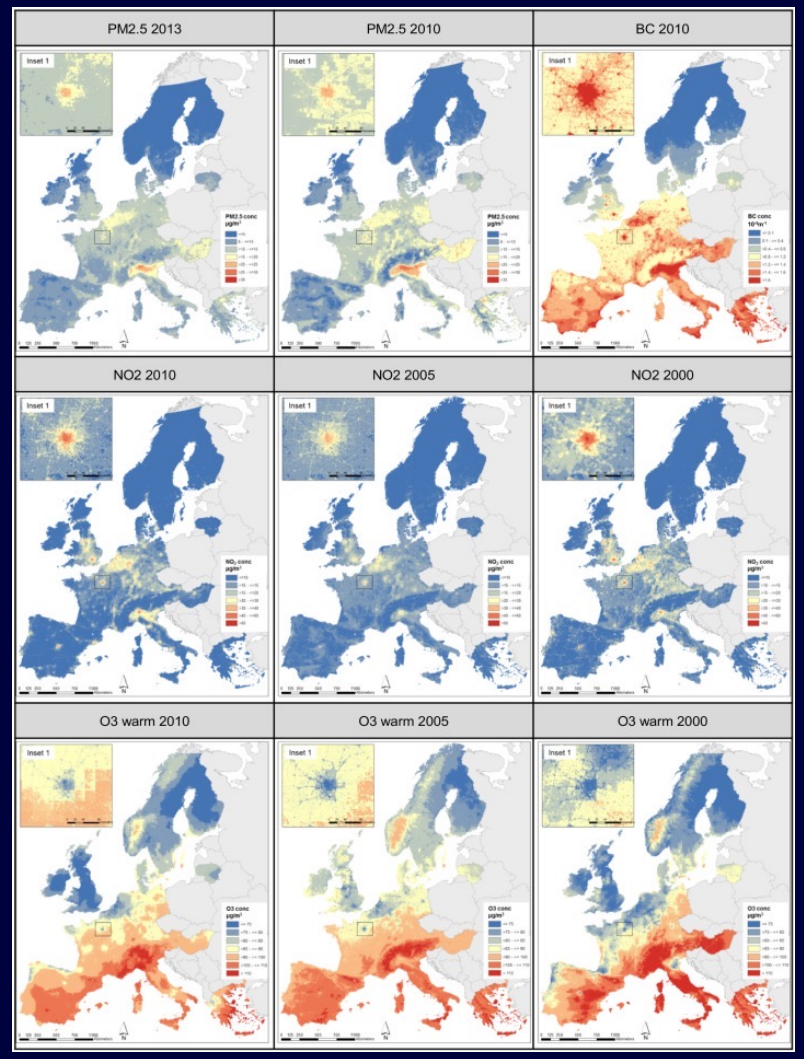
Pe

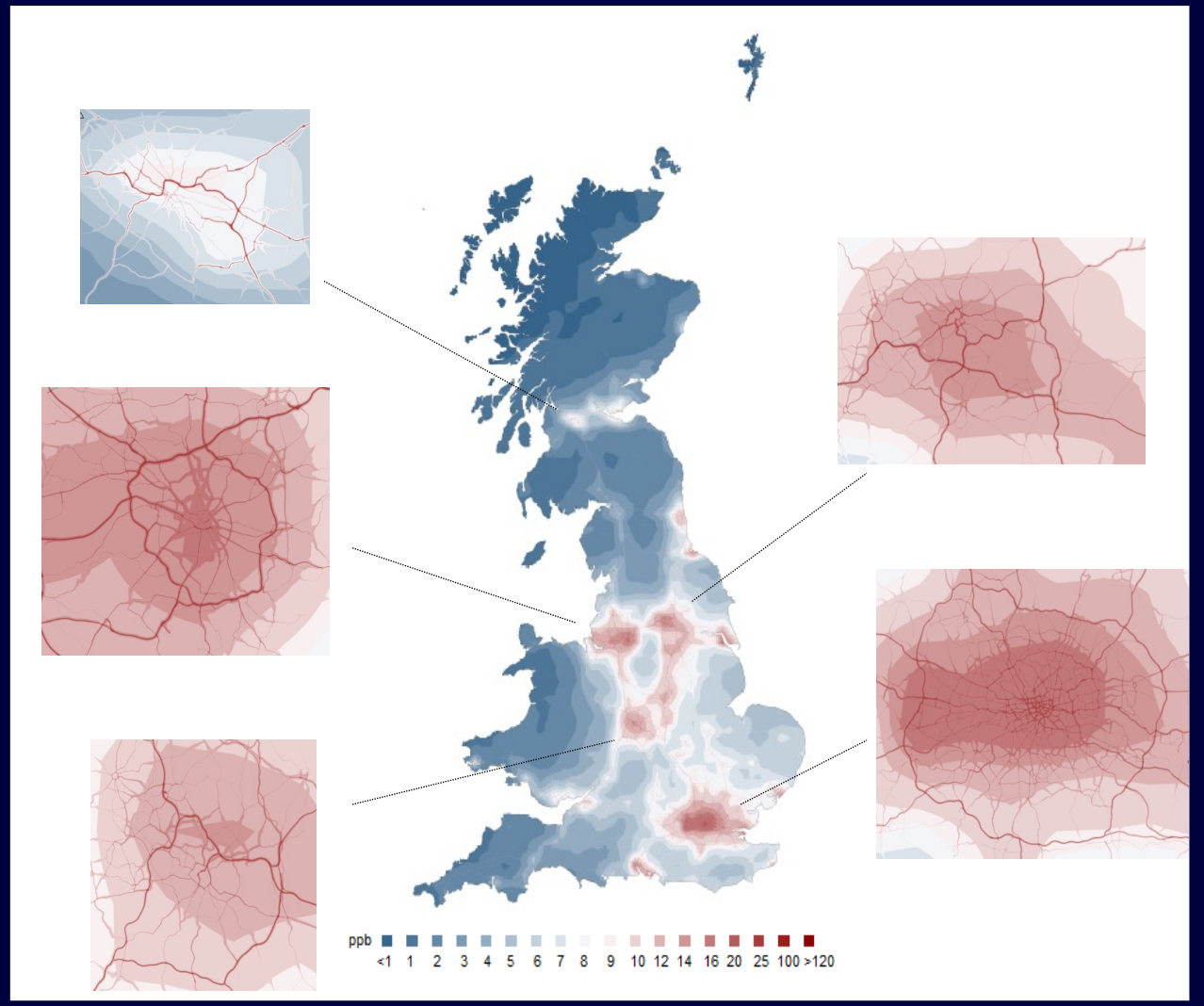


3-4657

External exposome

Enhanced modelling capacity

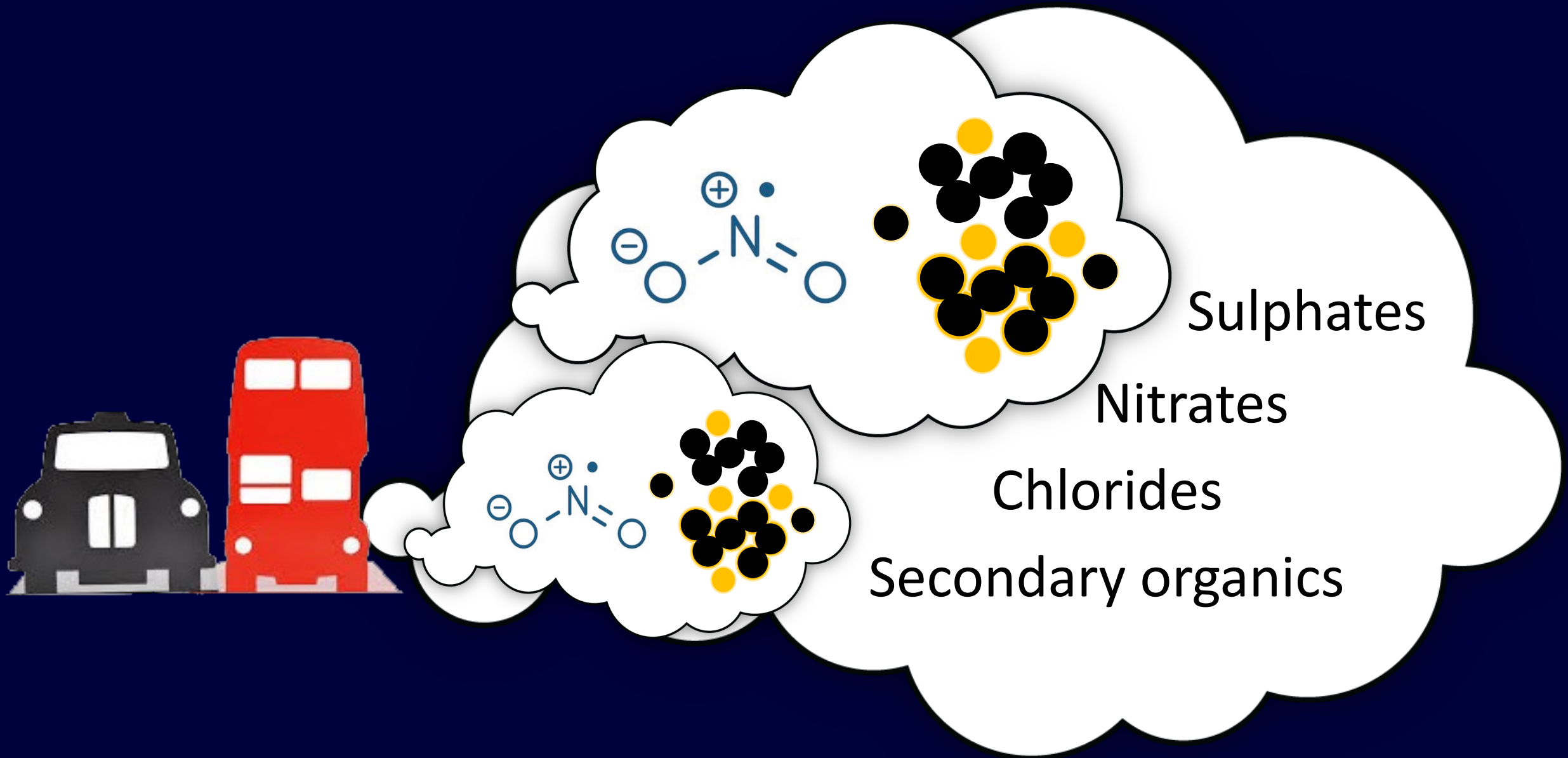




Environ Int. 2018;120:81-92.

External exposome developments

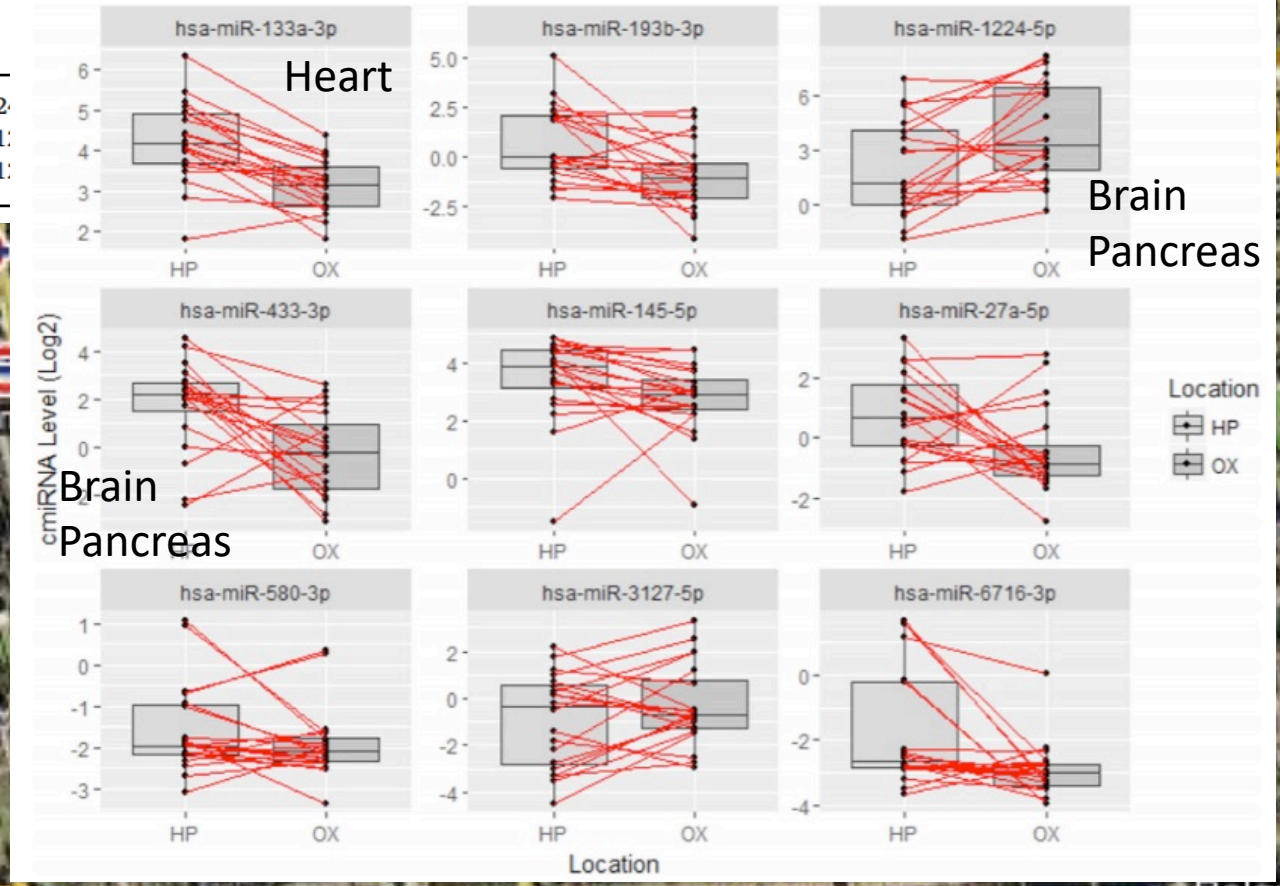
Unpicking causal associations

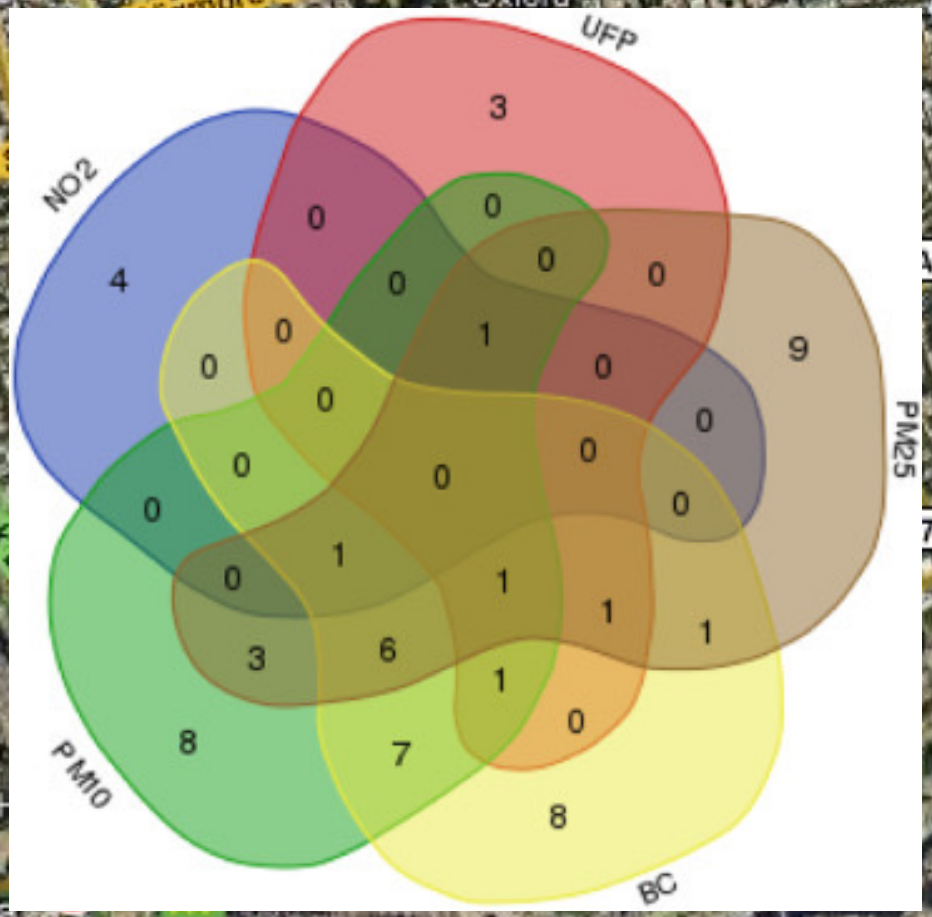


Human circulating miRNome and short-term exposure to traffic-related air pollution

Study population data.

	# Subjects	Age,	BMI,	# Healthy	# COPD	# IHD
All subjects	2					
Male	1					
Female	1					





Krauskopf et al. Environ Int. 2018;113:26-34.

Challenges for exposomics for policy integration

1. Refinement of exposure assessment to air pollution and wat… minants using a combination of personal exposure monitoring and 'omi…
2. Will such a validated refinement lead to more accu… of the association with… educing measurem…
3. Will … the investigati… ts of mixtures in addition to single components?
4. Will they improve the investigat… sponse relationsh…
5. Is it possible to strengther… ng by using the "meet-in-the-middle" concept, i.e. investigate the te… ce of exposure, biological pathway perturbation and disea se ons…
6. Standard… s and analysis - validation

Long(er) term biomarkers

Accumulative tissues

Biological ageing

Epigenetics

Adductomics

BMC Public Health v… e 18, Article number: 260 (2018)

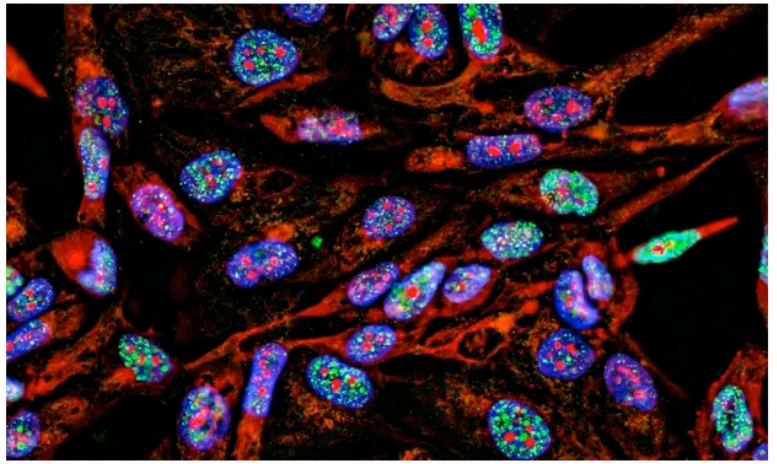
Brennan P et al. Eur J Epidemiol. 2017;32(9):741-749

biobank uk

Enabling scientific discoveries that improve human health

Millions invited to take part in UK scheme to diagnose diseases earlier

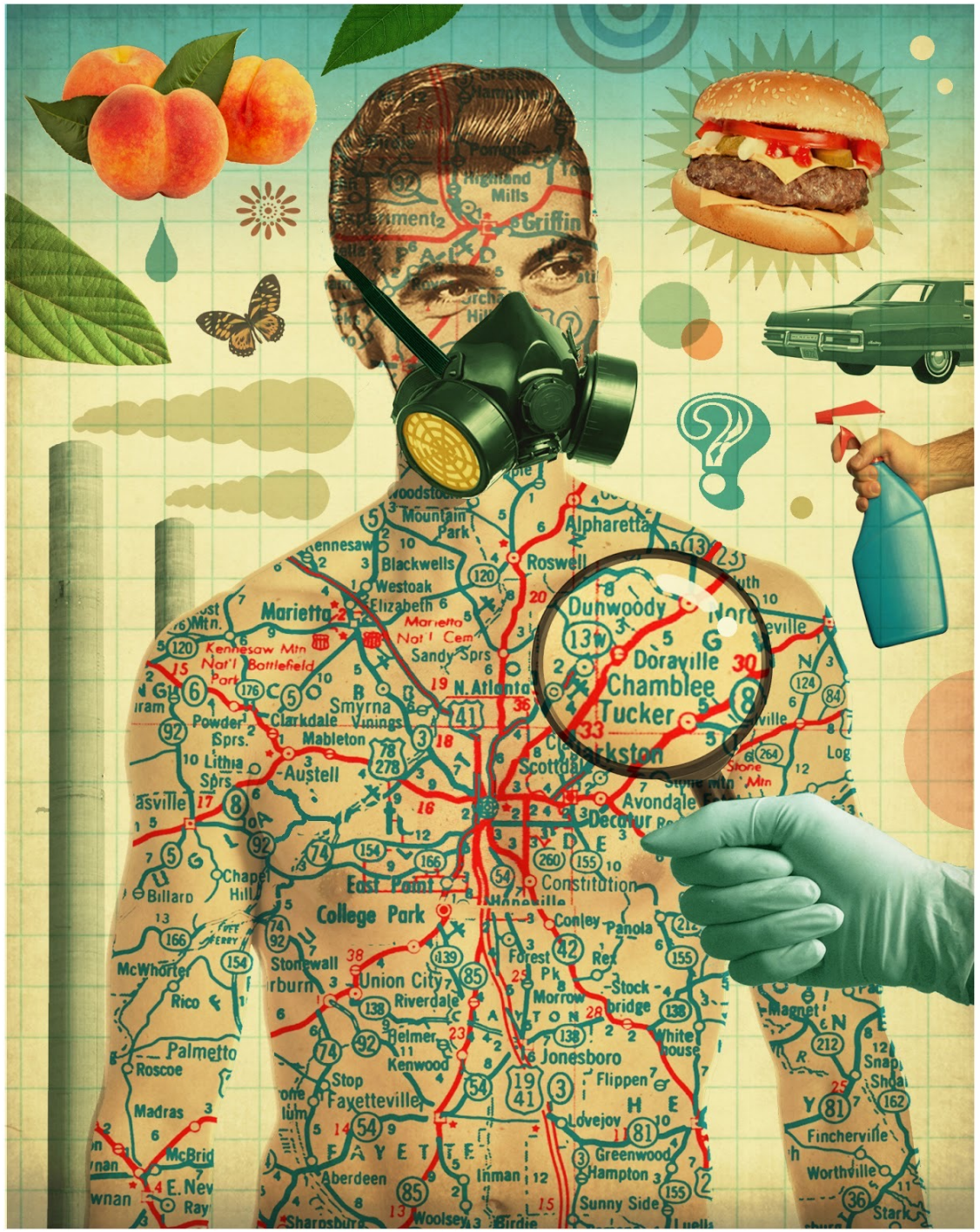
Our Future Health project to recruit 3m people to share health records, give blood samples and have DNA analysed



Fluorescent imaging of cancer cells. Earlier diagnosis and treatment could help those with conditions ranging from cancer to obesity and mental health. Photograph: Nicola Ferrari/Getty Images/iStockphoto

A project to diagnose and treat diseases early - or even prevent them from developing - has been launched in the UK, with 3 million people to be invited to take part this autumn.

The project, called Our Future Health, will eventually recruit 5 million or more people from all walks of life, with participants sharing their health records and giving blood samples, as well as having their weight, blood pressure and cholesterol measured, and their DNA analysed.


Griffin
Alpharetta
Roswell
Marietta
Duluth
Doraville
Chamblee
Tucker
Smyrna
Clarkdale
Mableton
Austell
Powder Sprs.
Lithia Sprs
Avondale
Decatur
East Point
College Park
Constitution
Union City
Riverdale
Jonesboro
Fayetteville
Palmetto
Roscoe
Madras
Aberdeen
Inman
Sunny Side
Lovejoy
Hampton
Greenwood
Fincherville
Worthville
Stockbridge
Conley
Panola
Forest Pk
Morrow
Rex
Kenwood
Helmer
Stonewall
McWhorter
Rico
Billard
Chapel Hill
Ferry
Sandy Sprs
N. Atlanta
Blackwells
Westoak
Elizabeth
Mountain Park
Highland Mills
Kennesaw Mtn Nat'l Battlefield Park
Marietta Nat'l Cem
Woodstock
Log
Stone Mtn

Questions