Definition of exposome and perspectives

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From Harpers Collins Dictionary, 2021:
A collection of environmental factors, such as stress and diet, to which an individual is exposed and which can have an effect on health

Wild C. (2005). Cancer Epidemiol Biomarkers Prev 14(8): 1847:
The concept of the exposome refers to the totality of environmental exposures from conception onwards, and includes both external and internal components

US-NIOSH:
The exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health.
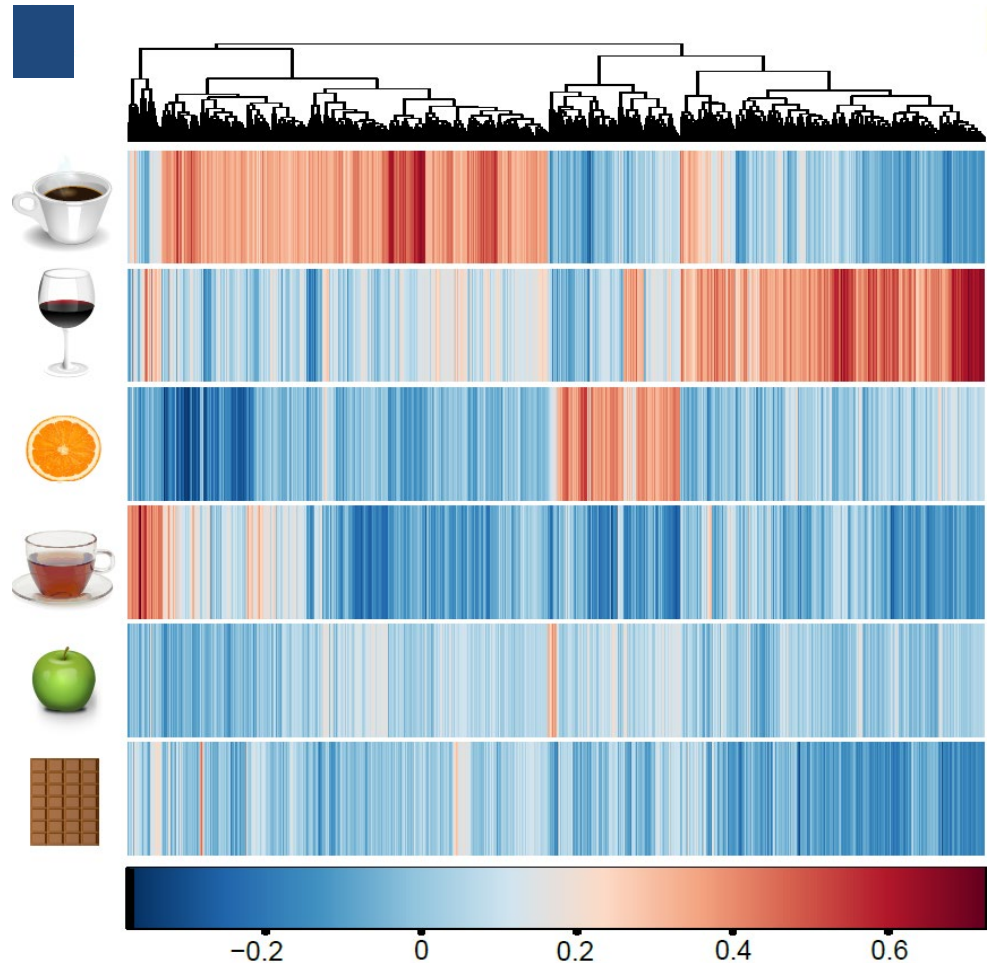
The exposome
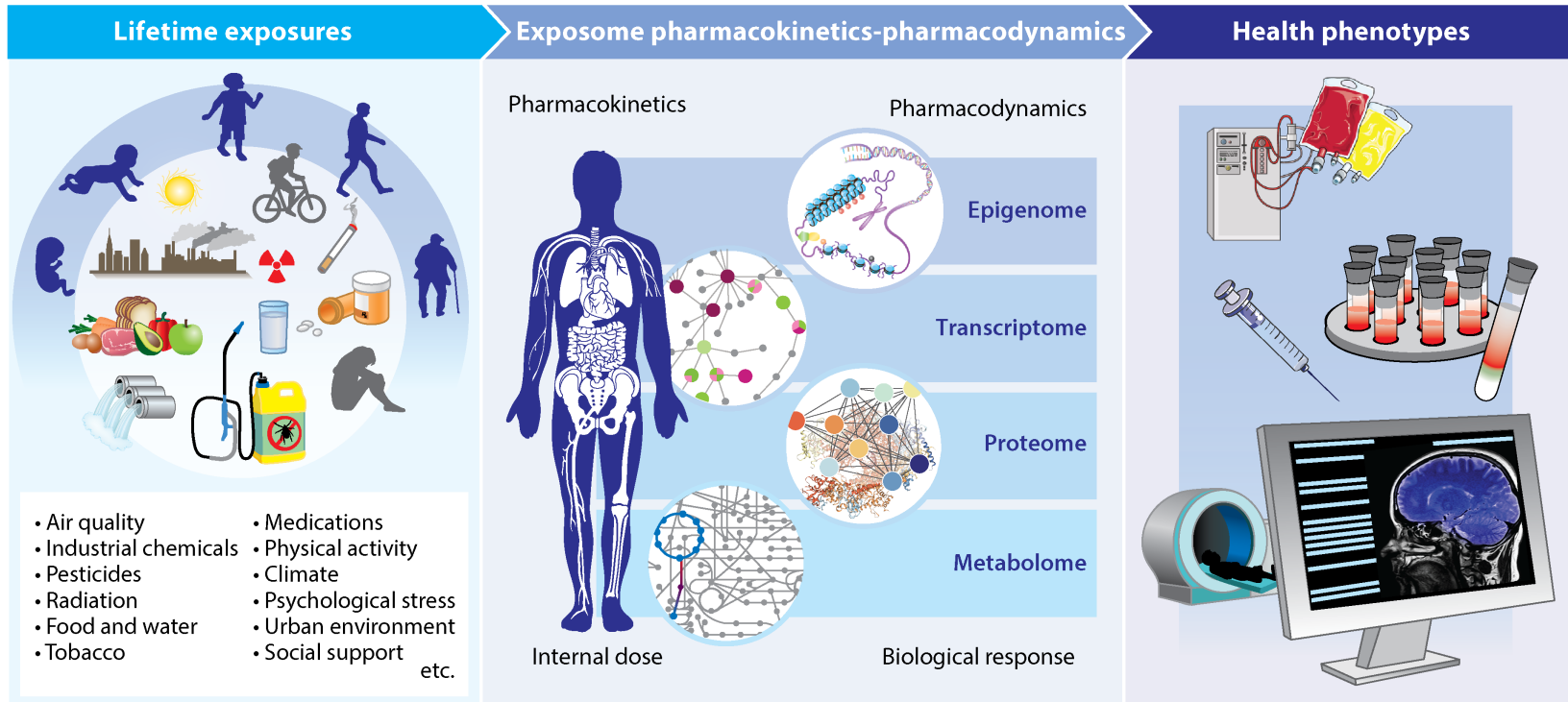
Diagram courteous of Niedzwiecki et al., 2019

Exposure assessment: Metabolic signals associated with food intake

481 subjects from 4 countries
24-hr Dietary recalls
24-hr Urine samples
High-resolution mass spectrometry
  (UHPLC-QTof-MS, neg ionization)
Iterative regression analyses

1 uL injected

- 14,000 mass spectrometry features detected
- 2,272 features correlated to intake of six different foods

Edmands et al., 2015, *Am J Clin Nutr*

THE RIVER EXPOSOME (Egli, Barron)

Tributary rivers have unique chemical signatures → River 'omics'

Tributaries are different contamination sources of the Thames

River water contamination may poLondon population (drinking water, fise a risk for the shing, swimming)

River Classification possible ✓
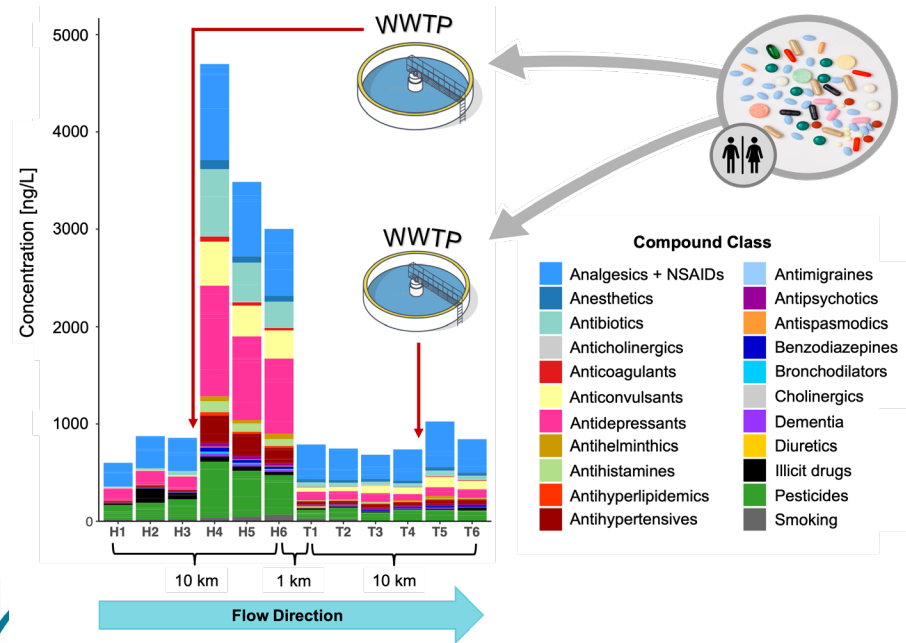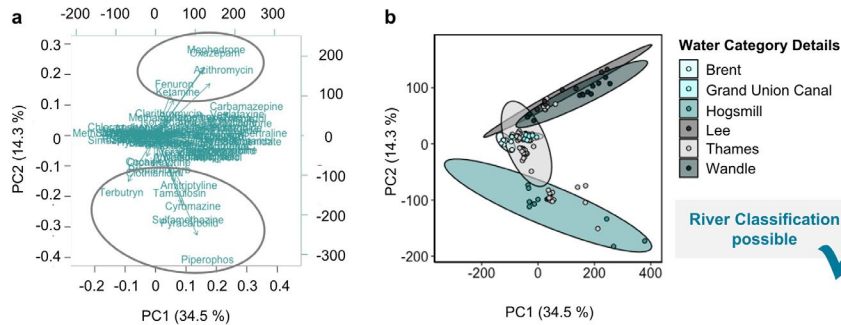
Fingerprints of exposures: certain exposures may leave characteristic fingerprints in DNA

CANCER ETIOLOGY

Mutational signatures associated with tobacco smoking in human cancer

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Tobacco smoking increases the risk of at least 17 classes of human cancer. We analyzed somatic mutations and DNA methylation in 5243 cancers of types for which tobacco smoking confers an elevated risk. Smoking is associated with increased mutation burdens of multiple distinct mutational signatures, which contribute to different extents in different cancers. One of these signatures, mainly found in cancers derived from tissues directly exposed to tobacco smoke, is attributable to misreplication of DNA damage caused by tobacco carcinogens. Others likely reflect indirect activation of DNA editing by APOBEC cytidine deaminases and of an endogenous clocklike mutational process. Smoking is associated with limited differences in methylation. The results are consistent with the proposition that smoking increases cancer risk by increasing the somatic mutation load, although direct evidence for this mechanism is lacking in some smoking-related cancer types.

obacco smoking has been associated with | cancer genome sequencing, we recently described

Fig. 2 — Signature 2, Signature 13, Signature 5, Signature 4, Signature of benzo[a]pyrene exposure in vitro

Tobacco smoke as a mixture that leaves different signatures depending on the cancer site and possibly on the chemicals involved – e.g. PAH for lung cancer: signature 4

Science, 4 November 2016
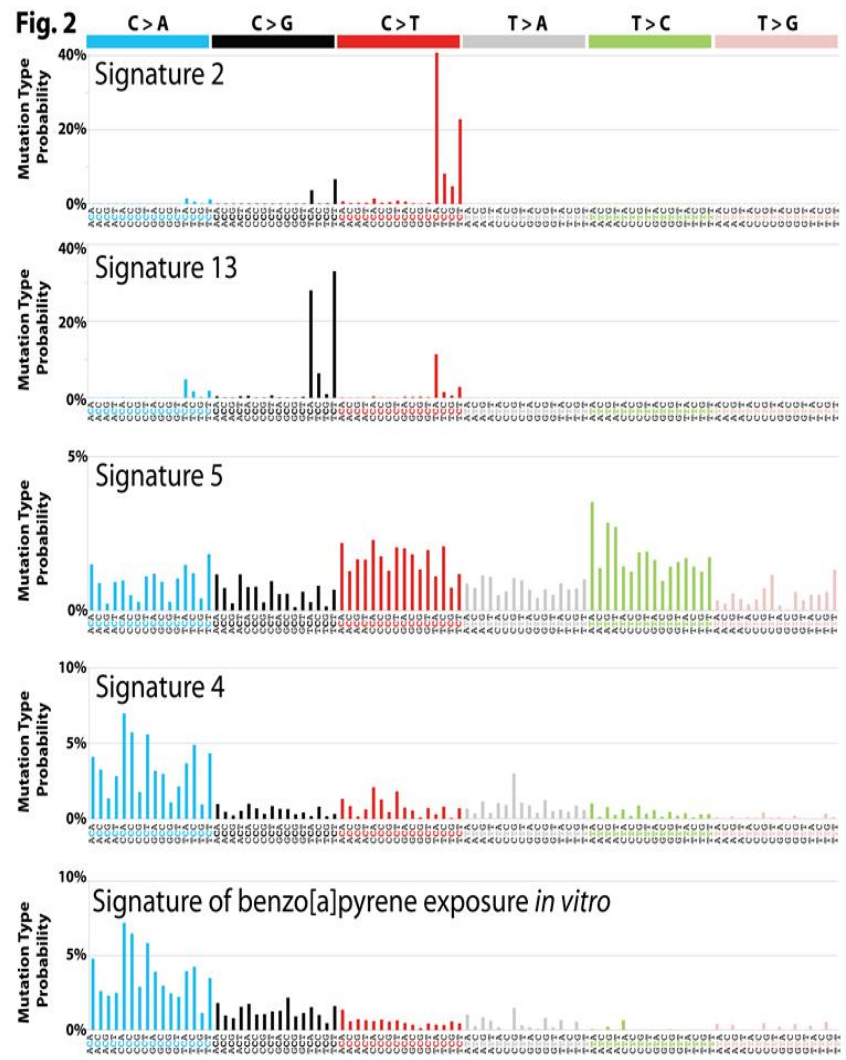
Pathways - «Meet-in-the-middle»
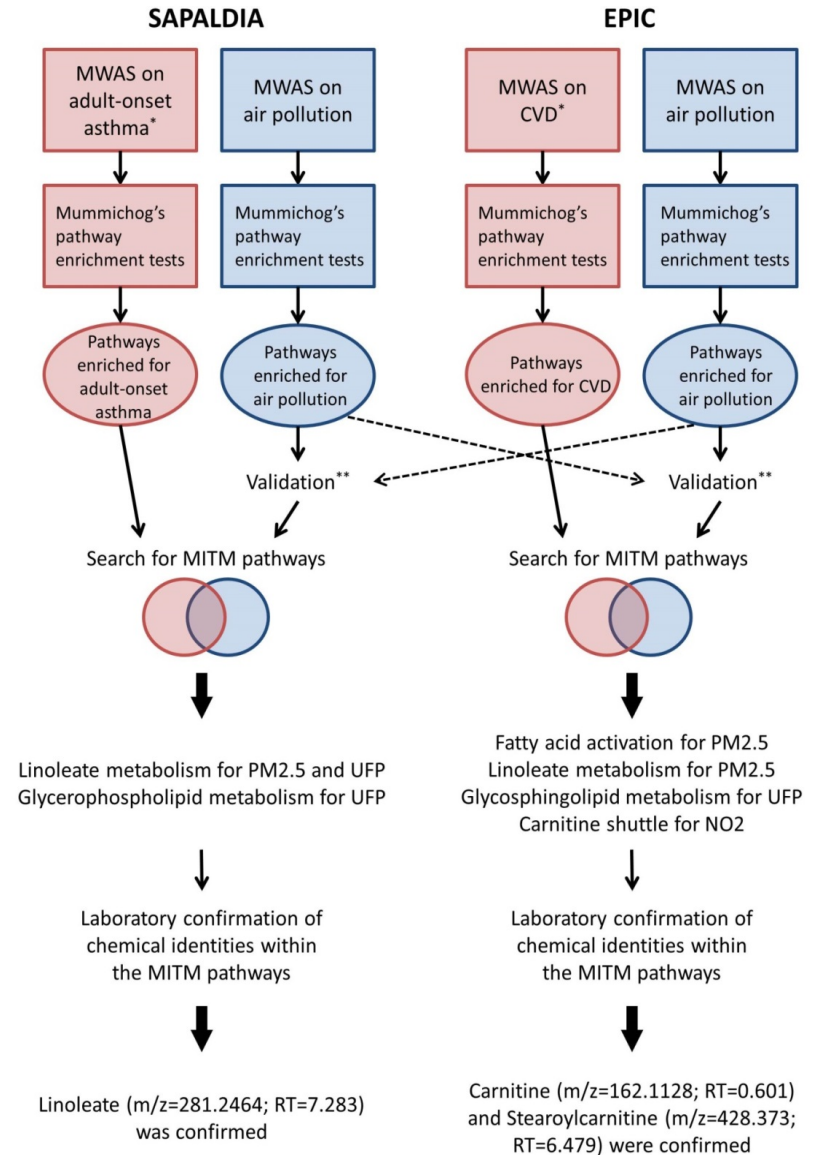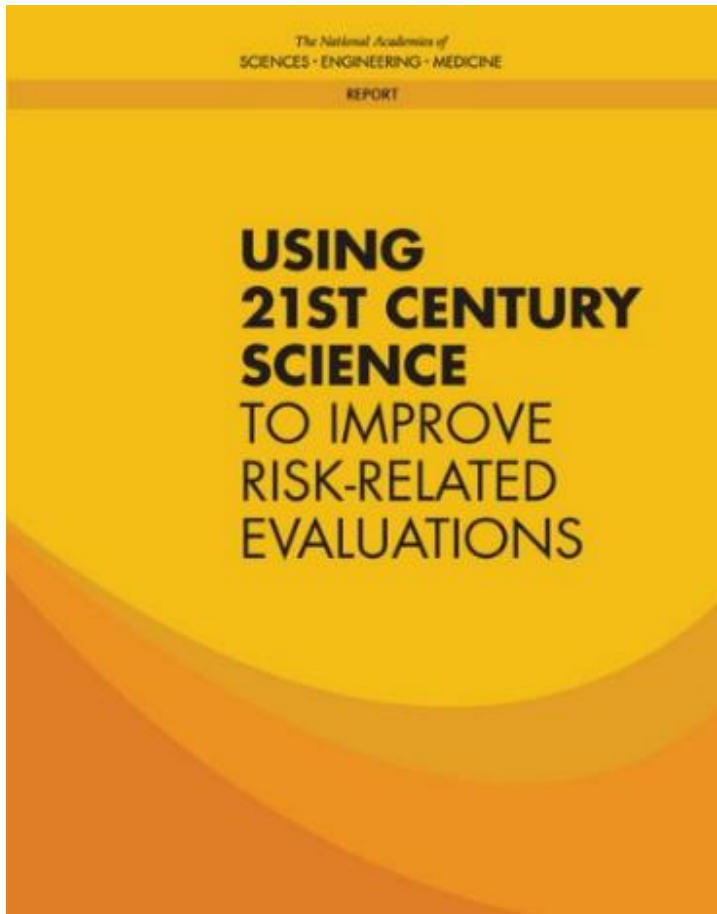
SOCIAL EXPOSOME

The French sociologist Pierre Bourdieu has explained the role of **economic, social and cultural capital** in the functioning of societies and in social inequality. Like "the social world is accumulated history" , so is the individual life at any particular time/age: it is the accumulated history of all economic, social, cultural and eventually biological experiences that had an impact on the body.

Biology (Zoe) and biography (Bios) meet for example through health status, depending on social position at a given age.

This connects to biology is not explained by Bourdieu, and biological capital is the missing concept. However, the ability to access the three other forms of individual capital and therefore position in life depends on **inherited biological health/skills, epigenetic imprinting and the accumulation of embodied biological changes that make an individual more or less successful in life.**

Relationship between cumulative mortality and the biomarkers used to create the allostatic load score (Castagné et al. 2018
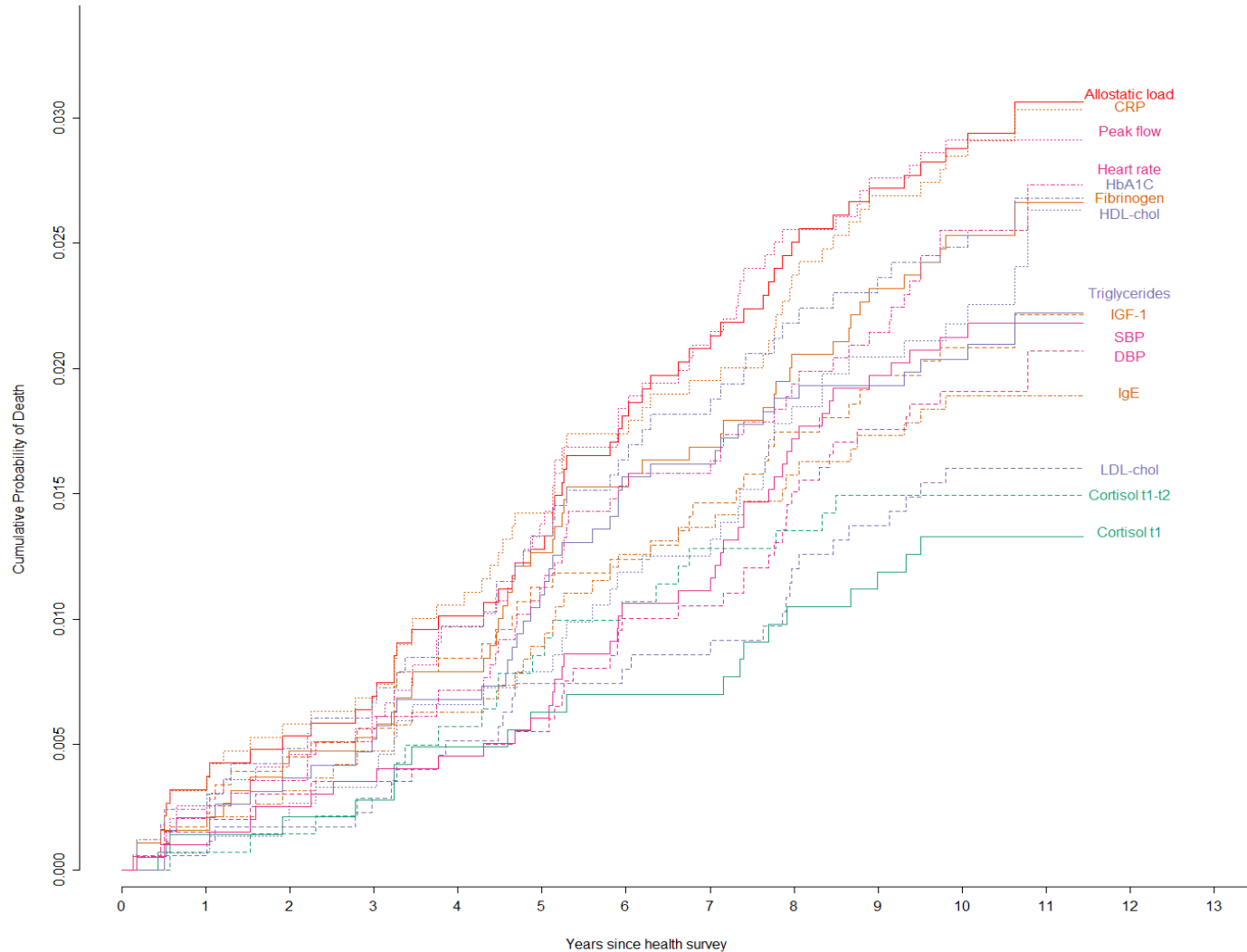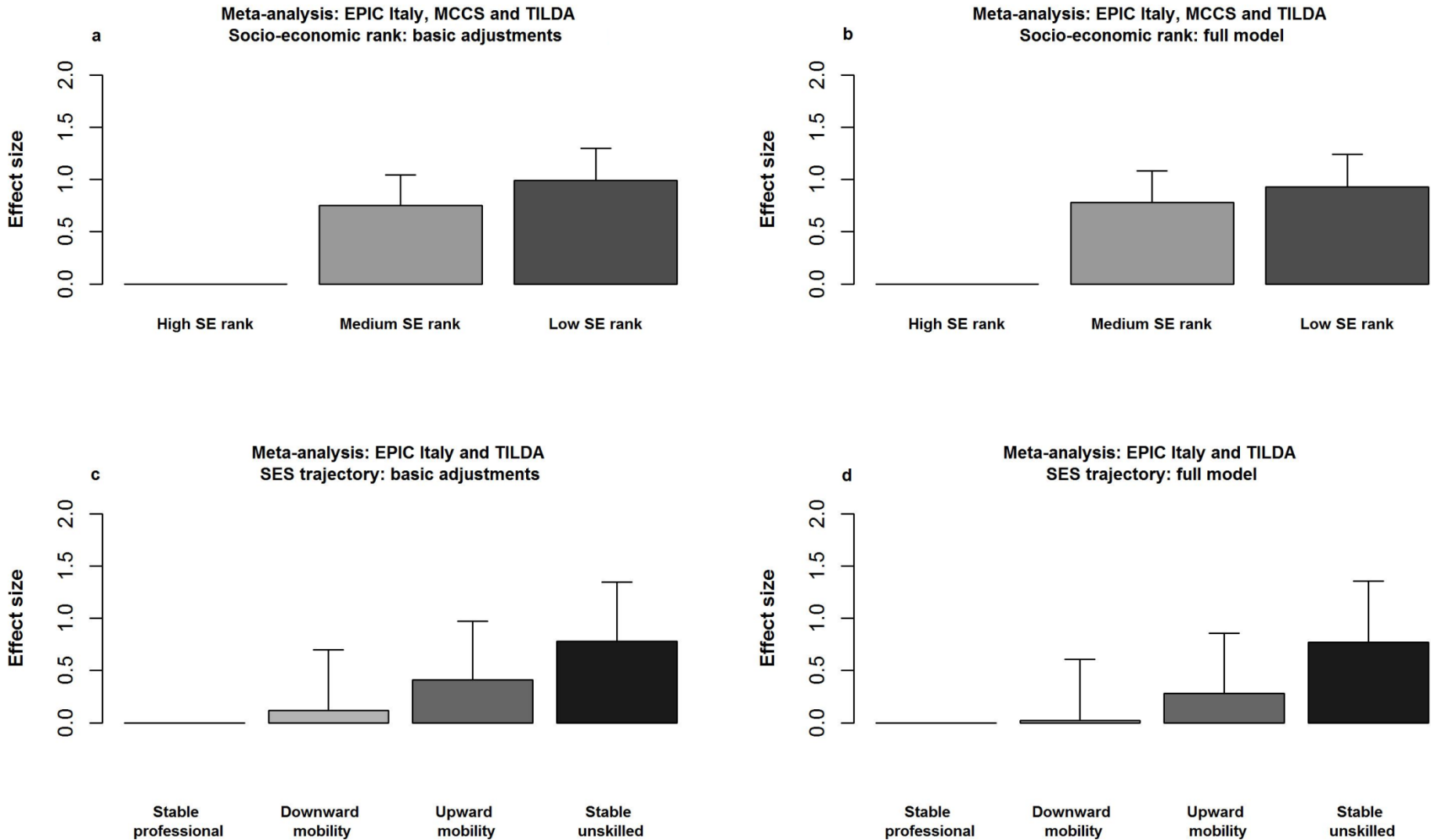
Biological clocks in LIFEPATH

- Ageing has been defined as the **"time-dependent decline of functional capacity and stress resistance, associated with increased risk of morbidity and mortality"**

- Environmental stressors can affect ageing rates at both the 'build-up' and 'decline phase'

- Recently, epigenetic clocks have been developed to assess *biological age*

- Horvath developed the DNA methylation clock to predict age with high accuracy using 353 CpG sites

- From this Age Acceleration may be derived as a discrepancy between methylation age and chronological age
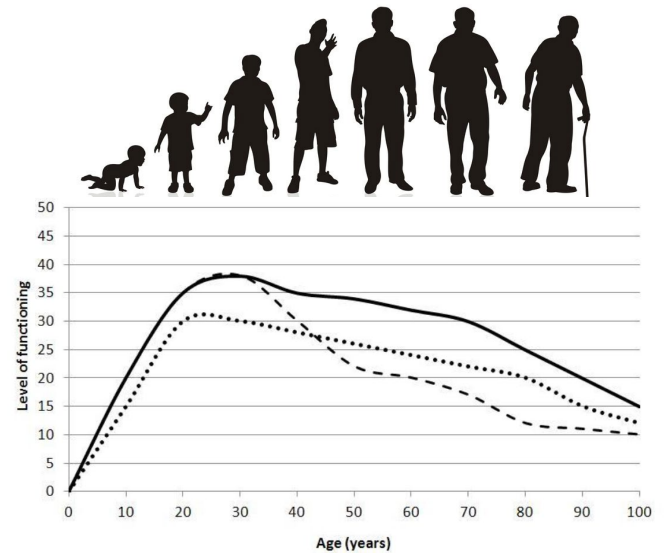
(Source: Strachan & Sheikh 2004)

Age acceleration based on DNA methylation in EPIC Italy, MCCS and TILDA

Meta-analysis: EPIC Italy, MCCS and TILDA
Socio-economic rank: basic adjustments

Meta-analysis: EPIC Italy, MCCS and TILDA
Socio-economic rank: full model

Meta-analysis: EPIC Italy and TILDA
SES trajectory: basic adjustments

Meta-analysis: EPIC Italy and TILDA
SES trajectory: full model

Fiorito G, 2017.

Risk factors for epigenetic age acceleration

- Meta-analysis of 16,000 people across 18 cohorts)

- Comparison of effects of leading NCD risk factors on epigenetic ageing

- Horvath, Hannum and Levine measures of **methylation-based age acceleration and stochastic epigenetic mutations (SEMs) assessed**

- SEMs are sites with extreme methylation levels, randomly distributed throughout genome, which accumulate with age ("epigenetic drift")
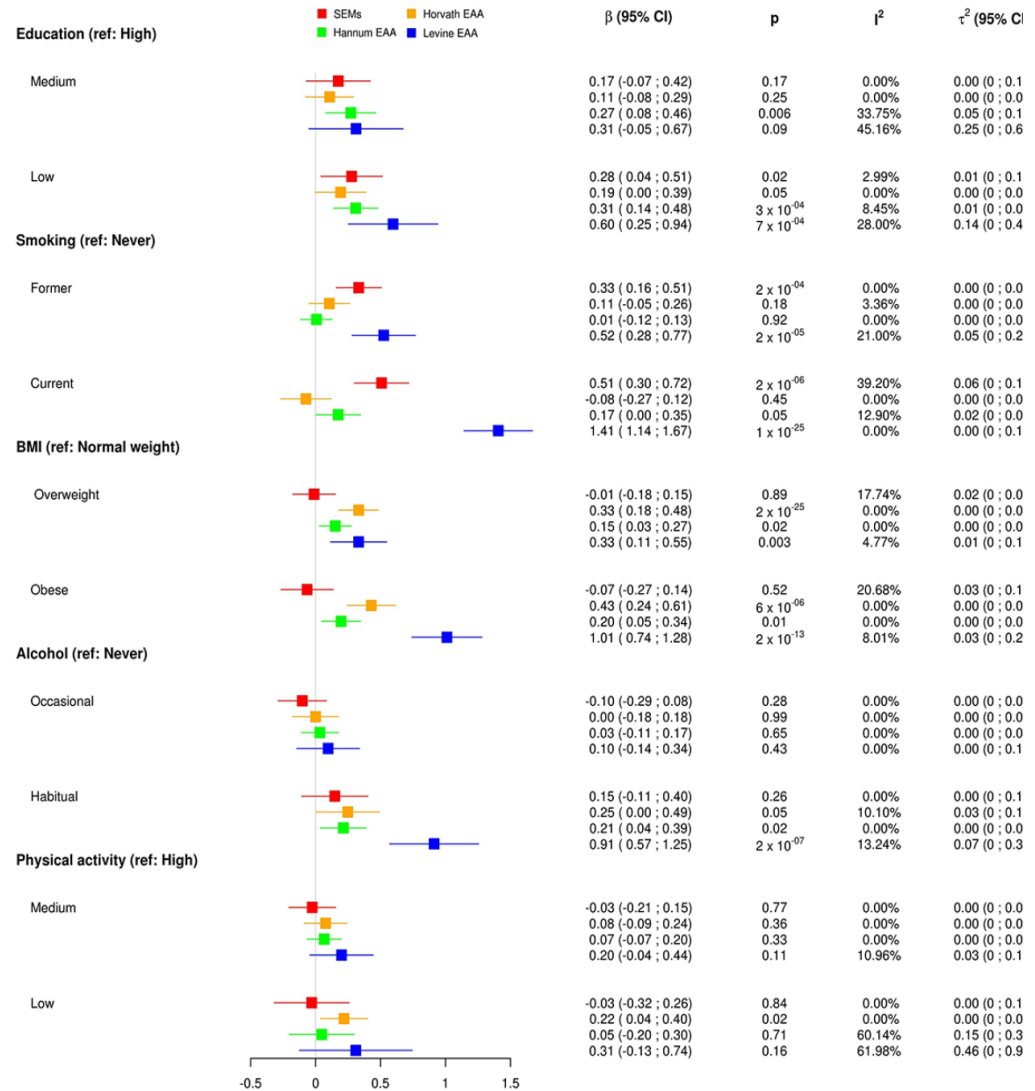
Fiorito et al 2019

Figure 1. Effect sizes (interpretable as years of increasing/decreasing epigenetic age) of the association between different risk factors and four epigenetic aging biomarkers: total number of stochastic epigenetic mutations (SEMs, red), Horvath epigenetic age acceleration (orange), Hannum epigenetic age acceleration (green) and Levine epigenetic age acceleration next-generation clock (blue).

What are the gaps?

- Conceptual gaps, e.g. temporal sequence of hallmarks of disease …

- What is the environment: not only biomedically relevant events!

- Lifecourse approach: only partially explored

- Agnostic approaches: immature

- Omics: incomplete coverage (e.g. CpGs in Illumina platforms, annotation of metabolomics), sensitivity of assays (for low levels)

- Rapid developments in molecular technologies, e.g. RNA sequencing (ncRNA), high costs

- Sensors not yet developed for field use

- Good advancements in biostatistics, gaps in cross-omics

- ….

Thank you