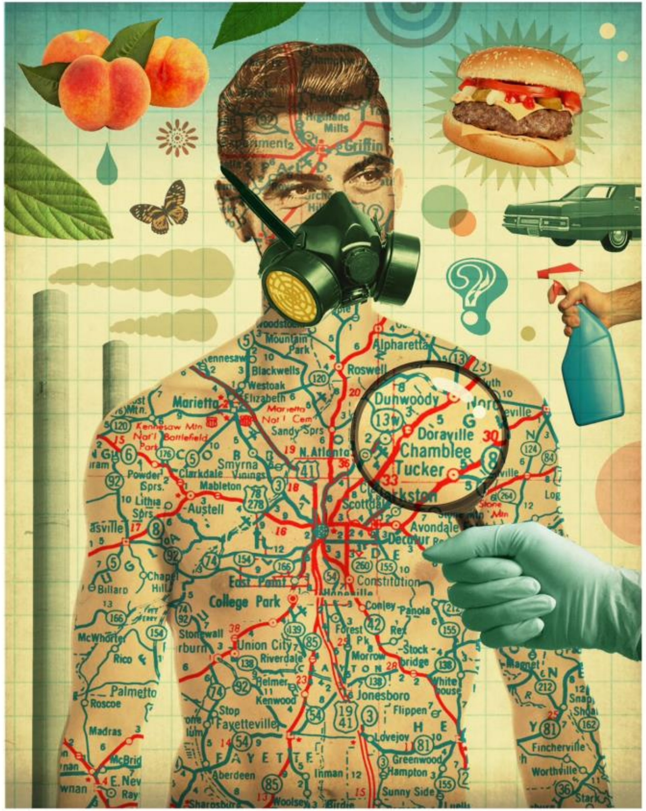
Queen Mary University of London
Medicine and Dentistry

The exposome concept: the totality of exposures as an integrated environmental health factor

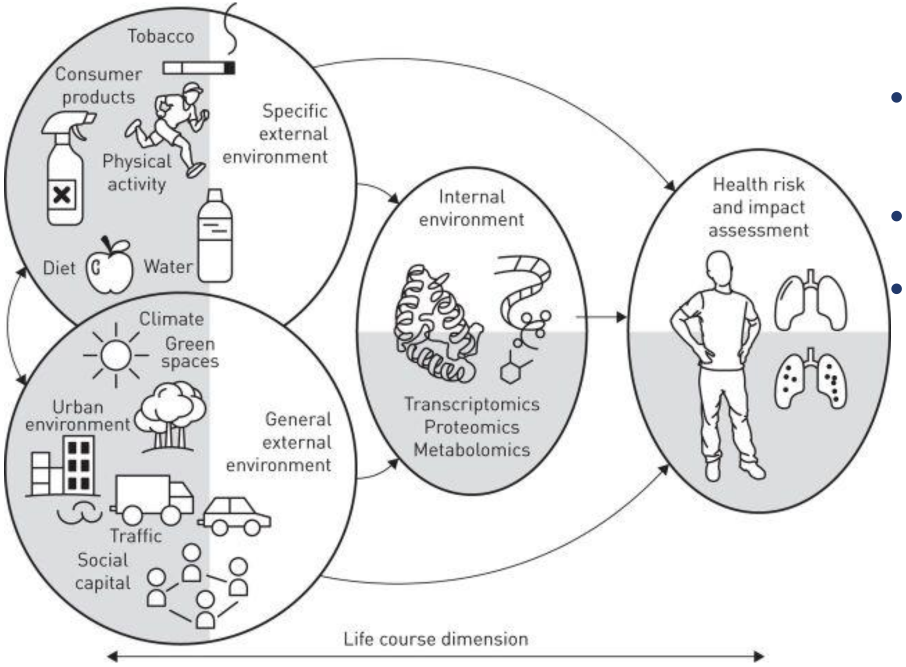
Stavroula Kanoni, PhD, PGCAP, FHEA
Reader (Associate Professor) in Nutrigenetics and Cardiovascular Health
Academic Lead (Dep) Environment & Health Multi-Disciplinary Theme
Fellow Digital Environment Research Institute (DERI)
s.kanoni@qmul.ac.uk

Outline

- What is the exposome
- How can we model the exposome and analyse it
- Exposome-wide association studies
- The role of AI
- Sensors and wearables
- The Health Digital Twin



The exposome concept

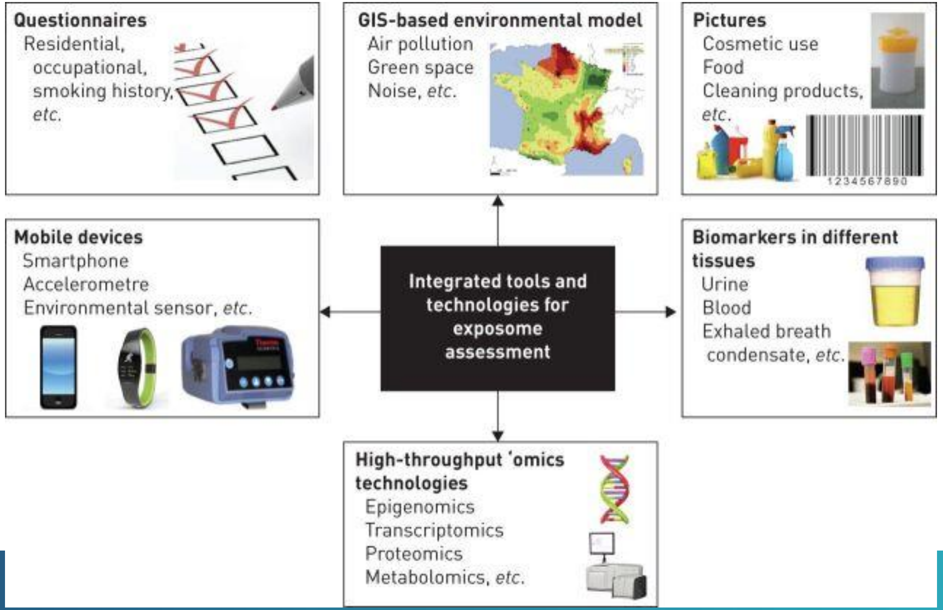


- First defined in 2005
- All environmental exposures through the lifetime that could cause or contribute to disease
- Lifelong exposure and co-exposures
- Factors to be measured:
  - General external environment (urban–rural environment, climate factors, social capital or education)
  - Specific external environment (diet, physical activity, tobacco, infection, occupation)
  - Internal environment (biological factors, metabolic factors, gut microbioflora, inflammation, oxidative stress or ageing)

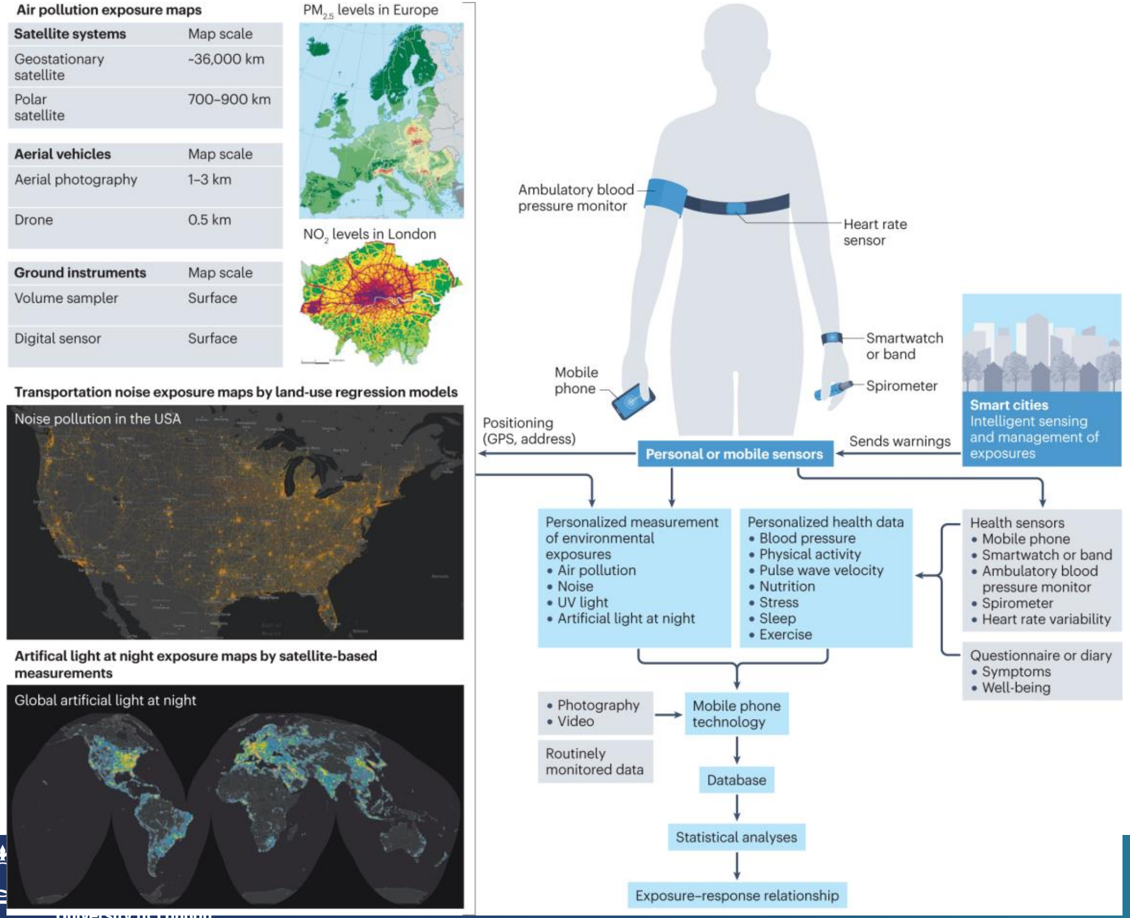
Exposome-wide association studies

- Exposome-wide association studies (ExWAS) -> agnostic, untargeted and hypothesis-generating approach -> identification of associations between environmental factors and diseases outcomes
- Simultaneously consider multiple exposures and prioritize outcome-associated risk factors

- Inclusivity of environmental factors assessed
- Validity of the measurements
- Statistical models applied



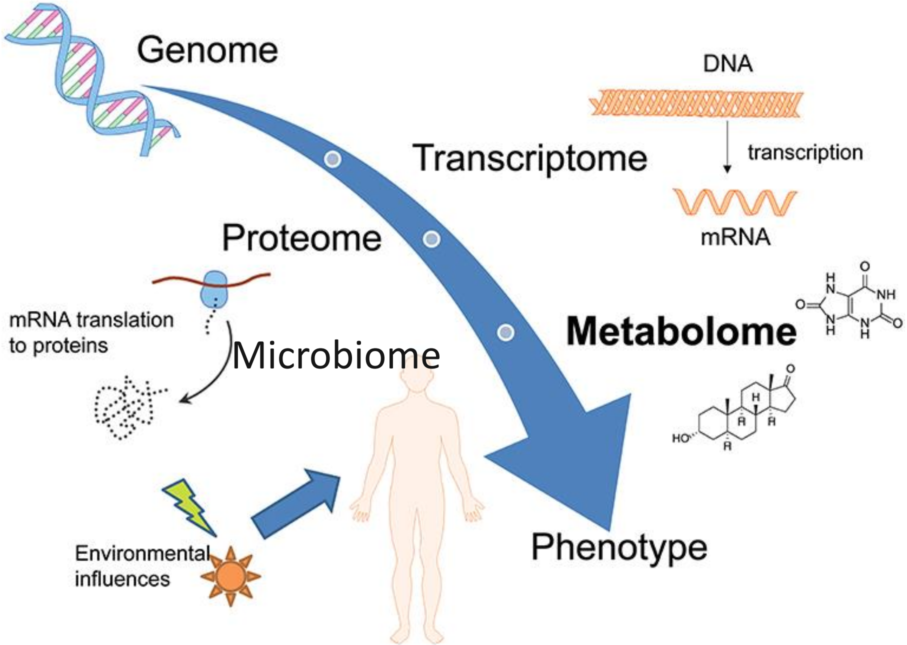
Assessment of the exposome



- Evaluate the exposome in real-time

Münzel T, *et al. Nat Rev Cardiol*, 2023
doi.org/10.1038/s41569-023-00873-3

Biomarkers of the exposome - Omics



- Internal exposome environment

Methodologies	
Transcriptomics	RNA sequencing[103,104]
	Single-nucleotide polymorphism-based arrays (metabochip, immunochip)[103,104]
Epigenomics	DNA methylation (EPIC, BeadChip, bisulfate sequencing)[123–125]
	Hydroxymethylation (5hmC)
	Histone modifications
	MicroRNAs[126]
	Long non-coding RNAs
Proteomics	Protein expression[103,104]
	Post-translational protein modifications (oxidation: 3-nitrotyrosine, S-oxo-Met, carbonylation; reactive aldehyde adducts: malondialdehyde, 4-hydroxynonenal)[54,114]
	Redox and phospho-proteome[106,107]
Lipidomics	Fatty acid composition of lipid membranes (saturated versus unsaturated fatty acids)[103,104,118,185]
	Oxidized lipids (oxidized LDL, isoprostanes)[114]
Metabolomics	Lipid metabolism[103,104,131]
	Glucose metabolism[131]
	Stress hormones (cortisol)[109,110]
	Cytokines[35,116,123,125,129,130]
	Vasoconstrictors and vasodilators (angiotensin II, endothelin 1)[35,182]

Münzel T, *et al. Nat Rev Cardiol*, 2023
doi.org/10.1038/s41569-023-00873-3

Biomarkers of the exposome – Present and Future

Type	Biomarker	Type of exposome study
Pathways and functions		
Circadian rhythm	Melatonin[111]	Large human cohort
	Circadian rhythm-related genes and proteins (*PER1*, *CRY*, *CLOCK*, *BMAL*, *NPAS*)[112,113]	Field study in humans
	Diurnal rhythms of expression and levels of genes, proteins and metabolites that are controlled by the circadian clock[112,113]	Animal models
Neurohormonal pathways	Cortisol, precursors and regulators (adrenocorticotropic hormone, corticotrophin-releasing hormone)[110]	Large human cohort
	Catecholamines (adrenaline, noradrenaline), urine stable metabolites (3-methoxy-4-hydroxyphenylglycol)[109]	Large human cohort
	Molecules downstream of catecholamine signalling (angiotensin II, endothelin 1)[35,182]	Large human cohort
Inflammation	Lipid peroxidation products (malondialdehyde, 4-hydroxynonenal, 8-isoprostane)[54,114]	Field study in humans and mice
	Products of direct oxidation of proteins, nucleic acids and lipids (3-nitrotyrosine, 8-oxoguanine, oxidized LDL)[38,54,112,114]	Field study in humans and mice
	Inflammation markers (C-reactive protein, interleukins)[35,116,123,125,129,130]	Large human cohort
	Mitochondrial DNA copy number and mutations	Large human cohort
DNA damage	DNA oxidation (8-oxoguanine)[38,112]	Large human cohort
	DNA methylation (O6-methylguanine)	Large human cohort
	Mutations	Large human cohort
	Micronuclei formation	Large human cohort
	Single-strand and double-strand breaks	Large human cohort
Toxic compounds	Heavy metals (mercury, lead, cadmium), metalloids (arsenic)[34,35,89]	Large human cohort
	Pesticides[67,89,152–155]	Large human cohort
	Phthalates, bisphenols, polychlorinated aromatic compounds[67,152–155]	Large human cohort
	DNA adducts (chemicals)[132–134]	Large human cohort
	Protein adducts (malondialdehyde, 4-hydroxynonenal, chemicals)[115,132–134]	Large human cohort
Other pathways and processes	Receptor activity assays (androgen receptor, oestrogen receptor, G protein signalling, aryl hydrocarbon)[104]	Large human cohort
	Stress-responsive genes (*NRF2*, *HMOX1*) by reporter cell assays[108,183,184]	Animal models
	Functional assays (endothelial function, heart rate variability, arterial stiffness)[117,135,137–140]	Field study in humans
	Autophagy, senescence, telomere length	Animal models

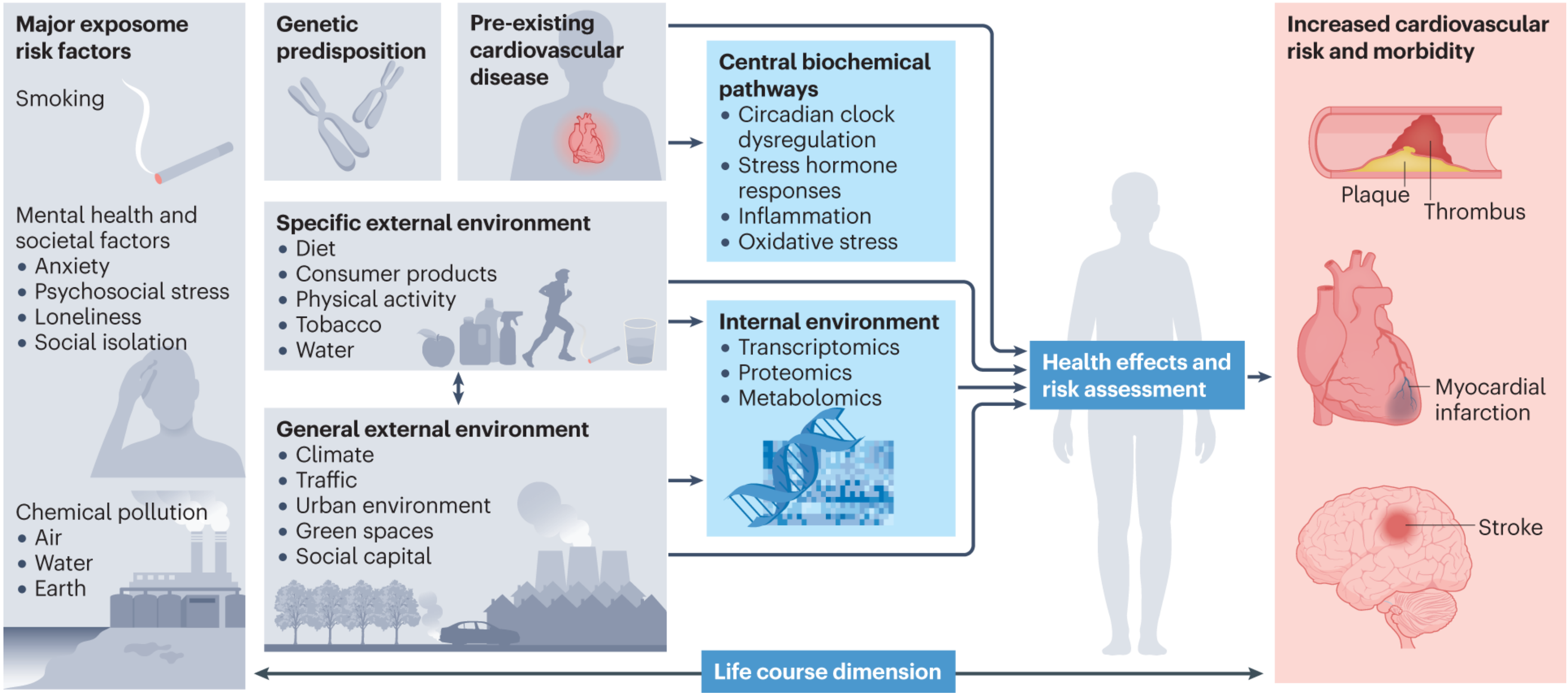
Münzel T, *et al. Nat Rev Cardiol*, 2023
doi.org/10.1038/s41569-023-00873-3

Exposome-wide association studies – Functional links

- EXPOsOMICS consortium:
  - oxidative stress and inflammation markers are associated via DNA methylation with the adverse effects of air pollution on cardiovascular and cerebrovascular disease
  - association between air pollution and cardiovascular disease via dysregulation of metabolic pathways using metabolomics
- Exposure to air pollution -> ↑ plasma C-reactive protein levels
- HELIX cohort -> prenatal exposure to mercury is associated with an increased risk of non-alcoholic fatty liver disease and inflammation in childhood
- SAPALDIA study -> association between arterial stiffness and night-time noise exposure
- The European Human Exposome Network
  - Initiated in 2020 with a € 106 million grant from the EU
  - 9 large-scale research projects
  - 4 of them -> investigate the effects of the exposome on CVD (external and internal exposures over the life course)

Münzel T, *et al. Nat Rev Cardiol*, 2023
doi.org/10.1038/s41569-023-00873-3

Exposome-wide association studies and CVD

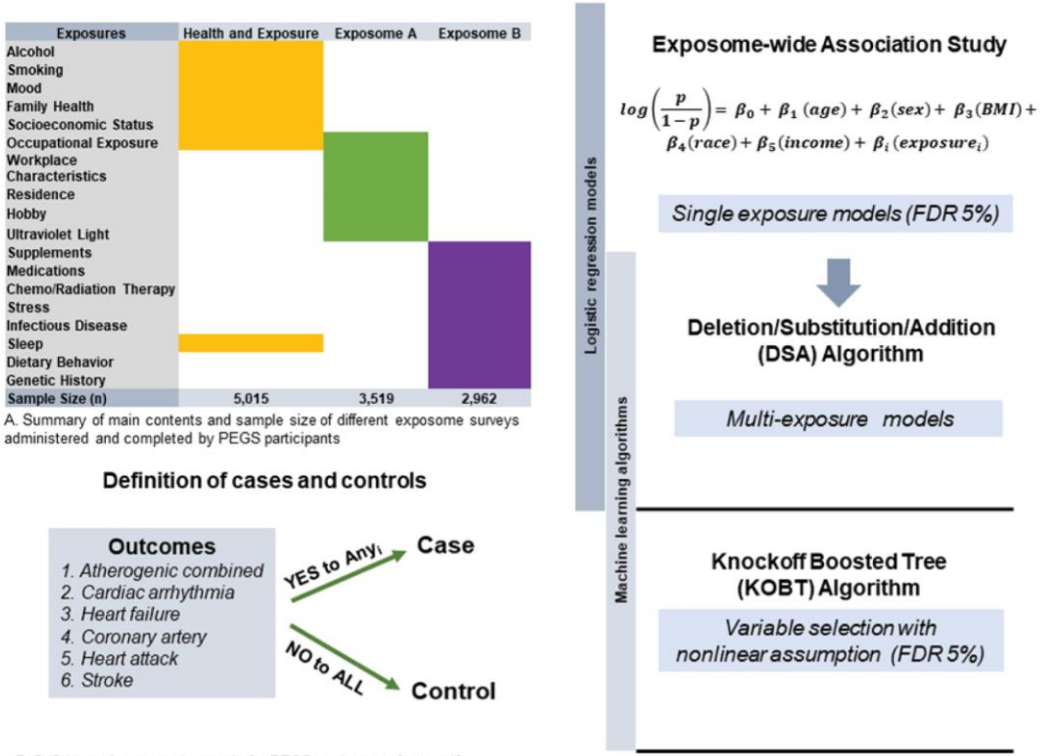


Queen Mary University of London
Medicine and Dentistry

Münzel T, *et al. Nat Rev Cardiol*, 2023
doi.org/10.1038/s41569-023-00873-3

Exposome-wide association studies and CVD

- Questionnaire-based ExWAS study for CVD outcomes
- Part of the National Health Information Survey and the National Health and Nutrition Examination Survey (NHANES)
- The Personalized Environmental and Genetics Study (PEGS) in North Carolina
- 19,672 individuals



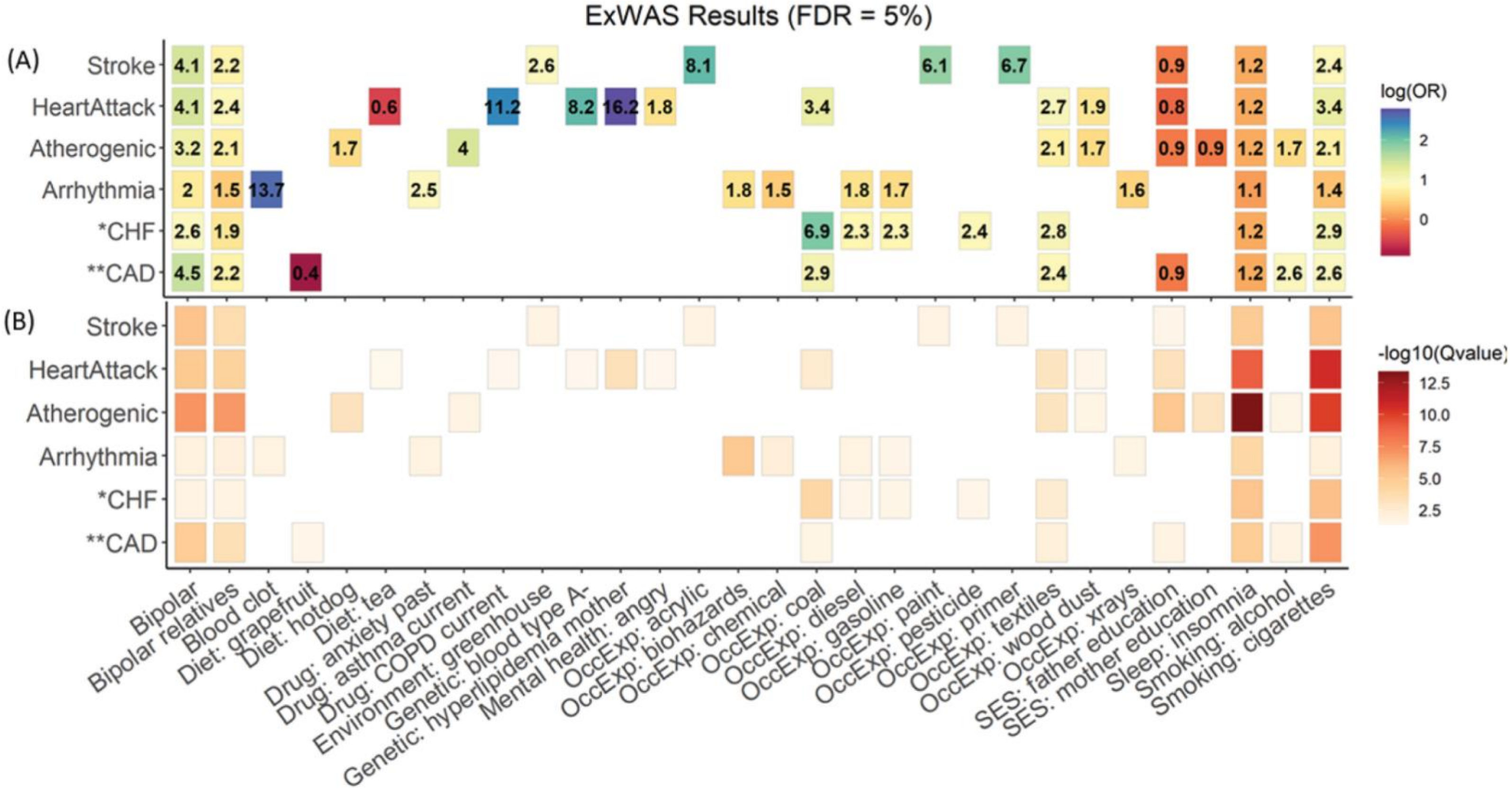
A. Summary of main contents and sample size of different exposome surveys administered and completed by PEGS participants

B. Definition of cases and controls for PEGS participants for specific cardiovascular-related outcome

C. Summary of the main analyses

Lee EY et al. Environ Res. 2022
doi: 10.1016/j.envres.2022.113463

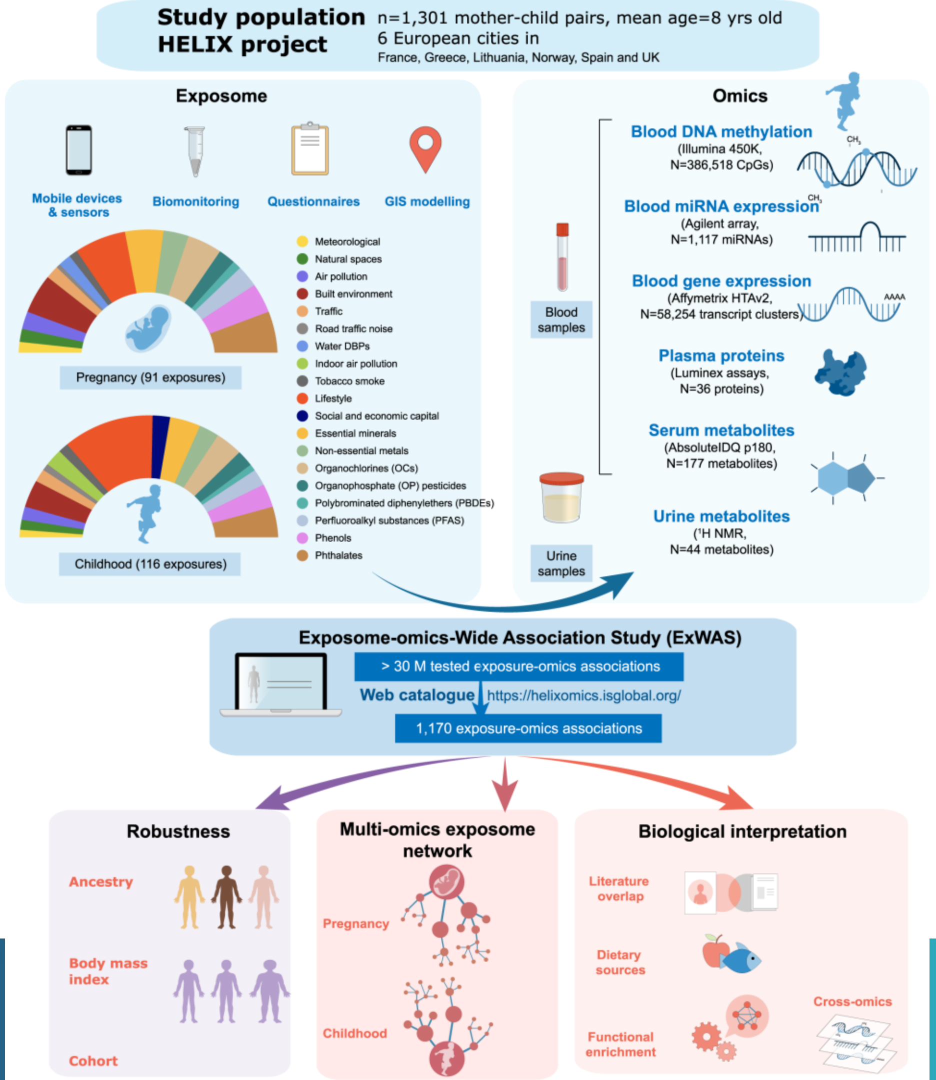
Exposome-wide association studies and CVD



Lee EY et al. Environ Res. 2022
doi: 10.1016/j.envres.2022.113463

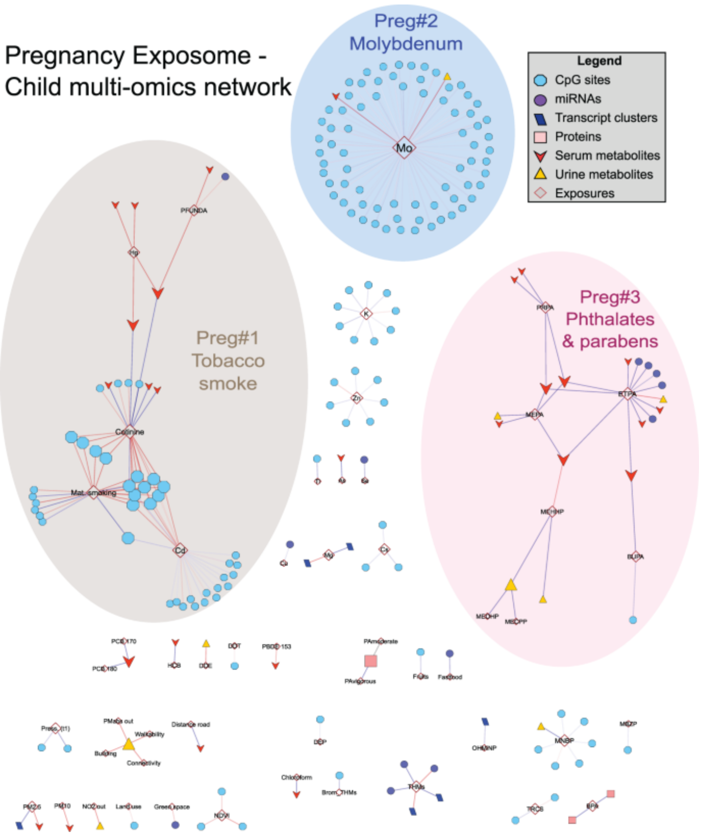
The human early life exposome

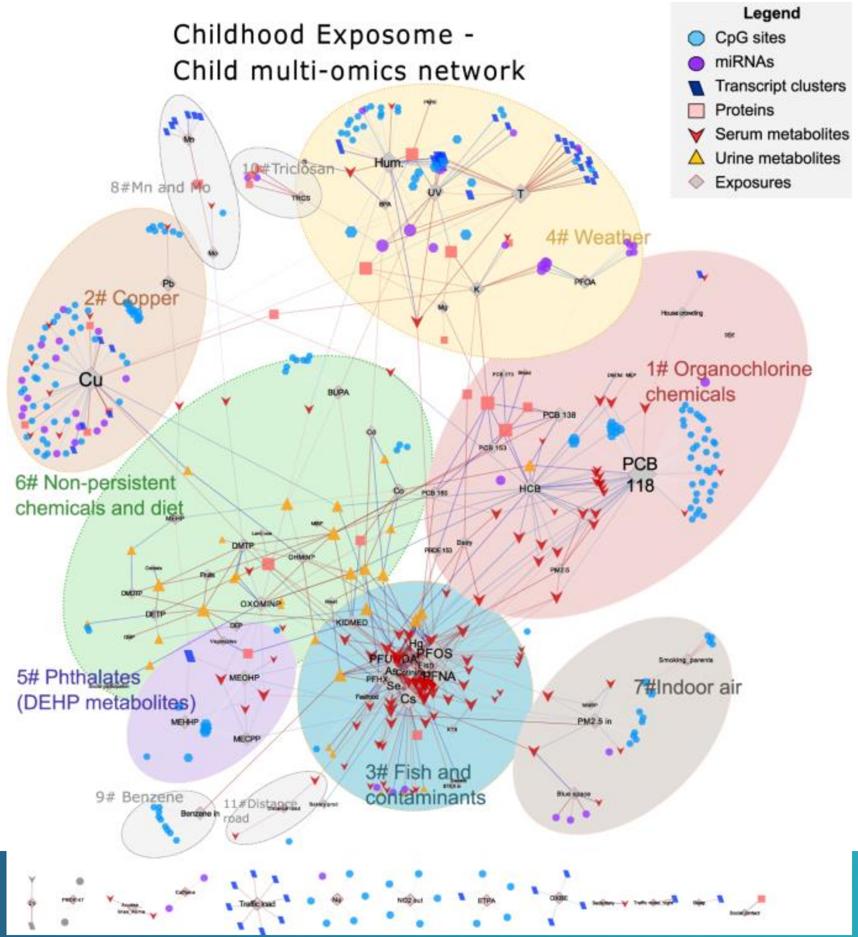
- Multi-centre cohort of 1301 mother-child pairs
- Individual exposomes consisting of >100 chemical, outdoor, social and lifestyle exposures assessed in pregnancy and childhood
- Multi-omics profiles (methylome, transcriptome, proteins and metabolites) in childhood
- 1170 unique associations between exposures and molecular features
  - 249 relating to pregnancy
  - 921 to childhood exposures



Maitre L., *et al. Nat Commun* (2022
doi:. 10.1038/s41467-022-34422-2

The human early life exposome

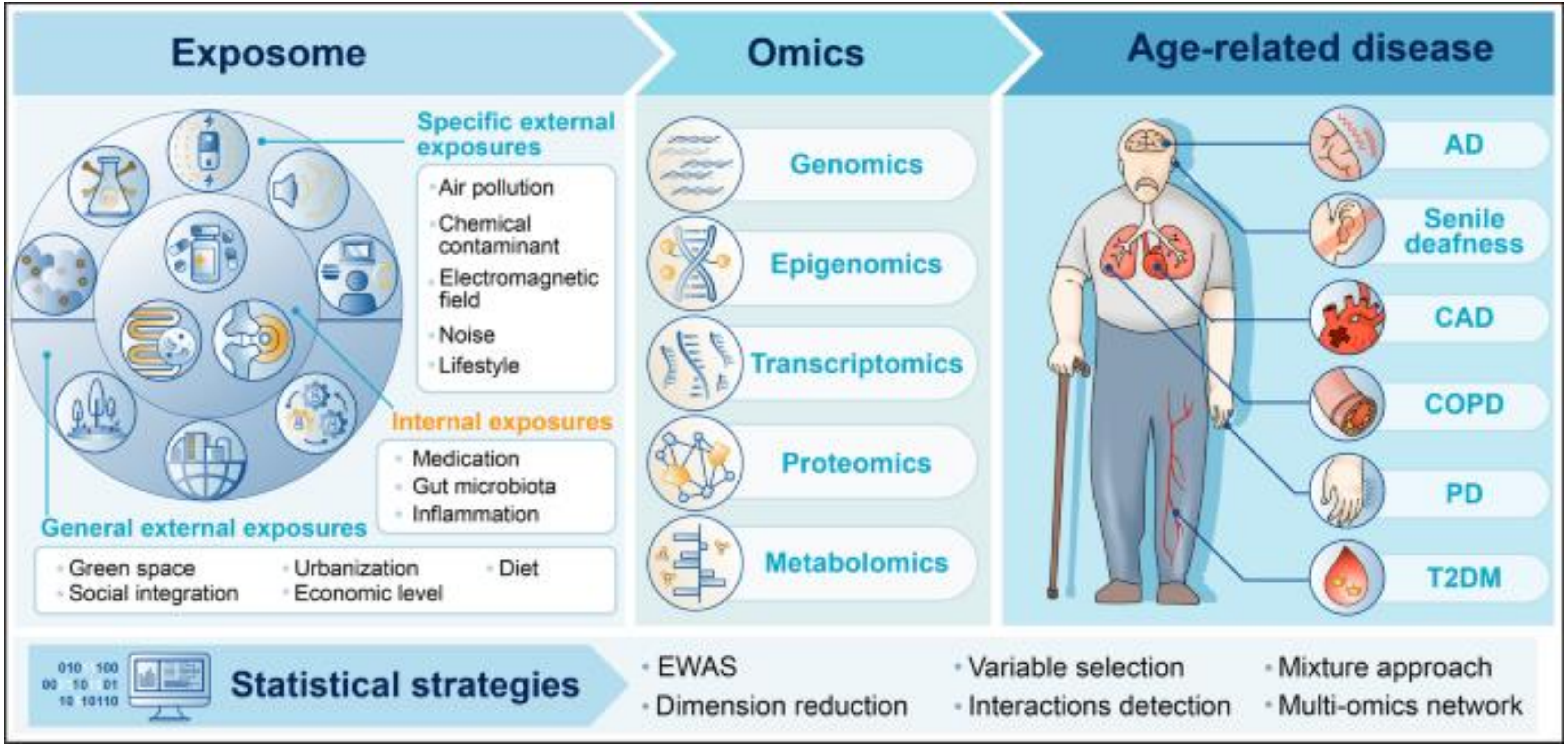




Queen Mary
University of London
Medicine and Dentistry

Maitre L., *et al. Nat Commun* (2022
doi:. 10.1038/s41467-022-34422-2

Mortality and aging exposome



Extended Data Table 1 | Types and dates of data collection in UK Biobank

	Type of data	Date of data collection	Number of participants
			Anticipated
Questionnaire and interview	Sociodemographic data	Recruitment: 2006-2010[a]	500,000
	Family history and early life		500,000
	Psychosocial factors		500,000
	Lifestyle		500,000
	Medical history		500,000
	Cognitive function		500,000
Physical measures	Blood pressure	Recruitment: 2006-2010	500,000
	Hand grip strength		500,000
	Anthropometry		500,000
	Spirometry		500,000
	Heel bone density		500,000
	Arterial stiffness		200,000
	Hearing test		200,000
	Cardiorespiratory fitness plus ECG		100,000
	Eye measures		100,000
Web-based questionnaires	Diet	2011-2012	210,000[b]
	Cognitive function	2014	120,000
	Occupational history	2015	120,000
	Mental health	2016	150,000
	Irritable bowel syndrome	2017	150,000
Enhancements	Physical activity monitor	2013-2014[c]	100,000
	Biochemistry markers[d]	2006-2010	500,000
	Genotyping	2006-2010	500,000
	Multi-modal imaging[e]	2014-2022	100,000[f]
Electronic medical records	Death registry	2006-current	14,000
	Cancer registry	1971-current	79,000
	Hospital inpatient data	1996-current	400,000
	Primary care data	Birth-current	pending

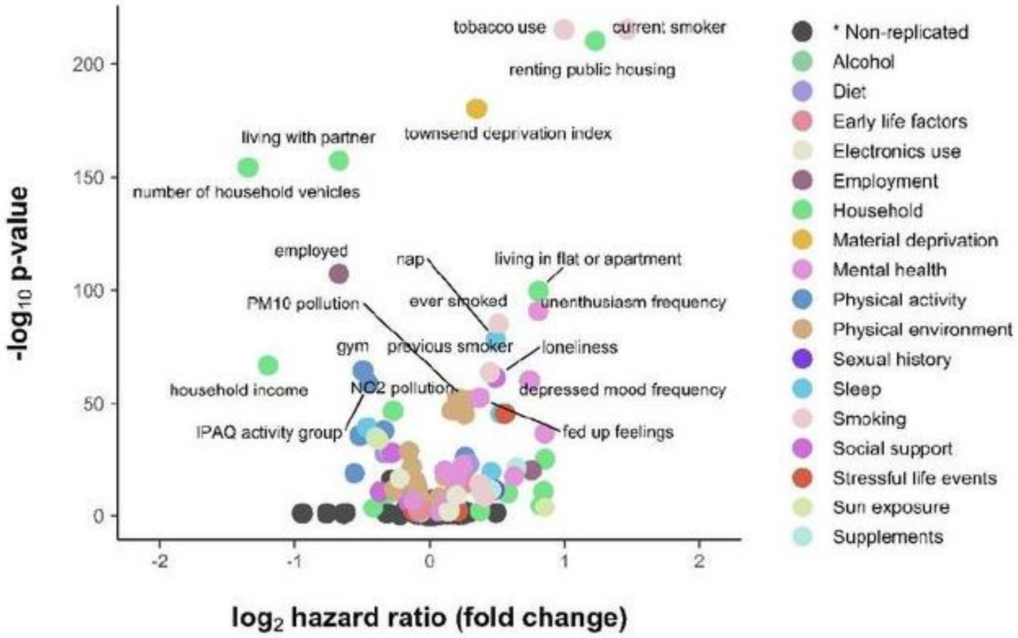
Bycroft et al. *Nature*. 2018
https://doi.org/10.1038/s41586-018-0579-z

Mortality and aging exposome

- Exposome-wide analysis using data from the UK Biobank (n=492,567) -> systematically identify exposures associated with mortality and multiple stages of the aging process
- Exposures that associate with the most critical outcome of all age-related diseases – mortality:
  - Incidence of age-related diseases that are either major causes of death or highly prevalent in aging populations (25 total)
  - Cross-sectional patterns of all age-related blood biomarkers available in the UK Biobank (25 total)
  - Prevalence of three major cardiometabolic risk factors (obesity, hypertension, dyslipidemia)

Argentieri MA, 2023
medRxiv doi:/10.1101/2023.03.10.23286340

Mortality and aging exposome



- 110 exposures significant associated with mortality
- Exposures associated with ↓ mortality risk -> associated with ↓ risk of obesity, dyslipidemia, and hypertension & ↑ levels of biomarkers indicating better health & ↓ levels of detrimental biomarkers
- Exposures associated with ↑ mortality risk -> associated with opposite patterns of these same diseases, risk factors, and biological mechanisms

Queen Mary University of London
Medicine and Dentistry

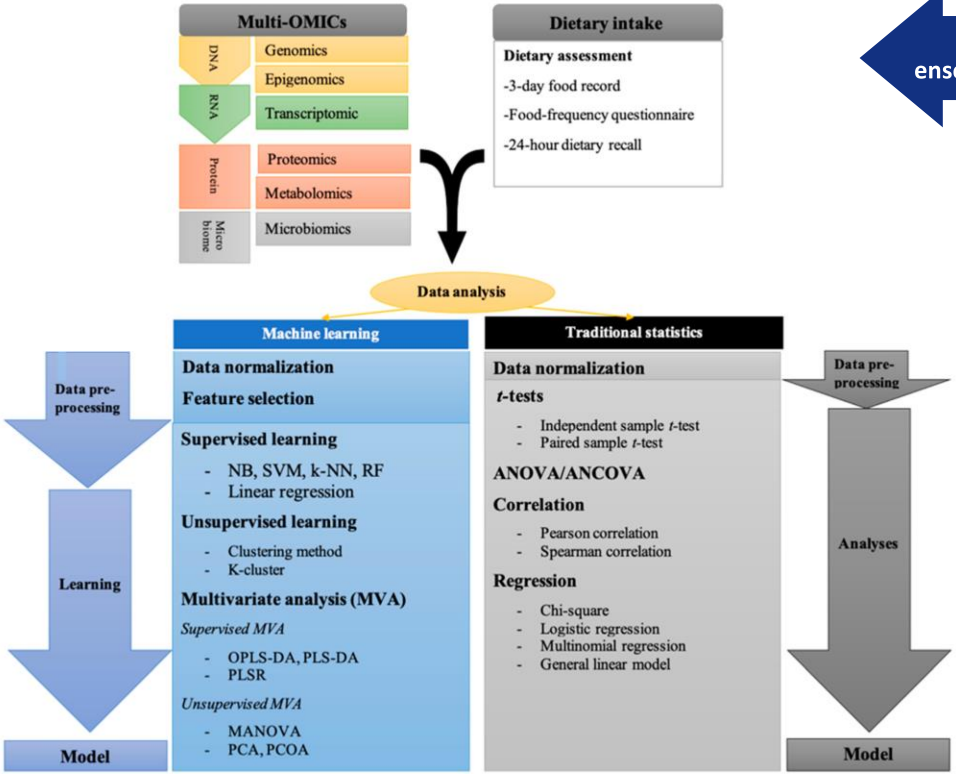
Argentieri MA, 2023
medRxiv doi:/10.1101/2023.03.10.23286340

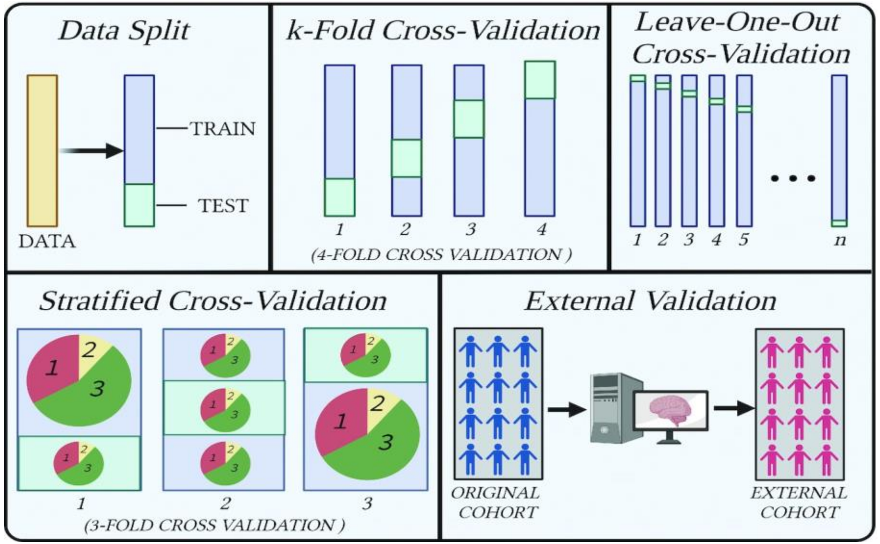
AI analytical approaches

- xAI -> explainable AI (SHAP)

Statistical superiority ensemble/deep neural networks

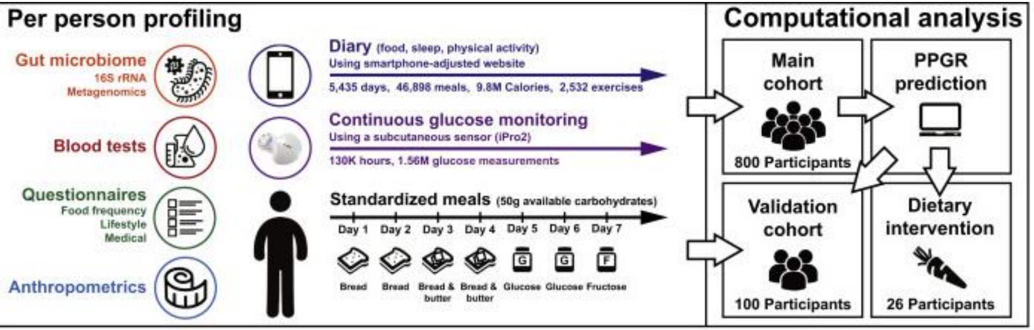
Need for model interpretability



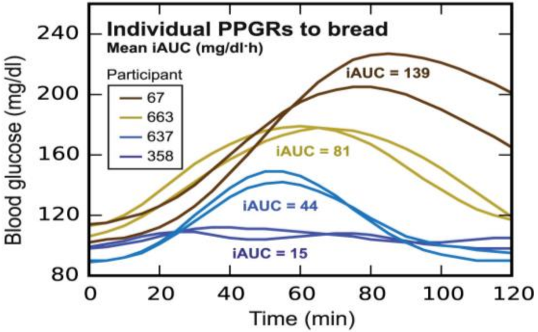


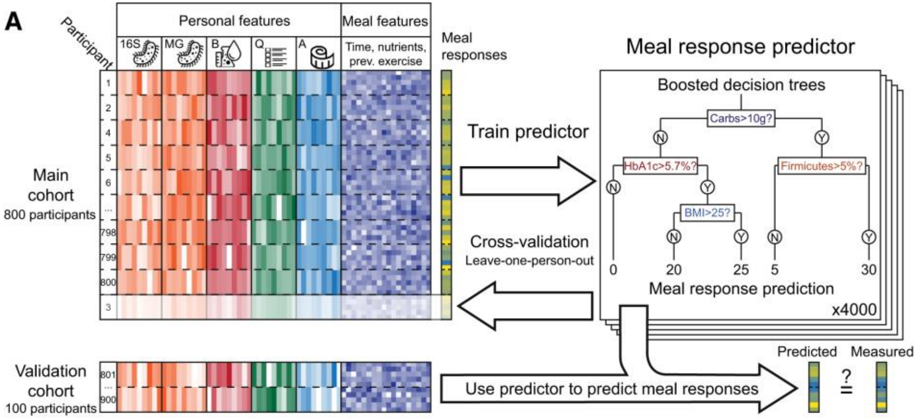
Kirk et al. *Advances in Nutrition*, 2022
doi: 10.1093/advances/nmac103

AI and precision nutrition



- ↑ interpersonal and ↓ intrapersonal variability of glycemic response to the same meal -> **one size does not fit all**
- Clinical and microbiotic profile -> algorithm of the glycemic response prediction: previous meal, sleep duration, physical activity, microbiota





- AI-based dietary intervention trial (100 participants for 1 week) -> significant improvement in glucose metabolism

Zeevi et al. *Cell*, 2015
10.1016/j.cell.2015.11.001

AI and precision nutrition

Zeevi et al. *Cell*, 2015 10.1016/j.cell.2015.11.001

Wearables and sensors measuring the exposome

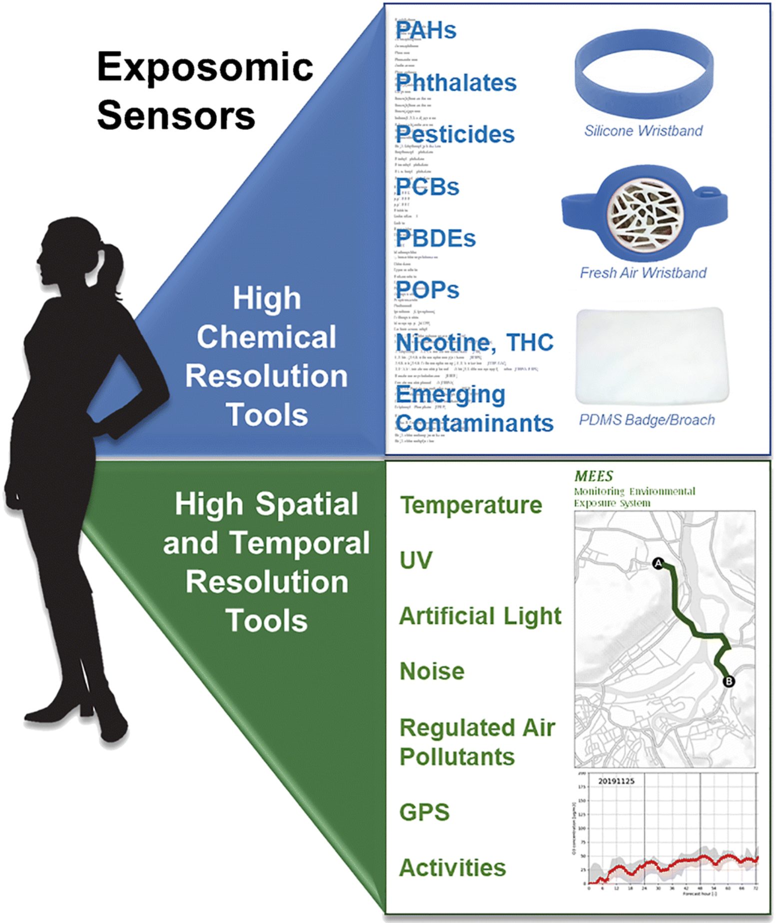
Specific External Exposures

Physical activity
Sleep behaviour
Diet
Drug Use
Smoking
Alcohol use

Lifestyle

Physical-Chemical

Temperature/ humidity
Electrometric fields
Ambient light
Noise
Air pollution
Agricultural activities
Pollen/mold/fungus
Pesticides
Fragrances
Flame Retardants (PDBEs)
Persistent Organic Pollutants (POPs)
Plastics, plasticizers
Food contaminants (water, soil, food)
Occupational exposures

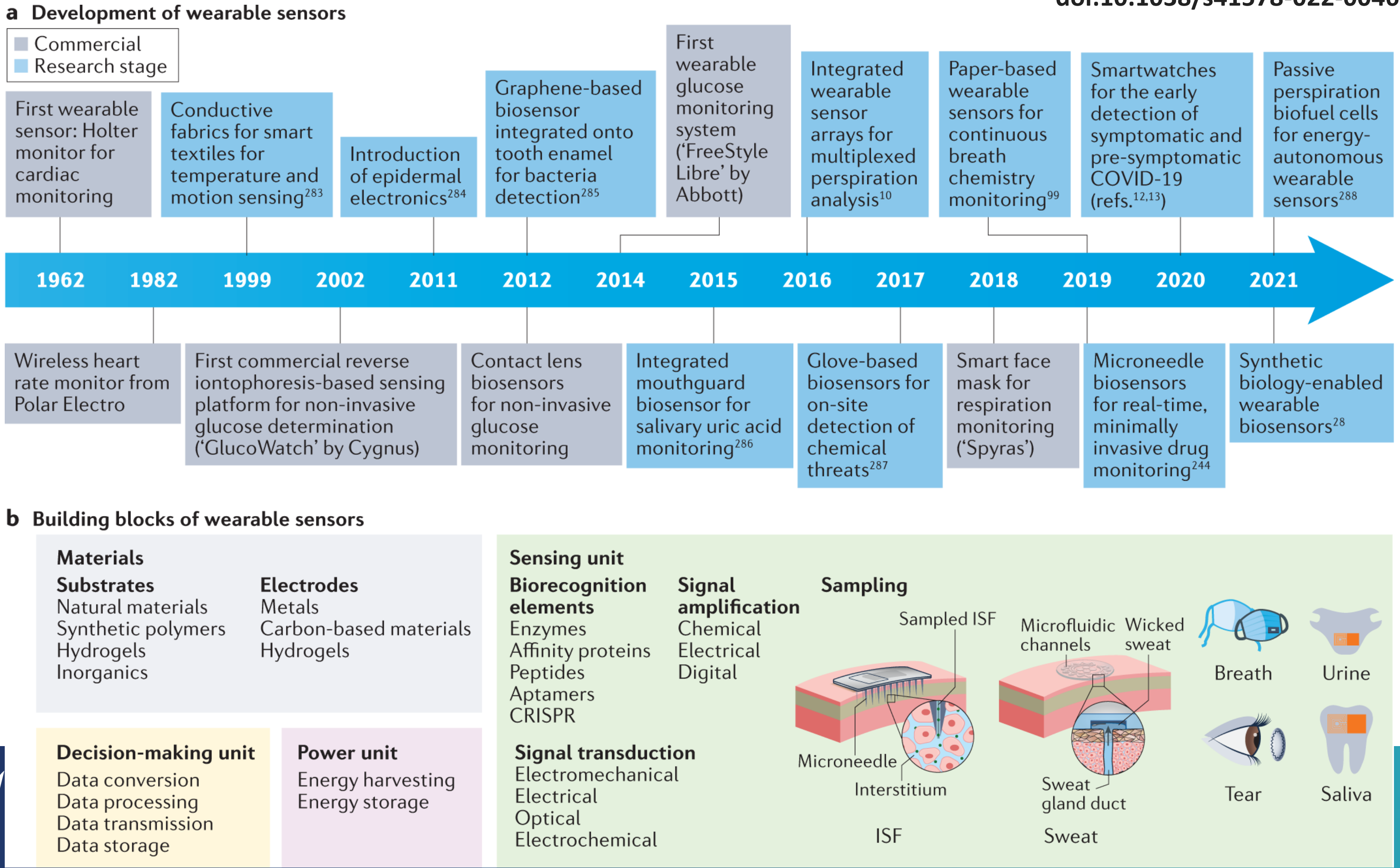


Wearable Passive Samplers

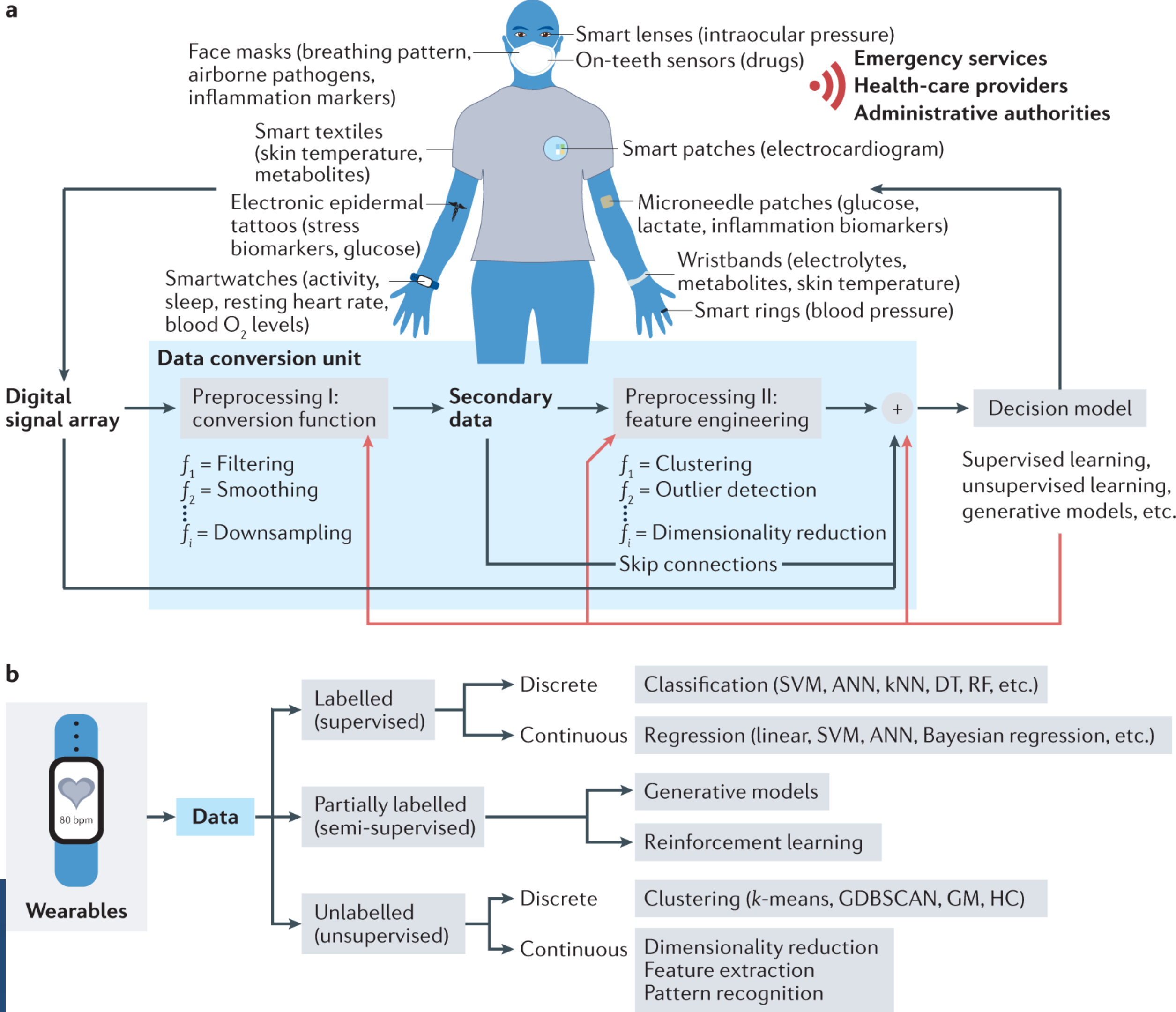
Personal Environmental Modelling Tools

Biosensors and health care

Ates HC *et al.* *Nat Rev Mater* 2022
doi:10.1038/s41578-022-00460-x



Biosensors and health care



Ates HC *et al. Nat Rev Mater* 2022
doi:10.1038/s41578-022-00460-x

Biosensors and precision nutrition

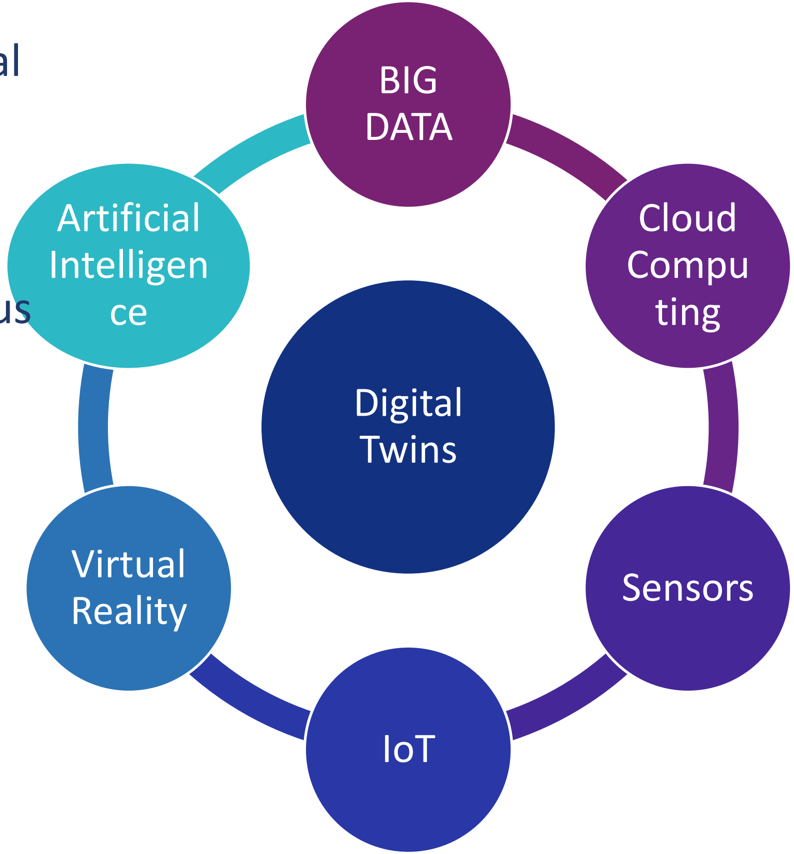
- NutriTrek
- Continuous measurement of metabolites (9 amino acids, vitamins and lipids) in the sweat
- Personalised, non-invasive metabolic and dietary monitoring -> lifestyle and dietary intervention
- Validation in small pilot studies

- **Users are empowered -> responsible of their health and wellbeing -> self-monitoring -> lifestyle changes**

Wang M et al. , *Nat Biomed,* 2022
10.1038/s41551-022-00916-z

Digital Twins

- Digital twins -> virtual representation of a physical object or process
- BIG DATA:
  - Vast volumes of structured, semi-structured, and unstructured data generated from various sources
  - 3 V's: volume, velocity, and variety
- Cloud computing: Large-scale computational infrastructure on demand
- IoT - Internet of Things: a network of physical objects, devices, and sensors that are interconnected and embedded with software, enabling them to collect and exchange data over the internet



Sun T, et al. DIGITAL HEALTH. 2023
doi:10.1177/20552076221149651

Health Digital Twins

- Health digital twins -> virtual representations “digital twin” of patients “physical twin”
- Generated from:
  - multimodal patient data
  - population data
  - real-time updates on patient
  - environmental variables
- Gain insight into the expected behaviour of the physical twin:
  - Precision medicine
  - Clinical trials
  - Public health

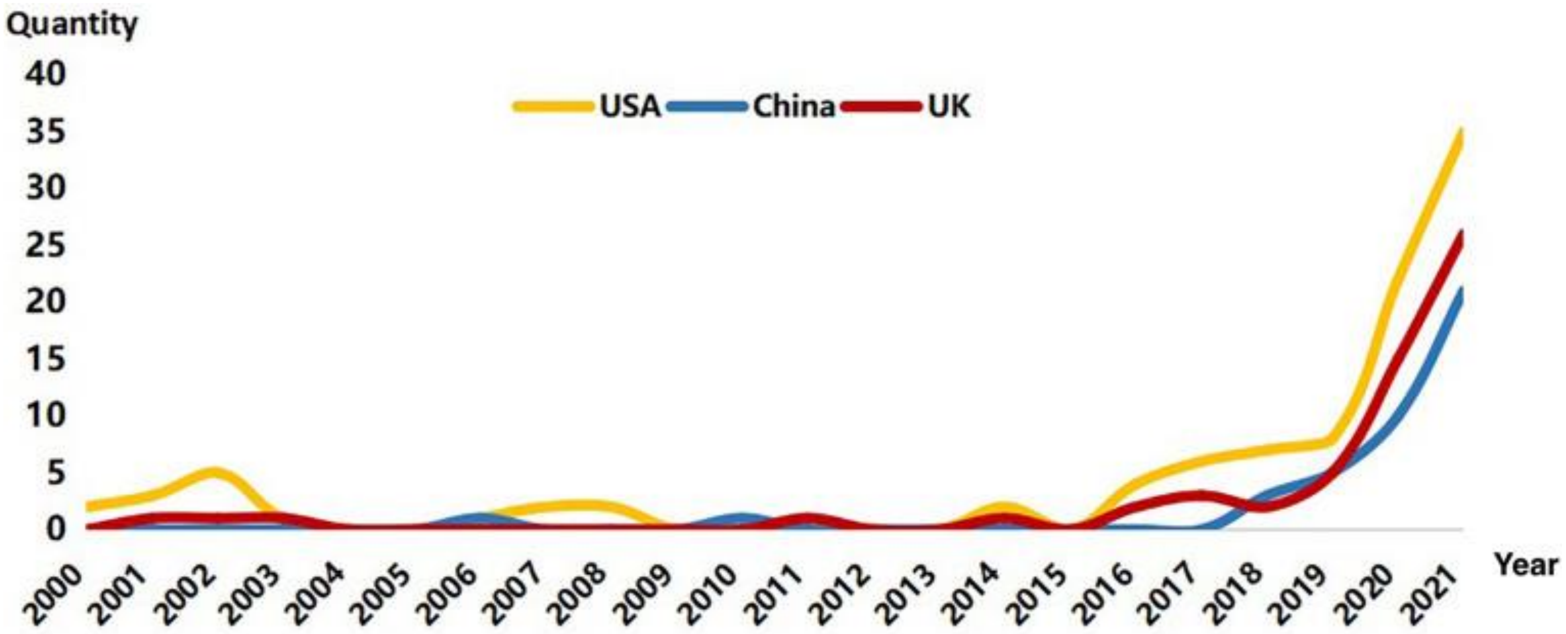
Queen Mary University of London
Medicine and Dentistry

Sun T, et al. DIGITAL HEALTH. 2023
doi:10.1177/20552076221149651

Health Digital Twins

Health Digital Twins

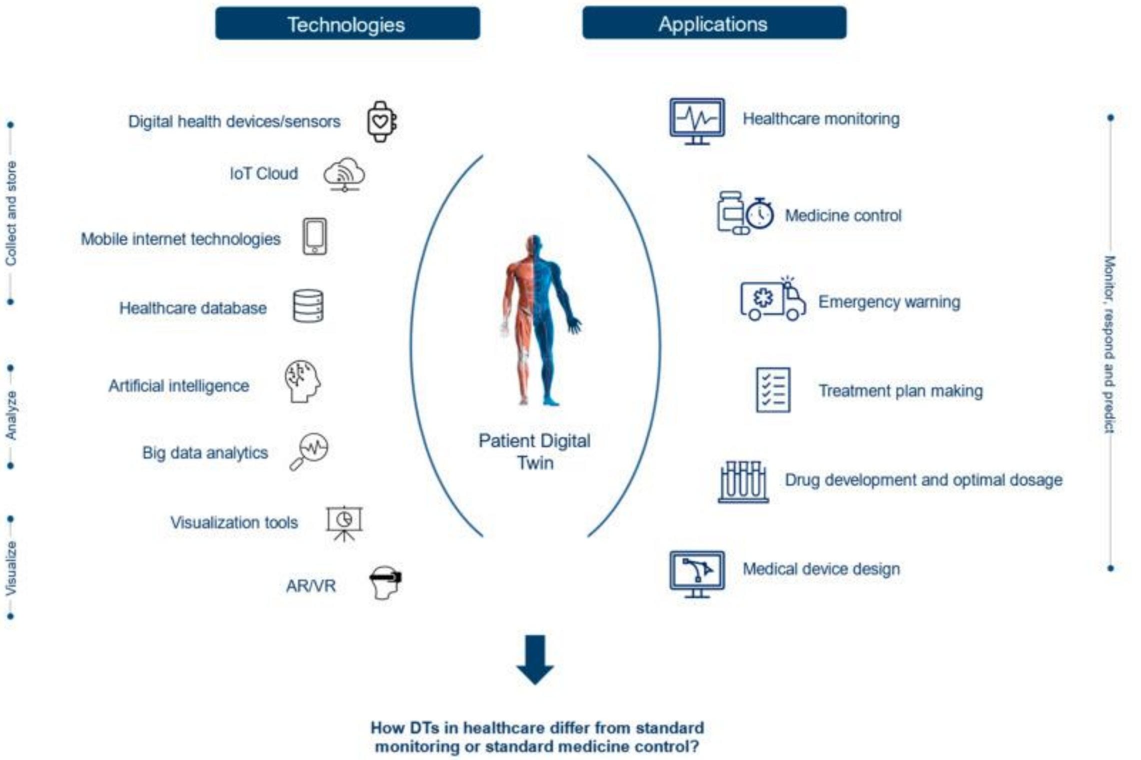
- Studies on medical digital twins



Sun T, et al. DIGITAL HEALTH. 2023
doi:10.1177/20552076221149651

Health Digital Twins

Health Digital Twins



Digital Twins allow

- Real-time information interchange between physical and virtual copy of the patient/object/environment
- Use of data to predict individual patient-specific evolutions

Armeni P, et al. J Pers Med. 2022
doi: 10.3390/jpm12081255

Health Digital Twins

Target Organ/Disease	Reference (Company, Journal etc.)	Description
Heart [1]	Living Heart Project, Dassault Systèmes	The Living Heart Project is the first DT organ considering all aspects of the heart's functionality, such as blood flow, mechanics, and electrical impulses. The 3D model of the organ has built with a 2D scan of the heart. The Living Heart Model on the 3DEXPERIENCE platform can be used to create new ways to design and test new devices and drug treatments. For instance, physicians can run hypothetical scenarios like adding a pacemaker or reversing the heart chambers to predict the outcome of treatment on the patient.
Heart [12]	CardioInsight, Medtronic	The CardioInsight Noninvasive 3D Mapping System collects chest electrocardiogram (ECG) signals and combines these signals with computerized tomography (CT) scan data to produce and display simultaneous 3-D cardiac maps. The mapping system enables physicians to characterize abnormal rhythms of the heart through a personalized heart model.
Heart [1]	Siemens Healthineers	Another heart DT has been developed by Siemens Healthineers and used for research purposes by Cardiologists of the Heidelberg University Hospital (HUH) in Germany. Although the first study is still in the data evaluation process, preliminary results are promising. Siemens Healthineers developed the DT model by exploiting a massive database containing more than 250 million annotated images, reports, and operational data. The AI-based DT model enables digital heart design based on patient data with the same conditions of the given patient (size, ejection fraction, and muscle contraction).

Armeni P, et al. J Pers Med. 2022
doi: 10.3390/jpm12081255

Health Digital Twins

Brain [17]	Blue Brain Project, EPFL and Hewlett Packard Enterprise	Hewlett Packard Enterprise, partnering with Ecole Polytechnique Fédérale de Lausannes (EPFL), builds a DT of brain called the Blue Brain Project. The project is one of the sub-projects of the Human Brain Project and aims to build biologically detailed digital reconstructions (computer models) and simulations of the mouse brain. In 2018, researchers published the first 3D cell atlas for the entire mouse brain [22].
Human air-way system [1]	Oklahoma State University's Computational Biofluidics and Biomechanics Laboratory	Researchers developed a prototype of human DT, named "virtual human V1.0", with the high-resolution human respiratory system covering the entire conducting and respiratory zones, lung lobes, and body shell. The project aims to study and increase the success rate of cancer-destroying drugs in targeting tumor-only locations.

Armeni P, et al. J Pers Med. 2022
doi: 10.3390/jpm12081255

Health Digital Twins

Target Organ/Disease	Reference (Company, Journal etc.)	Description
Brain aneurysm and surrounding blood vessels [1]	Sim&Cure	Sim&Cure developed a DT to treat aneurysms, which are enlarged blood vessels that can result in clots or strokes. DT of the aneurysm and the surrounding blood vessels (represented by a 3D model) allow brain surgeons to run simulations and understand the interactive relationship between the implant and the aneurysm. Although preliminary trials have shown promising results, further evaluation is required.
Multiple Sclerosis (MS) [9]	Frontiers in Immunology (journal)	Multiple sclerosis, also called the 'disease of a thousand faces', has high complexity, multidimensionality, and heterogeneity in disease progression and treatment options among patients. This results in extensive data to study the disease. Human DTs are promising in the case of precision medicine for people with MS (pwMS), allowing healthcare professionals to handle this big data, monitor the patient effectively, and provide more personalized treatment and care.
Viral Infection [23]	Science (journal)	Human DTs can predict the viral infection or immune response of a patient infected with a virus by integrating known human physiology and immunology with population and individual clinical data into AI-based models.
Trauma Management [24]	Journal of Medical Systems (journal)	Trauma management is highly critical among time-dependent pathologies. DTs can participate from the pre-hospital phase, where the physician provides the patient first aid and transfers them to the hospital emergency department, to the operative phase, where the trauma team assists the patient in hospital emergency. Although there is no real implementation yet, a system prototype has been developed.
Diabetes [25]	Diabetes (journal)	Human DT can also participate in diabetes management. California-based start-up Twin Health has applied DTs by modeling patient metabolism. The DT model tracks nutrition, sleep, and step changes and monitors patients' blood sugar levels, liver function, weight, and more. Ongoing clinical trials show that daily precision nutrition guidance based on a continuous glucose monitoring system (CGM), food intake data, and machine learning algorithms can benefit patients with type 2 diabetes.

Armeni P, et al. J Pers Med. 2022
doi: 10.3390/jpm12081255

Further reading

- Ding, E., Wang, Y., Liu, J. *et al.* A review on the application of the exposome paradigm to unveil the environmental determinants of age-related diseases. *Hum Genomics* 16, 54 (2022). https://doi.org/10.1186/s40246-022-00428-6
- Münzel, T., Sørensen, M., Hahad, O. *et al.* The contribution of the exposome to the burden of cardiovascular disease. *Nat Rev Cardiol* (2023). https://doi.org/10.1038/s41569-023-00873-3
- Armeni P, Polat I, De Rossi LM, Diaferia L, Meregalli S, Gatti A. Digital Twins in Healthcare: Is It the Beginning of a New Era of Evidence-Based Medicine? A Critical Review. J Pers Med. 2022 Jul 30;12(8):1255. https://doi.org/10.3390/jpm12081255
- Ates, H.C., Nguyen, P.Q., Gonzalez-Macia, L. *et al.* End-to-end design of wearable sensors. *Nat Rev Mater* 7, 887–907 (2022). https://doi.org/10.1038/s41578-022-00460-x

Thank you

@StavroulaKanoni

Queen Mary
University of London
Medicine and Dentistry