INFORMES DE L'INSTITUT, 10

Unveiling the exposome: Navigating environmental influences on health

A report of the Institut d'Estudis Catalans

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SECCIÓ DE CIÈNCIES BIOLÒGIQUES

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A report by the Biological Sciences Section of the Institut d'Estudis Catalans

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Unveiling the exposome: Navigating environmental influences on health

New research tools to make the invisible visible

A report of the Institut d'Estudis Catalans

Prepared by the Biological Sciences Section

Barcelona, 2025

Institut d'Estudis Catalans

SECCIÓ
DE CIÈNCIES
BIOLÒGIQUES

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Prologue
A brief reflection on the exposome

We live in complex times. Increasingly, our lives are being played out in cities with millions and millions of fellow inhabitants. We can travel practically anywhere in the world in 24 hours. Sitting at a computer, we can access all kinds of resources and with a simple click of the mouse order a limitless variety of goods and services, including the food that sustains us, sourced if we so wish from the other side of the globe. A plethora of devices makes our lives easier, enabling us to carry out numerous activities efficiently and safely. And when we run into a problem, we have developed highly diverse procedures and treatments that allow us, more often than not, to address it successfully.

From the moment we are born, we find ourselves inhabiting a complex environment, carefully created to ensure we are fed, kept warm, protected from infection and safeguarded against accidents. In this universe, one person cannot begin to comprehend how everything that sustains this environment works. We are oblivious to the price we pay for living a life that is, on the one hand, so easy, and on the other, so rich in possibilities. As this report is at pains to show, we are exposed to the action of a multitude of physical, chemical and biological agents that act as determinants of just how our lives will unfold. The complexity of the world and our incomprehension of how it functions compel us to develop concepts that allow us to understand and control, in the measure that this is possible, the factors to which we are exposed.

The exposome – as defined in this report – encompasses that set of factors to which an individual is exposed throughout their life and which has an impact on their health. And as the exposome expands, it becomes more and more evident that we cannot isolate ourselves from it and its diverse actions. Even factors produced thousands of kilometres from the place we live can end up impacting us. Indeed, the globality of the exposome leads us, in turn, to accept the globality of the health of human populations.

Understanding the exposome at any given moment should allow us to better plan a life that minimises its harmful effects. While we can sometimes mitigate these effects, our control is nevertheless limited. Modifying genetic factors, for example, lies largely beyond our current powers, as does that of many other factors. Additionally, the body's internal machinery has inherent flaws that contribute to the development of certain diseases. Life is also seldom free from random accidents. In essence, we are subject to both good and bad luck, and there is little we can do to change that.

Developing an awareness of all the factors that make up the exposome is today possible thanks to the powerful new tools of big data processing and, for this reason, it seems safe to say that the concept is here to stay. The Biological Sciences Section of the Institut d'Estudis Catalans accepted with great interest the proposal of the coordinators of this report, Josep Peñuelas and Josep Tabernero, since we believe it offers an authoritative and comprehensive perspective that relates the concepts of environmental analysis with the origins of human pathologies. It is our conviction that the approach adopted here will be one that we will turn to time and again in the future.

Pere Puigdomènech
President of the Biological Sciences Section
of the Institut d'Estudis Catalans

Preamble

Pesticides, air pollution, lead, ultraviolet radiation, ozone, DDT, climate change… The full set of environmental factors with an impact on human health forms a vast jungle that is far from easy to navigate. Some of these factors and their related health effects result in all too *visible* environmental disasters – the case, for example, of Seveso, Chernobyl, Yusho, and Minamata, while others have been dubbed silent disasters associated with the *invisible* contaminants in our environment.

The epidemiological transition in industrialised societies and the Anthropocene have ushered in the era of chronic diseases (cancers, cardiovascular pathologies, mental disorders, etc.). These health problems are multifactorial by nature and pose a challenge to causality in medicine. Yet, understanding the complex interactions between environmental factors and health is fundamental for prevention and risk management; meanwhile, the debate rages as to whether we are best advised to prevent or cure, inform or prohibit, or act in accordance with the tenets of the precautionary principle. *Today, the conducting of environmental health research is more opportune than ever but it needs to find new research tools that can make the invisible visible.*

The Lancet Commission on Pollution and Health reported that pollution was responsible for 9 million premature deaths in 2022, corresponding to one in six deaths worldwide (Fuller et al., 2022), which makes it the world's largest environmental risk factor for disease and premature death. But while a reduction has been achieved in the number of deaths attributable to the types of pollution associated with extreme poverty (that is, household air pollution and water pollution), they have simply been offset by increased deaths attributable to ambient air pollution and toxic chemical pollution (most notably lead). Deaths from these "modern" pollution risk factors – the unintended consequences of industrialisation and urbanisation – have risen by 7% since 2015 and by over 66% since 2000.

Today, it is widely recognised that an individual's characteristics result from the combination of their genes and other non-genetic factors, and that only a small percentage of diseases are exclusively attributable to their genetic makeup. Yet, biomedical research in recent decades has continued to focus its efforts primarily on characterising genes. With the aim of correcting this imbalance, we have seen *the emergence of the exposome concept, defined as: "the integrated compilation of all of the environmental factors, whether they are the physical, chemical, biological or psychosocial factors, and their interactions, which have an impact on biology and health"* (adopted definition during the meeting at the Banbury Center at Cold Spring Harbor Laboratory, New York, USA, 3-6 December 2023).

Thanks to technology advances in both measurement and analysis in recent years, the exposome has gained a certain prominence in biomedical research for investigating the diseases. Indeed, causal relationships have been established between non-genetic factors that make up the exposome and specific pathologies, including, for example, exposure to solar UV radiation and the development of melanoma and the presence of endocrine disruptors and their involvement in individuals' hormonal and metabolic dysregulation, leading to a variety of developmental pathologies.

Despite these advances, studying the exposome is extremely complex. The diversity and quantity of molecules or agents involved, together with the fact that the exposome is dynamic (and as such varies over time), combine to complicate its study. This means efforts to understand the exposome must be multidisciplinary, drawing on knowledge from such disciplines as toxicology, epidemiology, clinical medicine, the omics sciences, and data science, to name just a few.

Through the integration of information from these disciplines within the broader framework of exposome studies, it should be possible to identify risk biomarkers for the development of certain pathologies associated with specific exposures, design initiatives for preventing specific diseases, and formulate recommendations for healthy habits (diet and physical exercise) both for population groups and individuals.

Although the application of information derived from exposome studies in clinical practice is currently limited to very specific cases, and many significant challenges have yet to be addressed, it seems likely that this valuable knowledge will be fundamental in designing preventive, diagnostic, and therapeutic actions in future medicine and an indispensable tool in public health policies.

1. Introduction: The utility of the exposome research framework

Diverging from conventional approaches that link a singular exposure to a specific health outcome, the exposome introduces a novel perspective. In encompassing the totality of our environmental exposures, it provides an original conceptual framework for the study of a myriad of environmental factors, including urban settings, chemicals, lifestyle choices, and social dynamics, that converge to shape our health. This more refined framework is not simply concerned with dissecting individual hazards, rather it seeks to comprehend the complex interplay of multiple exposures and their collective, potentially cumulative impact (Figure 1).

Environmental health policy areas that are set to benefit from an exposome approach include those required to deal with processes of priority setting and which, hence, demand a systematic approach to a range of suspected environmental risk factors. Policy areas that should profit most are those that tackle more than one risk factor or pollutant at a time and which require knowledge of how such factors act together to influence health: ranging from chemical regulations (e.g. relating to endocrine disruptors, chemical mixtures, pesticides, food contact materials, cosmetics, and air quality) to strategies for enhancing urban management (e.g. the EU's Thematic Strategy of the Urban Environment) and disease-specific prevention policies (e.g. the EU's initiative on the prevention of NCDs). It is becoming increasingly clear that approaches that do not examine complex multi-factor effects can be ineffective in explaining, let alone preventing, the onset of most common diseases. Here it is important to recognise the interplay of multiple exposures and the complex "system" in which efforts to reduce the harmful exposome are made (encompassing individuals, communities, organisations, the natural and built environment, and economic and political forces) (Barton & Grant, 2006). This particular vision – that afforded by the "system" – is

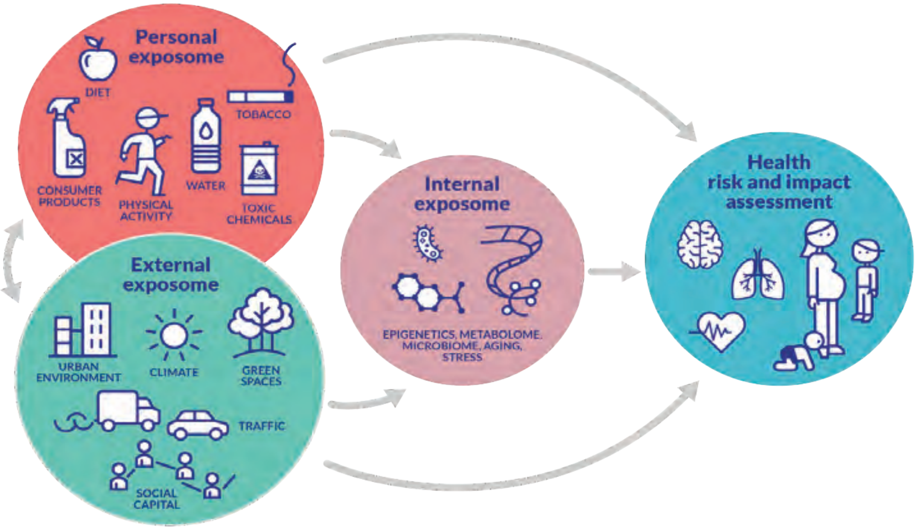

FIGURE 1. The three overlapping domains of the exposome.
SOURCE: Image extracted and adapated from the ATHLETE Project website, https://athleteproject.eu/.

further developed in the last section of this report, "Exposome and planetary health".

As an integral part of the exposome, internal biological responses to exposures can be measured at the molecular level using high-throughput omics techniques: metabolomics, proteomics, transcriptomics, and epigenomics, which have great potential for the broad and powerful characterisation of complete sets of biological molecules. Of particular interest is the identification of biological responses and pathways that respond to and interact with the exposures, resulting in adverse health, i.e. early pathway perturbations. This information may be used to improve biological plausibility of associations, to understand how different exposures may act on common pathways, and, ultimately, to predict environmental health related disease. Similar to developments in the fields of toxicology and pharmacology, the identification of perturbed pathways of well characterised exposures may facilitate the prediction of the public health burden of more recent, less characterised exposures.

The early part of the life course is a particularly important period in which to study early pathway perturbations: exposures during vulnerable periods may have pronounced effects at the molecular level but may remain clinically undetectable until adulthood. Each child is made up of a unique molecular profile at the methylome, transcriptome, proteome, or metabolome levels, as the result of the interaction between his or her genome and early life events partially captured in the external exposome. Children may also display differences in susceptibility to their environment and in the era of personalised medicine, a personal exposome assessment should consider molecular susceptibility. For example, the toxicity of arsenic, a ubiquitous metal whose exposure occurs mainly through the consumption of fish and crustaceans, will depend heavily on the capacity of the liver and potentially gut microbiota to methylate arsenic species (Claus et al., 2016).

FIGURE 2. Key traits of the exposome.
SOURCE: Created by Léa Maitre.

2. Characterising the exposome

Exposure is commonly assessed by means of a spectrum of questionnaire data and ecological, environmental, and biological measurements.

2.1. The chemical exposome

Léa Maitre
Cristina Balcells Nadal

A significant subset of the exposome is made up of the chemical exposome. This subset encompasses all chemical species (and their associated transformation products), either of biological or synthetic origin, capable of entering the human body via different pathways, including ingestion, inhalation, and dermal absorption. These molecules can originate from a range of sources that include diet, pharmaceutical drugs, and dietary supplements, personal care and consumer products (PCCPs), as well as water and airborne substances.

The best techniques for measuring these chemicals in human tissues or biofluids involve the use of liquid chromatography (LC) and gas chromatography (GC), coupled to either tandem or high-resolution mass spectrometry (MS/MS or HRMS, respectively), and nuclear magnetic resonance (NMR) spectroscopy (Balcells et al., 2024). Over the years, these analytical techniques have evolved from methods that accurately analyse and quantify a few pre-optimised metabolites or chemicals at a time (*targeted methods*) to wide-scope approaches capable of profiling thousands of chemicals in a biospecimen with little a priori knowledge about them (*untargeted methods*). In what follows, current use cases, examples, and applications of both types of method in exposomics are discussed.

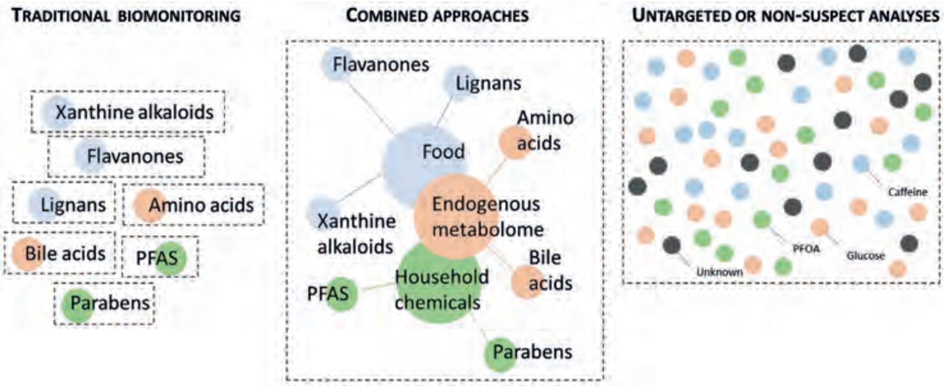

FIGURE 3. Evolution of the characterisation of the chemical exposome.
SOURCE: Created by Cristina Balcells Nadal.

Targeted analyses or traditional biomonitoring

Biological indicators of exposure, which assess internalised doses, are frequently favoured because of their direct relevance to the health outcomes under study. Conventional analytical measurements, commonly known as *targeted analyses*, involve assessing specific chemicals, metabolites, or reaction products in biological mediums such as urine or blood. These established biomonitoring methods have evolved into a fundamental element of exposure assessment in numerous epidemiological studies that aim to establish connections between exposures and health outcomes. Targeted, quantitative methods are still widely used to measure the chemical exposome, given the need for reliable biomonitoring data and the desire to define quantitative exposure-adverse health outcome associations for regulatory authorities and policymakers. Numerous governmental agencies and national laboratories worldwide periodically publish exposure biomonitoring data of their populations (e.g. PARC in the EU and NHANES in the US). Most targeted analytical methods employed to characterise the exposome are tailored to distinct groups of established exposures. Typically, these methods measure either single or up to a few tens of compounds and are validated for a specific biofluid or matrix. Moreover, they can be used to characterise molecules of different origin, from endogenous or dietary metabolites to man-made chemicals.

Examples of the most common families of chemical exposures targeted by current biomonitoring programmes include:

— *Plasticisers*: phthalates.
— *Combustion products*: polycyclic aromatic hydrocarbons (PAHs).

— *Tobacco smoke*: tobacco-specific nitrosamines (TSNAs), cotinine, heterocyclic aromatic amines (HAAs).

— *Pesticides, insecticides, and insect repellents*: pyrethroids, organochlorine pesticides, dialkyl phosphate pesticides and other organophosphate pesticides, carbamate insecticides, insect repellent, and metabolites (DEET).

— *Herbicides*: atrazine and metabolites, 2,4-D, 2,4,5-T and metabolites, sulfonylurea and metabolites.

— *Fungicides.*

— *Industrial and PCCPs*: per- and polyfluorinated substances (PFAS), parabens, phthalates, bisphenols.

— *Pharmaceuticals.*

— *Natural products*: mycotoxins, phytoestrogens.

— *Multiple sources*: volatile organic compounds (VOCs) and metabolites, polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs) and dibenzofurans.

Another major source of chemical exposure is diet. Some of the most reproducible biomarkers (metabolites) of food intake include:

— *Coffee, tea and cocoa*: caffeine, theobromine, theophylline.

— *Meat*: specific fatty acids and amino acid derivatives.

— *Fish*: specific fatty acids and amino acid derivatives.

— *Fruit and vegetables*: flavones, flavanones, coumarins.

Combined approaches

The realisation that these analytical techniques are suitable for the measurement of most small molecules, regardless of their origin, has paved the way for efforts to cover wider windows of the chemical space in a single analytical assay. In this way, and with the emergence of more sensitive, faster-scanning instrumentation, targeted assays typically aimed at a single chemical family as described above are giving way to more comprehensive targeted strategies, in an effort at simultaneously capturing various combinations of molecules from the endogenous metabolome, the food-related and microbiota-derived metabolomes, pharmaceuticals, environmental contaminants, and household chemicals.

Untargeted or non-suspect analyses

With only a few hundred chemicals routinely measurable using targeted methods, exposomic approaches are critical for understanding the thousands of chemicals people are exposed to on a daily basis through direct chemical exposures, as well as the consequences of such exposures (e.g. oxidative stress markers).

Moreover, all the information obtainable from targeted methods, even wide-scope approaches, necessarily concerns previously characterised molecules, which means the potential for the discovery of unknown exposures or exposure biotransformations is limited. By resorting to untargeted biomonitoring approaches, such as high-resolution metabolomics (HRM), thousands of chemical species can be monitored using just a relatively small amount of biological specimen (≤ 100 μL) and for the cost of a single traditional biomonitoring analysis of 8-10 target chemicals.

In principle, HRM provides the most comprehensive description of small molecular composition possible, including biomarkers of exogenous exposure as well as endogenous metabolites, which together make up a major component of the internal exposome. This field is currently in a stage of rapid development, capable of measuring and annotating hundreds and thousands of small molecules in each analytical run. This is gradually allowing light to be shed on the "dark exposome" or "unknown" chemical risk factors of disease (i.e. not yet identified as suspected risk factors and for which no high-accuracy measurement tools are available). One of the main challenges in measuring the chemical exposome is covering the range of compound abundance in the human body. The concentration of endogenous metabolites, food biomarkers, and drugs present in the blood can span roughly eight orders of magnitude; however, when combined with environmental pollutants, the required range for detecting all exposome compounds present in the body increases to over ten orders of magnitude from femtomoles to millimoles (Rappaport et al., 2014). This exceeds the linear dynamic range of modern mass spectrometers by 10,000-100,000 fold. However, recent developments in separation science, by increasing the resolution of existing separation methods (ultra-performance liquid chromatography or UPLC), and augmenting the complexity of data to detect more compounds (ion mobility spectrometry or IMS), are addressing this problem. Another strategy involves the use of (ultra) high-resolution mass spectrometry ((U)HRMS), which allows a radical increase in the number of detected features and an enhancement of the mass resolution, by exploiting such instruments as Orbitraps and Fourier-transform ion cyclotron resonance (FT-ICR). Other options to boost the number of features obtained include combining complementary stationary phases (e.g. reversed-phase chromatography and hydrophilic interaction liquid chromatography, or GC and UPLC) or removing high abundant analytes and concentrating low abundant exposome compounds, as used in targeted or semi-targeted analyses with the integration of standard reference compounds to allow for quantification (Gil-Solsona et al., 2021).

Finally, the development of mass spectral libraries promises improved annotation of metabolic features. Often referred to as "dark matter", the majority of features measured by untargeted MS cannot be annotated with high confidence to a given compound, where the level of confidence can range from unknown (level 5, simply knowing the mass of the molecule); elucidating its molecular formula (level 4, thanks to the isotope pattern detected); assigning functional groups or a compound class (level 3, by detecting diagnostic fragments); assigning a probable structure (level 2, by matching its fragmentation pattern to a spectral library) to finally validating the annotation with a chemical standard (level 1) (Schymanski et al., 2014).

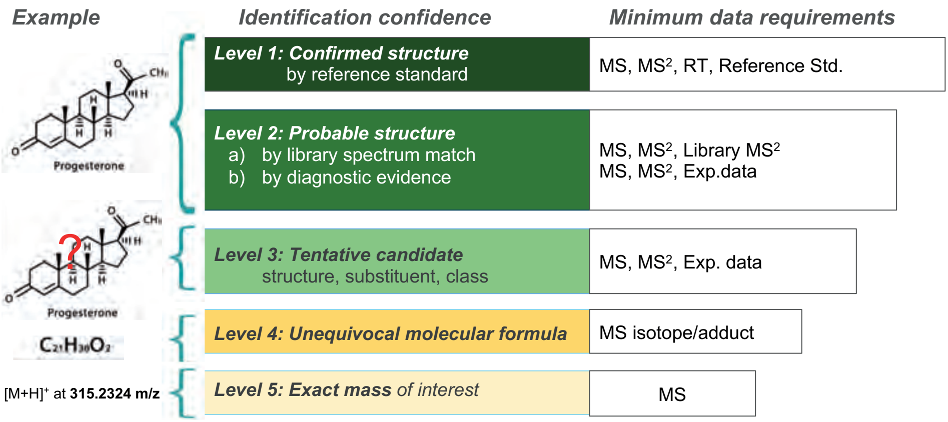

FIGURE 4. Identification confidence levels in high resolution mass spectrometric analysis.
SOURCE: Created by Cristina Balcells Nadal.

Indeed, more than 40 million compounds are listed in PubChem and ChemSpider but spectra are available for only one hundredth of these. Metabolome-wide databases are building on endogenous compound libraries and incorporating environmental toxicants, food contaminants and supplements, as well as drugs and their biotransformation products (METLIN; The Human Metabolome Database (HMDB); Warth et al., 2017) and metabolic databases dedicated to biomarkers of exposure to environmental risk factors are also being developed (e.g. http://exposome-explorer.iarc.fr/). Likewise, other tools are becoming available to help identify compounds uncovered in untargeted analyses and which rely on additional compound characteristics such as fragmentation patterns (tandem MS), exact mass (HRMS), retention time modelling, or ion mobility (collision cross section or CSS), aided by advanced computation and machine learning (Dührkop et al., 2015).

2.2. The urban exposome

By 2030, more than 80% of Europe's population will live in an urban environment. As urbanisation accelerates worldwide, understanding the intricate web of multiple exposures within the urban environment becomes increasingly crucial. The urban exposome encapsulates the myriad factors shaping the health of city dwellers, extending beyond traditional environmental risk assessments. In the hustle and bustle of urban life, individuals are subjected to a diverse array of exposures – from air pollution and noise to food deserts and socio-economic disparities. Traditionally, health research in urban environments has singled out exposures such as the social environment, indoor and outdoor air pollution, noise, heat, the lack of green and blue spaces, and water and food contamination; however, by applying the exposome concept to the urban domain it becomes possible to establish interrelations between these features and upstream factors and to explore how they contribute jointly to individual health.

The assessment of exogenous exposures at the population level can provide local-scale exposure estimates over broad geographical areas, facilitating large epidemiological investigations that link exposures with health outcomes. Generally, population-level exposure assessment relies on the integration of sensor technologies with mathematical modelling approaches.

Remote sensing

Remote sensing, the science of obtaining information about objects or areas from a distance, typically from an aircraft or satellite, can be used to identify multiple exposures related to the urban environment, including air pollution, temperature, and green spaces. New remote sensing technologies, such as the TROPOspheric Monitoring Instrument, are able to provide more spatially and temporally resolved data on air quality, in addition to data on specific atmospheric constituents (e.g. formaldehyde, methane, and nitrogen dioxide). Satellites can also estimate the normalised difference vegetation index, an indicator of greenness – which can be integrated with Google Street View images to provide a comprehensive assessment of the quality, accessibility, and aesthetics of the urban environment – and outdoor light-at-night exposure. While remote sensing data are becoming increasingly available at these higher temporal and spatial resolutions, they do not necessarily translate to exposure at the individual level, but require validation and integration with individual-level information.

Mobile and stationary sensing

External exposure information is often sampled at a limited number of locations, generally as part of a national measurement network or through study-specific measurement campaigns. Both approaches though have limitations: national networks (e.g. for air pollution) have limited geographical coverage, while study-specific measurements are usually conducted over short periods of

FIGURE 5. The AirView car, donated by Google, to collect high resolution air pollution data on all types of roads in Barcelona as part of the EXPANSE Project led by the University of Utrecht in collaboration with ISGlobal. This campaign contributes to building a hyper-local map showing the spatial distribution of different pollutants: nitrogen dioxide, ultrafine particles (UFPs), and black carbon (BC).
SOURCE: Cathryn Tonne and Mark Nieuwenhuijsen (2021), Google's Car Arrives in Barcelona to Measure Air Quality, *Blog ISGlobal*, (20 December), https://www.isglobal.org/en/health isglobal/-/custom-blog-portlet/google-s-car-arrives-in-barcelona-to-measure-air-quality.

time. In order to provide denser spatial information over a longer period, one solution is to use distributed sensor networks, that is, low-cost sensors deployed in large numbers in urban environments. Although the application of such networks remains limited because of the restricted validity of low-cost sensors, technological advances to improve both their effectiveness and pricing should help produce dense information on air quality, noise, and temperature in urban environments. Mobile monitoring platforms, which can be equipped with high-grade measurement equipment so as to cover a large geographical area, have also been proposed for this purpose. Mobile measurement campaigns to date have been unambitious, but recent efforts have seen the implementation of sensors in professionally driven fleet vehicles, including trams in Karlsruhe and Zurich, and in Google Street View cars in European cities, including Barcelona. This last campaign has resulted in the production of unprecedented citywide concentration maps of annual daytime nitrogen monoxide, nitrogen dioxide, and black carbon levels at a 30 m spatial scale.

Modelling

The growing availability of satellite measurements and geospatial information means increasingly accurate estimations of population-level exposures can be made. However, as well as being collected at different geospatial resolutions, such data are often temporally and spatially incomplete. As such, modelling approaches are required that can concatenate information and distil stable, long-term spatial patterns from time-resolved data. Empirical and geostatistical models, including land use regression, kriging, and maximum entropy models, have been considered but will need further elaboration, especially as temporal and spatial data resolution increases.

Sensors and personal monitors

Recent advances in sensor technologies and personal monitors facilitate more accurate, exposome-wide measurements in the external environment. Personal measurements have the unique ability to quantify levels of exposure and the variability in these levels accurately. However, until recently, the cost and inconvenience of personal assessment methods have prevented their extensive use in research.

A recent study demonstrated the feasibility of using wearable air-pump devices to collect information about biotic (biological) and abiotic (chemical) compounds simultaneously from environmental airborne exposures, which was then analysed by next-generation sequencing and LC-MS technologies (Jiang et al., 2018). The authors found 2,796 unique formulae of the chemical exposome, including the insect repellent diethyltoluamide (DEET), the pesticide omethoate, and the carcinogen diethylene glycol (DEG), which were present in every sample. The airborne biological diversity observed in this study was enormous with over 2,500 species identified, 5.11M single-nucleotide polymorphism (SNPs) in 108 pan-domain species across all samples. This number is comparable to the number of SNPs evaluated in the human gut microbiome (101 bacterial species; 3.98M SNPs at the individual level, 10.3M for all samples) (Schloissnig et al., 2013).

Based on the same analytical advances described above in relation to metabolomics in biological samples, the external exposome also benefits from untargeted LC-MS technologies. They allow the chemical compounds present in air, water, and surfaces in human habitats and the workplace to be profiled in an exposome-wide manner (McCall et al., 2019). They have even been proposed as a tool for use in forensic science (Kapono et al., 2018).

2.3. Biological responses: incorporating omics into exposome research

Early biomarkers of effect, that is, before clinical symptoms appear, are needed to identify early environmental exposures in humans, in particular during sensitive windows of exposure, such as pregnancy:

> Biomarkers of effect are measurable molecular, cellular, biochemical, physiologic, behavioural, structural or other alterations in an organism occurring along the temporal and mechanistic pathways connecting exposure to chemicals and an established or possible health impairment or disease. (National Research Council, 2006)

Ideally, effect biomarkers reflect subclinical changes before the onset of disease. Consequently, they range from early biological changes (e.g. enzyme induction responses) to altered structure and function. Effect biomarkers can help in identifying early effects at low doses, establish dose–response relationships, explore mechanisms, and increase the biological plausibility of epidemiological associations. In addition, they can improve the risk assessment of specific chemical families as well as exposure to chemical cocktails.

The use of omics platforms, once reserved for improving clinical diagnosis, patient stratification, and personalised medicine, is becoming increasingly common in the detection of subtle biological changes in the non-diseased general population (Everson & Marsit, 2018; Maitre et al., 2023). This is partly due to the feasibility of their application in large populations (N > 1000) in epidemiological settings, and thanks to their high throughput at reduced costs. Until recently, omics efforts have focused mainly on the identification of altered genes at the genome-wide level (genomics), allowing geneticists to move beyond the analysis of single candidate genes and to perform whole DNA sequence screening. However, while the genome represents the inherited set of DNA instructions needed for the creation and functioning of an organism, it is the environment that shapes and channels the biological potential of an individual during its normal or pathological development. Therefore, more recently other omes have come to the fore leading to the emergence of new omics techniques that facilitate the study of the interplay and intermediate steps between the biological blueprint and an individual's physiological responses and interactions with the environment (Peters et al., 2021). These include epigenomics, the identification of the epigenetic markers of gene expression acting without alteration of the genetic sequence and considered the "cell memory"; transcriptomics, the study of the expression levels of protein-coding messenger RNA (mRNA) and non-coding microRNA (miRNA); and proteomics, the field concerned with the production, behaviour, and interactions between proteins.

Among more recently developed omics are those that complement the other methods by enabling studies of the internalisation of exogenous exposures and immediate physiological response. These include metabolomics aimed at identifying, quantifying, and performing profiling of metabolites (as described in section 3.1 above) as well as metagenomics which allows the characterisation and quantification of all the genomes of the gut microbiota (microorganisms, including bacteria, archaea, fungi, and viruses, that live in the digestive tracts).

The abundance of existing omics techniques allows the events leading to pathological development or the adverse health outcomes at the early stages of the affected process to be pinpointed. For instance, different omics have proved useful in detecting early biological perturbations before the appearance of clinical symptoms in longitudinal epidemiological settings (Maitre et al., 2022), predicting later cardio-vascular and metabolic diseases or neurodegeneration (Liu et al., 2019; Westerlund et al., 2021; Wingo et al., 2022). These platforms have also been used in vivo and in vitro toxicological studies of endocrine disrupting chemicals to improve understanding of these mechanisms.

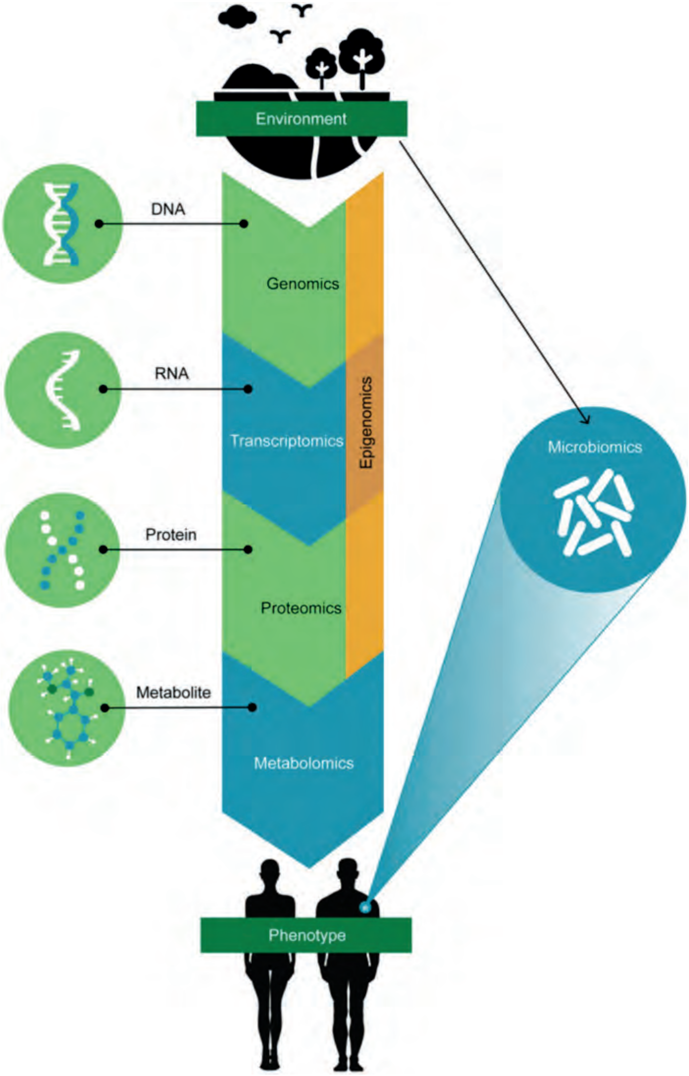

FIGURE 6. Overview of -omics technologies used to profile biological responses to the environment, leading to phenotype changes. Commensal microorganisms residing within (gut and other organs) and on (skin) the human body, collectively known as the *microbiome*, are largely influenced by host-microbe interactions that are reflected in the microbiome compositional and functional profiles.
SOURCE: Yu et al. (2022), An evaluation of the National Institutes of Health grants portfolio: Identifying opportunities and challenges for multi-omics research that leverage metabolomics data, *Metabolomics*, *18*, 29 (30 April), https://doi.org/10.1007/s11306-022-01878-8, under Creative Commons Licence Attribution 4.0 International, https://creativecommons.org/licenses/by/4.0/.

3. Describing the exposome: Variability, determinants, and patterns across the population

3.1. Correlation structure of the exposome

One of the outstanding challenges of interpreting exposure-disease associations is unravelling the dense correlations between all exposures. According to the third Bradford Hill criteria (1965):

> We must not […] over-emphasize the importance of the characteristic. […] One-to-one relationships are not frequent. Indeed, I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answer we might get back to a single factor.

The exposome framework allows the specificity of exposure-health associations to be examined. Indeed, the dense correlation pattern between exposures makes it hard to identify the directionality of the potential causal relation between exposures and outcome. The data-driven approach assumes little to no collinearity between environmental predictors, but it is almost impossible to select any single uncorrelated exposures from the dense exposome. One strategy for addressing these analytical issues is to characterise the correlations in diverse cohorts to provide reference levels, within and between families of exposures or "fields", to gauge the biological significance of associations.

The HELIX Project describes the correlation structure of the exposome based on the assessment of over 100 environmental exposures in 1,301 pregnant women and their children across six European birth cohorts (Tamayo-Uria et al., 2019). This exercise constituted an initial step towards identifying the mixture of exposures occurring simultaneously as a result of common routes of exposure, e.g. to arsenic, mercury, and perfluorinated compounds related to fish intake, or arising from common participant behaviour. The correlation structure was further exemplified in an exposome-metabolome wide association study in pregnant women, in which cotinine levels were strongly associated with urinary coffee metabolites (Maitre et al., 2018). Another potential source of variation may be due to the nature of the measurement or exposure characteristics, e.g. lipophilic persistent pollutants measured in blood are associated with blood lipids and fat mass and are, therefore, highly inter-correlated (Maitre et al., 2022). Temporal, behavioural, and geographical variations can also be interpreted with this type of exercise. For example, in the LIFE study, it was suggested that the individual (see Figure 7) rather than the shared environment of a household could be a major factor influencing the covariation of the exposome (Chung et al., 2018). Clearly, understanding exposure correlations has important analytical and sampling implications for research in exposomics.

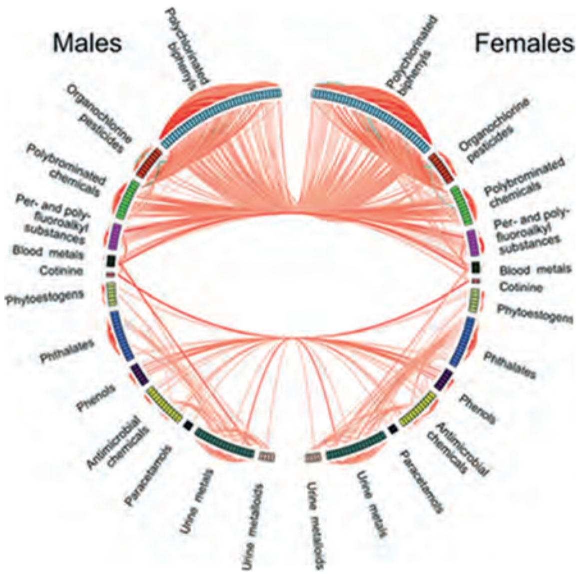

FIGURE 7. Exposome (128 endocrine disrupting chemicals) correlation globe showing the relationships of biomarkers between females, males, and couples.
SOURCE: M. K. Chung et al. (2018), Toward Capturing the Exposome: Exposure Biomarker Variability and Coexposure Patterns in the Shared Environment, *Environmental Science & Technology*, *52*(15) (4 July), 8801-8810, https://pubs.acs.org/doi/10.1021/acs.est.8b01467 (requests for further permissions related to this image should be addressed to the ACS).

3.2. Temporal variability of the exposome

Individual temporal variability - short-term variations

Various factors, including lifestyle changes, seasonal variations, and geographic mobility, cause environmental exposures to fluctuate over short periods of time. For instance, studies of air pollution exposure report significant intra-individual variability, with individuals experiencing fluctuations in pollutant levels depending on such factors as commuting patterns. Individual temporal variability is particularly pronounced in the case of chemicals with short biological half-lives (e.g. non-persistent chemicals) which are rapidly cleared from the body. Studies have shown, for instance, fluctuations in exposure to phthalates and bisphenols, with levels varying over weeks, days, even hours as a result of such factors as dietary intake, personal care product use, and indoor environment conditions.

Panel studies have been critical in investigating the temporal variability of exposures and its impact on health, as they provide insights into how individuals' environmental exposures fluctuate in relation to such factors as daily activities, seasonal variations, and life events. Panel studies exploit a longitudinal study design in which a group of individuals – the panel – is repeatedly measured over time to assess changes in exposure to environmental factors and their health outcomes. These studies typically involve collecting samples and data from the same individuals at multiple time points, thereby allowing researchers to examine how exposures vary within individuals over time and how these variations may influence health outcomes. As discussed above, the HELIX Project is an example of one such study conducted, in this instance, in children and pregnant women (Casas et al., 2018).

Long-term variations

Longitudinal cohort studies provide valuable data on temporal trends in environmental exposures, allowing researchers to track changes in the exposome over time. For example, analyses of historical air pollution data have documented declines in levels of particulate matter and nitrogen dioxide in urban areas, attributed to regulatory interventions, technological advances, and shifts in energy sources. Conversely, emerging contaminants, such as per- and polyfluoroalkyl substances (PFAS), present upward trends in exposure due to their widespread use in consumer products and industrial processes.

A persuasive example of the temporal variability of environmental exposure, including across society, is provided by that of lead exposure. Accurate historical analyses are possible by examining ice cores and their encapsulated air bubbles. These studies reveal a marked escalation in mercury and lead emissions attributable to human activities since the conclusion of antiquity, following a temporary decline during the Middle Ages (McConnell et al., 2019).

Historically, lead has been associated with varying degrees of exposure across the different social classes. In ancient Rome, lead exposure was prevalent among the affluent who used *defrutum*, a costly syrup made from cooked grapes stored in lead containers, to sweeten their food. Over time, the widespread use of lead-based paints and, later, leaded gasoline, resulted in a more ubiquitous exposure across the population. However, as the wealthier nations phased out leaded gasoline, older, unrenovated housing emerged as a significant source of lead exposure, primarily affecting the socio-economically disadvantaged. This historical trajectory of lead exposure highlights the complex interplay between environmental hazards and social dynamics, underscoring the importance of sociological perspectives in understanding how environmental exposures intersect with broader social determinants of health and contribute to health inequities, even in affluent societies.

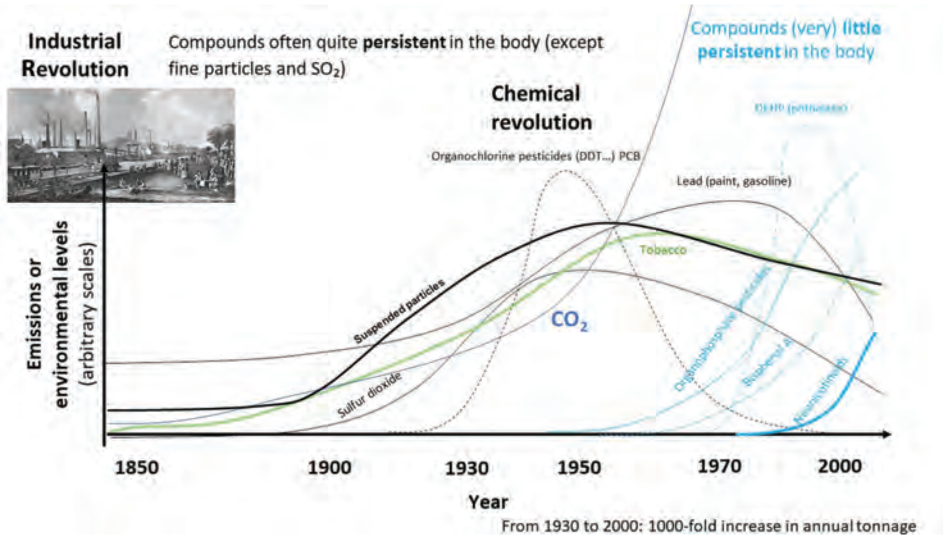

FIGURE 8. Historical evolution of the chemical exposome.
SOURCE: Rémy Slama (personal communication).

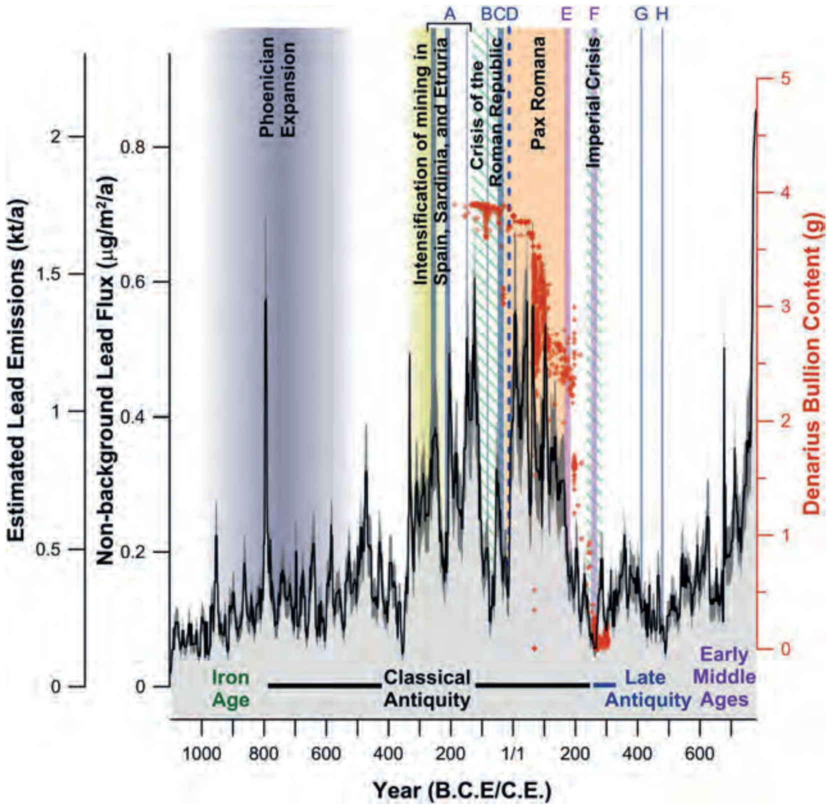

FIGURE 9. Annual lead pollution deposition during the past 2,200 years has been documented in an array of ice cores spanning nearly half the Arctic, including 12 ice cores from Greenland and one from Severnaya Zemlya in the Russian Arctic.

SOURCE: Joseph R. McConnell et al. (2018), Lead pollution recorded in Greenland ice indicates European emissions tracked plagues, wars, and imperial expansion during antiquity, *PNAS* (*Proceedings of the National Academy of Sciences*), *115*(22) (29 May), 5729, https://www.pnas.org/doi/pdf/10.1073/pnas.1721818115.

FIGURE 10. In Roman times, the wealthy classes were "privileged" in being able to sweeten their food with *defrutum*, a costly grape syrup cooked in a lead container that released lead acetate, a potentially deadly sweetener.
SOURCE: Image by HerrBudlanski in *Wikimedia Commons*, https://commons.wikimedia.org/wiki/File:Beuverie_Latine.jpg, under Creative Commons Licence Attribution-ShareAlike 4.0 International, https://creativecommons.org/licenses/by-sa/4.0/.

3.3. The exposome and health inequalities

STEFAN SIEBER

Health inequalities are commonplace and can be found virtually anywhere, occurring in low- and middle-income countries as well as in their high-income counterparts. Such inequalities are not only manifest across a range of medical factors, including genetic predisposition, access to health care, and health service quality, but they also occur in association with a slew of non-medical factors, including gender, race, education, income, housing, and food security, the so-called *social determinants of health* (Neufcourt et al., 2022). Health inequalities are an outcome of the conditions in which people live, work, and age, which are in turn shaped by broader political, social, and economic forces (World Health Organization & UN-Habitat, 2010). Moreover, health inequalities are not distributed randomly across the population but show consistent patterns according to socio-economic standing. In 2010, Sir Michael Marmot and colleagues published a seminal report on health inequalities in England entitled "Fair Society, Healthy Lives", and, in so doing, created awareness for an issue often overlooked by policy

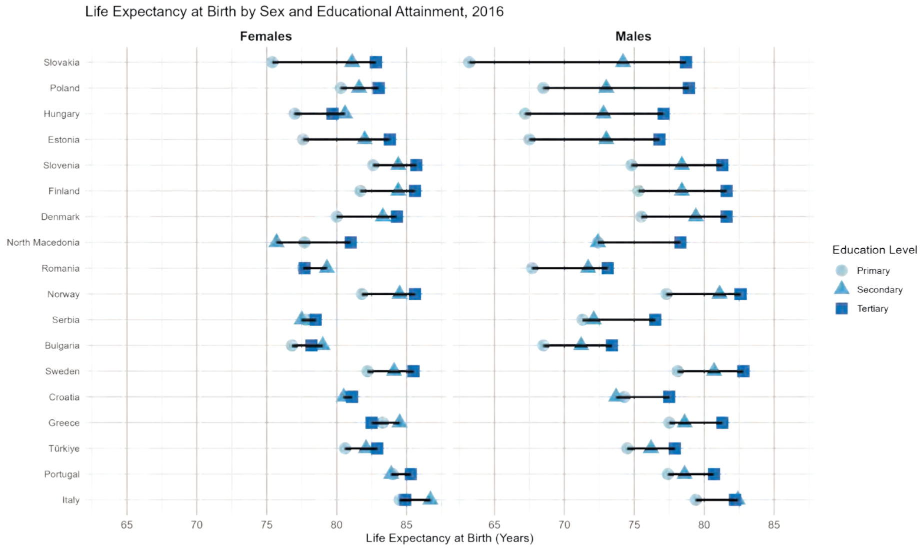

FIGURE 11. Life expectancy at birth, by education level, 2016.
SOURCE: Creation of Stefan Sieber using data from "Life expectancy by age, sex and educational attainment level", *Eurostat*, https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_MLEXPECEDU.

makers and the public at large (Marmot, 2010). The report concludes that each year between 1.3 and 2.5 million years of life are lost in England due to premature death as a consequence of health inequalities. These health inequalities result from social inequalities, something that becomes patent when examining the "social gradient in health": the lower a person's social position, the worse his or her health, a finding applicable to almost every country and context around the world (World Health Organization, 2008).

While the literature on the social determinants of health has grown substantially in recent decades, scientists investigating the exposome have only recently taken an interest in the non-medical factors influencing health outcomes, well-being, and quality of life. Increasingly, these scientists are interested in how the social determinants of health may be integrated in their research into the exposome and how, more specifically, they might be incorporated as part of the external exposome (Vineis et al., 2020). Traditional health risk factors, such as tobacco use, excessive alcohol consumption, sedentary lifestyle etc., partly explain the social health inequalities and tend to follow a social pattern, with unhealthy behaviours being more prevalent among lower social positions (Gallo et al., 2012). Nevertheless, a substantial part of these inequalities remains unexplained.

The exposome framework has great potential for investigating other pathways that might link social factors with health inequalities. The hypothesis of a biological embodiment of the social environment seeks to explain how social factors may lead to biological alterations (Blane et al., 2013), which makes it particularly interesting for exposome research. The social-to-biological transition suggests that the social environment may have an impact on health through exposures either of exogenous or endogenous origin (Neufcourt et al., 2022). Those of exogenous origin emerge from the specific external exposome and include pollution, pesticides, tobacco, alcohol, diet, etc.; those of endogenous origin influence the internal exposome via psychosocial factors involving the subjective interpretation of conditions, such as challenges, interpersonal relationships, etc., that trigger the response of internal biological mechanisms linked in the main to stress perception and stress response systems. This link between the social factors in the general external exposome and the biological responses that form the internal exposome makes the exposome framework a powerful tool to explore how social inequalities translate into health inequalities.

4. Exposome and health

4.1. Early-life exposome and health development

The early stages of life are critical periods in an individual's health development, with environmental exposures during this time having profound and lasting effects. Indeed, the developmental origins of health and disease (DOHaD) hypothesis posits that environmental exposures during critical periods of early development – especially during prenatal and early postnatal life – can significantly influence long-term health outcomes. The suggestion is that adverse environmental exposures during sensitive developmental stages may programme physiological systems, leading to increased susceptibility to non-communicable diseases (NCDs) later in life.

One of the best known examples illustrating the DOHaD hypothesis is the Dutch famine study, conducted by Professor David Barker and colleagues. This landmark investigation examined individuals who had been exposed to severe undernutrition during gestation *in utero* during the Dutch famine of 1944-1945. Researchers found that individuals who had been prenatally exposed to famine exhibited higher rates of chronic diseases, including obesity, cardiovascular disease, and diabetes, later in life compared to unexposed individuals. These findings provided compelling evidence of the link between early-life exposures and subsequent health outcomes, and lay the foundations for further research testing the DOHaD hypothesis (Barker et al., 1989).

Numerous studies worldwide have since provided evidence both supporting and expanding the DOHaD hypothesis by studying the impact of various early-life exposures on health development. This body of research, among others, has explored the effects of maternal nutrition, exposure to environmental pollutants, stress, and other factors during pregnancy and infancy on the risk of NCDs in offspring.

In Spain, for example, the *INfancia y Medio Ambiente* (INMA) cohort profile is a large-scale birth cohort study that investigates the effects of environmental exposures on child health and development (Guxens et al., 2012).

FIGURE 12. The INMA birth cohort network.
SOURCE: INMA Project (2018), *INMA - INfancia y Medio Ambiente*, https://www.proyectoinma.org/en/inma-project/study-design/.

Some of the key findings to emerge from the INMA cohort include:

— *Prenatal exposures*: Various prenatal exposures, such as air pollution, tobacco smoke, and maternal diet, are associated with adverse health outcomes in children. For example, exposure to air pollutants during pregnancy has been linked to decreased birth weight and respiratory problems in infants.

— *Neurodevelopmental outcomes*: Prenatal exposure to certain environmental pollutants, such as polychlorinated biphenyls (PCBs) and organophosphate pesticides, may be associated with neurodevelopmental delays and cognitive impairments in children.

— *Childhood asthma*: Prenatal and early-life exposures to air pollution and tobacco smoke are risk factors for childhood asthma and respiratory allergies.

— *Growth and development*: Environmental exposures have an impact on growth patterns and physical development in children. For instance, maternal exposure to endocrine-disrupting chemicals during pregnancy has been linked to altered growth trajectories in offspring.

The early life course also presents important windows of opportunity for prevention. Health and disease are full life-course processes and it is, today, widely recognised that the early parts of this course, from conception and even preconception, are especially vulnerable to environmental influences with life-long consequences. At least part of the origin of the most common NCDs lies in the first 18 years of life, and prevention during these periods will not just improve child health, but also benefit life-long health and disease trajectories. This means that building exposome tools and data for the future needs to start in the early life course.

4.2. Exposome and reproductive and sexual health: The case of endocrine disruptors

Recently, it has been demonstrated that certain compounds can act as endocrine disruptors, *interfering with the normal functioning of hormonal pathways*. These compounds have structures at the molecular level that resemble those of hormones and which replace them in carrying out their functions, ultimately causing alterations in the hormonal system. Exposure to these endocrine disruptors can be detrimental at any stage of life, but the effect is most marked during certain windows of susceptibility, particularly during pregnancy, lactation, and childhood, critical periods in an individual's development when their hormones play an essential role. Recent advances in omics technologies enable the characterisation of each of the molecules to which we are exposed and, thanks to this, the exposome can be seen to be playing a decisive role in determining the extent to which endocrine disruptors pose a risk to human health.

One example of a family of synthetic compounds that can act as endocrine disruptors are the phthalates, commonly found in plastics, PVC, cosmetics, and personal care products. When these compounds come into direct contact with blood or fluids containing lipids, they can readily enter the bloodstream and migrate to any part of the body. If these compounds reach the testes or ovaries, they can disrupt their hormone secretion function, leading to reproductive problems, spontaneous abortions, growth issues, and low birth weight, among others.

The role played by endocrine disruptors in the development of type II diabetes mellitus (DM) has also been well documented. While there is a genetic predisposition to DM, characterised by elevated blood glucose levels (hyperglycaemia) due to insulin resistance and a progressive failure in pancreatic insulin secretion, non-genetic factors such as poor diet, a sedentary lifestyle, and certain environmental pollutants can be critical in the development of this condition. Indeed, exposure to these factors during the prenatal stage has been identified as a risk factor for future diabetes. Specifically, bisphenol-A (BPA) has been identified as a compound that acts as an endocrine disruptor and which is related to the development of DM. Since 2011, its use has been prohibited or restricted in certain applications in Europe.

While the number of such molecules to which we are exposed is low, studies show that the effects of these disruptive compounds can be potentiated, so even though we are exposed to low doses, their effect can be much greater. This underscores the importance of identifying those compounds that act as endocrine disruptors. Several European projects are currently addressing this very issue, including the EURION cluster. This initiative aims to identify endocrine disruptors related to an increased risk of certain diseases and to develop diagnostic tests based on that information.

4.3. Exposome and non-communicable diseases

Apolline Saucy

The association between environmental factors and non-communicable diseases (NCDs) is gaining increasing recognition. According to the WHO, 12.6 million deaths globally (24% of all deaths) can be attributed to the environment, of which two thirds (ca. 8.2 million deaths) are caused by NCDs (Prüss-Üstün et al., 2016). Air pollution contributes to 5 million deaths from cardiovascular diseases each year and is considered the 5th leading cause of death, ranking just after smoking (GBD 2017 Risk Factor Collaborators, 2018). Other environmental exposures are being increasingly recognised for their adverse effects on health, including climate (Vicedo-Cabrera et al., 2021; Watts et al., 2018), environmental noise (Münzel et al., 2021; Vienneau et al., 2015), urbanisation (World Health Organization, 2021), and green space (Barboza et al., 2021).

Cardiovascular diseases

Cardiovascular diseases (CVDs) – covering a range of health disorders of the heart and blood vessels, including coronary heart diseases and cerebrovascular diseases – make the largest contribution to the environmental burden of disease worldwide. In 2017, they contributed to 17.8 million deaths and 35.6 million disability-adjusted life years or DALYs worldwide, making it the leading cause of death globally (Wang et al., 2023). The action of environmental conditions on CVDs can be direct (e.g. the impact of air pollution on respiratory function and blood pressure) but it can also be mediated by changes in behaviour or in social interactions, which may in turn lead to cardiovascular diseases. For instance, physical activity and a healthy lifestyle can be promoted by better access to public green spaces and public transport, and by improving street safety.

Mental health

Complex environments, including both environmental hazards and the social environment, have been shown to affect mental health and cause behavioural disorders. Wang et al. (2023) conducted exposome-wide association analyses in a twin cohort and found that more than half of the exposures were significantly associated with depressive symptoms in young adulthood. More specifically, influences from the family domain and the social exposome were particularly important drivers of depressive symptoms in late adolescence and early adulthood. Other environmental exposures such as environmental noise can also affect mental health, possibly via sleep alterations and effects on the central nervous system (Hahad et al., 2024). In a recent study conducted near a military airport, Wicki et al. (2024) showed a strong link between exposure to loud military aircraft noise events and symptom exacerbations and medical prescriptions in patients with psychiatric treatments.

NCDs and health disparities

The impact of environmental contaminants on health varies across regions, sexes, and age groups. The contribution of NCDs compared to infectious diseases is greatest in the adult and elderly population, and in high-income countries. However, the health impacts of modifiable environmental conditions globally have a disproportionate effect on low- and middle-income countries. With the epidemiological transition to an increasing prevalence of NCDs in developing countries and with a growing proportion of the population living in urban settings, environmental inequities are likely to grow in the future. Promoting healthy living environments is therefore essential in reducing mortality and morbidity from chronic diseases worldwide and in stemming the ever-increasing associated healthcare costs (Hajat & Stein, 2018).

4.4. Exposome and infectious diseases

Environmental exposures, including exposures to endocrine disrupting chemicals (EDCs), can influence an individual's susceptibility to infection. Suspected to exert their effects via hormonal pathways, certain EDCs, including phthalates, bisphenols, organochlorine pesticides, and perfluorinated alkane substances (PFAS), stand out as potential triggers for aggravated infections. Compelling evidence suggests that exposure to these substances may impact the immune defence mechanisms, potentially heightening vulnerability to infectious diseases such as COVID-19 (Tsatsakis et al., 2020).

Epidemiological findings underscore the significance of these concerns, particularly in the case of children exposed to PFAS, revealing, as they do, diminished immune responses to routine vaccines (Grandjean et al., 2012). Moreover, such exposure is associated with an increased risk of developing infectious diseases. As the exposome framework broadens our understanding of environmental influences on health, the complexity of the links between pollutants and infectious diseases clearly warrants careful exploration. The identification of these links not only furthers our understanding of disease pathways but also serves to underscore the importance of mitigating exposures to foster a resilient and responsive immune system in the face of infectious challenges.

Exposure to outdoor air pollution may impact the transmission, susceptibility to, and severity of infectious diseases such as COVID-19. Air pollution might affect the viability and movement of viral particles, potentially increasing the risk of infection by suppressing lung defences, altering receptor recognition, and affecting expression levels of key proteins involved in viral entry. Chronic exposure to air pollution could also worsen COVID-19 outcomes by exacerbating underlying chronic conditions and impairing immune function. A recent study in Catalonia (COVIDCAT) found that air pollution exposure was positively associated with the magnitude of antibody response among seropositive participants and that exposure to NO_2 and $PM_{2.5}$ was positively associated with COVID-19 disease and with the severity of the disease (Kogevinas et al., 2021).

5. Data science and the exposome

The main advantage of the holistic exposome framework over traditional "one-exposure-one-disease" approaches is that it provides an unprecedented conceptual structure for the study of multiple environmental hazards (including urban, chemical, lifestyle, and social risks) and their combined effects. Indeed, classical single pollutant models are unclear as to whether the analysed association can be attributed to the pollutant effect or to another correlated exposure not considered directly in the analysis. Such models are also unable to capture the interactions and cumulative effects derived from the exposure mixture. Furthermore, given the increasing availability of complex environmental health data thanks to the emergence of new technologies (including electronic health records, high throughput omics platforms, wearable sensors, etc.), there is a growing need for more advanced statistical approaches that focus on complex mixtures of exposures.

However, the analysis of such complex data comes with numerous challenges, including, for instance, the typically high correlations between exposures of the same family (e.g. air pollutants and lifestyle), and the ability to capture cumulative low dose effects, assess interactions, and identify important components of the mixture. Recently, a series of different methods have been developed to take into account multiple exposures and their interactions, including the use of mixture analysis methods; the integration of the selection, shrinkage and grouping of correlated variables (e.g. LASSO, elastic-net, adaptive elastic-net); the application of dimension reduction techniques (e.g. principal component and partial least square analyses); Bayesian model averaging (BMA), and Bayesian kernel machine regression (BKMR). Among the limitations of these approaches, however, are the lack of model selection stability (the case of shrinkage methods), the lack of interpretability of the latent variables (the case of dimension reduction techniques), and an overall computational inefficiency (the case of Bayesian models). Moreover, they are rarely applied in the context of large (>100 variables), heterogenous exposome data (omics, categorical/continuous variables).

Dimensionality reduction

One way of handling multivariate exposomic data (even without resorting to omics) is to employ methods of dimensionality reduction, especially that of feature selection. Feature extraction, by contrast, is less frequently employed since it can complicate the interpretation of the results, given our interest in the effect of a particular exposure on health. However, a number of methods have been developed that seek to analyse groups of correlated exposures. In this way, the dimensionality of the input can be reduced while ensuring interpretability of results.

Combined effect of exposures

Index methods serve to measure the combined effect of exposures. As well as being easy to interpret, they provide both a single parameter estimate for the mixture of exposures and weights to show the contribution of each exposure. However, all index methods suffer from an inability to consider the interactions between the exposures that contribute to the same index. This can, in part, be addressed by using response surface methods, albeit that it potentially hinders interpretation. This tension between interpretability and complexity when choosing between the two types of model has been eased somewhat by recently developed methods (i.e. multiple index models) that combine some of the advantages of both methodologies. These have the advantage of providing readily interpretable indices, while accommodating non-linear and non-additive relationships between exposure indices and the health outcome (McGee et al., 2023).

Bayesian techniques[1] are also useful since they can be used in a manner that naturally penalises complex models yet they are sufficiently flexible to incorporate a variable selection mechanism. They also help obtain the distributions of any quantity that can be derived from the model output.

1. These are statistical methods that involve updating beliefs or probabilities about hypotheses based on prior knowledge and observed data, allowing for the incorporation of uncertainty and the estimation of parameters through probability distributions.

Machine learning and prediction

Machine learning methods – including ensemble methods (such as random decision forests and XGBoost), neural networks and support vector machines – have the potential to increase the predictability of the outcome by capturing more complex information (e.g. complex interactions, non-linear relationships, etc.) from the exposome data. Models that combine multiple statistical techniques into an ensemble can provide even better results, since the different methods employed may be able to capture different data patterns.

Causal models

Finally, causal models – including mediation analyses using omics data, g-computation methods, and the causal random forest – have gained popularity in environmental epidemiology (Bind, 2019), including when making estimates for mixtures of exposures. Indeed, causal questions are what ultimately drive interventions and policy change. Causal mediation analysis with exposome data can help prioritise the environmental factors that have the greatest impact on health.

6. Potential for translating exposome research into clinical practice and policy

6.1. The modifiable exposome

The modifiable exposome refers to environmental exposures that can be altered or influenced through *individual or collective actions*.

By identifying and understanding exposures that are amenable to change, exposome research provides a roadmap for targeted interventions. This involves recognising lifestyle factors, behavioural choices, and environmental conditions that individuals or communities have the ability to modify. For example, reducing exposure to air pollution by promoting sustainable transportation options or mitigating noise pollution through urban planning strategies.

Mitigating exposures to endocrine disruptors

Numerous interventions have demonstrated the potential to modify exposure to the common endocrine disruptors (including phenols, phthalates, and parabens) frequently found in personal care products (PCPs) and dietary sources. Interventions promoting increased exposures, for example, using PCPs containing triclosan and serving meals based on canned foods likely to release BPA, consistently resulted in elevated urinary concentrations of the targeted chemicals. Conversely, interventions removing or substituting these exposure sources generally led to decreased biomarker concentrations. *Lifestyle modifications, label scrutiny, and product replacement* have emerged as feasible strategies, illustrating the individual's capacity to reduce exposure effectively.

However, notable gaps remain, especially as regards the potential health impacts of exposure to glycol ethers and the limited development of bisphenol A (BPA) substitutes. In a recent systematic review including 26 interventions (Yang et al., 2023), BPA and phthalate metabolites were reported as being the most targeted chemicals, possibly reflecting heightened media scrutiny. Dietary interventions, particularly those focused on BPA, were generally successful either alone or combined with PCP-related measures. Unexpected outcomes, including even increased metabolite concentrations in certain PCP studies, underscore the complexity of exposure reduction. Overall, the studies emphasise the need for interventions to consider participant compliance and motivation, and the ease with which the changes proposed can be adopted to enhance effectiveness.

The challenges of identifying "safer" replacement products were evident, with unintentional contamination from these replacements sometimes posing a risk. Participants, moreover, expressed difficulties in adhering to long-term changes, emphasising the need to promote sustainable interventions. Although varied participant demographics and the lack of long-term follow-up limit the generalisability of some of the interventions reported, successful instances showcase the potential for the widespread impact of policy measures that target exposure sources, transcending individual behavioural changes.

Urban exposome interventions

Mònica Ubalde López

Traditional urban structures have been designed primarily to promote mobility in private vehicles and not to meet the needs of the more vulnerable, i.e. children, youth, the elderly, and those with chronic conditions. However, motorised vehicular traffic is a major contributor to poor air quality in most urban areas which, if they also fail to comply with international air quality directives and WHO recommendations, suffer the weighty burden of premature mortality and increased morbidity. This traditional urban planning model, moreover, typically ignores the possibilities of creating more naturalised and inclusive open spaces that can satisfy the diverse needs of daily life, and contribute to reducing other harmful urban exposures: for example, high noise levels, the heat island effect, and the lack of green/blue spaces and areas for physical activity and social interaction. However, in recent decades, cities have responded by developing traffic calming measures aimed at reducing motorised vehicle traffic. Urban re-designs that limit vehicular parking, reduce speed limits or eliminate traffic entirely can improve air quality, safety, and encourage active modes of transportation.

It is evident that effective preventive actions are urgently required to reduce the health and economic burden of the harmful urban exposome. These actions need to recognise the "complex systems" affecting population exposure, including "upstream" (e.g. economic, political, and global forces, as well as the natural and built environment) and "downstream" (e.g. individual and organisational behaviour) influences on the effectiveness of exposome-reduction interventions (Rutter et al., 2017). The rapid translation of evidence into practice requires engaging communities, stakeholders, and decision-makers in the development and evaluation of interventions (Eldredge et al., 2016). In this sense, it is critical to develop, implement, and evaluate co-produced effective, scalable interventions to reduce personal exposure to the harmful effects of the urban exposome. New technologies (e.g. wearable air pollution sensors, smartphone apps) have the potential to provide a richer understanding of outdoor and indoor personal exposures (Larkin & Hystad, 2017). In this way, real-time information can help individuals make informed decisions to reduce exposome exposure (e.g. by choosing less polluted routes for active travel).

Interventions in the public space – synonymous, we might claim, with public health interventions – need to be developed in close partnership with communities and key stakeholders to ensure that the co-produced actions are both acceptable and feasible, and can thus guarantee their rapid translation into practice. Indeed, a number of tools designed to guide urban planning specifically incorporate this critical dimension of citizen participation, whereby greater participation provides a democratic mandate and serves to leverage political will. One example of such a tool is provided by the EU's Sustainable Urban Mobility Plans (SUMPs), a strategic policy that is tellingly built upon people's needs and which mobilises specific self-assessment toolkits (Rupprecht et al., 2019). However, to date, little attention has been paid to the barriers to and facilitators of governance when designing interventions in the public space. It is apparent that participation should not only be possible, but that it needs to be significant as well. Yet, the value of public participation only becomes evident when a plan's results are clearly and systematically integrated in a sustainable urban mobility project. Future projects need to address these challenges of governance head-on. Interventions to reduce multiple exposures can be co-produced, but meaningful reductions require structural changes as well as changes to individual behaviour.

Urban interventions aimed at re-naturalising the built environment, eliminating traffic and fostering active mobility and public transport are critical in improving the urban exposome. Traffic restriction measures, such as the low traffic neighbourhoods (LTNs) implemented in London, help create healthier, safer places for the community not only because of a potential reduction in air pollution (without the problem being displaced to neighbouring streets) (Yang et al., 2022), but also because of their impact on noise levels and their ability to win back urban sites for people and naturalised infrastructures. The benefits of increasing street greenery, boosting biodiversity and introducing new ecosystem services and climate-resilience have been estimated for mental health in adults and the

FIGURE 13. Community participation, co-production, and action aimed at enhancing the urban exposome.
SOURCE: Created by Mònica Ubalde.

related burden in public health services (Yañez et al., 2023), as well as for behavioural and cognitive development in children (Opbroek et al., 2024).

In some urban settings, schools are often urban exposome "hotspots", located in areas with extreme levels of pollution and noise, compounded by high levels of car use during the school run. Indeed, home-to-school commuting is reported as being responsible for 20% of a child's daily dose of air pollutants. Clearly, if we envisage health from a public health perspective and adopt a life-course approach (Kalache & Kickbusch, 1997), there is a more than pressing need to begin to design healthy, safe urban environments for and with children and young people (Bishop & Corkery, 2017), since health outcomes in later life are strongly influenced by an individual's early habits and behaviours, which in turn are strongly conditioned by the urban environment.

Urban school environments should therefore be seen as priority spaces for the health and well-being of children and their families. Yet, as schools are distributed across all neighbourhoods, their urban environments should be understood as a strategic point of entry for achieving a healthier, safer city. Implementing interventions in school environments and prioritising the health of the most vulnerable (i.e. taking an equity perspective) can ultimately benefit all by reducing their urban exposome. School streets' programmes seek to improve the quality of these public spaces through street re-designs, traffic-calming measures, the elimination of car parking zones, and the addition of street furniture and greenery; however, to date, few urban planning programmes have actually been subject to rigorous impact assessments. The few that have specifically been conducted in school environments report that street-calming measures do improve the urban exposome by reducing traffic flow and related pollutants (i.e. NO_2), increasing available public space for citizens, promoting play areas for children in the street, and providing spaces for physical activity and social interaction (Ferrer-Fons et al., 2023; Ubalde-López et al., 2023).

The transformative potential of school environments is, of course, indisputable, the goal being to ensure schools continue to be a great educational resource that can safeguard childhood growth as well as foster the well-being and health of the entire city. Yet, despite the key role of urban school settings, interventions to modify outdoor stressors in the built and natural environment that act as urban exposures target primarily individual behavioural change (e.g. increasing time spent in green spaces and active travel) rather than seeking to implement structural changes that can promote healthy behaviour and reduce urban exposure at the population level (Fernandes et al., 2023). Ultimately, built environment changes (e.g. infrastructure and support for bikes and walking) are required to support sustainable behavioural changes and an impact evaluation strategy needs to be integrated from the early design phase of the intervention. In common with all public policy design and practices, it is essential to identify what works and for whom, taking steps to identify barriers and enablers for implementation and evaluation.

6.2. Health impact assessment and policy

Risk and health impact assessment are moving away from the "one-chemical one-health outcome" model toward a new paradigm of monitoring the totality of exposures that individuals may experience in the course of their lifetime. Today, health impact assessment (HIA) and risk assessment are powerful tools that contribute to informed decision-making in public health and policy development. They can systematically evaluate the potential health effects of policies, programmes, or projects, and provide valuable insights into the risks and benefits associated with different interventions. The amalgamation of scientific evidence, community input, and policy considerations they offer is central to the success of their assessments.

Unlike traditional assessments that tended to focus on singular exposures or risks, the exposome broadens the scope, encompassing the totality of environmental exposures that individuals encounter throughout their lives. By considering the *cumulative impact of multiple exposures* (Tulve et al., 2024) – ranging from air quality and lifestyle factors to socio-economic determinants –, the exposome provides a holistic understanding of health influences. The need for cumulative impact assessments emerges from the growing recognition of the urgency for actionable science to address the *needs of overburdened communities*.

As we navigate the intersection of exposome research, health impact assessment, and policy development, we identify new avenues for *precision public health interventions* and policies that address the complex interplay of environmental factors on human health.

7. Future perspectives

7.1. Large-scale exposome research

To be able to study the plethora of environmental pollutants and the many physical, lifestyle and social risk factors and their combinations, while, at the same time, incorporating high-dimensional omics data, it is critical that exposome research begins to look beyond simple, self-contained projects and starts to build a large platform for the efficient generation of evidence and the replication of findings. However, the field's research tools and data are currently scattered and information remains largely embedded in scientific publications. Efforts are underway though to harmonise existing exposome data across multiple locations and to make them readily accessible (both as regards omics and exposome-wide association studies or ExWAS, e.g. the HELIX database and, in the case of metabolomics data, COMETS). Multi-centre exposome research needs to implement the FAIR data infrastructure to ensure the findability, accessibility, interoperability, and reuse of exposome data. The ongoing EU Horizon 2020 LifeCycle Project, which consolidates European pregnancy and child cohort studies in one harmonised data sharing platform, has begun to implement the FAIR principles, building on 80,000 mother-child pairs at baseline in 15 cohorts from 10 countries across Northern, Eastern, Southern, and Western Europe (Figure 14). Other initiatives have been taken, including the Children's Health Exposure Analysis Resource (CHEAR) in the US, aimed at providing access to standardised laboratory tools for exposome research in children's health studies, so as to ensure the comparability and replication of findings. In 2019 this initiative was expanded to include its Data Repository, Analysis and Science Center.

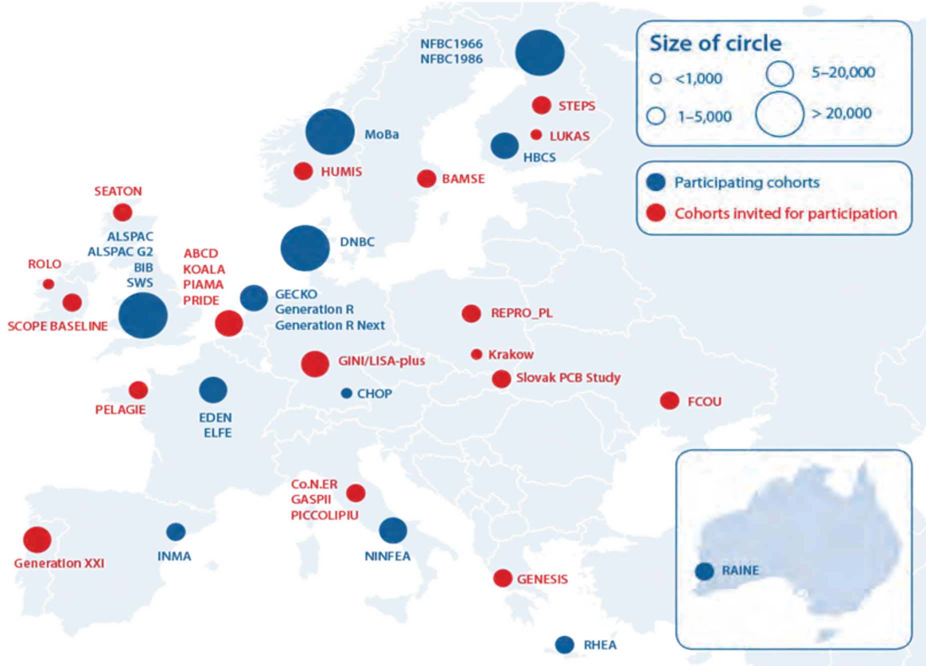

FIGURE 14. The EU Child Cohort Network.
SOURCE: *EU Child Cohort Network*, https://euchildcohortnetwork.eu/.

More recently, the International Human Exposome Network (IHEN) Project has been heralded as a ground-breaking endeavour in the realm of exposome research, insofar as it seeks collaboration and coordination at the global scale. This initiative, comparable to the Human Genome Project (1990-2003) in its scope and ambition, aims to map and understand the full breadth of environmental exposures encountered by individuals throughout their lives, akin to the genome's role in decoding genetic information.

7.2. Exposome in the Global South

ARIADNA CURTO

While much of exposome research has been conducted in the Global North, there is a growing expectation that the concept will have to be increasingly applied to the Global South, a term coined by the UN Conference on Trade and Development (UNCTAD) to designate countries of low socioeconomic status and, while not strictly geographical (Australia and New Zealand, for example, lie in the Southern Hemisphere but are considered high-income), it is increasingly being used to refer to low- and middle-income countries.

Unlike the Global North, many countries of the Global South have to face the challenges of poverty, restricted access to education and services (including piped water, waste disposal, and electricity), and weak health systems, among others. These factors – recognised drivers of health – have yet to be addressed fully in exposome research, which has tended to focus its interest on the challenges faced by high-income countries. This research gap is even more significant if we consider the social environment, a domain that has attracted very little research interest (both in the Global North and South), but which is of enormous significance for populations in the Global South who find themselves frequently exposed to adverse life events.

Global South populations also face environmental and socioeconomic exposures that are less prevalent in (or absent altogether from) the Global North (see Figure 15). Limited access to clean water, sanitation facilities, and proper hygiene practices (all of which are associated with waterborne diseases) in combination with restricted access to clean household fuels and technology (responsible for household air pollution) pose significant health challenges. Children living in these conditions are particularly vulnerable as they typically have a higher preexisting burden of chronic infections and nutritional deficiencies, exacerbating the challenges to their health and development.

In some countries of the Global South, rapid environmental changes, including those associated with urbanisation and industrialisation, hinder both the monitoring and understanding of these changing exposures. In India, for example, an increase in urbanised land use (and the associated reduction in green spaces) in residential areas between 1995 and 2009 has been associated with higher cardiometabolic risk factors due to reduced physical activity and increased air pollution exposure (Milà et al., 2020).

The methodological challenges encountered by exposome research in the Global North are magnified in the Global South by prevailing socioeconomic conditions, insufficient infrastructure and limited resources, all of which undermine both data availability and data quality. Inadequate health infrastructure, for instance, frustrates the ability to conduct large-scale longitudinal epidemiological studies and to collect quality clinical data. The coverage provided by environmental monitoring is also scant. For example, in the case of air quality monitoring, 60% of countries (the majority in Africa), representing 18% of the world's population, conduct no regular $PM_{2.5}$ monitoring (Martin et al., 2019).

Despite these challenges, there are instances that point to the feasibility of conducting exposome research in the Global South based on collaborative efforts and the use of advances in technology. One notable example is the study conducted

FIGURE 15. Environmental and socioeconomic factors affecting populations in the Global South.
SOURCE: Created by Ariadna Curto.

on 100 South African children, who were provided with wearable samplers (Koelmel et al., 2022). In this way, 637 environmental exposures could be identified, some of which had never previously been measured in children. The study identified 50 airborne chemical exposures of concern, including pesticides, plasticisers, organophosphates, and combustion products, among others. Primary monitoring campaigns can also serve as an effective means to obtain environmental data in these contexts. An illustrative example here is provided by a study involving

50 adults in South India, where comprehensive ambient and personal monitoring was carried out (Milà et al., 2018). This study exemplifies advanced data integration techniques in resource-limited settings by combining personal and ambient air pollution concentrations with questionnaires, GPS, and wearable camera data, which allowed identification not only of activities associated with increased exposure but also of the times of day and the locations where these exposures occurred.

To further exposome research in the Global South and enhance global collaboration in the field, various initiatives have been taken. Most notably, the International Human Exposome Network (IHEN) Project, funded by the European Commission, seeks to unite stakeholders from various sectors at the global scale. Such a collaborative approach is crucial for maximising the impact of future exposome research, particularly in the many Global South countries where research has historically been limited or undervalued.

7.3. Exposome and planetary health

Albert Bach
Quim Zaldo-Aubanell

The exposome concept has evolved to encompass not only the chemical exposures but also the broader environmental factors affecting human health (Price et al., 2022). This holistic view of the exposome, especially as regards the external exposome, assesses the links between human health and the intricate web of interactions within ecosystems, including the impacts of lifestyle, social determinants, and natural environments. In considering the interconnectivity between an individual's exposures and these broader ecological and environmental factors, the exposome framework can be aligned with that of *One Health*, which advocates for a unified health perspective across humans, animals, and their shared environments. Furthermore, study of the exposome could also contribute to considerations of the importance of safeguarding *planetary health* as a means of preventing disease and of promoting well-being, insofar as it highlights the exposure-related challenges and opportunities for mitigating global environmental changes derived from environmental degradation.

Although the three concepts highlighted converge, they can be distinguished from each other in certain respects:

— Exposome and studies conducted in this field are concerned with mapping individual environmental exposures and their health effects.

— One Health framework emphasises the interconnected health of humans, animals, and the environment, particularly the links between zoonotic diseases and ecosystem health (Erkyihun & Alemayehu, 2022; Wilcox & Steele, 2021).

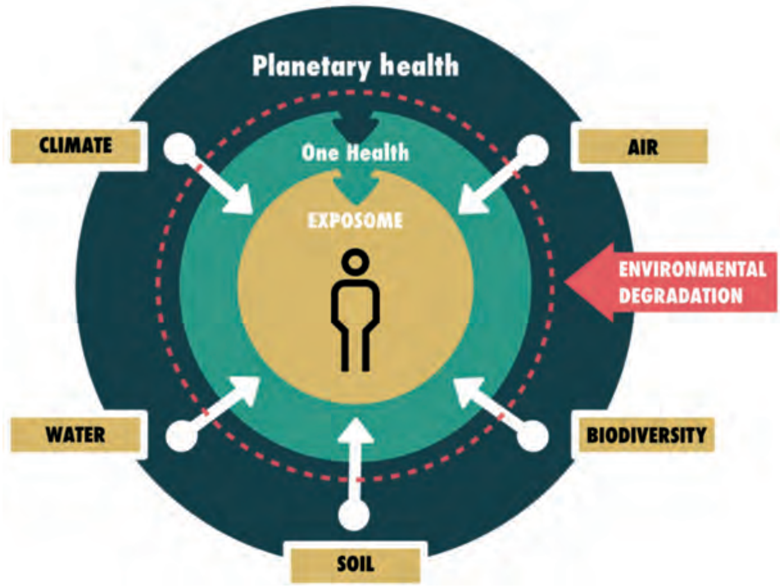

FIGURE 16. Diagram illustrating the interconnections between planetary health, One Health, and the exposome in the context of environmental degradation.
SOURCE: Created by Albert Bach.

— Planetary health takes a broader view by examining the human health impacts of human-caused disruptions of Earth's natural systems (Martens, 2024).

Each approach, associated with its own focus and methodology, underscores, however, the critical need for integrated health strategies that consider the complex interconnections between human activities, health, and the environment.

The concept of the exposome highlights the critical role played by environmental health in either enhancing or impairing human well-being. Broadly speaking, environmental influences on human health originate from one of the Earth's five key domains: namely, water, soil, climate, air, and biodiversity (Figure 16). However, the Earth functions as an intricately connected system, underscoring the complex interplay between human development and the environment (Ragnarsdottir, 2022). This perspective encourages a shift from examining isolated impacts within specific areas to exploring their interconnected consequences. In this regard, environmental degradation, largely driven by human activity, constrains or reverses the benefits and services provided by the environment, potentially leading to adverse effects and ultimately pushing ecosystems and human survival to the limit.

At the forefront of environmental transformation, climate change acts as a catalyst for a series of interconnected environmental disturbances. Driven by increasing greenhouse gas emissions, between 2011 and 2020, the global surface temperature rose 1.1 °C above pre-industrial levels. This warming has disrupted the balance of precipitation and accelerated the retreat of glaciers at unprecedented rates, contributing to a sea level rise of 3.4 mm per year since 1993 (Nerem et al., 2018). These alterations in water resources challenge their availability and quality and impact the fabric of biodiversity. Species are compelled to migrate or face extinction, disrupting ecosystems that have provided essential environmental services, from pollination to climate regulation, for millennia.

The effects of degradation extend to air quality. Air pollution from urban and industrial regions exacerbates planetary warming, promoting a cycle that jeopardises the development of all living organisms and the integrity of ecosystems. These sources of pollution have a number of environmental consequences including acid rain, forest decline, ground-level ozone fluctuation, and eutrophication. More than 90% of the global population is exposed to air quality that exceeds World Health Organization (WHO) guidelines because of significant pollutant concentrations (WHO, 2022). The burden is particularly severe in low- and middle-income nations, where the highest levels of exposure are recorded (Rentschler & Leonova, 2023), leading to an estimated 7 million premature deaths each year.

Against this backdrop, biodiversity is faced with an array of unprecedented threats. The Anthropocene, characterised by significant changes in atmospheric and oceanic chemistry, urbanisation, habitat fragmentation, land use alterations, and globalisation, has significantly degraded the biosphere. This degradation is contributing to the global biodiversity loss crisis, with estimates indicating that between 150,000 and 260,000 species have become extinct since 1500, marking the onset of the planet's sixth mass extinction (Ceballos & Ehrlich, 2018; Cowie et al., 2022). Biodiversity loss not only jeopardises the functioning of the biosphere but also impairs the role it plays in climate regulation and water quality maintenance, among others.

Alongside this loss of biodiversity, the threat of chemical pollution, heavy metal contamination and erosion posed by conventional farming and infrastructure development critically undermines the vital functions and services of the soil. Healthy soils in temperate climates should maintain at least 2% soil organic carbon, yet European farmlands are depleting carbon at a rate of 0.5% annually (Bruni et al., 2022; Lal, 2020). As soil organic carbon is depleted, soils lose their capacity to act as effective carbon sinks, contributing to increased atmospheric carbon dioxide levels (Nazir et al., 2024). This process not only potentially exacerbates the risk of water aquifer contamination due to diminished soil filtration capacities but can also influence nitrous oxide (N_2O) emissions (Guenet et al., 2021).

Direct human health impacts of climate change-induced exposures include the exacerbation of respiratory, cardiovascular, renal, and mental health issues due to increased temperatures and heatwaves, alongside injuries and diseases triggered by extreme weather events like torrential rains and floods. Indirect effects encompass a rise in infectious diseases through shifts in vector and host distributions, aggravated allergic reactions due to changes in allergen profiles, and health issues associated with the toxins produced by marine organisms affected by warming waters. Additionally, climate change is anticipated to indirectly affect human health through socioeconomic factors such as worsened air pollution, decreased availability of water and food, and the strain place on health systems by climate-induced migrations (Marrasé et al., 2020).

Impacts from biodiversity loss-induced exposures encompass all the derived effects of environmental degradation on the multiple pathways connecting biodiversity to human health. The crucial function of biodiversity in supplying medicinal resources and ensuring food security is at risk, increasing the likelihood of malnutrition and the loss of prospective pharmaceutical discoveries. Furthermore, the natural filtration systems that safeguard water quality are under threat, augmenting exposure to waterborne diseases. Urban biodiversity loss exacerbates air and noise pollution, elevates urban temperatures, and increases exposure to extreme heat, collectively heightening the risk of respiratory disorders, cardiovascular diseases, and heat-related illnesses. Additionally, changes in wildlife populations and habitats can accelerate the spread of zoonotic diseases, altering the dynamics of disease hosts and vectors and increasing human exposure to infectious diseases. The alteration of plant and animal species compositions can also lead to increased exposure to airborne allergens (Marselle et al., 2021).

As this report has shown, the exposome research field has developed a variety of tools and methodologies to quantify and analyse the complex array of environmental exposures individuals face. The potential integration of these technological advances to the field of planetary health should help shed light on particular climate change-induced or environmental degradation-driven exposures and their potential health implications (Abdelzaher et al., 2022; Cui et al., 2016).

This scientific inquiry not only maps the myriad of exposures affecting individuals and communities but also lays the groundwork for developing strategic interventions aimed at mitigating these environmental challenges. Thus, exposome knowledge and tools are key to the development of science-based policies that can preserve public health and restore planetary health in this critical moment in our history. The narrative of interlinked impacts across life forms, continents, and populations highlights a critical truth that has yet to be fully integrated into policy agendas: the urgency of addressing environmental degradation. Given the extensive damage already evident, we must continue to question the motives for such degradation and whether the perceived benefits can ever truly outweigh the enormous costs.

8. Summary of the cycle of conference presentations

Urban exposome assessment: Lessons learned from the EXPANSE Project

Apolline Saucy

The exposome concept emerged in the early 2000s to recognise the importance of the sum of all the non-genetic factors that can affect health across the life course. With the development of powerful computers and satellite imagery, tools have been developed that can describe exposure to the external exposome (e.g. air pollution, green spaces, etc.) and these are being integrated into a growing number of large-scale, population-based cohort studies. As more and more of the world's population live in cities, the EXPANSE Project – EXposome Powered tools for healthy living in urbAN SEttings – aims to address one of the most pertinent issues for urban planners, policymakers, and European citizens: "How can we improve our health and well-being in a modern urban environment?".

The first task initiated by EXPANSE was to characterise the living environment across European countries using harmonised indicators with a high spatio-temporal resolution. For example, models were developed to estimate daily NO_2, O_3, PM_{10}, and $PM_{2.5}$ concentrations at 25 × 25 m resolution for the European region. Smaller-scale aspects of the living environment can also affect lifestyle and health, including, for example, the food environment (e.g. distance to shops, fast-food restaurants, etc.) and other neighbourhood-specific qualities (e.g. walkability, availability of parks and green spaces).

Combining these dimensions of the external exposome helps us understand the spatial distribution of environmental stressors across different groups of the population. For example, by evaluating relocation trajectories of adults and families as they move home, we found that socioeconomic characteristics but also household and family composition are important determinants of the choice of new neighbourhoods and that privileged groups are more likely to relocate to "healthier" environments and experience positive health outcomes. Overall, despite increasing evidence of the central role of social determinants and life stages as important contributors to health, efforts and tools to integrate the social environment as a central part of the external exposome remain scarce and insufficient. A systematic integration of these factors in large-scale cohort studies and exposome research should gradually alleviate social inequities in health and mitigate the emergence of new inequalities.

The chemical context of the exposome

Joan Grimalt

The exposome constitutes an inventory of the plethora of exposures to synthetic chemicals, dietary components, psychosocial stressors, and physical factors, as well as their biological responses that might impact human health. This talk outlines the main physico-chemical characteristics that determine the potential toxicity of environmental contaminants and discusses the environmental equivalence of Paracelsus' adage: "the dose makes the poison", considering the effects of chronic exposure to low concentrations of contaminants over long periods or an entire lifetime. The increasing incidence of various non-infectious diseases and their possible relationship with environmental contaminants are also examined. The talk concludes by lending support to the proposal currently under debate at the United Nations, as promoted by some 20 researchers and supported by about 2,000 more, to establish an international panel on chemical contaminants and residues.

An overview of 10 years of early-life exposome research

Léa Maitre

Chemical pollution, characterised by the shift from traditional pollution (e.g. wood stoves) to modern pollution (e.g. lead and air pollution), represents an enormous burden for human health worldwide. Current technologies to monitor pollution of this type are, however, manifestly underperforming: most organic constituents of biological and environmental samples go unidentified and potential chemical stressors are disregarded. The exposome seeks to change the dominant paradigm and shift the focus in disease aetiology to the environment, escaping the genocentrism of the Human Genome Project.

Early-life exposome research at ISGlobal has been conducted in existing birth cohorts. This talk examines the application of interdisciplinary research – omics, environmental epidemiology, and toxicology – to understand early-life environmental influences on health and biological mechanisms and considers how this understanding can improve mental health outcomes in children and in their families by the close monitoring of environmental influences on the disease course. The influence of perinatal and childhood exposure to tobacco and mercury in children's gut microbiota is also described.

The impact of natural environments on maternal and child health

Payam Dadvand

Contact with natural environments, including green spaces, has been associated with a wide range of health benefits in humans. In this context, exposure to greenspace has been related to reduced risks of pregnancy complications (e.g. gestational diabetes and pre-eclampsia) and adverse pregnancy outcomes (e.g. low birth weight). Greenspace also plays a critical role in the growth and development of children, having been associated with improved neurodevelopment (e.g. cognition, behaviour, and motor) and lower risks of both neurodevelopmental (e.g. ADHD and autism spectrum disorders) and mental health conditions (e.g. depression and anxiety) in children and adolescents. Exposure to green spaces has also been related to better physical health, including cardiometabolic health, in these age groups. The association with respiratory and allergic outcomes remains heterogeneous. All in all, available evidence supports the beneficial role of greenspace in maternal and child health.

9. Conclusions

The exposome represents a comprehensive framework for understanding the myriad environmental exposures that people encounter throughout their lives and the way in which these exposures affect their health. The term, first coined by Dr. Christopher Wild in 2005, includes all non-genetic factors that influence health, from physical and chemical agents to social and behavioural environments.

The exposome is typically considered to comprise three broad types of exposure:

1. *General external exposures*: Broader social and environmental factors such as socioeconomic status, education, climate, and urban or rural environments.
2. *Specific external exposures*: More direct, quantifiable factors such as diet, pollution, food additives, pesticides, radiation, infections, and lifestyles such as smoking and physical activity.
3. *Internal exposures*: Internal biological responses to the external exposures, including inflammation, oxidative stress, gut microbiota composition and metabolic processes.

The implications of the exposome paradigm can be summarised as follows:

1. *Holistic perspective of health*: The exposome emphasises the importance of considering the whole spectrum of environmental influences on health, shifting the focus from genetic determinism to a more balanced view where the environment plays a critical role.
2. *Preventive health strategies*: By identifying harmful exposures and understanding their effects, public health initiatives can be tailored to reduce these risks, leading to better health outcomes at both the individual and population level.

3. *Personalised medicine*: Integrating exposome data with genetic information allows for more accurate and personalised health care, as treatments and preventive measures can be customised based on a person's unique exposure history.
4. *Research and policy*: The exposome framework encourages interdisciplinary research and informs policy decisions, promoting interventions that address environmental and lifestyle factors that contribute to disease.

In summary, the exposome represents a paradigm shift in health and life sciences in general, highlighting the intricate and cumulative impact of environmental exposures on human (and other organisms) health. It requires comprehensive data collection, innovative research methodologies, and integrated approaches to improve health outcomes through informed environmental and lifestyle modifications.

In this cycle of exposome conferences organised by the IEC and in the study presented herein, we have focused specifically on seven aspects of the exposome, which we list here together with a brief statement of the conclusions reached in each case:

1. *Prenatal exposures and child health*: Various prenatal exposures, such as air pollution, tobacco smoke, and maternal diet, are associated with adverse child health outcomes that include decreased birth weight and respiratory problems. Likewise, exposure to certain environmental pollutants can negatively affect neurological and cognitive development, and increase the risk of childhood asthma and respiratory allergies.
2. *Impact of environmental exposures on growth and development*: Environmental exposures during pregnancy can alter children's growth trajectories, especially when it comes to substances that affect the endocrine system.
3. *Importance of the first stages of the life course*: The first stages of life, from conception to the first years, are particularly vulnerable to environmental influences. Prevention during this period improves not only childhood health, but also lifelong health.
4. *Endocrine disruptors and reproductive health*: Compounds that act as endocrine disruptors can alter the hormonal system, especially during windows of susceptibility such as pregnancy, lactation, and childhood. These disruptors can have harmful effects at any stage of life.
5. *Modifiable exposure*: Identifying and understanding modifiable environmental exposures provides guidance for targeted interventions. This includes individual and collective actions to reduce exposure to factors such as air pollution and endocrine disruptors through strategies such as sustainable transport and urban planning.

6. *Interventions to reduce exposure to endocrine disruptors*: Intervention studies have shown that changing the use of personal care products and dietary modifications can effectively reduce exposure to chemicals such as phthalates and bisphenol A (BPA).
7. *Potential of machine learning tools and causal models*: The use of machine learning methods and causal models can increase the ability to predict health outcomes by capturing complex interactions of environmental data. This helps to prioritise environmental factors with a greater impact on health and promote more efficient interventions.

These findings underscore the importance of considering environmental exposures from the earliest stages of life for the prevention of chronic diseases and the improvement of public health.

Josep Peñuelas Reixach
Josep Tabernero Caturla

Bibliography

Abdelzaher, H., Tawfik, S. M., Nour, A., Abdelkader, S., Elbalkiny, S. T., Abdelkader, M., Abbas, W. A., & Abdelnaser, A. (2022). Climate change, human health, and the exposome: Utilizing OMIC technologies to navigate an era of uncertainty. *Frontiers in Public Health*, *10*. https://doi.org/10.3389/fpubh.2022.973000.

Athlete Project. *Athlete: Advancing tools for human early lifecourse exposome research*. https://athleteproject.eu/.

Balcells, C., Xu, Y., Gil-Solsona, R., Maitre, L., Gago-Ferrero, P., & Keun, H. C. (2024). Blurred lines: Crossing the boundaries between the chemical exposome and the metabolome. *Current Opinion in Chemical Biology*, *78*, 102407. https://doi.org/10.1016/j.cbpa.2023.102407.

Barboza, E. P., Cirach, M., Khomenko, S., Iungman, T., Mueller, N., Barrera-Gómez, J., Rojas-Rueda, D., Kondo, M., & Nieuwenhuijsen, M. (2021). Green space and mortality in European cities: A health impact assessment study. *The Lancet. Planetary Health*, *5*(10), e718-e730. https://doi.org/10.1016/S2542-5196(21)00229-1.

Barker, D. J., Osmond, C., Golding, J., Kuh, D., & Wadsworth, M. E. (1989). Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ: British Medical Journal*, *298*(6673), 564-567.

Barton, H., & Grant, M. (2006). A health map for the local human habitat. *The Journal of the Royal Society for the Promotion of Health*, *126*(6), 252-253. https://doi.org/10.1177/1466424006070466.

Bind, M.-A. (2019). Causal Modeling in Environmental Health. *Annual Review of Public Health*, *40*, 23-43. https://doi.org/10.1146/annurev-publhealth-040218-044048.

Bishop, K., & Corkery, L. (2017). *Designing cities with children and young people: Beyond playgrounds and skate parks*. Taylor & Francis.

Blane, D., Kelly-Irving, M., Errico, A. de, Bartley, M., & Montgomery, S. (2013). Social-biological transitions: How does the social become biological? *Longitudinal and Life Course Studies*, *4*(2). https://doi.org/10.14301/llcs.v4i2.236.

Bruni, E., Guenet, B., Clivot, H., Kätterer, T., Martin, M., Virto, I., & Chenu, C. (2022). Defining Quantitative Targets for Topsoil Organic Carbon Stock Increase in European Croplands: Case Studies With Exogenous Organic Matter Inputs. *Frontiers in Environmental Science*, *10*. https://doi.org/10.3389/fenvs.2022.824724.

Casas, M., Basagaña, X., Sakhi, A. K., Haug, L. S., Philippat, C., Granum, B., Manzano-Salgado, C. B., Brochot, C., Zeman, F., Bont, J. de, Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J. R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., … Vrijheid, M. (2018). Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. *Environment International*, *121*, 561-573. https://doi.org/10.1016/j.envint.2018.09.046.

Ceballos, G., & Ehrlich, P. R. (2018). The misunderstood sixth mass extinction. *Science*, *360*(6393), 1080-1081. https://doi.org/10.1126/science.aau0191.

Chung, M. K., Kannan, K., Louis, G. M., & Patel, C. J. (2018). Toward Capturing the Exposome: Exposure Biomarker Variability and Coexposure Patterns in the Shared Environment. *Environmental Science & Technology*, *52*(15), 8801-8810. https://doi.org/10.1021/acs.est.8b01467.

Claus, S. P., Guillou, H., & Ellero-Simatos, S. (2016). The gut microbiota: A major player in the toxicity of environmental pollutants? *Npj Biofilms and Microbiomes*, *2*(1), 1-11. https://doi.org/10.1038/npjbiofilms.2016.3.

Cowie, R. H., Bouchet, P., & Fontaine, B. (2022). The Sixth Mass Extinction: Fact, fiction or speculation? *Biological Reviews*, *97*(2), 640-663. https://doi.org/10.1111/brv.12816.

Cui, Y., Balshaw, D. M., Kwok, R. K., Thompson, C. L., Collman, G. W., & Birnbaum, L. S. (2016). The Exposome: Embracing the Complexity for Discovery in Environmental Health. *Environmental Health Perspectives*, *124*(8), A137-A140. https://doi.org/10.1289/EHP412.

Donaire-Gonzalez, D., Curto, A., Valentín, A., Andrusaityte, S., Basagaña, X., Casas, M., Chatzi, L., Bont, J. de, Castro, M. de, Dedele, A., Granum, B., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Manzano-Salgado, C. B., Aasvang, G. M., McEachan, R., Meinhard-Kjellstad, C. H., Michalaki, E., … Nieuwenhuijsen, M. J. (2019). Personal assessment of the external exposome during pregnancy and childhood in Europe. *Environmental Research*, *174*, 95-104. https://doi.org/10.1016/j.envres.2019.04.015.

Dührkop, K., Shen, H., Meusel, M., Rousu, J., & Böcker, S. (2015). Searching molecular structure databases with tandem mass spectra using CSI:FingerID. *PNAS* (*Proceedings of the National Academy of Sciences*), *112*(41), 12580-12585. https://doi.org/10.1073/pnas.1509788112.

Eldredge, L. K. B., Markham, C. M., Ruiter, R. A., Fernández, M. E., Kok, G., & Parcel, G. S. (2016). *Planning health promotion programs*: *An intervention mapping approach*. John Wiley & Sons.

Erkyihun, G. A., & Alemayehu, M. B. (2022). One Health Approach for the Control of Zoonotic Diseases. *Zoonoses*, *2*, 963. https://doi.org/10.15212/ZOONOSES-2022-0037.

Everson, T. M., & Marsit, C. J. (2018). Integrating -Omics Approaches into Human Population-Based Studies of Prenatal and Early-Life Exposures. *Current Environmental Health Reports*, *5*(3), 328-337. https://doi.org/10.1007/s40572-018-0204-1.

Fernandes, A., Ubalde-López, M., Yang, T. C., McEachan, R. R., Rashid, R., Maitre, L., Nieuwenhuijsen, M. J., & Vrijheid, M. (2023). School-based interventions to support healthy indoor and outdoor environments for children: A systematic review. *International Journal of Environmental Research and Public Health*, *20*(3), 1746.

Ferrer-Fons, M., López, M. J., Brugueras, S., Continente, X., Cortés, E., & Artazcoz, L. (2023). *Avaluació del programa Protegim les Escoles*. Barcelona: Agència de Salut Pública de Barcelona. https://www.aspb.cat/wp-content/uploads/2023/03/Avaluacio-programa-Protegim-Escoles.pdf.

Fuller, R., Landrigan, P. J., Balakrishnan, K., Bathan, G., Bose-O'Reilly, S., Brauer, M., Caravanos, J., Chiles, T., Cohen, A., Corra, L., Cropper, M., Ferraro, G., Hanna, J., Hanrahan, D., Hu, H., Hunter, D., Janata, G., Kupka, R., Lanphear, B., … Yan, C. (2022). Pollution and health: A progress update. *The Lancet. Planetary Health*, *6*(6), e535-e547. https://doi.org/10.1016/S2542-5196(22)00090-0.

Gallo, V., Mackenbach, J. P., Ezzati, M., Menvielle, G., Kunst, A. E., Rohrmann, S., Kaaks, R., Teucher, B., Boeing, H., Bergmann, M. M., Tjønneland, A., Dalton, S. O., Overvad, K., Redondo, M.-L., Agudo, A., Daponte, A., Arriola, L., Navarro, C., Gurrea, A. B., … Vineis, P. (2012). Social Inequalities and Mortality in Europe - Results from a Large Multi-National Cohort. *PLoS ONE*, *7*(7), e39013. https://doi.org/10.1371/journal.pone.0039013.

GBD 2017 Risk Factor Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1923-1994. https://doi.org/10.1016/S0140-6736(18)32225-6.

Gil-Solsona, R., Nika, M.-C., Bustamante, M., Villanueva, C. M., Foraster, M., Cosin-Tomás, M., Alygizakis, N., Gómez-Roig, M. D., Llurba-Olive, E., Sunyer, J., Thomaidis, N. S., Dadvand, P., & Gago-Ferrero, P. (2021). The Potential of Sewage Sludge to Predict and Evaluate the Human Chemical Exposome. *Environmental Science & Technology Letters*, *8*(12), 1077-1084. https://doi.org/10.1021/acs.estlett.1c00848.

González-Domínguez, R., Jáuregui, O., Queipo-Ortuño, M. I., & Andrés-Lacueva, C. (2020). Characterization of the Human Exposome by a Comprehensive and Quantitative Large-Scale Multianalyte Metabolomics Platform. *Analytical Chemistry*, *92*(20), 13767-13775. https://doi.org/10.1021/acs.analchem.0c02008.

Grandjean, P., Andersen, E. W., Budtz-Jørgensen, E., Nielsen, F., Mølbak, K., Weihe, P., & Heilmann, C. (2012). Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds. *JAMA*, *307*(4), 391-397. https://doi.org/10.1001/jama.2011.2034.

Guenet, B., Gabrielle, B., Chenu, C., Arrouays, D., Balesdent, J., Bernoux, M., Bruni, E., Caliman, J.-P., Cardinael, R., Chen, S., Ciais, P., Desbois, D., Fouche, J., Frank, S., Henault, C., Lugato, E., Naipal, V., Nesme, T., Obersteiner, M., … Zhou, F. (2021). Can N_2O emissions offset the benefits from soil organic carbon storage? *Global Change Biology*, *27*(2), 237-256. https://doi.org/10.1111/gcb.15342.

Guxens, M., Ballester, F., Espada, M., Fernández, M. F., Grimalt, J. O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., & Sunyer, J. (2012). Cohort Profile: The INMA —INfancia y Medio Ambiente— (Environment and Childhood) Project. *International Journal of Epidemiology*, *41*(4), 930-940. https://doi.org/10.1093/ije/dyr054.

Hahad, O., Kuntic, M., Al-Kindi, S., Kuntic, I., Gilan, D., Petrowski, K., Daiber, A., & Münzel, T. (2024). Noise and mental health: Evidence, mechanisms, and consequences. *Journal of Exposure Science & Environmental Epidemiology*, 1-8. https://doi.org/10.1038/s41370-024-00642-5.

Hajat, C., & Stein, E. (2018). The global burden of multiple chronic conditions: A narrative review. *Preventive Medicine Reports*, *12*, 284-293. https://doi.org/10.1016/j.pmedr.2018.10.008.

Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, *58*(5), 295-300.

Jaddoe, V. W. V., Felix, J. F., Andersen, A. N., Charles, M. A., Chatzi, L., Corpeleijn, E., Donner, N., Elhakeem, A., Eriksson, J. G., Foong, R., Grote, V., Haakma, S., Hanson, M., Harris, J. R., Heude, B., Huang, R. C., Inskip, H., Järvelin, M. R., Koletzco, B., Lawlor, D. A., Lindeboom, M., McEachan, R. R. C., Mikkola, T. M., Nader, J. L. T., Pinot de Moira, A., Pizzi, C., Richiardi, L., Sebert, S., Schwalber, A., Sunyer, J., Swertz, M. A., Vafeiadi, M., Vrijheid, M., Wright, J., & Duijts, L. (2020). The LifeCycle Project-EU Child Cohort Network: A federated analysis infrastructure and harmonized data of more than 250,000 children and parents. *European Journal of Epidemiology*, *35*(7), 709-724. https://doi.org/10.1007/s10654-020-00662-z.

Jiang, C., Wang, X., Li, X., Inlora, J., Wang, T., Liu, Q., & Snyder, M. (2018). Dynamic Human Environmental Exposome Revealed by Longitudinal Personal Monitoring. *Cell*, *175*(1), 277-291.e31. https://doi.org/10.1016/j.cell.2018.08.060.

Kalache, A., & Kickbusch, I. (1997). A global strategy for healthy ageing. *World Health*, *50*(4), 4-5.

Kapono, C. A., Morton, J. T., Bouslimani, A., Melnik, A. V., Orlinsky, K., Knaan, T. L., Garg, N., Vázquez-Baeza, Y., Protsyuk, I., Janssen, S., Zhu, Q., Alexandrov, T., Smarr, L., Knight, R., & Dorrestein, P. C. (2018). Creating a 3D microbial and chemical snapshot of a human habitat. *Scientific Reports*, *8*(1), 3669. https://doi.org/10.1038/s41598-018-21541-4.

Koelmel, J. P., Lin, E. Z., DeLay, K., Williams, A. J., Zhou, Y., Bornman, R., Obida, M., Chevrier, J., & Godri Pollitt, K. J. (2022). Assessing the External Exposome Using Wearable Passive Samplers and High-Resolution Mass Spectrometry among South African Children Participating in the VHEMBE Study. *Environmental Science & Technology*, *56*(4), 2191-2203. https://doi.org/10.1021/acs.est.1c06481.

Kogevinas, M., Castaño-Vinyals, G., Karachaliou, M., Espinosa, A., Cid, R. de, Garcia-Aymerich, J., Carreras, A., Cortés, B., Pleguezuelos, V., Jiménez, A., Vidal, M., O'Callaghan-Gordo, C., Cirach, M., Santano, R., Barrios, D., Puyol, L., Rubio, R., Izquierdo, L., Nieuwenhuijsen, M., … Tonne, C. (2021). Ambient Air Pollution in Relation to SARS-CoV-2 Infection, Antibody Response, and COVID-19 Disease: A Cohort Study in Catalonia, Spain (COVICAT Study). *Environmental Health Perspectives*, *129*(11), 117003. https://doi.org/10.1289/EHP9726.

Lal, R. (2020). Soil organic matter content and crop yield. *Journal of Soil and Water Conservation*, *75*(2), 27A-32A. https://www.tandfonline.com/doi/full/10.2489/jswc.75.2.27A.

Larkin, A., & Hystad, P. (2017). Towards Personal Exposures: How Technology Is Changing Air Pollution and Health Research. *Current Environmental Health Reports*, *4*(4), 463-471. https://doi.org/10.1007/s40572-017-0163-y.

Liu, J., Carnero-Montoro, E., Dongen, J. van, Lent, S., Nedeljkovic, I., Ligthart, S., Tsai, P.-C., Martin, T. C., Mandaviya, P. R., Jansen, R., Peters, M. J., Duijts, L., Jaddoe, V. W. V., Tiemeier, H., Felix, J. F., Willemsen, G., Geus, E. J. C. de, Chu, A. Y., Levy, D., … Duijn, C. M. van (2019). An integrative cross-omics analysis of DNA methylation sites of glucose and insulin homeostasis. *Nature Communications*, *10*(1), 2581. https://doi.org/10.1038/s41467-019-10487-4.

Maitre, L., Bustamante, M., Hernández-Ferrer, C., Thiel, D., Lau, C.-H. E., Siskos, A. P., Vives-Usano, M., Ruiz-Arenas, C., Pelegrí-Sisó, D., Robinson, O., Mason, D., Wright, J., Cadiou, S., Slama, R., Heude, B., Casas, M., Sunyer, J., Papadopoulou, E. Z., Gutzkow, K. B., … Vrijheid, M. (2022). Multi-omics signatures of the human early life exposome. *Nature Communications*, *13*(1), 7024. https://doi.org/10.1038/s41467-022-34422-2.

Maitre, L., Jedynak, P., Gallego, M., Ciaran, L., Audouze, K., Casas, M., & Vrijheid, M. (2023). Integrating -omics approaches into population-based studies of endocrine disrupting chemicals: A scoping review. *Environmental Research*, *228*, 115788. https://doi.org/10.1016/j.envres.2023.115788.

Maitre, L., Robinson, O., Martinez, D., Toledano, M. B., Ibarluzea, J., Marina, L. S., Sunyer, J., Villanueva, C. M., Keun, H. C., Vrijheid, M., & Coen, M. (2018). Urine Metabolic Signatures of Multiple Environmental Pollutants in Pregnant Women: An Exposome Approach. *Environmental Science & Technology*, *52*(22), 13469-13480. https://doi.org/10.1021/acs.est.8b02215.

Marmot, M. (2010). *Fair Society Healthy Lives (The Marmot Review)*. Institute of Health Equity. https://www.instituteofhealthequity.org/resources-reports/fair-society-healthy-lives-the-marmot-review.

Marrasé, C., Camí, J., & Peters, F. (2020). *Report on climate change and health in Catalonia. Informe de la Secció de Ciències Biològiques de l'Institut d'Estudis Catalans*. https://publicacions.iec.cat/repository/pdf/00000301/00000025.pdf.

Marselle, M. R., Hartig, T., Cox, D. T. C., Bell, S. de, Knapp, S., Lindley, S., Triguero-Mas, M., Böhning-Gaese, K., Braubach, M., Cook, P. A., Vries, S. de, Heintz-Buschart, A., Hofmann, M., Irvine, K. N., Kabisch, N., Kolek, F., Kraemer, R., Markevych, I., Martens, D., … Bonn, A. (2021). Pathways linking biodiversity to human health: A conceptual framework. *Environment International*, *150*, 106420. https://doi.org/10.1016/j.envint.2021.106420.

Martens, P. (2024). Planetary health: The need for a paradigm shift. *BioScience*, *74*(3), 128-129. https://doi.org/10.1093/biosci/biad107.

Martin, R. V., Brauer, M., Donkelaar, A. van, Shaddick, G., Narain, U., & Dey, S. (2019). No one knows which city has the highest concentration of fine particulate matter. *Atmospheric Environment: X*, *3*, 100040. https://doi.org/10.1016/j.aeaoa.2019.100040.

McCall, L.-I., Anderson, V. M., Fogle, R. S., Haffner, J. J., Hossain, E., Liu, R., Ly, A. H., Ma, H., Nadeem, M., & Yao, S. (2019). Analysis of university workplace building surfaces reveals usage-specific chemical signatures. *Building and Environment*, *162*, 106289. https://doi.org/10.1016/j.buildenv.2019.106289.

McConnell, J. R., Chellman, N. J., Wilson, A. I., Stohl, A., Arienzo, M. M., Eckhardt, S., Fritzsche, D., Kipfstuhl, S., Opel, T., Place, P. F., & Steffensen, J. P. (2019). Pervasive Arctic lead pollution suggests substantial growth in medieval silver production modulated by plague, climate, and conflict. *PNAS* (*Proceedings of the National Academy of Sciences*), *116*(30), 14910-14915. https://doi.org/10.1073/pnas.1904515116.

McConnell, J. R., Wilson, A. I., Stohl, A., Arienzo, M. M., Chellman, N. J., Eckhardt, S., Thompson, E. M., Pollard, A. M., Peder Steffensen, J. (2018). Lead pollution recorded in Greenland ice indicates European emissions tracked plagues, wars, and imperial expansion during antiquity. *PNAS* (*Proceedings of the National Academy of Sciences*), *115*(22) (29 May), 5729. https://www.pnas.org/doi/pdf/10.1073/pnas.1721818115.

McGee, G., Wilson, A., Webster, T. F., & Coull, B. A. (2023). Bayesian multiple index models for environmental mixtures. *Biometrics*, *79*(1), 462-474. https://doi.org/10.1111/biom.13569.

Milà, C., Ranzani, O., Sanchez, M., Ambrós, A., Bhogadi, S., Kinra, S., Kogevinas, M., Dadvand, P., & Tonne, C. (2020). Land-Use Change and Cardiometabolic Risk Factors in an Urbanizing Area of South India: A Population-Based Cohort Study. *Environmental Health Perspectives*, *128*(4), 047003. https://doi.org/10.1289/EHP5445.

Milà, C., Salmon, M., Sanchez, M., Ambrós, A., Bhogadi, S., Sreekanth, V., Nieuwenhuijsen, M., Kinra, S., Marshall, J. D., & Tonne, C. (2018). When, Where, and What? Characterizing Personal $PM_{2.5}$ Exposure in Periurban India by Integrating GPS, Wearable Camera, and Ambient and Personal Monitoring Data. *Environmental Science & Technology*, *52*(22), 13481-13490. https://doi.org/10.1021/acs.est.8b03075.

Münzel, T., Sørensen, M., & Daiber, A. (2021). Transportation noise pollution and cardiovascular disease. *Nature Reviews Cardiology*, *18*(9), 619-636. https://doi.org/10.1038/s41569-021-00532-5.

National Research Council (2006). *Human Biomonitoring for Environmental Chemicals*. Washington: The National Academies Press. https://doi.org/10.17226/11700.

Nazir, M. J., Li, G., Nazir, M. M., Zulfiqar, F., Siddique, K. H. M., Iqbal, B., & Du, D. (2024). Harnessing soil carbon sequestration to address climate change challenges in agriculture. *Soil and Tillage Research*, *237*, 105959. https://doi.org/10.1016/j.still.2023.105959.

Nerem, R. S., Beckley, B. D., Fasullo, J. T., Hamlington, B. D., Masters, D., & Mitchum, G. T. (2018). Climate-change-driven accelerated sea-level rise detected in the altimeter era. *Proceedings of the National Academy of Sciences*, *115*(9), 2022-2025. https://doi.org/10.1073/pnas.1717312115.

Neufcourt, L., Castagné, R., Mabile, L., Khalatbari-Soltani, S., Delpierre, C., & Kelly-Irving, M. (2022). Assessing How Social Exposures Are Integrated in Exposome Research: A Scoping Review. *Environmental Health Perspectives*, *130*(11), 116001. https://doi.org/10.1289/EHP11015.

Opbroek, J., Pereira Barboza, E., Nieuwenhuijsen, M., Dadvand, P., & Mueller, N. (2024). Urban green spaces and behavioral and cognitive development in children: A health impact assessment of the Barcelona "Eixos Verds" Plan (Green Axis Plan). *Environmental Research*, *244*, 117909. https://doi.org/10.1016/j.envres.2023.117909.

Patel, C. J., & Manrai, A. K. (2014). Development of exposome correlation globes to map out environment-wide associations. In R. B. Altman, A. K. Dunker, L. Hunter, M. D. Ritchie, T. A. Murray, & T. E. Klein (Eds.). *Biocomputing 2015*. World Scientific, 231-242. https://doi.org/10.1142/9789814644730_0023.

Peters, A., Nawrot, T. S., & Baccarelli, A. A. (2021). Hallmarks of environmental insults. *Cell*, *184*(6), 1455-1468. https://doi.org/10.1016/j.cell.2021.01.043.

Price, E. J., Vitale, C. M., Miller, G. W., David, A., Barouki, R., Audouze, K., Walker, D. I., Antignac, J.-P., Coumoul, X., Bessonneau, V., & Klánová, J. (2022). Merging the exposome into an integrated framework for "omics" sciences. *iScience*, *25*(3), 103976. https://doi.org/10.1016/j.isci.2022.103976.

Prüss-Üstün, A., Wolf, J., Corvalán, C., Bos, R., Neira, M. (2016). *Preventing Disease through Healthy Environments: A Global Assessment of the Burden of Disease from Environmental Risks*. World Health Organization.

Ragnarsdottir, K. V. (2022). Setting the Scene: Viewing the World as Interconnected Systems. In P. Künkel, & K. V. Ragnarsdottir (Eds.). *Transformation Literacy: Pathways to Regenerative Civilizations*. Springer International Publishing, 115-131. https://link.springer.com/book/10.1007/978-3-030-93254-1.

Rappaport, S. M., Barupal, D. K., Wishart, D., Vineis, P., & Scalbert, A. (2014). The Blood Exposome and Its Role in Discovering Causes of Disease. *Environmental Health Perspectives*, *122*(8), 769-774. https://doi.org/10.1289/ehp.1308015.

Rentschler, J., & Leonova, N. (2023). Global air pollution exposure and poverty. *Nature Communications*, *14*(1), 4432. https://doi.org/10.1038/s41467-023-39797-4.

Rupprecht, S., Brand, L., Böhler-Baedeker, S., & Brunner, L. (2019). *Guidelines for developing and implementing a Sustainable Urban Mobility Plan (2nd edition)*. https://urban-mobility-observatory.transport.ec.europa.eu/system/files/2023-09/sump_guidelines_2019_second%20edition.pdf.

Rutter, H., Savona, N., Glonti, K., Bibby, J., Cummins, S., Finegood, D. T., Greaves, F., Harper, L., Hawe, P., Moore, L., Petticrew, M., Rehfuess, E., Shiell, A., Thomas, J., & White, M. (2017). The need for a complex systems model of evidence for public health. *The Lancet*, *390*(10112), 2602-2604. https://doi.org/10.1016/S0140-6736(17)31267-9.

Schloissnig, S., Arumugam, M., Sunagawa, S., Mitreva, M., Tap, J., Zhu, A., Waller, A., Mende, D. R., Kultima, J. R., Martin, J., Kota, K., Sunyaev, S. R., Weinstock, G. M., & Bork, P. (2013). Genomic variation landscape of the human gut microbiome. *Nature*, *493*(7430), 45-50. https://doi.org/10.1038/nature11711.

Schymanski, E. L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H. P., & Hollender, J. (2014). Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. *Environmental Science & Technology*, *48*(4), 2097-2098. https://doi.org/10.1021/es5002105.

Tamayo-Uria, I., Maitre, L., Thomsen, C., Nieuwenhuijsen, M. J., Chatzi, L., Siroux, V., Aasvang, G. M., Agier, L., Andrusaityte, S., Casas, M., Castro, M. de, Dedele, A., Haug, L. S., Heude, B., Grazuleviciene, R., Gutzkow, K. B., Krog, N. H., Mason, D., McEachan, R. R. C., … Basagaña, X. (2019). The early-life exposome: Description and patterns in six European countries. *Environment International*, *123*, 189-200. https://doi.org/10.1016/j.envint.2018.11.067.

Tsatsakis, A., Petrakis, D., Nikolouzakis, T. K., Docea, A. O., Calina, D., Vinceti, M., Goumenou, M., Kostoff, R. N., Mamoulakis, C., Aschner, M., & Hernández, A. F. (2020). COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence. *Food and Chemical Toxicology*, *141*, 111418. https://doi.org/10.1016/j.fct.2020.111418.

Tulve, N. S., Geller, A. M., Hagerthey, S., Julius, S. H., Lavoie, E. T., Mazur, S. L., Paul, S. J., & Frey, H. C. (2024). Challenges and opportunities for research supporting cumulative impact assessments at the United States environmental protection agency's office of research and development. *The Lancet. Regional Health - Americas*, *30*. https://doi.org/10.1016/j.lana.2023.100666.

Ubalde-López, M., Honey-Rosés, J., Núñez-Tobajas, Z., García-Malo, T., Abiétar, D. G., Daher, C., Márquez, S., Cirach, M., Ballbé, A., Calvo, R., Miquel, A., Antenas, G., Aparicio, O., Berrón, A., Colom, M., Cholbi, J., Fernández, G., Flores, G., Hurtado, A., Jurado, B., Palomeque, O., Sobrino, M., & Valls, I. (2023). *Informe final de l'avaluació d'impacte als entorns escolars pacificats a la ciutat de Barcelona pel programa Protegim les Escoles. Període, 2021-2023. ISGlobal*. Institut de Ciència i Tecnologia Ambientals de la Universitat de Barcelona (ICTA-UAB).

Vicedo-Cabrera, A. M., Scovronick, N., Sera, F., Royé, D., Schneider, R., Tobias, A., Astrom, C., Guo, Y., Honda, Y., & Hondula, D. M. (2021). The burden of heat-related mortality attributable to recent human-induced climate change. *Nature Climate Change*, *11*(6), 492-500.

Vienneau, D., Schindler, C., Perez, L., Probst-Hensch, N., & Röösli, M. (2015). The relationship between transportation noise exposure and ischemic heart disease: A meta-analysis. *Environmental Research*, *138*, 372-380. https://doi.org/10.1016/j.envres.2015.02.023.

Vineis, P., Robinson, O., Chadeau-Hyam, M., Dehghan, A., Mudway, I., & Dagnino, S. (2020). What is new in the exposome? *Environment International*, *143*, 105887. https://doi.org/10.1016/j.envint.2020.105887.

Wang, Z., Zellers, S., Whipp, A. M., Heinonen-Guzejev, M., Foraster, M., Júlvez, J., Kamp, I. van, & Kaprio, J. (2023). The effect of environment on depressive symptoms in late adolescence and early adulthood: An exposome-wide association study and twin modeling. *Nature Mental Health*, *1*(10), 751-760.

Warth B.; Spangler, S.; Fang, M.; Johnson, C. H.; Forsberg, E. M.; Granados, A.; Martin, R. L.; Domingo-Almenara, X.; Huan, T.; Rinehart, D.; Montenegro-Burke, J. R.; Hilmers, B.; Aisporna, A.; Hoang, L. T.; Uritboonthai, W.; Benton, H. P.; Richardson, S. D.; Williams, A. J.; & Siuzdak, G. (2017). Exposome-Scale Investigations Guided by Global Metabolomics, Pathway Analysis, and Cognitive Computing. *Analytical Chemistry*, *89*, p. 11505-11513.

Watts, N., Amann, M., Ayeb-Karlsson, S., Belesova, K., Bouley, T., Boykoff, M., Byass, P., Cai, W., Campbell-Lendrum, D., Chambers, J., Cox, P. M., Daly, M., Dasandi, N., Davies, M., Depledge, M., Depoux, A., Dominguez-Salas, P., Drummond, P., Ekins, P., … Costello, A. (2018). The *Lancet* Countdown on health and climate change: From 25 years of inaction to a global transformation for public health. *The Lancet*, *391*(10120), 581-630. https://doi.org/10.1016/S0140-6736(17)32464-9.

Westerlund, A. M., Hawe, J. S., Heinig, M., & Schunkert, H. (2021). Risk Prediction of Cardiovascular Events by Exploration of Molecular Data with Explainable Artificial Intelligence. *International Journal of Molecular Sciences*, *22*(19). https://doi.org/10.3390/ijms221910291.

Wicki, B., Vienneau, D., Schäffer, B., Müller, T. J., Raub, U., Widrig, J., Pervilhac, C., & Röösli, M. (2024). Acute effects of military aircraft noise on sedative and analgesic drug administrations in psychiatric patients: A case-time series analysis. *Environment International*, *185*, 108501. https://doi.org/10.1016/j.envint.2024.108501.

Wilcox, B. A., & Steele, J. A. (2021). One Health and Emerging Zoonotic Diseases. In I. Kickbusch, D. Ganten, & M. Moeti (Eds.). *Handbook of Global Health*. Springer International Publishing, 2099-2147. https://doi.org/10.1007/978-3-030-45009-0_88.

Wingo, T. S., Liu, Y., Gerasimov, E. S., Vattathil, S. M., Wynne, M. E., Liu, J., Lori, A., Faundez, V., Bennett, D. A., Seyfried, N. T., Levey, A. I., & Wingo, A. P. (2022). Shared mechanisms across the major psychiatric and neurodegenerative diseases. *Nature Communications*, *13*(1), 4314. https://doi.org/10.1038/s41467-022-31873-5.

World Health Organization (2008). *Closing the gap in a generation: Health equity through action on the social determinants of health. Final report of the Commission on Social Determinants of Health* (WHO/IER/CSDH/08.1). https://www.who.int/publications-detail-redirect/WHO-IER-CSDH-08.1.

World Health Organization (2019). *Healthy, prosperous lives for all: The European Health*

Equity Status Report. Copenhagen: WHO Regional Office for Europe. https://www.who.int/publications/i/item/9789289054256.

World Health Organization (2021). *Urban health*. https://www.who.int/news-room/fact-sheets/detail/urban-health.

World Health Organization (2022). Air pollution. In *Compendium of WHO and other UN guidance on health and environment, 2022 update*. https://www.who.int/publications/i/item/WHO-HEP-ECH-EHD-22.01.

World Health Organization, & UN-Habitat (2010). *Hidden cities: Unmasking and overcoming health inequities in urban settings*. https://iris.who.int/handle/10665/44439.

Yang, T. C., Jovanovic, N., Chong, F., Worcester, M., Sakhi, A. K., Thomsen, C., Garlantézec, R., Chevrier, C., Jensen, G., Cingotti, N., Casas, M., McEachan, R. R., Vrijheid, M., & Philippat, C. (2023). Interventions to Reduce Exposure to Synthetic Phenols and Phthalates from Dietary Intake and Personal Care Products: A Scoping Review. *Current Environmental Health Reports*, *10*(2), 184-214. https://doi.org/10.1007/s40572-023-00394-8.

Yang, X., McCoy, E., Hough, K., & Nazelle, A. de (2022). Evaluation of low traffic neighbourhood (LTN) impacts on NO_2 and traffic. *Transportation Research Part D: Transport and Environment*, *113*, 103536.

Yañez, D. V., Barboza, E. P., Cirach, M., Daher, C., Nieuwenhuijsen, M., & Mueller, N. (2023). An urban green space intervention with benefits for mental health: A health impact assessment of the Barcelona “Eixos Verds” Plan. *Environment International*, *174*, 107880.

Yu, C. T., Chao, B. N., Barajas, R., Haznadar, M., Maruvada, P., Nicastro, H. L., Ross, S. A., Verma, M., Rogers, S., & Zanetti, K. A. (2022). An evaluation of the National Institutes of Health grants portfolio: Identifying opportunities and challenges for multi-omics research that leverage metabolomics data. *Metabolomics*, *18*, 29 (30 April). https://doi.org/10.1007/s11306-022-01878-8.

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Títols publicats

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