Exposome, 2025, **5(1)**, osaf003
https://doi.org/10.1093/exposome/osaf003
Commentary

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Commentary

The exposome at twenty: a personal account

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Abstract

Non-communicable diseases represent a major global health burden of the 21st century, being responsible for over 70% of deaths annually worldwide. Environmental exposures as a whole (ie, non-genetic) are the main contributors to these diseases, although the identification of many of the specific risk factors remains to be defined. The exposome encompasses the totality of environmental exposures throughout the lifespan. This fresh perspective encourages a more comprehensive approach to exposure assessment when seeking to establish exposure-disease associations. The fact a number of the technologies applied to the exposome measure events on the disease pathway provides the additional benefit of indicating the biological plausibility of such associations. This article provides a personal history of the exposome, which serves to highlight the reasons why an exposome was needed to complement the genome. The article closes with indications of future priorities: in particular, it is vital to remain focused on the overall prize of establishing etiology as a basis for preventive interventions that in turn lead to a reduction in morbidity and mortality.

Key words: exposome, exposomics, environment, exposure, cancer, etiology, prevention.

Extinguish a fire while it is still small
A Kalenjin proverb

Introduction

In the 1980s, as a postdoctoral scientist in the Netherlands, I attended a lecture by a venerable and entertaining Professor who outlined the three stages of a research career. Stage 1: you are on your way up, marked by an invitation to present a late-breaking abstract at a major conference. Stage 2: you reach the top, marked by an invitation to give the keynote lecture at said conference. Stage 3: you are on a slow but inexorable decline, marked by an invitation to put your research into its ethical and social context. Over the years I wondered whether there was a Stage 4. Now I know: Stage 4 is marked by an invitation to give an historical account of your research. However, as the French philosopher and mathematician Auguste Comte said *"To understand a science, it is necessary to know its history."* So twenty years on, here is a brief personal history of the exposome. I hope it yields a measure of understanding with at least some relevance to the future.

Formative thoughts

The origin of an idea is difficult to pin down. However, I believe the foundation of the exposome was laid 25 years prior to the 2005 paper that introduced the concept.[1] During my PhD studies I was using the novel monoclonal antibody technology of Georges Köhler and César Milstein to study DNA repair of miscoding alkylated nucleosides in experimental hamster cell lines. In truth, I lacked interest in these mechanistic studies. At lunchtime I would eat in the cafeteria of the adjacent regional cancer center and while winding my way there I would pass by the children's cancer ward. In doing so I was struck by the lack of immediate relevance, as I saw it, of my basic science activities to the suffering of those young patients. With hindsight, I realize I was on the road to becoming an "applied scientist" (then a somewhat derogatory label). Furthermore, a deep-seated preference was emerging for research into prevention rather than cure.

In writing my PhD thesis I discovered that alkylating agents existed not only in the oncologist's armamentarium but also on people's plates. N-nitrosamines can be formed in the stomach from nitrates and amines, are present pre-formed in foods such as processed meats, as well as being constituents of tobacco smoke. This suggested that alkylated DNA bases could be occurring in people due to environmental exposures. Furthermore they might be detected by the newly-developed monoclonal antibodies aimed at them.[2] The latter possibility was of interest to Ruggero Montesano at the International Agency for Research on Cancer (IARC) in Lyon, France, with whom I went to work in 1984. As an important aside, my IARC training fellowship demonstrated to me the value of a supportive supervisor who places confidence in early career scientists, provides them credit for their own work, enables visibility at major scientific conferences and prime responsibility for writing manuscripts; this was an example that stayed with me throughout my career. However, the specific scientific question we were addressing in the mid-1908's was whether the novel immunoassays would provide the

Received: February 28, 2025; **Revised:** March 31, 2025; **Accepted:** April 3, 2025

requisite sensitivity to quantitate human exposure in epidemiological studies. If so, elucidation of etiology might be followed by preventive interventions. This period marked the beginning of what was termed "molecular cancer epidemiology".

Exposure struggles

In the early phase of this new field, laboratory scientists were focused predominantly on developing methods for exposure assessment. There was excitement that molecular and biochemical tools, including antibodies, could be applied to population-based studies. The hope was to transform the accuracy of exposure assessment, while reducing misclassification and confounding. Furthermore, the measurement of events on the pathway from exposure to disease promised to add biological plausibility to any observed associations.

Early molecular epidemiology studies did demonstrate the feasibility of measuring DNA adducts in human tissues following environmental exposure.[3,4] However, despite the promise, the majority of assays had low sample throughput and required relatively large quantities of tissue. Method validation was time consuming and costly. Consequently epidemiologists were unable to integrate these biomarkers into population-based studies where hundreds or thousands of samples required analysis. While this methodological struggle was ongoing, the polymerase chain reaction (PCR) was developed.

Testing susceptibility

PCR had a major impact on the nascent field of molecular cancer epidemiology. Genotyping single nucleotide polymorphisms (SNPs) offered a high-throughput approach applicable to tiny amounts of sample compared to DNA (and protein) adduct analyses. In addition, in contrast to exposure biomarkers, the genotype did not change over a lifespan, including being unaffected by disease (avoiding the risk of reverse causation). This made genotyping more suited to the common case-control design.

Case-control studies of SNPs in carcinogen metabolizing enzymes (eg, cytochrome P450s and glutathione S-transferases) and other candidate susceptibility genes proliferated. The initial phase comprised relatively small studies of individual SNPs, which were prone to false positive results; few of the initial associations have stood the test of time. The later emergence of genome-wide association studies (GWAS) involving tens of thousands of subjects has reduced false positive findings and resulted in a significant genetic component being assigned to various complex disorders.[5] Despite this, there has been little translation of the findings into strategies for disease prevention.

The arrival of PCR-based SNP genotyping resulted in hundreds of articles being published, many research grants awarded and numerous conferences organized. It kept us busy. Validating and applying exposure biomarkers attracted less funding and offered fewer opportunities to publish. In this context, many laboratory scientists shifted some or all of their focus away from exposure assessment to genotyping. I believe this slowed progress in understanding the major causes of cancer and other chronic diseases. While this shift was going on the Human Genome Project (HGP) was launched.

Genes rule

The HGP was irresistible. The opportunity to describe the genetic make-up of human beings offered fundamental knowledge about our species, origins, and relationship to the rest of life on Earth. Truly this was akin to landing a man on the moon. It was a category shift. DNA sequencing accelerated as costs dropped dramatically. International scientific cooperation was supported by billions of dollars of funding. The benefits are now plain to see in many domains. However, the HGP was never going to unravel the major causes and prevention of the non-communicable diseases (NCDs) that would dominate human health in the 21st century and pre-occupy governments worldwide. Many voices, including epidemiologists, sought to point this out but it was difficult not to sound self-serving. To question the eventual benefits in any context was to swim against the tide.

There is an old adage that advises: "If you can't beat them, join them." Could cooperation trump competition? Certainly the ability to examine hundreds or thousands of SNPs simultaneously had potential for understanding how environmental exposures might be modulated by underlying genetic susceptibility. But could the genetic technology associated with the HGP be harnessed to identify more directly the environmental and behavioral (non-genetic) causes of human disease? In addition, maybe the HGP provided lessons about the type of approach, scale and ambition needed. The HGP was all-encompassing. No more one gene at a time; no more one exposure at a time? Yet despite the HGP's success, the core challenge remained. If we could only measure one half the environment-gene conundrum, the solutions for disease prevention would remain out of reach.

Cohorts and biobanks

Around the time the HGP was maturing, enthusiasm emerged for establishing large prospective cohort studies with associated biobanks to identify those elusive causes of NCDs. Potentially the increase in scale would improve the statistical power to detect modest increases in risk, mitigating some of the problems of imprecise measurement of non-genetic exposures. The UK Biobank was one of the early frontrunners in this regard. As a member of the UK Biobank Ethics and Governance Council, I witnessed firsthand the significant investment in such cohorts and the scientific opportunities on offer. Yet, once again, unless the prevailing blunt tools of environmental exposure assessment could be sharpened, the full potential of this research infrastructure would not be realized. In particular, the precious banked biological material would not yield its full information content.

There was a clear need for a major investment in environmental exposure assessment during the period of grace while the cohorts matured to the point where nested case-control studies could be conducted. Could some of the emerging "omics" technology, such as microarrays for RNA expression, mutation or proteomics profiles, be used to develop biomarkers of exposure? If some of the measurable biological responses to external exposures ("early response markers") were on the pathway to disease, this could add biological plausibility to exposure-disease associations. Furthermore, as well as helping to identify hazard and risk, eventually this new generation of biomarkers might serve as modifiable outcome measures in intervention studies. The possibilities were far-reaching. The outstanding challenge of exposure assessment needed an ambitious response. A fresh perspective was called for.

Exposome: a difficult birth

The routine sequencing of an individual's complete genome was several years away as the HGP came to fruition. But the potential

was staggering: to fully characterize, with exquisite precision, the complete genetic make-up of an individual. Was there an equivalent for an individual's complete exposure history, encompassing the totality of exposures in a dynamic fashion over the lifespan? Was there an exposome to complement the genome (I do remember trying out alternatives at the time (none of which I now recall) but the word exposome seemed best suited both to the entity to be captured and to complementing the genome. It sounded right.)? Although practically unmeasurable in its entirety, there was a logical case that this entity exists for each individual. Furthermore, even a partial characterization would offer major opportunities to understand disease etiology, including through exposome studies applied to the large prospective cohorts that were being assembled. The way forward was not to argue about whether the study of genes or environment should take precedent but to see both as being necessary and complementary.

If the need for an exposome could be established this might help rejuvenate scientific interest and investment in exposure assessment. Greater equality might be achieved between commitment to characterization of the genome and exposome. At the time, the image of the male Fiddler Crab, with its cancer connotations, seemed to represent the predominating imbalance rather comically, having invested more than half its body weight in one claw while relying on its second, tiny claw to feed itself. Something was out of kilter.

The original paper on the exposome went to a couple of top-cited general scientific and medical journals but was met with rejection; all scientists are familiar with that experience! However, as a senior editor for the AACR journal Cancer Epidemiology, Biomarkers and Prevention, I was required to contribute an editorial every so often. I used this prerogative to introduce the exposome.[1] At the time, the CEBP editor-in-chief, John Potter, remarked that the paper was "out there"; I wasn't sure whether that was good or bad. And then nothing; five years later the paper had attracted virtually no attention.

Exposome: a lively rebirth

The exposome underwent a rebirth in 2010 when Steve Rappaport and Martyn Smith published a short article in Science drawing attention to the exposome.[6] In addition, Steve had co-organized a meeting earlier in 2010 under the auspices of the US National Academies entitled "The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influence on Human Disease" in Washington DC. The paper and the workshop were of great value in bringing the exposome to wider attention.

The Washington meeting encouraged me to write a more detailed description of the exposome, pointing to its specific external, internal and general external components.[7] The aim was to ensure the exposome concept was not limited to the external environment of physical, chemical and biological factors but included internal biological processes, such as inflammation, gut microflora, body morphology, aging etc., as well as the broader context of the general external environment, including the built environment, education, socio-economics, climate, social capital, etc, It was important to emphasize that dysregulation of biological processes could themselves be part of the exposome, driving pathogenesis. Furthermore, the paper stressed the need to focus on the application as being *"key to ensuring that the exposome is translated from concept to utility for better delineating the causes and prevention of human disease."* The trip to the cafeteria thirty years earlier was still a driver.

Most importantly the rebirth of the exposome has led to major and sustained funding, notably from the National Institute of Environmental Health Sciences (NIEHS) and the European Commission. The result has been an expansion in scope both in terms of disease, moving well beyond cancer, and international cooperation. Most recently the International Human Exposome Network (IHEN) (https://humanexposome.net/), funded by the EC, and the NIH-funded Network of Exposomics (NEXUS) (https://www.nexus-exposomics.org/), provide examples of leading initiatives. A similar scale of investment in east- and south-east Asia would be timely. The injection of funding has attracted a large community of researchers internationally, which in turn stimulates innovative, creative thinking about how to address the exposome and to what purpose. In conjunction with exposome-related developments there has been progress in bringing prospective cohort studies and biobanks into consortia, for example the NCI Cohort Consortium (https://epi.grants.cancer.gov/cohort-consortium/), and the European BBMRI-ERIC biobank network (https://www.bbmri-eric.eu/), are just two of a number offering excellent opportunities for application of the new methodologies at scale.

Future—parameters and possibilities

Exposome research is still in an early phase, with concerted effort and investment stretching back little more than a decade. In that context progress has been remarkable in terms of sharpening definitions, development of tools and methodologies as well as practical application into population-based studies. On a note of nomenclature, I believe the term exposome should remain defined as the totality of exposures over the lifespan. Therefore, terms such as "Social Exposome" or "Pregnancy Exposome" should be considered shorthand for the "social component of the exposome" or the "pregnancy component of the exposome" as these approaches, quite reasonably, set out to examine specific parts of the whole. They are maybe the equivalent of chromosomes or genes within the genome. There continue to be new insights and developments in these and other aspects of exposome research.[8-11] Nevertheless, the overall prize must remain: to identify the causes of disease, thereby enabling prevention and reducing the burden of human suffering.[12] Thinking to the future, I highlight a few points briefly below.

Comprehensiveness

The defining, innovative feature of the exposome is its comprehensive nature, encompassing the full breadth of exposures considered over the lifespan. The drive to capture breadth is reflected in the application of "omics," that is, "exposomics", technology to studies of the exposome. In this approach exposomics comes closest to doing for the exposome what genomics has done for the genome. That said, a range of different tools will be required to characterize different domains of the exposome. In addition to exposomics, for example, there are opportunities to draw on increasingly sophisticated questionnaires and electronic diaries to address dietary, psychosocial and socio-economic factors; individual monitors, for example, to measure physical activity; and geospatial technology (from sensors to satellites) for factors such as air pollution and climate. This breadth of approach will necessitate ever more commitment to inter-disciplinary research.

Capture of the time dimension of the exposome remains crucial. The level of a given exposure will vary over time; the same exposure may have different effects depending on the period of life during which that exposure occurs. In this regard, long-term financial and institutional support to longitudinal cohort studies is vital, albeit challenging. Furthermore, studies are needed in different age groups, from birth through to middle- to late-age. While there are a number of cohorts at the two ends of life, currently the adolescent and early adult age groups are less well-represented, albeit with some notable exceptions.[13] Ideally, future longitudinal cohorts, with the exposome in mind, should involve collection of several types of biospecimens (at least urine and blood) at more than one timepoint. This additional investment will likely be repaid by the validity of the scientific findings and the translation into public health benefits.

Biology

Another key feature of the exposome is the integration of exposure, biology and disease. If such an integration can be achieved, the exposome offers not only a powerful way to assess exposure but to establish biological plausibility and indicate opportunities to interrupt the disease pathway.

Vineis and colleagues have highlighted one outworking of this potential through their "meet-in-the-middle" concept.[14] In this case intermediate biomarkers (eg, of inflammation and oxidative stress) within longitudinal cohort studies, can be related back to measurements of external exposures and forward to health outcomes. High-resolution mass spectrometry metabolomics offers one approach to non-targeted acquisition of intermediate biomarkers.[15] However, to be useful the biomarkers must be characterized (annotated) and linked not only to a health outcome but also to one or more modifiable exposures. Without the latter link being established there is no basis for an eventual preventive intervention.

Big data

Analogous to the genome, studies of the exposome generate vast amounts of high-dimensional data. The large complex datasets carry with them challenges that require complementary tools to those used in generating the data. Notably, there is a need for innovation in computational workflows and bioinformatics for data processing as well as in statistical analysis.[16] Methods are needed to deal with the correlation structure between many of the exposures to permit identification of independent exposures associated with mortality, specific diseases, or other endpoints. Artificial intelligence and machine learning will further contribute to establishing causes of disease from complex environmental data.

The data collected as part of exposome-wide association studies (EWAS) are personal and potentially highly sensitive. The ethical aspects of study design as well as data confidentiality and security must evolve along with the science.[17] Each of these areas must be developed as the exposome field moves forward.

Absence of hypothesis but not purpose and value

Exposome-wide research represents a shift from hypothesis-driven to discovery-driven, or agnostic, research designs. The latter allow novel, unanticipated associations to emerge from the large datasets generated, with parallels to genome-wide association studies. However, emerging associations may themselves be a trigger to subsequent hypothesis-driven research. This is a reasonable strategy, leading to a powerful, comprehensive integration of discovery-driven and hypothesis-driven research designs.

When adopting a discovery-driven approach, however, it is important to avoid detaching the generation of data from scientific theory, purpose and values, all of which should impinge on the design and analytical plan of a study. Consideration of these elements needs to be maintained in the discovery-driven approach, not least to ensure the benefits from research reach as many people as possible. For example, a study that is discovery-driven may need to be designed such that it doesn't yield insights into only one ethnic group, age range or sex. In the same way that there has been recognition of the need to expand genome research beyond the initial focus on White, Western populations, the same need to study different populations and groups within populations is present for exposome research.

From concept to utility

There have been many studies applying an exposome approach in recent years. In the first phase a majority were conducted to establish a proof-of-principle while in a second phase they tended to address a particular domain (or segment) of the exposome in relation to a specific disease endpoint. Much has been learned from these applications. Now the field is ripe for studies that can be truly classed as EWAS, incorporating a broad scope of environmental exposures and disease endpoints. Novel observations are starting to indicate causes of disease and the underlying biological processes resulting from environmental exposure. For example, applying metabolomics to blood samples in the study of drinking water contaminants and colorectal cancer resulted in identification of a number of potential mechanisms of disease development.[18] The HELIX project has revealed multiple associations between environmental factors and serum metabolome, blood DNA methylation and gene expression, urinary metabolites and more, pointing to putative links between biological changes and exposures *in utero* and in early childhood.[13] These studies also raise the challenge of disentangling the genetic and environmental contributions to the phenotype captured by exposomics approaches, demanding innovative data analytical techniques to complement those applied in data acquisition.[19]

A recent example from Argentieri et al.[20] illustrates many of the principles as well some of the "Future parameters and possibilities" outlined above. The authors conducted their EWAS on over 490,000 UK Biobank participants, examining the relative contributions of environmental and genetic factors to aging. In terms of comprehensiveness, premature all-cause mortality and twenty-five age-related diseases in relation to 164 environmental exposures, as well as indicators of genetic variation (polygenic risk scores), were studied. A number of statistical approaches were employed to deal with the correlation structure across the exposome.

The analysis identified smoking and lower physical activity linked to mortality and age-related multimorbidity as well as several socio-economic markers, including deprivation, lower household income, lower education level, and a number of psychosocial factors, including sleep, mental and physical wellness and home occupancy, among other exposures. This illustrates the value of the broad discovery-driven approach of the exposome, drawing on measures other than the omics technologies. Unfortunately, the authors did not conduct any "omics" analyses

eg, metabolomics that could have revealed a wider range of exposures from both external and internal components of the exposome. Nevertheless, it was of interest that the vast majority of the identified risk factors were modifiable and hence potentially subject to intervention.

In relation to biology the authors employed a proteomic age clock, previously shown to be related to mortality, as well as a set of age-related biomarkers. They were able to link, therefore, a subset of the exposures with these markers of biological aging. Notably there were indications that early-life exposures (maternal smoking around birth and height and body size age 10 years) affected mortality and aging. This emphasizes the importance of the age-specific element of exposome research and the need to consider exposure and preventive intervention across the lifespan.

Of particular importance, the above study revealed a far greater impact of the exposome on variation in mortality than polygenic risk scores, over and above the effect of age and sex; while polygenic risk scores explained less than two percentage points of additional mortality variation, the exposome explained seventeen percentage points. At the same time, it was notable that each environmental factor alone contributed a small proportion to the total. Instead it was the ability to take an integrated exposome-wide view that revealed the underlying associated pattern of exposures and health outcomes.

Conclusions

The seeds of the exposome were sown in a simple and perhaps naïve desire to address the causes and prevention of human disease. The germination occurred during a period of frustration and hope. Frustration at the neglect of investment in exposure assessment in comparison to genome research. Hope at the potential in applying the latest molecular and biochemical methodologies to a new generation of longitudinal, population-based cohorts with associated biobanks.

The coming years provide the time to harvest the fruit of the exposome: to identify risk factors for the dominant NCDs of the 21st century and in doing so to enable strategies to reduce morbidity and mortality. The political focus of the United Nations on NCDs within the Sustainable Development Goals provides a top-down impetus to the above bottom-up, research-led exposome initiatives.[21] The scientific community should make this link more explicitly, addressing what is all too often an unbridged chasm from research to policy.

Post-script

It is not without irony that the most cited paper of a forty-year research career should be one of the shortest written and contains not a single data point. It does, however, contain an idea. Maybe that is a reminder that during all the "business" of research it is worthwhile, on occasion, to look up, to survey the horizon and not to neglect the creative speculation that is a feature of science, whatever the fashions of the day. You may even change end-up changing something.

And so to Stage 5.

Funding

None declared.

Author contributions

Christopher Wild (Conceptualization [lead], Writing - original draft [lead], Writing - review & editing [lead])

Conflicts of interest

None declared.

Data availability

No new data were generated or analyzed in support of this research.

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Exposome, 2025, 5, 1–6
https://doi.org/10.1093/exposome/osaf003
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