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Putting the exposome into practice: An analysis of the promises, methods and outcomes of the European human exposome network

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ABSTRACT

Objectives: Contemporary research on the exposome, i.e. the sum of all the exposures an individual encounters throughout life and that may influence human health, bears the promise of an integrative and policy-relevant research on the effect of environment on health. Critical analyses of the first generation of exposome projects have voiced concerns over their actual breadth of inclusion of environmental factors and a related risk of molecularization of public health issues. The emergence of the European Human Exposome Network (EHEN) provides an opportunity to better situate the ambitions and priorities of the exposome approach on the basis of new and ongoing research.

Methods: We assess the promises, methods, and limitations of the EHEN, as a case study of the second generation of exposome research. A critical textual analysis of profile articles from each of the projects involved in EHEN, published in Environmental Epidemiology, was carried out to derive common priorities, innovations, methodological and conceptual choices across EHEN and to discuss it.

Results: EHEN consolidates its integrative outlook by reinforcing the volume and variety of data, its data analysis infrastructure and by diversifying its strategies to deliver actionable knowledge. Yet data-driven limitations severely restrict the geographical and political scope of this knowledge to health issues primarily related to urban setups, which may aggravate some socio-spatial inequalities in health in Europe.

Conclusions: The second generation of exposome research doubles down on the initial ambition of an integrative study of the environmental effects of health to fuel better public health interventions. This intensification is, however, accompanied by significant epistemological challenges and doesn't help to overcome severe restrictions in the geographical and political scope of this knowledge. We thus advocate for increased reflexivity over the limitations of this conceptually and methodologically integrative approach to public and environmental health.

1. The exposome so far: between promises and limitations

Over the last two decades, in the fields of public and environmental health, the 'exposome' has been developed as an integrative approach to disease etiology. It is defined as a complement to the 'genome' by encompassing all the exposures experienced by individuals throughout their lifetime (Wild, 2005). It proposes a partition of the environment into general external (i.e. education), specific external (i.e. infectious agents) and the internal (i.e. metabolism). As large-scale genomic and sequencing projects failed to deliver expected payoffs in terms of scientific understanding and therapeutic applications, the ambition of the exposome is to bring more attention towards the role of the environment in the etiology of disease and to harness the latest developments in big data techniques. The exposome is often presented as a new integrative

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and 'holistic'[1] approach build to overcome the limitations of traditional epidemiology and toxicology by deciphering long-term cumulative effects of multiple exposures.

HELIX (2013–2017), EXPOsOMICS (2012–2017) and Lifepath (2015–2019) together constitute a first generation of projects that established the exposome as a novel concept, target of funding, and research methodology. They proposed an innovative combination of evidence-making practices: questionnaires on diet and well-being meet high-throughput molecular analysis of blood and air samples (Giroux, 2023). Data from large epidemiological cohorts were supplemented with laboratory knowledge from toxicology, and most notably with the wide-scale application of 'omics' technologies (high-throughput molecular data acquisition techniques). This led to the inclusion of experts in public health policy and risk assessment, as in EXPOsOMICS (Canali, 2016). The exploration, in Lifepath, of the biological processes underpinning social inequalities was also premised on its ability to provide more precise targets for policy interventions (Ghiara and Russo, 2019; Vineis et al., 2020).

Taken literally, the exposome approach portrays itself as the apex of public and environmental health research. It combines breadth of scope and precision, scientific excellence and policy relevance. This idealistic interpretation has not resisted the scrutiny of social scientists and philosophers, who have flagged a variety of obstacles and tensions at play in the first concrete instantiations of the approach (Shostak & Moinester, 2015; Ghiara and Russo, 2019; Giroux et al., 2021; Canali, 2022). Their main concern is the primacy, in practice, of the internal over the external environment (Giroux, 2021). The centrality of omics technologies – combined with the overall absence of social scientists – turned the exposome into a hunt for bio- and sociomarkers that track the 'presence of molecules or processes that can be connected to exposures to environmental elements' (Canali and Leonelli, 2022). External exposures were measured insofar as their effects can be tracked down to a molecular and individual level. This 'molecularization' of the environment (Shostak, 2005; Landecker, 2011) comes at the expense of a variety of determinants that act at a population level, most notably social factors (Neufcourt et al., 2022). This, in turn, raised doubts on the scope of policy relevance of exposome research, as molecularization entails a depoliticization and technification of environmental and public health (Guchet, 2019; Giroux, 2023). Facing a trade-off between precision and breadth of scope (Giroux, 2021), exposome research in fact needs to address a classically encountered dilemma (Levins, 1966; Cartwright and Hardie, 2012).

One way to respond to such criticism is through conceptual engineering, as illustrated by the proposition of 'socio-exposome' (Senier et al., 2017) or 'social exposome' (Gudi-Mindermann et al., 2023) as more inclusive substitutes to the exposome as currently practiced. Another is to rely on methodological improvements that would enable a truly exhaustive coverage of the external environment, a horizon that has been contested on technical and economic grounds (Fayet, 2023).

The limited coverage of the exposome raised also fears of potential side-effects on spatial inequalities in health (Fayet, 2023), which is a major public health issue in Europe. At the national level, the highest life expectancies at birth reach 83 years (in Spain, Sweden, Luxembourg and Italy) while the lowest ones barely surpass 70 years (Bulgaria, Romania and Latvia). A fifteen-year difference can be seen between regions of the same country, such as in Spain, Finland and Bulgaria (Eurostat, 2023). Evidence for marked health inequalities between urban and rural areas are more controversial (Riva et al., 2009; Ayuso-Álvarez et al., 2022). While rural inhabitants are better off in the United Kingdom (Allan et al., 2019) and the Netherlands (van Hooijdonk et al., 2008), the reverse situation has been described in France (Fayet et al., 2020), Cyprus (Lamnisos et al., 2019) and Scandinavian countries (Bremberg, 2020).

The European Human Exposome Network (EHEN) is part of Horizon (2020), the EU's research and innovation funding scheme. It stems from the SC1–BHC-28-2019 call for proposals on 'The Human Exposome Project: a toolbox for assessing and addressing the impact of environment on health'. The 9 selected projects, gathering 126 laboratories for a total funding of 106 million euros, have been encouraged by the European Commission to form a research network, organizing joint conferences and working groups. The EHEN represents a second generation of exposome projects and, as of today, the largest and most ambitious instantiation of the exposome approach. Its emergence raises a number of questions about (a) the commitments and priorities of second generation exposome projects, (b) its ability to move beyond limitations identified in the first generation, and (c) how it addresses the trade-off between precision and breadth of scope.

2. Tracking the concrete development of the exposome research

2.1. Objectives

This paper is the outcome of a collaboration between researchers from different disciplines (philosophy of science, philosophy of medicine, social geography) interested in the possibilities, implications, and limitations of the exposome approach in public and environmental health research and policy. The emergence of the EHEN provides an opportunity to better situate the ambitions and priorities of the exposome approach on the basis of new and ongoing research. We discussed, in *Section 1*, the tensions and limitations raised by the integrative outlook of exposome research. As they concerned the first generation of exposome projects, this critical literature thus necessarily lacks hindsight and could derive from the immaturity of the approach. In this sense, we see the EHEN as providing a window into the concrete development of exposome research. Our aim is to identify its priorities, as well as its methodological and conceptual commitments. We could thereby assess whether and how second generation exposome projects address, incorporate, or reject previous criticism. Particular attention was paid to the overall representativeness of those studies, given the integrative ambition of the exposome concept and the EHEN claim for political actionability of its results.

2.2. Data sources

The first joint action of the EHEN was to publish a profile paper for each project in the journal *Environmental Epidemiology*. These profile papers are useful and informative documents insofar as they outline the aims, concepts, methods, data and challenges of each EHEN project. We therefore chose these as our main source material. One could downplay the value of profile papers as mere repetitions of the expectations from the funding body. The call for projects set by the European Commission only identified three general priorities: (a) to harness 'the last decade's rapid technological advances' in data collection and analysis, (b) to devise and evaluate interventions that could 'contribute to sustainable healthcare' and (c) to develop 'a long-term host and a single shared data infrastructure' (European Commission, 2018). In our view, these are rather loose constraints that leave open a series of significant choices (i.e. the types of disease and conditions to study, the data to be collected and used, the policy interventions to suggest) that could be traced as commitments and priorities of EHEN projects. Throughout the paper we mention the profile paper for each project by the project's acronym (Table 1 provides an overview of the projects).

[1] The usage of term 'holistic' by exposome researchers is essentially rhetorical, and mostly denotes the ideal of comprehensiveness at play in these research projects (for more about this, see Giroux et al., 2021 et Giroux, 2023). Contrary to its philosophical meaning, holistic here doesn't imply a form of irreducibility at work at a higher-level. Thanks to the anonymous reviewer for their remark that helps us to clarify this point.

Table 1
Overview of the EHEN projects.

Acronyms	Full names	Claimed commitments and priorities
ATHLETE	Advancing Tools for Human early Lifecourse Exposome research and Translation	Measuring a wide range of environmental exposures to better understand how the exposome impacts human health from pregnancy to adolescence.
EPHOR	Exposome Project for Health and Occupational Research	Developing methods and tools to characterize the working-life exposome
Equal-Life	Early environmental quality and life-course mental health effects	Developing and test combined exposure data using a new approach to multimodal exposures and their impact on children's mental health and development
EXIMIOUS	Mapping exposure-induced immune effects: connecting the exposome and the immunome	Bringing about a new way of assessing the human exposome by linking innovative ways of characterizing and quantifying multiple and combined environmental exposures with high-dimensional immunophenotyping and profiling platforms to map early immune effects induced by these exposures
EXPANSE	Exposome powered tools for healthy living in urban settings	Studying the complex mixture of social and environmental factors in the urban environment that collectively have an impact on health.
HEAP	Human exposome assessment platform	Developing an informatics platform to analyze large datasets on environmental exposures and their health effects
LongITools	Dynamic longitudinal exposome trajectories in cardiovascular and metabolic noncommunicable diseases	Measuring how exposure to air and noise pollution and the built environment, and an individual's lifestyle, psychological and social situation, interact with genetic factors, and contribute to the risk of developing diseases such as obesity, type 2 diabetes, heart disease and atherosclerosis
HEDIMED	Human exposomic determinants of immune mediated diseases	Identify the exposomic determinants that are driving the rapid increase of immune-mediated diseases (IMDs) such as type 1 diabetes, celiac disease, allergies and asthma
REMEDIA	Impact of exposome on the course of lung diseases	Better understanding the contribution of the exposome to two untreatable respiratory diseases: chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF)

2.3. Data analysis

We performed critical textual analysis of the profile papers for each of the nine EHEN projects, in line with previous interdisciplinary investigations (Giroux et al., 2023). Unlike a systematic review, our assessment does not review available evidence, identify research gaps or indicate future directions. Instead, our purpose was to provide a close individual analysis to derive common priorities, innovations, methodological and conceptual choices across EHEN that can help to assess whether and how EHEN studies meet the integrative ambition of the exposome and its claim for political actionability.

After a first close reading of the profile papers and related publications of the nine projects, we assessed this research's integrative nature along four dimensions:

- Areas: Are the data and indexes used in these projects geographically restricted?
- Risk factors: What type of risk factors is accounted for by these exposome projects?
- Diseases: Are studies focusing on/relevant to particular diseases?
- Population: What is the provenance of cohort participants/analysts?

Our focus on these four dimensions was based on the limitations identified in previous analyses of the exposome and the related assumption that these topics would help us spot possible limitations and uproot implicit reductionist commitments. This analysis was used to provide a global overview of the projects (Table 1) and to identify their spatial coverage, given the integrative ambition of the exposome and the EHEN claim of political actionability (Table 2). In Table 2, the coordinating and participating countries have been highlighted in different colors according to their belonging to one of the four European subregions in the United Nations geoscheme[2] in order to assess the EHEN representativity. We also analyzed considered environments and areas in those projects for the same purpose.

The initial analysis of the profile papers also allowed us to identify the main zones of innovation – data collection, data analysis, and policy relevance – which were in turn subjected to scrutiny through closer and collective reading of each paper (Section 3). This provides the basis for tentative answers to how EHEN plans to address previous tensions and challenges identified in Section 1. The critical analysis performed in Section 4 draws from the literature in social sciences about data-intensive sciences and health and spatial inequalities applied to the case at hand. It also builds on an extended experience from earlier works on the exposome and public health, frequent discussions, interviews and seminars with exposome researchers as part of two fund research projects funded by the French *Agence Nationale de la Recherche*.[3]

2.4. Strengths and limitations

Our interdisciplinary analysis of profile papers is useful to shed light on the 'best possible version' of second generation exposome research. However, this does not take into account developments and possible changes to projects and the EHEN as a whole as it progresses. Our research aims at fostering increased reflexivity about the possibilities of exposome research, and is thus relevant beyond the scope of our disciplinary expertise (i.e. exposome researchers and policy-makers). We make the choice to treat the nine EHEN projects as a core entity with shared commitments and methodology. Our study would thus benefit from being complemented with in-depth analyses of individual projects that might display a different picture of exposome research. It results should also be confronted with actual developments of EHEN research, through empirical studies of scientific practice and analysis of published scientific results.

3. The commitments and priorities of the European human exposome network

3.1. Overview of common ambitions

Our initial characterization of individual projects, summarized in Table 1, gave us a first grasp of EHEN's overall ambitions. We observed a reinstatement of the commitment, inherent to exposome research, to an integrative analysis of the health impact of the environment. The EHEN also marks an extension to previously unaddressed public health priorities of central importance, such as occupational health (EPHOR), noncommunicable diseases (LongITools) or health inequities (Equal-life).

[2] https://unstats.un.org/unsd/methodology/m49/#ftn13.
[3] "EPIEXPO: Epistémologie critique de l'Exposome" and "EnviroBioSoc: The environment and human health across life and social sciences".

Table 2
Spatial coverage of EHEN projects.

Acronyms	Coordinator place	Participating countries	Considered environments and areas
ATHLETE	Barcelona Institute for Global Health (ISGlobal), Spain	Spain, UK, The Netherlands, France, Belgium, Norway, Czechia, Denmark, Greece, Lithuania, Italy.	Integrative approach with use of social data
EPHOR	Netherlands Organization for Applied Scientific Research (TNO), Utrecht, The Netherlands	The Netherlands, UK, France, Spain, Germany, Belgium, Denmark, Sweden, Norway, Finland, Greece, Cyprus.	Working life exposome data only
Equal-Life	National Institute for Public Health and the Environment (RIVM), Utrecht, The Netherlands	The Netherlands, Spain, Austria, Sweden, Macedonia, Slovenia, Italy, Germany, Finland, Belgium, UK.	Integrative approach with use of social data. Use of non-exhaustive "national" or "regional" cohorts
EXIMIOUS	Unit of Environment and Health. KU Leuven, Belgium	Belgium, Norway, Denmark, UK, Spain, Switzerland, Romania.	Focus on exposures mainly linked to urban environments (air pollution, built environment)
EXPANSE	Institute for Risk Assessment Sciences, Utrecht University, The Netherlands	Czechia, Spain, Greece, France, Poland, The Netherlands, Italy, Switzerland, Germany, Estonia, UK, Sweden, and the USA	Integrative approach but explicit focus on the urban exposome
HEAP	Karolinska University Hospital, Solna, Sweden	Sweden, Denmark, Finland, Austria, The Netherlands, Poland.	Non applicable — Technical platform
LongITools	Center for Life-Course Health, University of Oulu, Finland	UK, Finland, The Netherlands, Sweden, France, Norway, Spain, Italy	Focus on risk factors mainly linked to urban environments (air pollution, built environment, noise, green spaces)
HEDIMED	Tampere University Foundation, Finland	Finland, Sweden, Norway, Estonia, Italy, Czechia, Austria, Switzerland, Germany, Greece, Denmark.	Little mention of environmental data
REMEDIA	National Institute of Health and Medical Research (INSERM), Paris, France	France, Denmark, Norway, Hungary, Switzerland, Germany, Greece, Belgium.	Focus on physical and chemical environments despite mention of social factors

UN Geoscheme subregions: Southern Europe, Northern Europe, Eastern Europe, Western Europe

The exposome's emphasis on a life-course perspective is also visible on the proposed in-depth investigations of common etiological pathways to several disorders (HEDIMED; ATHLETE; Equal-Life; EXPANSE). Upon closer analysis, these projects display no moderation to their integrative ambitions. EHEN projects aim at a *full* description of the exposome they study, of its effects on health, and of the whole pathway mediating these effects. This exhaustive understanding would serve, in turn, the formulation of public health interventions to address the issues of concern. This is well exemplified in EXIMIOUS, which aims to 'holistically explore and integrate the human immunome', by studying 'the entire pathway from exposome, to immune fingerprints, to disease during a person's lifetime' and 'direct preventative actions and policies at the individual, group, and population levels, and so contribute to better healthcare' (EXIMIOUS, p. 8; see also Equal-Life, p. 5, 8; REMEDIA, p. 8). At first sight, the EHEN is willing to address tensions identified in *Section 1* by a broader consideration of the environment and a stronger dedication to generate policy-relevant knowledge. This implies the use of improved tools, data, and theoretical models (ATHLETE, p. 2; REMEDIA, p. 5). Through a broader inclusion of scientific and non-scientific stakeholders, EHEN projects strive to create a panoramic view of the issues at stake and facilitate the formulation of policy interventions (Equal-Life, p. 8; LongITools, p. 3). The following subsections unpack these all-encompassing ambitions by identifying novelties at the level of data collection, data analysis and knowledge to policy translation strategies.

3.2. Expanding data volume and resolution

When it comes to data use, the general impetus behind EHEN's development is to augment volume and variety, as well as precision and resolution. In other words, EHEN projects aim to 'increase the coverage of the external exposome by extending the number of exposures that are included and by refining the resolution with which these exposures are assessed in space and time' (EXPANSE, p. 3). In this particular project, adults and matured birth cohorts (in which participants have reached adulthood) are combined through an 'accelerated longitudinal design' to reconstitute entire life-course trajectories. The reliance on cohort populations spanning twelve European countries attests its coverage of wide terrestrial grounds (an issue we discuss again in Section 4). Explicit efforts are made to diversify the external environmental factors, including a wide array of elements from the physical and social environments. This includes, among several elements, the age of buildings, physical safety, electromagnetic fields, and, at the level of individuals, patterns of activities as well as information related to ethnicity and migration status (Equal-Life; REMEDIA). A particular emphasis is found on an improved resolution within the urban context (to track individual behaviors) and outside (to determine land use). To do this, EHEN projects plan to harness the increasingly common availability of minimally invasive sampling methods such as wearable devices and data generated through engagement on digital platforms (EPHOR, HEAP; REMEDIA; Equal-Life). Improvements in high-throughput omics technologies, such as mass spectrometry and chromatography, underpin an intensified exploration of several layers of chemical components found in internal and external environments and collected through biological samples. This multidimensional expansion in data collection abilities, covering several aspects of the external environment, provides an answer to previously voiced concerns over a restrictive focus on mere molecular components. At the same time, this increasingly heterogenous evidence basis puts tremendous pressure on data *analysis*.

3.3. Innovative tools for data integration and data analysis

As the most commonly mentioned challenge in profile papers (i.e. LongITools, pp. 8–9; HEDIMED, p. 6), EHEN's general struggle for the development of operational data infrastructure is best exemplified by the HEAP project. The latter's sole mission is the development of 'a global research resource […] for the efficient management and processing of massive data from geographically distributed large-scale population cohorts' (HEAP, p. 1). It strives to create interoperability between 'exposome data analysis focused on epigenomics, microbiomics, metabolomics, wearable sensors, advanced statistics, and Artificial Intelligence (AI)' (HEAP, p. 2). Issues of data harmonization and accessibility are addressed by alignment to existing standards, such as the FAIR Principles (Wilkinson et al., 2016), the use of already harmonized data (i.e. from the E. U. Child Cohort Network, ATHLETE, p. 4) and the use of open source software. In line with a project like HEAP, improvements in data interoperability rely on the use of Artificial Intelligence (AI) derived tools. These innovations also aim to foster the *agnostic* exploration of the vast multidimensional data spaces being created, overcoming the traditional epidemiological focus on one

exposure at a time, with the idea of uprooting unexpected but robust associations and patterns (ATHLETE, p. 10; EPHOR, p. 2) and not leave data underanalyzed, a concern already voiced on first generation exposome projects (Canali, 2020). As with data sources, EHEN projects thus strongly rely on recent technical innovation to overcome previous limitations.

3.4. From knowledge to policy

Broader (and better exploited) data appear a major step in the production of policy-relevant, actionable knowledge. They contribute to the broader objective of translating 'data and knowledge into simple and available predictive tools for scientists, citizens, policy-makers, or other end users' (LongITools, p. 8). The emphasis is placed on the transferability and replicability of the knowledge produced. EHEN projects plan to achieve this mostly through the devising of scores and indicators that can predict external exposures, and link it to possible individual risks or population-level health and economic impacts. This includes 'Job Exposure Matrices' (EPHOR), 'poly-environmental scores', a 'Health Impact Assessment' database (ATHLETE), or the 'Exposome Map' and the 'Exposome Navigator' (EXPANSE). This information would then be turned into individual-level recommendations, diagnostic tools for preclinical risks, help the identification of vulnerable subgroups and the proposition of population-level interventions. The latter are evaluated through the randomized controlled trial (RCT) methodology (i.e. HEDIMED) or through the training of an AI algorithm that integrates data from cohorts and available RCTs (LongITools). The data infrastructure is judged ripe to attempt to replicate findings from first generation exposome projects (ATHLETE, p. 8). An increasingly recognized condition is a successful involvement of a wider array of stakeholders 'from the earliest stages of the project' to ensure that proposed policy interventions 'are both acceptable and feasible'. This motivates the presence of participatory aspects in several EHEN projects (ATHLETE, p. 10; HEDIMED, p. 8; Equal-Life, p. 8; EXPANSE, p. 3) and the devising of 'toolboxes' that enhances the accessibility and interpretation (mostly through tailored cost-benefit analyses) of project results for researchers as well as citizens and decision-makers. A wide variety of strategies is thus mobilized to improve the policy relevance, and the overall usability of the vast array of exposome data.

3.5. Summary

In our analysis, EHEN's broad ambition hinges on the integration of diverse types of knowledge that compensate blind spots from individual perspectives and, together, exhaustively account for the complex impacts of the exposome. This strongly depends on technical innovations that both enable expanded data collection, improved data analyses, and automated evaluations of policy recommendations. The explicit inclusion of elements from open science and community-based participatory research are deemed to enhance the adequation of proposed interventions to its context of applications. We argue that this mobilization of this array of technical and epistemic tools is a way to *overcome*, rather than *embrace*, the tensions identified in *Section 1*: this latest generation of exposome research explicitly promises to deliver more precise *and* more broadly applicable knowledge, for an expanded array of pressing public health issues. The next section, however, raises a critical discussion of this ultimate ambition.

4. Scope and relevance of recent exposome research

4.1. The data-driven spatial limitation of the exposome approach

Seeking to 'achieve both wide and accurate exposome coverage' (ATHLETE, p. 5), a central feature of EHEN projects is the extension of data collection and use for exposome research. As discussed before, expansions in data volume and variety notably allow for a better characterization of physical and social environments, notably in the EXPANSE, ATHLETE and Equal-life projects (Table 2). However, we argue that limits in the availability of data make them face practical difficulties in meeting this integrative ambition. As a consequence, EHEN projects have tilted towards the investigation of *urban* contexts. This orientation is openly admitted in EXPANSE, which claims to study the 'complex mixture of social and environmental factors in the urban environment' and makes use of the concept of *urban exposome*. In other projects, the urban bias is implicit and can be tracked at the level of data sources. Indeed, several measures (i.e. air pollution, noise, and built environment) and indexes (i.e. 'walkability' scores, accessibility to food outlet or green spaces) describing the external environment are strongly tied to urban contexts. Finally, we found that the EHEN projects variously meet the exposome promise of integration in terms of environments and areas (see Table 2).

This limitation is connected to the fluctuating availability of spatial data. Indexes measuring environment require precise spatial data which are often not routinely produced. Characterizing the social environment (i.e. the 'deprivation index') depends on administrative data but their precision and quality at the neighborhood level can vary greatly across European countries. Only a few exposures, such as air pollution or noise, which are easier to model statistically from measurement stations, are reliably findable. Exhaustive and updated recordings are then needed to assess other exposures (i.e. air and water pollution) and environmental features (i.e. accessibility to food/tobacco/alcohol outlets or the walkability of an area). Again, the availability of these measurements is very heterogeneous in Europe (with the North and the West of Europe being the most affluent in these regards).

The spatial limitations of these studies raise broader questions about the ability of exposome studies to meet its integrative ambitions, as well as its search for actionable knowledge. The sophisticated resources needed to measure the external exposome as comprehensively as possible are generally much easier to deploy in major urban areas of the wealthiest European countries, and depend strongly on national political will. This translation of spatial inequalities into data infrastructure has serious consequences for the spatial scope of EHEN studies since areas without precise data are excluded from the analysis. This already happened in the first-generation HELIX project, which only included geographical areas with data on air pollution and the built environment (Maitre et al., 2018). This risk is particularly salient at the European scale, where geographical heterogeneity in data availability is strongly present, and hampers the current practical implementation of the exposome concept.

As an overall result of this data-driven spatial limitation of the exposome approach, Table 2 shows that Western and Northern European countries are far more represented in the EHEN studies, as coordinators or participants. For example, Western and Northern Europe have at least two countries in each of the 9 EHEN projects, while Eastern European countries are missing from 3 projects. We can, of course, imagine that these differences are not intentional, but they underline the probable current difficulty of finding the resources needed to actually set up exposomic studies across the European continent. Given the reduced spatial coverage of EHEN studies and their limited representativeness of the exposome at the European level, we caution against the high levels of actionability claimed by the EHEN, as we discuss below.

4.2. Situating the actionability of EHEN studies

EHEN means to be a political impactful scientific project. This is also visible in its overt affiliation to the *European Green Deal*, which aims 'to protect citizens' health and well-being from pollution and environmental deterioration by providing new evidence for better preventive policies' (European Human Exposome Network, 2020). Similarly, some EHEN stakeholders are involved in the *Health Environment Research Agenda* consortium 'to set the priorities for an environment, climate and health research agenda in the EU' (Hera Research EU, 2020). Yet these

political ties place enormous expectations from EHEN studies. Reiterating the integrative mindset of the exposome, these studies portray themselves as exhaustive and broadly representative of the various health risks at the European level. In this view, the outputs of these projects would constitute a legitimate touchstone of evidence-based health policy-making in the Union. Our analysis suggests conversely that issues of representativeness are limiting the scope of political action resulting from the findings of EHEN studies. Indeed, ambitious and evidence-based actions on external exposures addressed by EHEN studies (i.e. pollution, food environments, green spaces …) would mostly improve life conditions and health outcomes within areas mostly concerned by these factors and where spatial data collection tools are the most advanced and the most extensive, i.e. (largest) urban areas of European countries, notably in the North and West of Europe. On the opposite, actions arising from EHEN results would be mostly irrelevant to Eastern European countries and above all non-urban areas, which are poorly covered hence represented by exposome research.

This inclination towards the 'urban exposome' can be defended on several grounds. A large breadth of socio-spatial and environmental inequalities in health can be addressed inside urban areas neighborhoods (Costa et al., 2019). Moreover, EHEN studies address major health risk factors (air pollution, noise, green spaces, …), impacting large populations and which are related to other ecological priorities, such as climate change mitigation. From a policy (and economic) perspective, large cities are the most cost-effective areas, since each action can affect millions of people and save a lot of public money compared to smaller town or rural areas. Finally, urban contexts are host to a majority of the world population, and Europe is no exception. One can find in EXPANSE that '72% of Europe's population lives in an urban environment' and that 'this percentage is expected to grow to more than 80% by 2030' (EXPANSE, p. 2). We would like, however, to relativize this purported number of potential beneficiaries. The estimation indeed comes from a harmonized definition of 'urban areas' that includes, in many countries, any municipality or locality with at least 5000 inhabitants. Therefore, the estimation encompasses not only cities, but also less dense urban areas such as small towns and suburbs, where the environmental exposures measured in the EHEN studies are comparatively irrelevant and are thus likely to fall outside the political scope of EHEN projects.

These considerations lead us to temper the claim that the EHEN can provide objective knowledge to support policies on a vast array of public health issues. More centrally, *we argue for an increased awareness and recognition of the spatial limitations and thus the restricted scope of political actions coming from the results of EHEN studies.* We emphasize the need to invest in fine-tuned, harmonized tools, for aspects of the external exposome that are difficult to measure across contexts. The improvement of tools measuring various aspects of the external exposome is especially salient as the search for biomarkers as proxies for external exposures entrenches a biologisation of socio-spatial inequalities, a move with risky and unpredictable policy consequences (Lynch, 2017; Serviant-Fine et al., 2023).

The narrative of the EHEN consortium (e.g. 'providing new evidence for better preventive policies') suggests that research outputs in the form of actionable knowledge are essential to sound health-promoting policy actions. We would like to question this close link between scientific and policy outputs. This vision, promoted by the EHEN, indeed sidesteps unresolved debates on the role and necessity of causal mechanisms in evidence-based policy (see Parkinnen et al., 2018; Reiss, 2007). In substance, one might wonder about the added value of causal mechanistic knowledge where the health impact of several environmental factors (air pollution, green spaces, food environments for example) is already well documented. This question matters as the investigation of these sophisticated pathways is costly and complex. In this view, the option to wait for evidence at the biological level to trigger policy action could be seen as an epistemic justification for political inaction, a far cry from the precautionary principle put forward in European environmental legislation.

Moreover, the policy orientation of the EHEN gives rise to an unusual configuration. Indeed, a scientific network mostly constituted by biomedical disciplines is expected to play a direct contributing role in European policy-making in fields such as environmental health, sustainable development, ecological transition and regional planning on the basis of innovative, highly complex and sophisticated studies that have limited spatial and policy scope. This discrepancy between the precise scientific relevance and contributions of the EHEN in environmental health research and the much broader scope of its political objectives raises questions about the extent to which the guidelines that could stem from this research properly account for matters of spatial justice, at least at the inter-regional and intra-regional level.

4.3. Potential side effects on spatial inequalities in health

The limited spatial coverage of EHEN projects raises questions about their ability to account for spatial inequalities in health. The latter constitutes a major issue across Europe. At the national level, the highest life expectancies at birth reach 83 years (in Spain, Sweden, Luxembourg and Italy) while the lowest ones barely surpass 70 years (Bulgaria, Romania and Latvia). A fifteen-year difference can be seen between regions of the same country, such as in Spain, Finland and Bulgaria (Eurostat, 2023). Evidence for marked health inequalities between urban and rural areas are more controversial (Riva et al., 2009; Ayuso-Álvarez et al., 2022). While rural inhabitants are better off in the United Kingdom (Allan et al., 2019) and the Netherlands (van Hooijdonk et al., 2008), the reverse situation has been described in France (Fayet et al., 2020), Cyprus (Lamnisos et al., 2019) and Scandinavian countries (Bremberg, 2020).

Health inequalities between rural and urban areas are primarily linked to socio-economic differences. For example, lower incomes in rural areas can undoubtedly contribute to these spatial inequalities, given the extent of the social gradient in health (Bremberg, 2020). Nonetheless, the extent of this phenomenon is such that some European countries administratively split their major urban area (usually the capital) from its surroundings. The creation of two distinct regions allows the lesser-developed area to be eligible to more European funds (Lambrechts, 2019). These opposing dynamics in terms of economic development could contribute to raising spatial inequalities in health. In the United Kingdom, for example, the largest increases in life expectancies are reported in metropolitan districts (especially in London), which are the wealthiest and most dynamic areas (Rashid et al., 2021). Spatial inequalities in health may result from higher levels of social deprivation, lower access to healthcare, specific environmental exposures linked to industrial and agricultural activities and increased risk of unhealthy lifestyle behaviors. In particular, studies point at social factors such as deprivation and behaviors (smoking, alcohol drinking, food intakes, physical activity) as the main factors responsible for national differences in life expectancy in Europe (Stefler et al., 2016; Trias-Llimós et al., 2018; Janssen, 2021). A recent study analyzing determinants of inequalities in life expectancy across 15 European countries found that smoking, low income and high body weight were the risk factors contributing most to the gap in life expectancy (Mackenbach et al., 2019).

The focus provided by EHEN projects on factors related to physical environment in urban settings (air pollution, noise, built environment, walkability, food environments, green spaces) may have a limited relevance towards those risk factors leading to spatial inequalities in health at the national, inter-regional and intra-regional levels in Europe. This focus will, at best, help the design of healthier urban environments, which might help to reduce spatial inequalities in health within these places. But it risks widening other spatial inequalities at regional, national and European scales since affluent urban areas are already benefitting from the best overall health outcomes in many European countries. At the same time, specific risks affecting rural areas and Eastern European countries inhabitants (notably exposure linked to

intensive agriculture and industrial activities, as well as health-related behaviors) are also underrepresented in exposome studies. In addition, there may be concerns that the discrepancy between the limited scope of the EHEN and its claim for policy actionability reinforce the belief that all public health issues (including social risk factors leading to spatial inequalities) could be effectively addressed simply by improving living environments.

Despite significant progress described above, the EHEN faces extant epistemological and political challenges in the successful implementation of its ideals. Putting the exposome concept into practice thus reveals concrete issues of spatial justice, which resonates with current studies of *agnotology*, the production of ignorance in environmental health (Counil and Henry, 2021) and also, in another way, with criticisms of reductionist leanings of the first generation exposome studies. Our analysis helps to better situate the political scope of the exposome, in its current forms and limits. We might thus consider the EHEN as *promoting an evidence-based approach to the design of healthier urban environments.* This analysis also shows how current spatial disparities in terms of data availability and quality (health, biological, environmental and social data) currently undermine the feasibility of the epistemological and political ambitions of the exposome. Indeed, the reduced scope of application of EHEN results calls for a revision of political promises to 'provide new evidence for better preventive policies' (European Human Exposome Network, 2020). Following these results, we argue for an increased awareness and recognition of the current spatial limitations as well as the restricted scopes of actions derived from EHEN results. Far from discrediting the potential of the exposome approach, recognition of these limitations could support the strategic development of exposome measurement tools (and in particular the blind spots of the social and physical environment) on a European scale, to improve its ability to study the full range of public health issues in Europe.

5. Conclusion

The EHEN is a representative example of the cutting-edge and highly funded generation of exposome research. The ambitious integrative if not holistic leanings, the vast range of partners and intensity of scientific interaction at play in the EHEN testify to the concrete intensification of the exposome concept. Focusing on its respective projects helps reveal its core commitments, priorities and limitations for putting the exposome concept into practice. Our analysis of profile papers shows that this novel research address existing limitations by sidestepping, rather than embracing, the criticisms and tensions leveled at the first generation exposome projects. The technology-driven expansion of the type and volume of data collected, of the data analysis infrastructure, and the inclusion of aspects of open and participatory science, are stated as grounds to overcome previous limitations. The EHEN in fact doubles down on its dual promise for an exhaustive knowledge of the role of the environment in health and a delivery of targeted evidence-based public health interventions. We argued that data-driven spatial limitations undermine the representativeness, actionability, and political scope of their results.

The entrenched reliance of exposome studies on complex and costly technological infrastructure and intensive data collection proves in fact double-edged. The exposome appears becoming an approach mostly applicable to affluent urban environments. Doing so, it invisibilizes large swathes of areas (and their associated public health issues) while catering for the issues and needs of the wealthiest and healthiest portion of the population. This contests the virtue of the EHEN ambitions on two grounds. First, it provides boundaries to the claimed integration of exposome research. Second, and more importantly, while tackling some health issues, we argue that EHEN research could contribute to *reinforce* some spatial inequalities of health. Our analysis of profile papers thus exhibits the highly situated – rather than holistic and inclusive – nature of exposome research. In this sense, the limit to its contribution to public and environmental health needs to be explicitly recognized.

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CRediT authorship contribution statement

Yohan Fayet: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Conceptualization. **Thomas Bonnin:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Conceptualization. **Stefano Canali:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Conceptualization. **Elodie Giroux:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Data availability

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References

Primary sources – EHEN profile papers (published in Environmental Epidemiology)

ATHLETE, Vrijheid, M., et al., 2021. Advancing tools for human early lifecourse exposome research and translation (ATHLETE). https://doi.org/10.1097/ee9.0000000000000166.

EPHOR, Pronk, A., et al., 2022. 'Applying the exposome concept to working life health: The EU EPHOR project' https://doi.org/10.1097/EE9.0000000000000185.

Equal-Life, van Kamp, I., et al., 2021. Early environmental quality and life-course mental health effects: the Equal-Life project. https://doi.org/10.1097/EE9.0000000000000183.

EXIMIOUS, Ronsmans, S., et al., 2022. The EXIMIOUS project – mapping exposure-induced immune effects: connecting the exposome and the immunome. https://doi.org/10.1097/EE9.0000000000000193.

EXPANSE, Vlaanderen, J., et al., 2021. Developing the building blocks to elucidate the impact of the urban exposome on cardiometabolic-pulmonary disease: the EU EXPANSE project. https://doi.org/10.1097/EE9.0000000000000162.

HEAP, Marinez, R.M., et al., 2021. 'Human exposome assessment platform' https://doi.org/10.1097/EE9.0000000000000182.

HEDIMED, Laiho, J.E., et al., 2022. Exposomic determinants of immune-mediated diseases: special focus on type 1 diabetes, celiac disease, asthma, and allergies: the HEDIMED project approach. https://doi.org/10.1097/EE9.0000000000000212.

LongITools, Ronkainen, J., et al., 2021. LongITools: dynamic longitudinal exposome trajectories in cardiovascular and metabolic noncommunicable diseases. https://doi.org/10.1097/EE9.0000000000000184.

REMEDIA, Benjdir, M., et al., 2021. Assessing the impact of exposome on the course of chronic obstructive pulmonary disease and cystic fibrosis: the REMEDIA European Project Approach. https://doi.org/10.1097/EE9.0000000000000165.

Other sources

Allan, R., Williamson, P., Kulu, H., 2019. Gendered mortality differentials over the rural-urban continuum: the analysis of census linked longitudinal data from England and Wales. Soc. Sci. Med. 221, 68–78. https://doi.org/10.1016/j.socscimed.2018.10.005.

Ayuso-Álvarez, A., Ortiz, C., López-Cuadrado, T., Rodríguez-Blázquez, C., Fernández-Navarro, P., González-Palacios, J., et al., 2022. Rural-urban gradients and all-cause, cardiovascular and cancer mortality in Spain using individual data. SSM Popul Health 19, 101232. https://doi.org/10.1016/j.ssmph.2022.101232.

Bremberg, S., 2020. Rural-urban mortality inequalities in four Nordic welfare states. Scand. J. Publ. Health. 48 (8), 791–793. https://doi.org/10.1177/1403494820921684.

Canali, S., 2016. Big Data, epistemology and causality: knowledge in and knowledge out in EXPOsOMICS. Big Data & Society.

Canali, S., 2020. What is new about the exposome? Exploring scientific change in contemporary epidemiology. Int. J. Environ. Res. Publ. Health 17 (8), 2879. https://doi.org/10.3390/ijerph17082879.

Canali, S., 2022. A pragmatic approach to scientific change: transfer, alignment, influence. Euro Jnl Phil Sci 12, 48. https://doi.org/10.1007/s13194-022-00477-7.

Canali, S., Leonelli, S., 2022. Reframing the environment in data-intensive sciences. Stud. History and Philos. Sci. 90, 203–214. https://doi.org/10.1016/j.shpsa.2022.04.006.

Cartwright, N., Hardie, J., 2012. Evidence-based Policy: A Practical Guide to Doing it Better. Oxford University Press. https://doi.org/10.1093/acprof:osobl/9780199841608.001.0001.

Costa, C., et al., 2019. Population health inequalities across and within European metropolitan areas through the lens of the EURO-HEALTHY population health index. Int. J. Environ. Res. Publ. Health 16 (5), 836. https://doi.org/10.3390/ijerph16050836.

Counil, É., Henry, E., 2021. When scientific knowledge and ignorance make it difficult to improve occupational health: a French and European perspective. New Solut. 31 (2), 141–151.

European Commission, 2018. The Human Exposome Project: a toolbox for assessing and addressing the impact of environment on health. https://cordis.europa.eu/programme/id/H2020_SC1-BHC-28-2019. (Accessed 7 December 2023).

European Human Exposome Network, 2020. About. https://www.humanexposome.eu/about/. (Accessed 7 December 2023).

Eurostat, 2023. 'Life Expectancy by Age and Sex', 7 December eap.2023.

Fayet, Y., 2023. Place of integrative approaches in the study of spatial dimension of health outcomes. Integrative Approaches in Environmental Health and Exposome Research: Epistemological and Practical Issues. Palgrave Macmillan, pp. 209–238. https://doi.org/10.1007/978-3-031-28432-8_8.

Fayet, Y., et al., 2020. Beyond the map: evidencing the spatial dimension of health inequalities. Int. J. Health Geogr. 19, 46. https://doi.org/10.1186/s12942-020-00242-0.

Ghiara, V., Russo, F., 2019. Reconstructing the mixed mechanisms of health: the role of bio- and sociomarkers. Longitudinal Life Course Stud. 10 (1), 7–25. https://doi.org/10.1332/175795919X15468755933353.

Giroux, E., 2021. L'exposome : entre globalité et précision. Bulletin d'Histoire et d'Épistémologie des Sciences de la Vie 28 (2), 119–148. https://doi.org/10.3917/bhesv.282.0119.

Giroux, E., 2023. A critical assessment of exposures integration in exposome research. In: Giroux, E., Fayet, Y., Merlin, F. (Eds.), Integrative Approaches in Environmental Health and Exposome Research: Epistemological and Practical Issues. Palgrave Macmillan, pp. 129–171. https://doi.org/10.1007/978-3-031-28432-8_6.

Giroux, E., Fayet, Y., Serviant-Fine, T., 2021. L'exposome : tensions entre holisme et réductionnisme. Méd./Sci. 37 (8–9), 774–778. https://doi.org/10.1051/medsci/2021092.

Giroux, E., Merlin, F., Fayet, Y. (Eds.), 2023. Integrative Approaches in Environmental Health and Exposome Research: Epistemological and Practical Issues. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-28432-8.

Guchet, X., 2019. 'De la médecine personnalisée à l'exposome : environnement et santé à l'ère des big datas'. Multitudes 75 (2), 72–80. https://doi.org/10.3917/mult.075.0072.

Gudi-Mindermann, H., White, M., Roczen, J., Riedel, N., Dreger, S., Bolte, G., 2023. Integrating the social environment with an equity perspective into the exposome paradigm: A new conceptual framework of the Social Exposome. Environ. Res. 233, 116485 https://doi.org/10.1016/j.envres.2023.116485.

Hera Research EU, 2020. Our mission. https://www.heraresearcheu.eu/. (Accessed 7 December 2023).

Janssen, F., 2021. 'The role of smoking in country differences in life expectancy across Europe, 1985–2014'. Nicotine Tob. Res. 23, 152–160. https://doi.org/10.1093/ntr/ntaa011.

Lambrechts, M., 2019. Why Budapest, Warsaw, and Lithuania split themselves in two. The Pudding. https://pudding.cool/2019/04/eu-regions/. (Accessed 7 December 2023).

Lamnisos, D., Middleton, N., Kyprianou, N., Talias, M.A., 2019. Geodemographic area classification and association with mortality: an ecological study of small areas of Cyprus. Int. J. Environ. Res. Publ. Health 16 (16), 2927. https://doi.org/10.3390/ijerph16162927.

Landecker, H., 2011. Food as exposure: nutritional epigenetics and the new metabolism. BioSocieties 6, 167–194. https://doi.org/10.1057/biosoc.2011.1.

Levins, R., 1966. The Strategy of model building in population biology. Am. Sci. 54 (4), 421–431.

Lynch, J., 2017. Reframing inequality? The health inequalities turn as a dangerous frame shift. J. Publ. Health 39 (4), 653–660. https://doi.org/10.1093/pubmed/fdw140.

Mackenbach, J.P., Valverde, J.R., Bopp, M., Brønnum-Hansen, H., Deboosere, P., Kalediene, R., et al., 2019. Determinants of inequalities in life expectancy: an international comparative study of eight risk factors. Lancet Public Health 4 (10), e529–e537. https://doi.org/10.1016/s2468-2667(19)30147-1.

Maitre, L., de Bont, J., Casas, M., et al., 2018. Human Early Life Exposome (HELIX) study: a European population-based exposome cohort. Epidemiology 8, e021311. https://doi.org/10.1136/bmjopen-2017-021311.

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. Environ. Health Perspect. 130 (11), 116001 https://doi.org/10.1289/EHP11015.

Parkinnen, V.P., et al., 2018. Evaluating Evidence of Mechanisms in Medicine: Principles and Procedures. Springer Link. https://doi.org/10.1007/978-3-319-94610-8.

Rashid, T., Bennett, J.E., Paciorek, C.J., Doyle, Y., Pearson-Stuttard, J., Flaxman, S., et al., 2021. 'Life expectancy and risk of death in 6791 communities in England from 2002 to 2019'. Lancet Public Health 6 (11), e805–e816. https://doi.org/10.1016/S2468-2667(21)00205-X.

Reiss, J., 2007. Do we need mechanisms in the social sciences? Philos. Soc. Sci. 37 (2), 163–184. https://doi.org/10.1177/0048393107299686.

Riva, M., Curtis, S., Gauvin, L., Fagg, J., 2009. Unravelling the extent of inequalities in health across urban and rural areas: evidence from a national sample in England. Soc. Sci. Med. 68 (4), 654–663. https://doi.org/10.1016/j.socscimed.2008.11.024.

Senier, L., Brown, P., Shostak, S., Hanna, B., 2017. The socio-exposome: advancing exposure science and environmental justice in a postgenomic era. Environ. Sociol. 3 (2), 107–121. https://doi.org/10.1080/23251042.2016.1220848.

Serviant-Fine, T., Arminjon, M., Fayet, Y., Giroux, E., 2023. Allostatic load: historical origins, promises and costs of a recent biosocial approach. BioSocieties. https://doi.org/10.1057/s41292-023-00303-0.

Shostak, S., 2005. The emergence of toxicogenomics: a case study of molecularization. Soc. Stud. Sci. 35 (3), 367–403. https://doi.org/10.1177/0306312705049882.

Shostak S, Moinester M. The missing piece of the puzzle? Measuring the environment in the postgenomic moment. In: Postgenomics: Perspectives on biology after the genome. 2015. p. 192–209.

Stefler, D., Pikhart, H., Kubinova, R., Pajak, A., Stepaniak, U., Malyutina, S., Simonova, G., Peasey, A., Marmot, M.G., Bobak, M., 2016. Fruit and vegetable consumption and mortality in eastern Europe: longitudinal results from the health, alcohol and psychosocial factors in Eastern Europe study. Eur. J. Prevent. Cardiol. 23, 493–501. https://doi.org/10.1177/2047487315582320.

Trias-Llimós, S., Kunst, A.E., Jasilionis, D., Janssen, F., 2018. The contribution of alcohol to the East-West life expectancy gap in Europe from 1990 onward. Int. J. Epidemiol. 47 (3), 731–739. https://doi.org/10.1093/ije/dyx244.

van Hooijdonk, C., Droomers, M., Deerenberg, I.M., Mackenbach, J.P., Kunst, A.E., 2008. Higher mortality in urban neighborhoods in The Netherlands: who is at risk? J. Epidemiol. Community Health 62 (6), 499–505.

Vineis, P., Robinson, O., Chadeau-Hyam, M., Dehgham, A., Mudway, I., Dagnino, S., 2020. What is new in the exposome? Environ. Int. 143, 105887 https://doi.org/10.1016/j.envint.2020.105887.

Wild, C.P., 2005. Complementing the genome with an 'exposome': the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol. Biomarkers Prev. 14 (8), 1847–1850. https://doi.org/10.1158/1055-9965.EPI-05-0456.

Wilkinson, M.D., et al., 2016. The FAIR Guiding Principles for scientific data management and stewardship. Sci. Data 3, 160018. https://doi.org/10.1038/sdata.2016.18.