



• Perspective

The exposome and the future of epidemiology: a vision and prospect

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It is widely accepted that a relatively small proportion of chronic disease can be explained by genetic factors alone. Although information about environmental exposure is important to comprehensively evaluate chronic diseases, this information is not sufficiently or accurately assessed by comparison with genomic factors. To emphasize the importance of more complete evaluation of environmental exposure, the concept of the exposome, which indicates the entirety of environmental exposure from conception onwards, was introduced in 2005. Since the 2010s several epidemiological studies, such as the Human Early-Life Exposome project, have applied the exposome concept. The exposome consists of three overlapping domains: the general external, the specific external, and the internal environments. General external factors include the broader socioeconomic environment, and specific external factors include lifestyles, occupations, and pollutant exposures. Internal factors include biological effects and responses. Because the exposome covers exposures from conception to death, the birth cohort is an important part of the exposome study. Although there is not yet an established consensus in selecting what, when, and where to measure concerning the exposome, the use of omics analyses, especially analysis of the metabolome, should be considered in order to implement the exposome concept in the birth cohort. The exposome needs to be measured repeatedly in certain important phases of life, such as during pregnancy and infancy. To perform exposome-informed epidemiological studies, untargeted data-driven approaches in conjunction with dimension reduction techniques need to be developed and refined. The exposome concept has the potential to make a breakthrough in overcoming some of the limitations of conventional epidemiology. Concerted national and international efforts are required for future exposome studies.

Keywords: Exposome, Omics analysis, Metabolome, Birth cohort, Untargeted data-driven approach

INTRODUCTION

Now that thousands of genome-wide association studies have been conducted, it is widely accepted that a relatively small proportion of chronic disease can be explained by genetic factors alone [1]. Therefore, to comprehensively evaluate the cause and

progress of chronic diseases, more extensive assessment of non-genetic factors, “environment”, should be performed, to complement assessments of genetic variation. However, in contrast to genome analysis, environmental factors are still being evaluated using questionnaires, geographic information, or a few targeted biomarkers, and are not assessed with sufficient comprehensive-

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ness or accuracy.

In this context, the concept of the exposome, which represents the entirety of environmental exposure from conception onwards, was first introduced in 2005, to emphasize the need for more complete measurement of environmental exposure [2]. The exposome encompasses not only environmental chemicals and pollutants but also lifestyle, socioeconomic status, social capital and the social environment, and even biological responses.

Due to rapid advances in omics technology, sensor technology, data science, and information and communication technology, the exposome concept is now realizable, and has been applied to recent epidemiological studies in Europe and the US, while not yet in Asia [3,4]. The exposome concept has the potential to change the methodology, study subjects, goals, and visions of epidemiology. Therefore, in the present article, we summarize the current status, and discuss issues that should be considered, the expected utility, and future research topics related to application of the exposome.

RESEARCH INITIATIVES RELATED TO THE EXPOSOME

Several exposome-related studies have been launched in Europe and the US since the 2010s. The Health and Environment-Wide Associations Based on Large Population Survey projects (http://cordis.europa.eu/project/rcn/110918_en.html) has been conducted to develop a refined methodology for performing environment-wide association studies, using omics-derived exposome data from population studies across Europe. The EXPOsOMICS project (<http://www.exposomicsproject.eu/>) specifically focuses on developing new methods to measure air pollution and water contaminants, such as using personal exposure monitoring systems, and links the measured external exposure to biochemical changes in the body. The Health and Exposome Research Center: Understanding Lifetime Exposures project (<http://emoryhercules.com>) is funded by the National Institute of Environmental Health Sciences (NIEHS), and aims to develop and provide greater access to new tools and technologies related to the exposome. The Human Early-Life Exposome project (<http://www.projecthelix.eu/>) is a European collaboration of birth cohorts that focuses on the early-life exposome of mothers and children and its associations with various health outcomes.

Because the exposome is defined as the totality of exposure from conception onwards [2], the birth cohort is conceptually essential and a core part of exposome studies. In addition, cross-sectional studies can be subject to potential biases, even when using exposome information [5]. However, birth cohort studies

employing the exposome framework are relatively rare, which emphasizes the need for the construction and reformulation of birth cohorts from the perspective of the exposome concept.

THREE DOMAINS OF THE EXPOSOME AND POTENTIAL TOOLS TO MEASURE THEM

The exposome covers not only longitudinal environmental exposure from conception to death but also three comprehensive overlapping domains of exposure: the general external, specific external and internal environments [6]. General external factors include the broader socioeconomic environment such as social capital, education level, home location, urban-rural environment, and climate factors. More active and appropriate use of geographic information systems and social media networks can improve the measurement of the general external environment. Specific external factors include lifestyles, occupations, and pollutant exposure. Personal monitoring using sensor technologies and omics analyses such as metabolomics and adductomics can improve the measurement of the specific external environment. Internal factors include biological factors such as metabolism, circulating hormones, gut microflora, oxidative stress, and inflammation. The internal environment reflects not only the biological effects of external exposure but also biological responses to them [7]. Analyses of the transcriptome, proteome, metabolome, epigenome, and microbiome can improve the measurement of the internal environment [8].

APPLICATION OF THE EXPOSOME CONCEPT IN THE BIRTH COHORT

As in the Human Genome Project, concerted national and international efforts for data sharing and coordination, control of measurement error, and methodological development, rather than scattered efforts by individual research teams, would be more appropriate to develop and refine methodologies to evaluate the exposome [9]. Although the NIEHS have supported the building of centralized infrastructure to provide tools, methods, and data for exposome study, there have been a limited number of proof-of-concept studies, and there is as yet no established consensus in selecting what, when, and where to measure in exposome studies [10].

However, in general, to implement the exposome concept in the birth cohort, it can be said that the use of omics analyses, especially of the metabolome through high-resolution metabolomics, should be considered for untargeted discovery of chemicals with potential harmful effects[3]. The metabolome com-

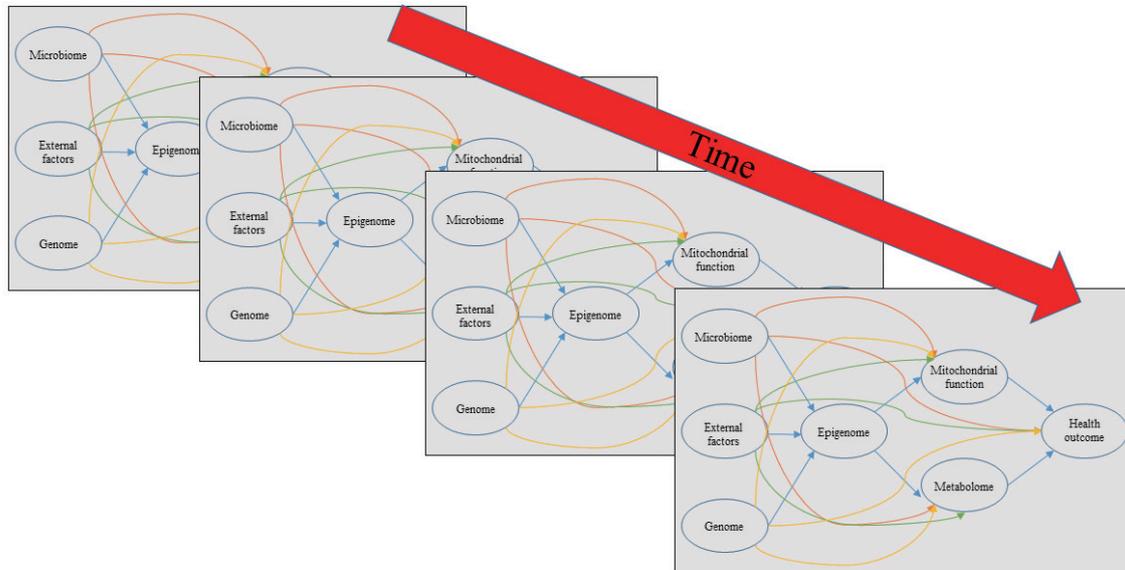


Figure 1. Longitudinal changes in pathways from the exposome to health outcomes.

prises not only endogenous compounds created by metabolic processes in the body but also exogenous compounds such as environmental pollutants, and reflects all aspects of exposure, susceptibility, and outcome [11]. However, because concentrations of pollutants are generally much lower than concentrations of endogenous compounds, and untargeted high-resolution metabolomics analyses cannot reliably detect low concentrations of small molecules, complementary conventional targeted analyses could also be conducted [11,12].

Because it is not feasible to measure all components of the exposome continuously, it is more realistic to assess the exposome regularly at certain important phases of life (Figure 1), such as during pregnancy and infancy, which are known to impact disease susceptibility later in life [4].

Finally, collection and storage of biospecimens such as blood and urine, widely used and typically considered to be the preferred matrices, should also be conducted cautiously in studies applying the exposome concept, because some methods used in omics analyses are known to be sensitive to biospecimen quality [3].

SPECIFIC RESEARCH SUBJECTS

The investigation of complex associations between the exposome and health outcomes is one of the challenges that must be overcome in the future exposome-informed epidemiological studies. Untargeted data-driven approaches employing various dimension reduction techniques such as regression shrinkage methods and principal components analysis can be used to propose new hypotheses and draw conclusions [13]. However, ana-

lytical strategies analogous to genome studies are not appropriate in exposome studies, because exposome data is highly heterogeneous and some components such as pollutants are correlated [5]. Further methodological improvement is warranted.

We suggest the following research directions to be investigated in exposome-informed epidemiological studies. First, data-driven data exploration and analysis methodologies suitable for exposome data structures need to be developed and refined. Second, health impacts due to multiple pollutant exposure needs to be assessed. In addition, molecular fingerprints of specific exposure can be used practically in epidemiological investigations [8]. Third, interactions between pollutant exposure and lifestyle factors with respect to various health outcomes warrant investigation. Fourth, interactions between pollutant exposure and the general external environment can be investigated in the context of health inequality. Fifth, exposome data can be used to strengthen causal reasoning by assessing exposure, biological pathways, and health outcomes (the “meet-in-the-middle” approach) [13]. Sixth, the developmental origins of health and disease hypothesis [14] can be evaluated using epigenome data, in exposome-informed life-course epidemiological studies. Finally, exposome-genome interactions also require investigation in order to comprehensively understand health and disease phenomena.

CONCLUSION

Although precision medicine and exposome-informed epidemiology have some similarities in their use of technologies and data sources such as omics analyses, claims data, medical re-

cords, and life-log data, their goals and motivation differ substantially. Precision medicine mainly focuses on personalized clinical treatment of patients, and therefore is more hospital-centered. In contrast, exposome-informed epidemiology focuses on finding etiological factors and predicting and preventing diseases, and cohorts of the general population, especially mothers and children, are considered to be an important component.

The goal of exposome-informed epidemiology is to comprehensively understand health and disease and to improve the health status of populations by preventing disease. The exposome concept has the potential to make a breakthrough in overcoming the limitations of conventional epidemiology, related to exposure misclassification, complex interactions between exposures, and causal inference. Concerted national and international efforts are required for the active application of the exposome concept.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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