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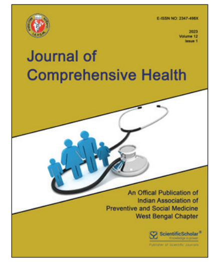

Review Article

Exposome within the Context of the Public Health Perspectives

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ABSTRACT

Genetics account for a small proportion of diseases, and the remaining causes appear to be environmental. The classic epidemiological approach is to study each cause-effect relationship separately. This does not consider the linked and complex interactions between different exposures throughout the life course. The exposome is a new concept in health research. It focuses on integrating environmental exposures from conception to death with the human genome to study their effects on human health. It complements but does not mirror the genome. It is dynamic and includes many domains, and the relationship between different domains is complex. These domains include the internal biological processes, the general external environment, and the external individual's local immediate environment. Environmental exposures need to be studied to understand the causes and mechanisms of diseases to formulate prevention strategies. Many study designs, assessment tools, and methods are currently used to unravel its effects at levels of the population throughout the life span. While the application of the genome to health may be at the individual level, the exposome will be applied to the general population. Therefore, the exposome is likely to benefit public health rather than clinical practice. This narrative review aims to provide readers with the current status of exposome research, its relevance to public health and medicine, as well as its future challenges. The most important challenges are methodological and statistical issues, identification of novel biomarkers, big data management using artificial intelligence, ethical and economic considerations, integration with one health and syndemic approaches, and lastly, data sharing and international cooperation.

Keywords: Exposome, Genomics, EXPOsOmics, Epigenomics, Biomarkers, One Health, Syndemics

INTRODUCTION

Until recently, epidemiological studies focused on a single or few simultaneous exposures. The term "exposome" emphasizes the importance of integrating environmental exposures from conception to death with the human genome to study their effects on human health. This represents the non-genetic drivers of disease. The exposome is a comprehensive measurement of all human exposures from conception to death with a focus mainly on chronic diseases.[1-5]

Miller and Jones[6] expanded this definition as the cumulative measure of environmental influences and associated biological responses throughout the lifespan; the effects may be transmitted to new generations. This holistic approach to studying gene-environment interactions permits a more accurate assessment of disease risk. Exposome research requires multi-disciplinary partnerships to define the best study design and overcome analytical challenges.[7]

Exposome research is a growing field that is still being developed and refined.[8] The genetic variants explain a small fraction of this risk while the environmental exposures play the greatest role. This applies to non-communicable diseases (NCDs), for example, asthma, allergic diseases, type II diabetes, obesity, cancers, congenital anomalies, and neurodegenerative diseases.[9-11]

There are many justifications for the development of the concept of exposome including: (1) a major limitation of many epidemiological studies focus on a single or few environmental factor(s) at a single time-point and ignore effects, co-exposures, confounding, and synergy between different environmental factors;[12,13] (2) the major common diseases have an environmental etiology;[14] (3) simultaneous assessment of many exposures provide an accurate assessment of the impact on health; (4) currently the genetic polymorphisms is accurately assessed at a relatively low cost; (5) accurate assessment of environmental exposures enables the study of the interaction between the environment and the genome;[2] (6) the growing burden of NCDs caused by environmental and behavioral risks; (7) the lack of integrated approach for prediction and detection of NCD;[15] (8) understanding exposomes has significant implications for public health[16] and guide policy makers to apply valid preventive and treatment strategies;[17] (9) help individuals to understand the environmental factors that contribute to disease;[6,18] and (10) refinement of exposure assessment methods, and developing sophisticated computational approaches will revolutionize the fields of public health.[19,20]

CLASSIFICATIONS/DOMAINS

There are multiple overlapping classifications of the exposome. These types can be (1) external (e.g., economic and climatic factors) or internal (e.g., hormones, sex, and aging); (2) major (e.g., smoking, obesity, and cholesterol) or minor (e.g., sleep and stress); (3) modifiable (e.g., body weight and smoking) or non-modifiable (hormones and genes); and (4) general acting on population level (e.g., traffic risks and climatic factors) or specific acting on individual level (e.g., diet and physical activity).[21,22]

There are three interacting domains of exposome research.[2,3,5,23-25] These domains are as follows:

1. Internal biological processes, for example, inflammation, oxidative stress, hormones, epigenetic changes, aging, and sex.
2. General external environment, for example, climatic factors, traffic, economic factors, and urban environment.
3. Specific external individual's local environment, for example, diets, tobacco, occupation, radiation, chemicals, and physical activity

PUBLIC HEALTH RELEVANCE

Forms of exposome include public health exposome (PHE), occupational (work-related) exposome, military exposome, and fetal and early life exposome.[26] There are four domains of PHE, including natural (e.g., air, water, and land), built (residence, work, and transportation), social (demographics and socio-cultural), and policy environments.[27]

The PHE represents the general external environment. Adapting PHE principles will challenge the traditional public health policy, research methodology, and funding mechanisms.[27]

There are many potential national and international public health implications for the exposome. First, helps in designing interventions to reduce NCDs risks.[28] Second, it helps in the development of novel methods for assessing the cumulative effects of multiple exposures.[29] Personal monitoring devices can help scientists better track population exposures and assess the effectiveness of interventions.[30] Third, develop environmental intelligence services, for better control of exposure. Finally, the exposome tools can address public health challenges of communicable diseases to limit their spread.[31]

GLOBAL SITUATION

Large research projects related to exposome have been launched in developed countries. There are many interrelated, mixed, and synonymous terminology.[32-37] The following is a hint on these projects.

Genome-wide association study (GWAS)

GWAS identifies associations of genes with a particular disease. GWAS explores the genome (the entire set of DNA) in a large population to find out minor variations called single nucleotide polymorphism (SNP). Each study can look at thousands of SNPs at a time. Despite the genetic risk of disease being unmodifiable, GWAS identified that the genetic variation contributes to chronic diseases (e.g., cardiac disease and diabetes) and drug effects. However, individual SNPs accounted for a small percentage of disease risk.[38-40] Birth cohort studies found SNPs were associated with different outcomes, revealing the complexity of the genetic contribution to disease.[40] GWAS have several limitations including small sample sizes, non-control for possible confounders, the potential for false positive results, and the findings explain only a partial amount of heritability.[41-43]

Exposome (environment or environmental)-wide association study (EWAS)

EWAS examines the association between multiple environmental factors and complex diseases to decipher the environmental causes of disease. In EWAS, the associations are adjusted for a multiplicity of comparisons.[24,44] and were employed in type 2 diabetes[32] and the National Health and Nutrition Examination Survey.[45-47] Better data sources and rigorous methodologies are prerequisites for better utility of EWAS.[48] The statistical analysis in EWAS is similar to GWAS and aims to use a panel of exposures.[35,44,45]

EXPOsOmics

EXPOsOMICS is the study of the exposome[48] to assess environmental exposures, mainly water contamination and air pollution, using personal exposure monitoring and linking them to biochemical and molecular changes in the body.[2,24,26] This approach needs systematic simulation to characterize its efficiency.[49]

Epigenome-wide association studies (EpWAS)

Epigenetics is the discipline of non-genetic mitotically inherited variation in the gene potential.[50,51] EpWAS is the examination of epigenetic marks, such as DNA methylation, to find out the associations between epigenetic variation and a particular phenotype/trait.[51] Unlike the currently unmodifiable genetic risk of disease, the epigenetic risk may be modifiable and/or reversible.[52]

The life course of epigenetics, together with the exposome model, could allow a better understanding of the etiology of diseases and the role of epigenetically regulated gene expression.[53]

HERCULES (UNDERSTANDING LIFETIME EXPOSURES)

HERCULES refined new technologies for the assessment and application of the exposome.[2] Biomedical and health research have become progressively genome-centric due to the technological developments in the genomics sciences.[54] The HERCULES aims to (1) provide access to exposome-related methods, for example, temporal and spatial statistical models and high throughput toxicology, and (2) advance translation of new findings to develop new prevention or treatment strategies.[24]

Health and environment-wide associations based on large population surveys (HEALS)

HEALS integrates "omics" data with biochemical biomonitoring to create internal exposome at the individual level.[2,55] It aims to identify the links among environment, genes, and NCDs in large cohorts using new technologies in different settings of exposures.[56]

Human early-life exposome (HELIX)

HELIX combines all early-life environmental hazards that mothers and children are exposed to and links this to the growth, development, and health of children.[4,57] It is a European collaboration project established as a proof-of-concept study to illustrate children's exposomes through early life to measure environmental exposures for air, food, water, pesticides, ultraviolet rays (UVR), and noise of large samples of mother-child pairs.[24]

Children's health exposure analysis resource (CHEAR)

CHEAR project advances understanding of the impact of environments on children's health and development.[55] It provides access to statistical analyses to incorporate and expand environmental exposures in their research. The CHEAR Data Center created a public data repository that collects data from studies.[58]

Japan environment and children's study (JECS)

JECS is an ongoing birth cohort study that measures the environmental exposures during pregnancy and throughout childhood in 100,000 Japanese mother-child dyads. Children's health will be examined periodically until the age of 13.[55,59]

METHODOLOGICAL ISSUES

Exposome assessment

Many integrated tools and technology are used for systemic mapping of the exposome. Traditional methods (e.g., questionnaires) are useful for measuring external factors. Personal monitoring devices (e.g., smartphone applications and wearable sensors) collect real-time data on exposure.[2,4,28,45,60-63]

Biomarkers

Indicators (e.g., chemicals in urine, blood, and tissues) are incorporated into exposome and epidemiological studies that measure biological processes and characterize the internal exposome and biological response.[64-66] The high-throughput-omics measure thousands of biomarkers simultaneously and provide a detailed molecular profile of an individual at a given time.[24,67]

Geographic information systems (GIS)

GISs track the collection, editing, storage, analysis, and interpretation of geographic data and estimate the individual's exposure to environmental hazards based on spatial data, for example, air pollution and noise[68], to find out the associations between environmental exposures and health effects.[69,70] They allow for mapping of topographical, environmental, or health-related exposures.[70]

Computation and simulation approaches

Data generated by exposome projects require advanced computational and simulation methods for storage, analysis, and interpretation. Data mining techniques, including machine learning[71-73], are used to identify patterns and relationships within the complex exposome data.[32,73]

CHALLENGES

Over past decades, there has been a substantial argument on the concept of the exposome.[2,3,6,12,30,58,74] Many challenges face the practical application of the exposome concept and limit its progress. The following text summarizes these challenges.

Exposure assessment challenges

The main challenge is the thousands of different combinations of historical, current chemical, and physical and biological exposures together with diversity and complexity of exposure during an individual's lifetime with synergistic effects between diverse exposures.[75]

The exposome is dynamic and varies throughout a lifetime with critical windows of exposure. The impact of exposure differs for each individual due to differences in genetic and personal factors.[6,20,49,74,76,77]

At present, sensors are used to monitor clinical parameters such as glucose and blood pressure levels. New sensors to measure biomarkers have been developed.[78] The continuous, real-world, real-time assessment of exposures and their temporal variation with the individual's activity, location, and lifestyle can be monitored by devices with remote-sensing-based spatial referencing technologies. The use of smartphones and tablet technology is likely to provide greater opportunities to collect exposure information.[79,80]

Methodological challenges

There is a lack of validated standardized methods for measuring exposures addressing the dynamic, life-long nature of the exposome. Validated scales to characterize environmental exposures throughout life and endogenous events within the body are lacking. New technologies, such as high-throughput methods for measuring simultaneous multiple exposures, are being developed.[81,82]

Birth cohort studies are the best to understand the associations between longitudinal exposure to various environmental factors and incidence of diseases with unknown etiology.[83] Birth cohort studies are prone to potential biases in the collection of exposure and outcome data.[84]

Statistical challenges

The current statistical methods cannot disentangle the true effects from confounding exposures, variability of exposures, and effects over time (short vs. prolonged; low vs. heavy).[24] Another statistical challenge is exposure misclassification or recognizing synergistic effects between exposures. Analysis and assessment of the totality of exposure over the life course is difficult as the same exposure may have different effects at various periods of life, with some periods being more critical to health and disease.[7,12]

To explore the relationship between multiple external exposures–and outcomes, the following analysis has been used for example, latent class analysis, multiple-exposures regression-based methods, and single-exposure regression-based methods.[85]

Exposome research priorities

Exposome projects are opportunities for scientific innovation and tools to establish causes and risks, capture co-exposures and confounders, assess dose-response data for risk assessment and stratification, assess critical windows in a lifetime, evaluate potential interventions, and development of research methods. Priority should be given to research on NCD prevention, environment, and behavior.[75,86]

Identification of informative and novel biomarkers of exposure and effects

At present, the biomarkers of exposures can be analyzed in biological materials to assess the effects of different exposures during different stages of life-cycle.[87] The persistent chemical biomarkers (e.g., lead) persist in fat and can be detected in breast milk and blood to estimate long-term exposure.[88] Non-persistent chemicals (e.g., currently used pesticides) can be detected in blood and urine.[89] Biomarkers of effects reflect measurable changes in physiologic and biochemical parameters that occur as a result of exposure.[90] There are many known biomarkers, for example, immunoglobulins biomarkers of infections.[91-93] There is a need to identify agreed-on novel biomarkers for characterizing the exposome to support current and future exposome research. Development and validation of new biomarkers is critical for the exposome initiative to succeed and will help in understanding the pathogeneses of the exposure-disease relationship.[75,67,94]

Molecular epidemiology studies that identify the relationship between exposures and health outcomes provide the required information about disease processes and pathways. There is a need for both laboratory and field validation of biomarkers.[75,95]

Epidemiologists must understand the omics principles to define the appropriate time to include biomarkers and integrate omics outcomes to understand the causes of disease better.[96,97]

Management of big data challenges

Data mining techniques may help in finding statistical associations between exposures and their effects and genetics with disease. Data related to exposures and health outcomes can be collected from history taking during interview schedules, health records, local or national registries, direct clinical examinations, as well as GIS-based systems of environmental exposures and socioeconomic parameters, biological materials among others.[98-101]

Getting benefits of artificial intelligence (AI)

AI framework provides researchers with an understanding of when and how to apply AI algorithms to diverse types of data. The stepwise method starts from the initial data up to the evaluation and validation of results.[102]

In exposome research, AI helps to (1) analyze the complected data which is beyond the capabilities of the human brain; (2) understand the exposome simultaneously at different types of data; (3) predict disease risk with application of preventive and treatment measures; (4) augment stratification of patient risk and applying personalized approach to health care by considering confounders, interactions, and the increasing prevalence of multi-morbidity; and (5) enable accumulation of data across the different types and domains of the exposome.[102-106] Policymakers and clinicians need to decide how to apply newly generated models of disease prevention and treatment in real life.[106]

Ethical consideration

The proper bioethical assessment is needed with adherence to strict ethical principles of research to ensure the rights of individuals. In exposome research, the ethical considerations to be considered include exposome tools, the applicability of its findings, and the epidemiological and/or clinical norms applicable to research.[107]

Integration with syndemic approach

Syndemic is defined as a synergistically multiple interrelated epidemics occurring at the same time. There is a biological and social interactions that increase a person's susceptibility to adverse health outcomes.[108-110]

The social component of the syndemic is partially explained by unhealthy behaviors attributed to different factors, including social inequalities. Recently, high-throughput "omic" data were associated with measures of social inequalities.[111] Clearly, the idea of syndemic is strongly relevant to the exposome approach. In both cases, a life course approach is key. Researchers and policymakers need to develop more effective strategies for preventing and treating diseases with syndemic approaches by integrating environmental, whole-body health, and internal biologic exposome level.[112,113]

Integration with "One Health" approach

Both the exposome and the one health developed from the need to comprehend what affects human health. The one health concept serves as an embracing background with the exposome and exposomics nested within one health concept. Furthermore, the exposome framework provides the basis for planning and actions that address the components of one health concept (human, animal, and/or ecosystem). The one health and exposome concepts are highly synergistic, the merging of both concepts have the following benefits: (1) biomarkers analyses and exposomics provide significant insights for the human domain of one health; (2) exposomics provides the diagnostics to be used in one health's surveillance; (3) expands the scale and time of challenges of one health framework; (4) expands application of the exposome to non-human life; (5) applying exposomics issues in real time may resolve vague issues of one health framework; (6) current and future accommodation of human well-being in a worldwide culture; and (7) identify the highly interconnected chemical, physical, and biological stressors affecting humans, animals, and the environment (one health components); (8) integrating the traditional health surveillance with exposome and one health provides an innovative comprehensive public health approach for tailored interventions, and disease outbreak predictions; and (9) engagement of the efforts of stakeholder, policy makers, public, academic, and nonprofits organization.[16,113-121]

Cost challenges

Massive and sustained financial resources are needed to invest in exposure biomarkers' development. Training of a new generation of multi-national researchers operating in an interdisciplinary environment also needs funds.[2,12,74] This high cost is beyond the capabilities of many countries, especially developing ones where the environmental exposures are worse.

International cooperation and data sharing

Local and international data sharing will benefit the researcher, the scientific community, research sponsors, data repositories, and the general public. Involving developing countries in exposome research and projects is a component of international cooperation. The best practices to encourage international cooperation include: (1) clear data documentation with robust metadata assuring confidentiality; (2) proper data storage in repositories to be easily accessible; (3) available and affordable technology for data storage, processing, and transfer especially for countries with limited resources; (4) provide education and training for international research communities; (5) promote future collaboration in data mining and integration with genomic data; (6) coordination of research initiatives, resources and infrastructures; (7) consideration of the legal and ethical issues when sharing medical data; (8) adequate funding for creation and maintenance of shared data repositories; (9) bridging the international differences in cultural and scientific disciplines; and (10) promote inter-and multi-disciplinary, bioinformatics, epidemiology; biostatistics; laboratory sciences; and environmental sciences.[122-129] The knowledge transfer about the exposome is difficult from an educational perspective. Adoption and promotion of the exposome within academia is the responsibility of public and environmental health sciences. It is necessary to integrate the big data of exposome into elective courses for both undergraduate and postgraduate students.

CONCLUSION

Research on the human exposome has a broad range of applications in fields such as public, occupational, and environmental health, eHealth, and clinical medicine. Many potential challenges to be tackled by multidisciplinary teams to address the long-term effects of different exposomes. Scholars need to emphasize advanced data handling and statistical analysis of big data. It is important to merge exposome projects with one-health initiative and syndemics approach health as the three have the same framework. There is a need to include developing countries in a community-level exposomics approach.

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