Editorial

Measuring Exposome Associated with Health

Survey on life course history, built and ecological environment complements exposomics

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The concept of exposome has received increasing discussion, including the recent Special Issue of Science –"Chemistry for Tomorrow's Earth," about the feasibility of using high-resolution mass spectrometry to measure exposome in the body, and tracking the chemicals in the environment and assess their biological effect. We discuss the challenges of measuring and interpreting the exposome and suggest the survey on the life course history, built and ecological environment to characterize the sample of study, and in combination with remote sensing. They should be part of exposomics and provide insights into the study of exposome and health.

Approaches to conducting an etiological study of complex human disorders have changed in recent decades. With the completion of the Human Genome and multiple related projects, the development of microarray, the next-generation sequencing technology, and bioinformatics tools, investigators can rapidly integrate genomic variation with environmental exposure for a complete examination of potential etiological factors causing diseases or health outcomes. However, compared with the genetic variants in the genome, the measurement of environmental factors lacks a similar level of accuracy and coverage. In 2005, Wild (1) proposed the concept of the exposome and believed it would be useful to draw attention to developing the methodology for assessing exposure over time.

THE EXPOSOME AND EXPOSOMICS

The concept of exposome (**Box 1**) has received increasing interest and discussion in recent years, including the National Academy of Sciences workshop and meeting on exposome (2). Characterization of the exposome should include chemicals that are caused by both internal and external environments (3). For example, chemicals are produced by infection, inflammation, and oxidative stress, some of which can retrospectively partially capture past exposure events. Potential measurement and utility of the exposome were also discussed concerning the application of "omics" techniques to epidemiological study (4, 5). The exposomics were defined (Box1), and the internal exposures can be characterized by functions of genomics, metabolomics, and other "omics" (6). This expansion appears broader than the initial concept of the exposome in parallel comparison with the genome.

Very recently, a Special Issue of *Science* – "Chemistry for Tomorrow's Earth" focuses on chemicals in the environment (7). Investigators discuss the feasibility of turning the exposomics into precision sciences and propose new regulations of chemicals and reducing the exposure in the environment through green chemistry. High-resolution mass spectrometry (HRMS) is proposed for identifying and measuring the chemicals and metabolites (or small mole-cules) in the body (8), including those produced by both exogenous and endogenous exposure to known or unknown chemicals. With a careful study design, the high-throughput approach would advance environmental health and understanding of the underlying mechanisms. More importantly, the holistic approach allows discovering chemicals in the living organisms without a known history of exposures, such as second-hand smoke, afflation B1 that represents a risk factor for liver cancer(9). Measuring the exposome in the body allows individuals to be profiled, by identifying a group of chemicals or metabolites that can distinguish individuals in the risk pool; an essential component for the precision medicine and health.

Another discussion (10) is about tracking a group of chemicals in the changing environment and assessing for a combined risk for health. This is an excellent concept for the study of environmental health because a chemical from the source of pollution entering our environment may not be alone, and there may be mixture toxicity even though the concentration of individual chemicals is at a low level or below the occupational standard (e.g., benzene). Such toxicity has been demonstrated in the past regarding benzene exposure in humans (11). Tracking multiple chemicals may help to identify the source of pollution, which is important

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for taking preventive steps to reduce potential ongoing exposure. With non-target screening, one can perform analytical chemical analysis of indoor and outdoor environments and biological samples to detect and identify known and unknown chemicals. Further, with target analysis and bioanalytical tools, one can capture and assess a group of chemical mixtures that may pose risks for living organisms. Screening and monitoring the chemicals in the environment (e.g., water, soil, living organisms) may require a careful plan for sampling and sample preparation to address the variation in time, spatial space and composition (10), which may have to match the sampling in the human studies for assessing biological effect.

Box 1. Exposome, exposomics and life course history

The exposome was initially defined to "include environmental exposure (including lifestyle factors) across the life span from the prenatal period onwards."(1).In addition to the exogenous environment, the detection and concentration of internal chemicals may vary with who you are (genetic susceptibility or resistance), where you live, what you eat and lifestyle, and what activity and work you do. Socioeconomic status and social network may also contribute to the exposome.

Exposomics is defined as "the study of the exposome and relies on the application of internal and external exposure assessment methods"(6).

Life course history is defined with five principles(12), lifespan development, human agency, historical time and geographic place, time of the decision, and linked lives.

CHALLENGES OF MEASURING AND INTERPRETING THE EXPOSOME

Further discussions of measuring the exposome may help to turn this concept and discussion into better practice in research and to maximize the benefits of the new technologies. The measurement of the exposome in the body may not be comparable with that of the genome. It has been known that a limited number of polymorphisms are in the human genome, which can be measured with microarray or the next-generation sequencing technologies. The common genetic variants can be largely regarded as fixed attributes, i.e., little variation in the genetic variants within an individual over time. However, the measurement of the exposome is highly variable and dynamic, which might limit the progress of advancing this type of approach to molecular research if used alone. It may have to be combined with other approaches. While some internal chemicals may indicate exposures in the past, some others may be outcomes of a series of biochemical and chained reactions accumulated in the body, or at a specific time point, and therefore are determined or modulated by a number of factors (Figure 1). In addition, high-throughput technology may suffer from significant batch effects, even in measuring the genome, which may require a rigorous study design (13) and careful analytical processes and analyses. Due to variability and dynamics, in principle, the exposome should be measured longitudinally (1) to examine how the change in exposure would alter the biological effect or response. Of note, the uncertainty, measurement errors, and biological specimens may vary significantly with time and geographic location. This would make the population-based longitudinal measurements of exposome more challenging, in particular for low concentration of chemical and rare outcomes.

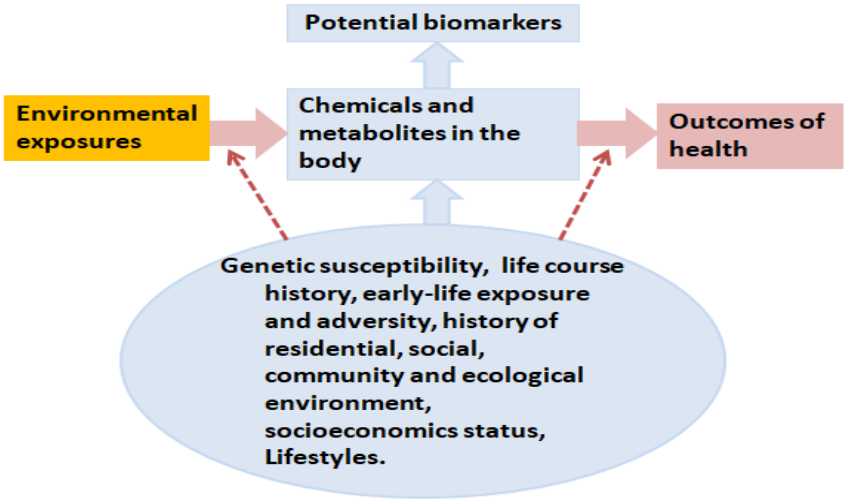

Figure 1. A framework of biomarker of exposure with environmental exposure and health outcomes in exposomics.1) Dashed arrow indicates modulation effect from environmental exposure to cause biological response and health outcomes; 2) factors in the ellipse circle are component to be observed or latent factors that can be measured.

More critically, interpretation of the internal chemicals and evaluation of their biological effect may have to be linked to the levels of exogenous exposure in the environment, which may help to take preventive steps to reduce further exposure and potential risks. Many factors may determine the biological effect or response including the source of exposure, the cumulative dose of an exposure in the environment, how individuals are exposed (e.g., skin, gastrointestinal tract, or inhalation), and an individual's susceptibility. For example, the level of internal nicotine indicates an overall burden of tobacco smoke exposure but may not reflect peak doses of tobacco exposure, which must be combined with the duration of tobacco smoking. Analytically, internal exposure measured at a specific time point can provide an association with biological effect or response but may not prove causation. The cumulative exposures may determine the biological response or effect, but also help to interpret the chemicals detected in the body, which may allow us to establish an exposure dose-response relationship at a population level. Except some special cases(14), the cumulative exposure may be difficult to obtain through the biological sample. The retrospective collection through a survey may be complementary.

SURVEY ON LIFE COURSE HISTORY, BUILT AND ECOLOGICAL ENVIRONMENT

Surveys are essential tools to complement the measurements by high-throughput technology. Humans are social animals and highly heterogeneous. A survey conducted with a well-designed multi-domain questionnaire is an integral part of measuring the exposome. Relevant do-mains may include the individual and family, build community, and ecological location. It has become clear that many chronic diseases or even cancers have developmental origins(15, 16). A survey of life course history may be a good approach to document sample heterogeneity in the early or critical stage of development in life. The concept of the life course originated in the methodology of sociology in the 1920s (17, 18) and developed in the 1960s for examining an individual's life history. Studies showed how early events affected future decisions and critical demographic events such as marriage, divorce, and mortality. Elder described the life course theory and defined five principles (12), of which the lifespan development, historical time, and geographic place may have implications for examining the environmental factors associated with human health. The life course history can be appropriately collected through a survey with structured, semi-structured questionnaires or even an ethnographic study of some individual cases. Stressful events, natural disasters such as famine or hunger, epidemics, or pandemics of a disease that the maternal organism experienced, and medications used during pregnancy may be adverse events that pose a risk of disease or health for the child in later life. Some historical events are fixed attributes and can be retrospectively collected through documentation or survey, with minimal recall errors. The dose of exposure associated with lifestyle or exposure to a fixed source of risk and dynamic social environment can also be collected through a survey.

Previous research has shown the missing link of both genes and the environment to the risk of human diseases and some adverse health outcomes. Over the past decade, a large number of genome-wide association studies have indiated that genetic variants only explained a small proportion of variation in the risk of human disorders, even for those with a substantial heritability (19), including human height (20). Other diseases such as cancers may be primarily caused by environmental factors, in particular unhealthy diet, inadequate physical activity, and tobacco use. For example, a twin study has indicated that inherited genetic factors contribute a minor portion of susceptibility to most types of cancers(21), and a non-shared environment may explain a majority (>70%) of variance in the incidence of most cancers (22). Therefore, measurement of the exposome would improve the identification of novel causal factors for health and diseases and help to explain the concentration of chemicals detected and measured in the body through the HRMS approach. In some cases, one can use special biological samples such as teeth to restructure the exposure to some organic chemicals in the prenatal and the early childhood stage that has been implicated for chronic diseases in later life (14). Such techniques can be very useful in study of some kinds of diseases and health outcomes.

The missing risk factors for health should be in the environment (23), which includes an individual's family environment, early life events, built environment and ecological environment one has experienced from the preconception period onwards. The indoor air quality might be major part of environment that has been missed, as the typical indoor air pollutants (e.g., smoke, benzene, and radon) have a high potential to cause harm to human health and individuals may be exposed for a substantial duration of time. A survey approach could help retrospectively collect information on the possible duration of exposure that occurred in early development or in parental life during one or more critical windows of reproduction and development. In addition, information on built community and environmental exposure, history of the residence, the distance to the nearest possible sources of pollutions, green space, and walk-ability may have important implications for public health such as cardiovascular disease and mental health(24), and all such information can be collected through a survey or geographic information systems (GIS). The built environment has become an emerging field of public health (25). One genome-wide epigenetic study conducted in a Detroit neighborhood found that a group of epigenetic biomarkers was associated with mortality risk. This association was largely driven by the built environment, such as availability of green space in the neighborhood (26). However, information on the duration of residence may be needed from a detailed survey to further study this association. Further, with the availability of all kinds of electronic "big" data, including the built environment, traffic, and remote sensing and spatial data, GIS can be used to map exposure and the risk of disease at a spatial level. Ecological and spatial informatics could provide the first intuitive evidence for conducting a study that aims to identify individual risk factors.

Surveys and the HRMS approach complement each other.

Survey research is a standard tool for a population-based observational study. Many social and epidemiological cohort studies have been carried out longitudinally in cardiovascular disease and aging (e.g., Framingham Study). Early efforts in the precision medicine initiative have primarily been made to the cohort study in the United States. However, the HRMS approach can be added to the cohort study, and investigators are allowed to conduct precision sciences and assess health outcomes. While the HRMS approach mostly collects data at a cross-sectional time, there is potential for the study of biological effect on specific target organs or systems, although these relationships are only at the level of association. In contrast, data retrospectively collected through the survey can be used to calculate the possible dose or duration of exposure, which provides more robust evidence for a dose-response relationship, although some measures are subject to recall bias. Also, survey data can help interpret the biomarkers that are discovered through HRMS and can provide good predictability to monitor the possible source of exposure, which can in turn reduce the possibility of continued exposure in the environment.

Development of a multi-domain questionnaire requires multidisciplinary knowledge and skills that usually depend upon a team effort. Depending on the diseases and outcomes under study, a better understanding of the underlying theory of how specific diseases are developed is crucial for developing a good instrument. For specific exposures such as smoke or pesticides, the information on when the exposure was started, how much, how often, how long, and on what occasion (e.g., indoor or open-air) the exposure occurred, should be consistently collected. A well-designed questionnaire should consider background knowledge in sociometry, psychometrics, biometrics, so that the exposure can be measured at an appropriate scale. The measurement scales in a questionnaire should be tested for item reliability and validity, while considering local cultures and languages.

In summary, we recommend that measuring the exposome should be combined with use of well-designed surveys that can facilitate the interpretation of chemicals measured in the body, contribute to understanding underlying mechanisms and prediction of the risks for health, and take necessary intervention.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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