Understanding the link between environmental exposures and health: does the exposome promise too much?

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ABSTRACT

Environmental exposures affecting human health range from complex mixtures, such as environmental tobacco smoke, ambient particulate matter air pollution and chlorination by products in drinking water, to hazardous chemicals, such as lead, and polycyclic aromatic hydrocarbons, such as benz(a)pyrene. The exposome has been proposed to complement the genome and be the totality of all environmental exposures of an individual over his or her lifetime. However, if measurements of the exposome in biological samples are the sole tool for exposure assessment there are a number of limitations. First, it has limited utility for fully capturing the impact of complex mixtures such environmental tobacco smoke or particulate matter air pollution. Second, a number of relevant environmental exposures such as noise, heat or electromagnetic fields do not have direct correlates as metabolites or protein adducts, but there is important evidence linking them with health effects. Third, functional genomic changes are likely in many instances to be both a susceptibility factor and a marker of internal doses in response to environmental exposures. Fourth, internal dose measurements of environmental exposures might have lost the distinct signature of the relevant sources. This paper emphasises the obligation of environmental epidemiology to provide robust evidence to assist timely and sufficient protection of vulnerable individuals. Environmental exposures in addition contribute to more general pathophysiological mechanisms, and increase the burden and potential health effects through repeated and prolonged exposures by influencing the development of disease over the life course of individuals. For example, the indirect effects of ambient particulate matter such as increased inflammation, increased prothrombotic states and altered autonomic function have been identified as reasons for the cardiovascular disease burden of fine particles. Biomarkers describing changes of physiological states upon exposures to environmental agents are therefore frequently both indicators of internal effective doses of mixtures and early physiological responses at the same time (figure 1). Many of the environmental exposures of primary concern for public health actually lack specific biomarkers of internal dose that fully reflect the exposure. This still applies to environmental exposures that are complex mixtures, such as environmental tobacco smoke, particulate air pollution and photochemical smog. Furthermore, some environmental exposures have no direct correlate as a biomarker of internal dose, such as noise, heat stress and electromagnetic fields. In contrast, exposures to heavy metals, air toxins and endocrine disruptors may be monitored with extremely sophisticated analytical equipment in bodily fluids, in metabolic states, or as adducts.

EARLY PHYSIOLOGICAL RESPONSES TO ENVIRONMENTAL EXPOSURES

Important pathways that are affected by multiple environmental exposures and can be well characterised by biomarker panels include markers of oxidative stress, inflammation, altered immune responses and hormonal regulation among others. Some of the links highlighted in figure 1 have been well documented, whereas others are still under investigation.

Current advances in studying the molecular bases for disease development and progression are utilising high throughput techniques and...
The exposome has been proposed to complement the genome and be the totality of all environmental exposures of an individual over his or her lifetime. Recent advances in biological chemistry allow the characterisation of metabolites and protein adducts originating from environmental exposures, and thereby provide novel insights into internal effective doses of environmental exposures, which have long been precluded from being proposed for next-generation sequencing. Documented associations are shown as solid lines while hypothetical associations are shown as dashed lines. *Named target organs are those for which the major impact of the environment is expected, but multiple other organs such as liver, bladder, kidney and reproductive systems among others may be affected. Electro Magnetic Fields (EMF).

**Figure 1** Schematic overview on a paradigm of environmental epidemiology linking traditional research and emerging biomarkers and altered functional genomics. Documented associations are shown as solid lines while hypothetical associations are shown as dashed lines. *Named target organs are those for which the major impact of the environment is expected, but multiple other organs such as liver, bladder, kidney and reproductive systems among others may be affected. Electro Magnetic Fields (EMF).

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**THE EXPOSOME—AN ADEQUATE INSTRUMENT FOR EXPOSURE ASSESSMENT?**

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**INTEGRATING THE EXPOSOME WITH TRADITIONAL AND NOVEL TOOLS FOR EXPOSURE ASSESSMENT**

We very well recognise that traditional approaches to characterising environmental exposures also have limitations. In addition, the novel approaches and the idea to introduce the concept of the exposome offer important impetus for advancements in science. We therefore propose to integrate state-of-the-art exposure assessment with state-of-the-art high-throughput approaches both for characterising internal doses of xenobiotics as well as early physiological responses representing altered functional genomics, important deregulation in metabolic pathways, and changes in immune function, inflammation and endocrine regulation. Furthermore, the novel techniques are likely to open new fields of investigation, such as interaction between environment and microbiome in the gut. Potentially, there will be the possibility to establish libraries of untargeted metabolomics that allow future interrogation in ways currently being proposed for next-generation sequencing.

A very valuable concept embedded into the exposome paradigm is to our mind the notion to study vulnerable periods and assess environmental exposures in a life-course fashion. We strongly agree that this is a missing feature in environmental epidemiology and combined analyses of studies from different life phases need conceptual and statistical methodological developments. An integrative exposures assessment is likely to be essential for these developments and ideally should combine traditional and novel approaches.

**CONCLUSION**

We would like to emphasise the obligation of environmental epidemiology to provide robust evidence to assist timely and sufficient protection of vulnerable subgroups of populations from environmental hazards. Therefore, in applying the exposome concept to environmental health problems, a strong link with the external environment needs to be maintained. We recognise the emerging wealth of methods and data, and support the necessity to integrate environmental questions into research on disease mechanisms that is overturning paradigms based on technical innovations.
Competing interests None.

Contributors The debate paper has been discussed and commented on by all authors. All authors read and approved the final version.

Provenance and peer review Commissioned; internally peer reviewed.

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*J Epidemiol Community Health* 2012 66: 103-105 originally published online November 11, 2011
doi: 10.1136/jech-2011-200643

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