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STATE-OF-THE-ART REVIEW

Health Consequences of Environmental Exposures: Causal Thinking in Global Environmental Epidemiology

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Abstract

The 2010 Global Burden of Disease estimates indicate a trend toward increasing years lived with disability from chronic noncommunicable diseases (NCDs). Risk factors examined included smoking, diet, alcohol, drug abuse, and physical inactivity. By contrast, little consideration was given to accumulating evidence that exposures to environmental chemicals, psychosocial stress, and malnutrition during fetal development and across the life span also increase risk of NCDs. To address this gap, we undertook a narrative review of early-life environmental contributions to disease. We documented numerous etiologic associations. We propose that future GBD estimates use an expanded approach for assessing etiologic contributions of environmental exposures to recognized disease risk factors. We argue that broadening the definition of environmental disease, together with improved methods of assessing early life exposures and their health outcomes across the life span, will allow better understanding of causal associations and provide the incentives required to support strategies to control avoidable exposures and reduce disease risk.

KEY WORDS children, pollution, non-communicable disease, burden of disease, public health

In 2010, the United Nations adopted a global plan of action to reduce poverty and to improve health by launching 8 Millennium Development Goals to be achieved by 2015. Significant progress has been made toward achieving these goals in many countries. At the same time, we have seen a substantial change in the global pattern of disease. Publication of the 2010 estimates of the Global Burden of Disease (GBD) and of 67 risk factors and risk factor clusters has demonstrated a significant shift toward chronic noncommunicable diseases (NCDs).[1,2] Early childhood deaths have

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PDS, M-NB-D, and WS conceived the concept for this article, PDS wrote the initial draft. All authors reviewed and edited the manuscript and PDS produced the final draft, which was approved by all authors.

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declined, but in contrast, years lived with disability (YLD) have increased.[2] Globally, YLD attributable to communicable, maternal, neonatal, and nutritional diseases have decreased by 19.5% between 1990 and 2010, whereas those attributable to chronic disease have increased: cardiovascular diseases by 17.7%; chronic respiratory disease by 8.5%; neurological conditions by 12.2%; diabetes by 30.0%; and mental and behavioral disorders by 5.0%.[3]

These estimates of disease burden and assessments of the hazards posed by their underlying risk factors are based on conservative methodology that requires a very high level of evidence before a risk factor can be included.[1] These estimates, therefore, included careful consideration of the contributions to GBD of such well-established risk factors as alcohol, tobacco, drug use, diet, and physical inactivity.[1] These exposures were considered to be "lifestyle" risk factors. By contrast, the current GBD methodology does not include estimates of the contributions to disease burden of many environmental risk factors. The methodology fails to consider the chemicals present in food and water that have toxic, carcinogenic, or endocrine disruptive actions. It does not consider the substantial body of evidence that chemical exposures and nutritional deficiencies in early life increase risks of chronic diseases such as hypertension, high blood glucose, and increased body mass index in childhood, during adult life, and in the elderly.[4] Furthermore, the current methodology fails to consider emerging evidence that behaviors currently classified as caused by "lifestyle" are, in fact, the result of much more than personal choice and are profoundly shaped by the social and cultural environment, genetics, and parts of the natural and the manmade environment. For example, although obesity is included as a risk factor, chemical exposures in early life that appear likely to contribute to obesity[5,6] are not. In short, these considerations indicate that the GBD analysis at present significantly underestimates the role of environmental exposures in human disease. Ambient noise is another environmental hazard with adverse consequences on health (in addition to hearing loss)[7] that is often omitted from environmental contributions to disease.

Quantifying the disease burden caused by the environment is difficult because evidence on causal links between exposure to many environmental factors and health outcomes is still evolving. Additionally, there is often a lack of reliable exposure data at the population level, especially in regard to exposures in early life that may have occurred years or decades ago.[8] An expert panel convened by the World Health Organization (WHO) estimated that 24% of the global disease burden and 23% of all deaths could be attributed to environmental exposures, based on data collected in the late 1990s and early 2000s.[9] Among children 0-14 years of age, WHO estimates that the proportion of deaths attributable to the environment could be as high as 36%.[9] The WHO has reported the fraction of disease attributed to the environment for 85 diseases. The WHO definition of the "environment" included a wide range of modifiable physical, chemical, and biological factors external to the human host that directly affect health and also increase unhealthy behaviors (eg, the impact of the structure of the environment on physical inactivity). However, even these estimates almost certainly did not go far enough and also did not include the contributions of early life chemical exposure or ambient noise to other risk factors.

ENVIRONMENTAL EXPOSURES AND CHRONIC, NONCOMMUNICABLE DISEASES

Recent data from the US Centers for Disease Control and Prevention national biomonitoring program[10] demonstrate the almost all Americans have detectable levels of a wide variety of environmental chemicals in their bodies, including many with known endocrine-disrupting, neurotoxic, and carcinogenic activities. These include organic chemicals that persist in the environmental long after their production and use have been stopped, such as polychlorinated biphenyls, and nonpersistent chemicals to which individuals are constantly exposed, such as the plastic components and plasticizers bisphenol A (and other bisphenols) and phthalates. Many of these chemicals may be present at levels that can cause biological or toxicologically relevant effects in animal models. There is strong evidence that such exposures increase the risk of diabetes,[5,6,11] hypertension,[12] cardiovascular disease,[13,14] obesity,[15,16] and cancer.[17] Table 1 gives an overview of the environmental exposures associated with chronic noncommunicable diseases, and Supplementary Tables 1-5 (available in the online version at http://dx.doi.org/10.1016/j.aogh.2016.01.004) provide more details.

Understanding is increasing that the risk of developing many chronic NCDs are increased by early-life exposure to toxic chemicals, nutritional imbalances, and psychosocial stress[18] and, as such,

these NCDs should be considered to be environmental diseases. Exposures to toxic or endocrine-disrupting chemicals in early life can influence metabolism to alter brain growth,[19] promote obesity via actions on adipocyte precursors,[15] and play a substantial role in initiation and progression of diseases,[20] including: respiratory diseases such as asthma, chronic obstructive pulmonary disorder, and lung cancer; neurobehavioral disorders, including attention-deficit/hyperactivity disorder (ADHD)[21]; depression and other mental disorders; mild mental disability; obesity and type 2 diabetes[22,23]; and cancer.[24] Chronic diseases such as these have not traditionally been thought of as being "environmental diseases," although environmental contributions to risk for these diseases are becoming more generally accepted.

Without a true understanding of the contribution of environmental exposures in early life to the risk of NCDs, especially of modifiable or avoidable exposures, there will be little impetus to reduce such exposures. For progress to be made, a new approach to causal thinking in global epidemiology[25] will be required, an approach that considers environmental risks and redefines environmental diseases.

BARRIERS TO EXPANDED CAUSAL THINKING IN GLOBAL ENVIRONMENTAL EPIDEMIOLOGY

Difficulties that need to be overcome to allow appropriate recognition of environmental risks in GBD estimates are summarized in the next sections. These include: individual susceptibility to chemicals related to genetic variation; particular widows of susceptibility to xenobiotics during vulnerable periods of pre- and postnatal development; chronic low-dose exposures to ubiquitous chemicals in the environment; nonmonotonic dose-response curves; the long latency between early-life exposure and chronic NCDs; and an incomplete acceptance that common, widespread exposures could play a role in apparently disparate diseases affecting different organ systems.

Traditionally, knowledge of the adverse human health consequences of chemical exposures has resulted from occupational exposures or from poisoning events. However, population exposure to the bulk of environmental chemicals occurs at low doses and the magnitude of adverse human health effects of many chemicals occurring at low doses in the environment or food is uncertain. Low-dose effects have been defined as biological changes occurring in the range of "typical" human exposures or occurring at doses below those tested in traditional toxicology assessments.[26] Ubiquitous exposures to environmental chemicals poses difficulties

Table 1. Environmental Exposures Associated with Chronic Noncommunicable Diseases

Disease	Exposure During Fetal Development or Early Life	Exposure in Later Life
Asthma	Tobacco smoke Ambient air pollution Household chemicals Bisphenol A	Tobacco smoke Ambient air pollution Household air pollution Ecological exposure to PCBs
COPD	Tobacco smoke Ambient air pollution	Tobacco smoke Ambient air pollution Household air pollution
Obesity	Tobacco smoke Bisphenol A POPs	Bisphenol A POPs Gastrointestinal dysbiosis
Type 2 diabetes	No data	POPs Bisphenol A/phthalates Ambient air pollution
Metabolic syndrome	Endocrine-disrupting chemicals	POPs Ambient air pollution
Hypertension	Tobacco smoke Organochlorine pesticides	Tobacco smoke POPs Ambient air pollution Arsenic (drinking water)
Cardiovascular diseases	Tobacco smoke	Tobacco smoke POPs Ambient air pollution Household air pollution Ambient noise
Low IQ	Tobacco smoke POPs Heavy metals PAHs Organophosphate pesticides Brominated flame retardants	Heavy metals POPs
ADHD/ASD	Heavy metals POPs Bisphenol A/phthalates	Tobacco smoke Bisphenol A/phthalates
Neurodegenerative disorders	No data	Heavy metals Air pollution Herbicides
Cancers	Tobacco smoke UV radiation Arsenic	Ambient air pollution Arsenic POPs Many carcinogens

For full details of the exposures, their effects, and references, see Supplementary Tables 1-5 in the online supplement.
ADHD, attention-deficit/hyperactivity disorder; ASD, autistic spectrum disorder; COPD, chronic obstructive pulmonary disease; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; UV, ultraviolet.

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in undertaking the studies required to provide a sufficient level of evidence required for inclusion in the GBD estimates.

Many environmental chemicals, especially those with endocrine-disrupting activity, have nonmonotonic dose-response curves—that is, where the slope of the dose-response changes from positive to negative (or vice versa) at some point in the dose range studied.[26] Such dose-response curves cause problems for the traditional risk assessment approach used by regulatory agencies, which assumes that the dose-response curve is monotonic and that the effects of low-dose exposure can be predicted from high-dose exposures.[26] Nonmonotonic dose-response curves occur naturally in biology, especially for naturally occurring hormones, including sex hormones, thyroid hormones, and corticosteroids.[26] Vandenberg et al[26] have comprehensively reviewed the literature and reported low-dose effects and nonmonotonic dose-response curves for natural hormones, pharmaceutical hormones, and a large number of environmental chemicals, including: chemicals added to plastics; detergents and surfactants; polycyclic aromatic hydrocarbons; heavy metals; phytoestrogens and natural anti-oxidants; herbicides, insecticides and fungicides; flame retardants; polychlorinated biphenyls; and dioxins and dioxin-like chemicals. These include many of the very chemicals implicated as contributing to chronic NCDs (Table 1, Supplementary Tables 1-5).

The concept of early-life exposures increasing the risk for later-life outcomes is not new, with many well-known examples in the literature. The adverse health consequences of maternal malnutrition during pregnancy occurring during the "Dutch famine" or of prenatal exposure to high concentrations of arsenic in drinking water in Antofagasta, Chile, were revealed many decades later (reviewed in Boekelheide et al[27]). This long latency between exposure and effect increases the difficulties in providing evidence from epidemiology linking early-life exposures with later health effects, especially where genetic variation in individual susceptibility is likely to exist in enzymes associated with detoxification systems. Both of these examples included exposures that could (later) be timed precisely and that were subsequently removed. Thus, it was relatively easy for epidemiologists to attribute causation to the metabolic and obesogenic effects of maternal starvation during specific periods of pregnancy and to the cancers and noncancerous lung diseases resulting from prenatal exposure to high concentrations of arsenic.[27] When exposures to environmental toxicants occur at low dose and are ongoing from ingestion of food or water or from inhalation of pollutants in air, the situation is far more challenging and "proving" causation is almost impossible, especially when the adverse heath outcome from prenatal and early-life exposures occurs many years or decades later.

Another area of confusion that potentially limits acceptance of the role that early-life environmental exposures play in the initiation and progression of chronic noncommunicable disease is the observation that seemingly common exposures can be linked to different diseases and different disease phenotypes. On face value, it is easy to understand why exposure to particulate matter in ambient air would increase the risk for respiratory disease, but why would the same exposure induce insulin resistance, obesity, and type 2 diabetes?[28] Among the mechanisms postulated to link respiratory and metabolic diseases are common exposures during fetal development (maternal smoking, maternal stress) and in early life (diet low in antioxidants and fresh fruit and vegetables, ambient air pollution) (reviewed in Chacko et al[29]). In addition, both respiratory and metabolic diseases are "inflammatory" conditions and oxidative stress plays a role in both.[28] Low lung function has been associated with obesity and type 2 diabetes and asthma symptoms are seen in those with the metabolic syndrome (reviewed in Chacko et al[29]). Although extreme obesity may impose mechanical limitations on the chest wall, reducing lung function, this is an uncommon situation and not likely to explain the links between metabolic and respiratory diseases.

An emerging field of research is how alterations of the gastrointestinal microbiome, known as dysbiosis, are associated with various chronic diseases such as inflammatory bowel disease, obesity, and asthma. The gastrointestinal microbiota contains literally billions of bacteria that perform key roles in maintaining normal homeostasis, extracting energy from food,[30] and biotransformation of environmental toxicants that may increase or decrease the toxicity of the chemical.[31] The gut microbiota is established in early postnatal life[32] and is influenced by environmental factors, including: place and mode of delivery[33]; the type of infant feeding[32]; and the presence of siblings and pets in the home in early life.[34] Gastrointestinal dysbiosis that is associated with chronic disease commonly involves a reduction in so-called probiotic species, including lactobacillus and bifidobacteria, with or without the outgrowth of potentially pathogenic bacteria.[35]

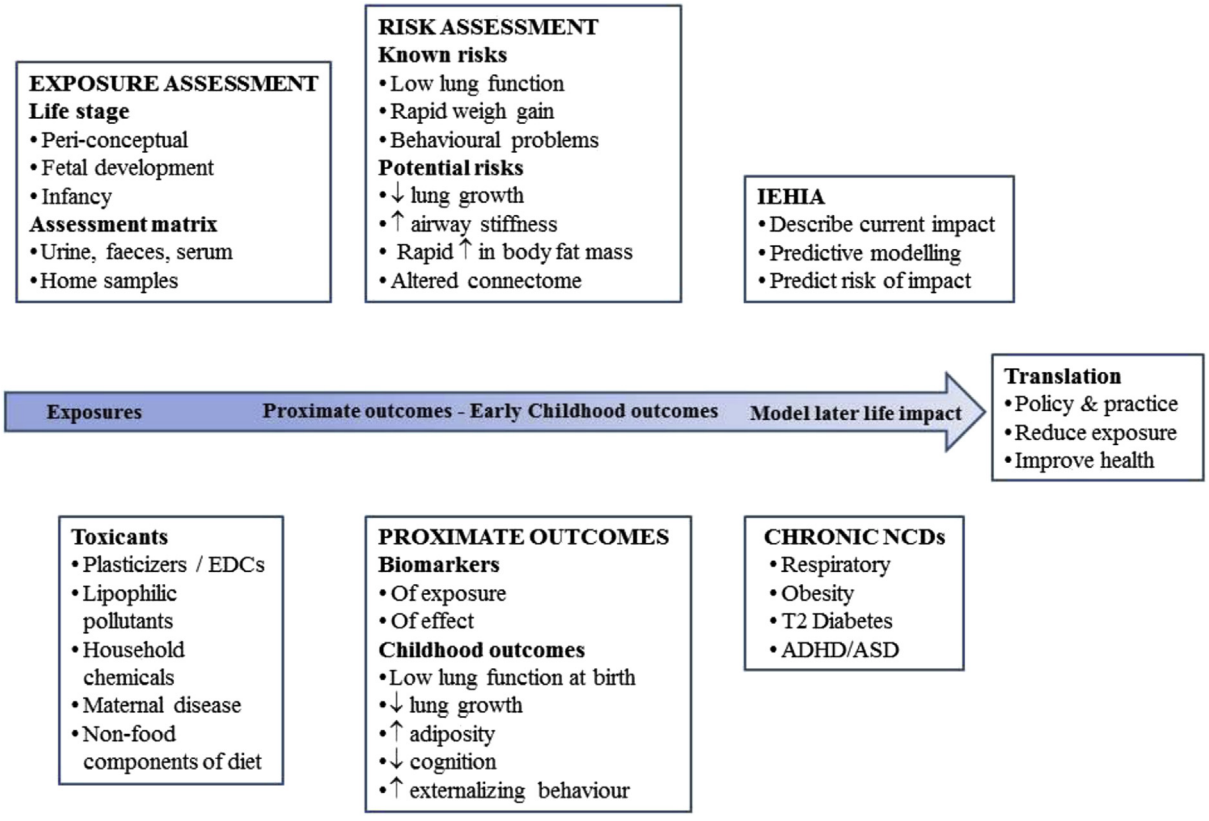

Figure 1. Schematic representation of methods to improve knowledge of the links between early life environmental exposures and chronic non-communicable diseases. Abbreviations: ADHD/ASD, attention-deficit/hyperactivity disorder / autism spectrum disorders; EDCs, endocrine-disrupting chemicals; IEHIA, integrated environmental health impact assessment; NCDs, noncommunicable diseases.

One possible set of mechanisms linking early-life environmental exposures to chronic noncommunicable diseases are epigenetic modifications of gene expression and function that may lead to transgenerational increases in risk of disease. Epigenetic changes occur via a variety of molecular mechanisms; the most commonly studied include: methylation of cytosine sited in CpG dinucleotides, most commonly in the promoter regions of genes; post-translation modification of histones responsible for chromatin packaging of DNA; and effects on gene expression occurring via regulation of noncoding RNAs such as microRNAs.[36] Epigenetic modifications can be inherited and third-generational (and beyond) inheritance of disease risk has been demonstrated in animals.[37] Despite epidemiologically studies suggesting that transgenerational risk of disease occurs in humans—for example, increased asthma risk from maternal and grandmaternal smoking[38]—definitive evidence for heritable environmentally induced epigenetic modifications in human disease is lacking.[36] Environmental epigenetics is a rapidly growing research field with an emphasis on explaining mechanisms by which early-life exposures increase long-term disease risk.[36,37,39] Early-life exposures to a variety of environmental toxicants, including tobacco smoke, traffic-related pollutants, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, heavy metals, and bioaerosols, have been linked to chronic disease via epigenetic mechanisms including alterations in gene methylation, histone modification, and microRNAs.[39] Low-dose exposure occurring during windows of susceptibility occurring during fetal development may have far greater effects that high-dose exposure in an adult.[39]

FUTURE DIRECTIONS

How can we advance the science linking early-life environmental exposures to long-term disease risk? Longitudinal birth cohort studies have provided a

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wealth of information about risk factors for various diseases; however, the long latency between early-life exposure and chronic disease in later life limits enthusiasm for undertaking new birth cohort studies. Many existing birth cohort studies did not collect the samples required to assess exposure to environmental toxicants in early life. The incorporation into epidemiologic studies of new approaches to exposure assessment that assess exposures in the distant past by analyses of calcified tissues such as teeth represents an exciting development.[40] It is also necessary to base future studies on an understanding of potential adverse effects of environmental exposures, which can come from in vivo experimental models for reproductive and developmental effects, supported by in vitro studies indicating human relevant/plausible mechanism of action or mode of action. In addition, few environmental epidemiology studies pay adequate attention to genetic and phenotype variations in study design.

We propose a new approach that combines improved assessment of environmental exposures occurring during fetal development and in early life with improved assessment of outcomes in early life through discovery and validation of biomarkers of exposure and improved assessment of proximate outcomes that link with long-term disease risk. This approach is shown schematically in Figure 1 and discussed in more detail in the review by Suk et al in this edition.[41] Using chronic lung disease as an example, low lung function is a known risk factor for acute and chronic lung disease[42]; however, methods for measuring lung function in infants have been limited and not suitable for large-scale epidemiological studies. Recent developments have seen new methods for measuring the mechanical properties of the airway and lungs in unsedated infants during natural sleep.[43] This technique can be used to study the effects of prenatal exposures suspected of restricting lung growth in utero, thus demonstrating a direct link between environmental exposures and long-term risk of lung disease.

CONCLUSIONS

The difficulties inherent in providing sufficient evidence linking environmental exposures, whether in early life or in adulthood, with chronic noncommunicable diseases have led to under-recognition and underestimation of the environmental contributions to disease. Diseases to which the environmental contribution have been underestimated include reproductive and developmental disorders and chronic diseases such as respiratory diseases, obesity, type 2 diabetes, metabolic syndrome, cardiovascular disease, low IQ, neurocognitive and behavioral disorders, and cancer. A broadening of the definition of what constitutes an environmental disease, together with improved methods of assessing early-life exposures and the outcomes of those exposures, will allow a better understanding of these links. A better understanding of disease risk from environmental exposures is necessary to provide the incentives required to support strategies aimed at reducing avoidable exposures and reducing disease risk. Annual updates of the GBD estimates are anticipated. If new and expanded etiologic thinking is not incorporated into these annual updates, they may result in enshrining the current bias against newly recognized and emerging risk factors, including early-life environmental exposures.

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SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.aogh.2016.01.004.

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