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Developmental Origins of Health and Disease: Integrating Environmental Influences

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There are now robust data supporting the Developmental Origins of Health and Disease (DOHaD) paradigm. This includes human and animal data focusing on nutrition or environmental chemicals during development. However, the term DOHaD has not been generally accepted as the official term to be used when one is concerned with understanding the pathophysiological basis for how environmental influences acting during early development influence the risk of later noncommunicable diseases. Similarly, there is no global research or public health program built around the DOHaD paradigm that encompasses all aspects of environment. To better inform the global health efforts aimed at addressing the growing epidemic of chronic noncommunicable diseases of environmental origin, we propose a two-pronged approach: first, to make it clear that the current concept of DOHaD comprehensively includes a range of environmental factors and their relevance to disease occurrence not just throughout the life span but potentially across several generations; and second, to initiate the discussion of how adoption of DOHaD can promote a more realistic, accurate, and integrative approach to understanding environmental disruption of developmental programming and better inform clinical and policy interventions. (*Endocrinology* 2016: 17–22, 2016)

Development is a plastic process that is sensitive to environmental perturbations including nutrition, stress, drugs, and environmental pollutants. Indeed, environmental influences during development have been shown to affect the etiology of and susceptibility to the noncommunicable diseases (NCDs) and dysfunctions that constitute major public health problems across the globe including obesity, diabetes, hypertension, cardiovascular disease, asthma and allergy, immune and autoimmune diseases, neurodevelopmental and neurode-generative diseases/dysfunctions, changes in timing of puberty, infertility, cancers, depression, and psychiatric disorders (1–4). Although prevention efforts to reduce NCDs have focused mainly on adults and on four factors, namely poor diet, physical inactivity, tobacco use, and alcohol consumption, evidence now suggests that more attention is needed on early-life optimization of nutrition, reduction of stress, and abatement of exposures to toxic environmental chemicals (4).

During the last two decades there have been a variety of terms used to denote the effects of over or under nutrition or environmental chemical exposures during development

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Abbreviations: DOHaD, Developmental Origins of Health and Disease; FOAD, fetal origins of disease; NCDs, noncommunicable disease.

that lead to increased disease/dysfunction later in life. These include fetal origins of disease (FOAD) and fetal beginnings of adult disease, both of which focused on the fetal period of exposure and adult diseases to the exclusion of diseases earlier in life. In 2002, the FOAD Society voted to change and expand its name to Developmental Origins of Health and Disease (DOHaD). Thus DOHaD is the official name of a society and a corresponding journal that focus mainly on the importance of nutritional insults during development on later-life disease susceptibility. The term DOHaD has not been generally accepted as the official term to be used when one is concerned with understanding the pathophysiological basis for how non nutritional environmental influences acting during early development influence the risk of later NCDs. Similarly, there is no global research or public health program built around the DOHaD paradigm that encompasses all aspects of environment. To better inform the global health efforts aimed at addressing the growing epidemic of chronic NCDs of environmental origin, we propose a twopronged approach: first, to make it clear that the current concept of DOHaD comprehensively includes a range of environmental factors and their relevance to disease occurrence not just throughout the life span but potentially across several generations; and second, to initiate the discussion of how adoption of DOHaD can promote a more realistic, accurate, and integrative approaches to understanding environmental disruption of developmental programming and better inform clinical and policy interventions.

"Environment" and DOHaD

The name most well associated with DOHaD is David Barker, because his studies from the late 1980s onward followed a tradition of research on how early life influenced later health (5). Barker and his colleagues focused on the role of undernutrition during fetal development (poor maternal nutrition) that resulted in low birth weight and associated risks for later life obesity, diabetes, and cardiovascular disease. Barker's emphasis on nutrition and low birth weight became dominant in the FOAD field. Later it was shown that birth weight is merely a crude proxy for fetal nutrition and endocrine environment and that risks for different diseases can be elevated throughout the entire range of weights at birth and early childhood. Thus, in the nutritional area, the DOHaD field covers not only extremes of low and high birth weight, in which there can be major changes in tissue weights and physiology, but also birth weights within the normal range, in which subtle functional changes can occur in tissues (6). In some cases, the developmental changes can promote fitness through the reproductive years at the expense of increased disease susceptibility later in life (5).

Important research relating to what would become DOHaD also came from early studies of environmental chemicals and disease focusing on diethylstilbestrol (7), fetal alcohol syndrome (8), lead (9), and work related to the fragile fetus hypothesis developed by Howard Bern (10). Thus, similar to the effects of nutritional perturbations during development, there are instances in which environmental chemical exposures during development can lead to a normally appearing fetus that has subtle functional changes in specific tissues resulting in increased susceptibility to disease/dysfunction later in life (11, 12). These subtle functional changes, in many cases, are due to altered gene expression leading to altered cell proteins, and in some cases altered numbers and/or location of cells. Environmental chemicals that alter developmental plasticity often interfere with the endocrine control of development and are called endocrine disrupting chemicals. Thus, the tissue specificity and timing of response depends both on the endocrine system being sensitive to the chemical and on the timing of specific windows of development. The sensitive window for environmental chemical exposures to affect developmental plasticity includes the time when the tissue is developing, which, in some cases is mainly *in utero* but in others, such as the respiratory, immune systems, and the brain, continues well into childhood and even early adulthood. Once a tissue is fully developed, it is less sensitive to functional changes that can lead to increased susceptibility to diseases later in life (1).

Prenatal stress is another environmental factor that is increasingly recognized as a cause of fetal developmental reprogramming, and that has been associated with multiple different diseases and disorders including include cardiovascular diseases such as hypertension, coronary heart disease and heart failure, and metabolic diseases such as obesity and diabetes (13, 14). A number of neurologic diseases and disorders, such as visuomotor problems, attention deficit, impaired cognition, and reduced brain volume in children have been shown to be the result of stress (15, 16). These findings from human studies are supported by findings in rodent and nonhuman primate models (17). The effects of prenatal stress exhibit marked sex differences (18), making it difficult to generalize outcomes across sexes. Numerous mechanisms have been proposed as a basis for the fetal effects of prenatal stress, among which are elevated fetal glucocorticoid exposures, increased proinflammatory cytokines, elevated levels of fetal serotonin or glutamate, shortened telomere length, and epigenetic alterations (13, 15, 18–20). The timing of prenatal stress during pregnancy is critical in determining associated outcomes (20).

For example, early gestational stress is related to adult coronary heart disease, midgestation to renal disease, and late gestation to metabolic consequences (21, 22). Consequences of prenatal stress are also dependent upon the type of stressor involved (18), and related to the uncontrollability and unpredictability of the stressor (23).

There are many common aspects across these DOHaD areas of nutritional, environmental chemical, and stress (1). Nutritional insults, environmental chemical exposures, and stress during development may:

- Act during specific windows of developmental plasticity.
- Cause subtle functional changes not necessarily detectable without sensitive molecular approaches and which may not be apparent without a second "hit" or challenge later in life.
- Result in latency between "exposure" and disease/dysfunction.
- Result in increased susceptibility to some similar diseases, creating the possibility or likelihood of interactions between the various environmental stressors to increase disease susceptibility, incidence and severity.
- Result in effects that in some cases can be transmitted via the germ line to future generations.
- Result in sex-specific effects.
- Interact with fixed genetic components.
- Act at least partially via alterations in epigenetic marks which may be irreversible.

The fact that both under-or overnutrition, environmental chemical exposures, and developmental stress have common features in terms of their phenotypic outcomes and in fact are likely to interact to result in increased susceptibility to disease and dysfunction make it imperative to integrate research and conceptual frameworks across these and other aspects of environment. Such integration can provide a more accurate and realistic picture of the effects of altered developmental environment on disease outcomes across the life span. Moreover, populations do not experience these stressors in isolation; low-middle and high-income countries all have problems with under-and overnutrition. Globally, populations also experience exposures to environmental chemicals including endocrine-disrupting chemicals, indoor and outdoor air pollutants, and poor water quality. Lastly, all populations are subject to a variety of stressful situations. Advancing the understanding of the role of early life experience in chronic disease etiology requires an integrated analysis of all aspects of the environment and how they interact together to cause disease.

Complex aspects of exposures are typically not integrated when assessing the role of environment during development in susceptibility to disease across the life span in animal studies, in human studies, or in policy statements. Indeed, the major International Conferences focusing on the role of early life exposures in chronic diseases, such as The DOHaD Society and Prenatal Programming and Toxicity conferences have not fully integrated nutrition, stress, and chemical exposures into their respective conference programs.

It is time to integrate all relevant environmental stressors into an overall program to understand the role of environment in disease and thus in disease prevention.

Common terminology for DOHaD

Over the last 20 years or so, as noted above, there have been several different terms and definitions pertaining to the developmental origins of disease. To foster an integrative approach to studying and understanding the importance and implications of the developmental origins of disease hypothesis it is critical to start with a definition that is comprehensive, inclusive, and accepted by all communities interesting in understanding the importance of environment in developmental plasticity and disease susceptibility. The definition developed and used by the DOHaD Society is the following:

"The Developmental Origins of Health and Disease is a multidisciplinary field that examines how environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with its environment in later life."

Although much of the focus of DOHaD as developed by this Society was on nutritional insults, this definition uses the more comprehensive wording, "environmental factors." This allows for consideration of all aspects of the environment, including environmental chemicals and stress.

We propose that the term "DOHaD" should be kept and used whenever research focused on developmental origins of health or disease is discussed regardless of the environmental stressor studied or phase of developmental plasticity studied.

Furthermore, when the term DOHaD is used it should be understood that it pertains to the following:

- Development (broadly defined as ranging from preconception, including paternal exposures through childhood and adolescence) is a sensitive time for environmental factors to affect developmental plasticity in either a positive or negative manner.
- Disease susceptibility during development can occur without an immediate physical change, such as altered birth weight or body composition, but can occur across the normal population ranges of such variables and

result from subtle functional changes in gene expression, including epigenetic changes that lead to altered proteins, cells, and cell locations, which often materialize at a later time in the life course.
- A latent period often occurs between the initial environmental influences on development and subsequent manifestation of disease or dysfunction, lasting years to decades in humans.
- Environmental factors that can affect developmental plasticity include not only nutrition, stress, and man-made environmental chemical exposures, which are the focus here, but also infections, the microbiome, and drugs.
- Diseases can occur at any time across the life span from childhood (*e.g.,* asthma, learning disabilities, and childhood cancers) to those that occur during puberty, pregnancy, adulthood, and aging.
- Environmental influences during development can be transmitted intergenerationally: multigenerationally (to grandchildren) or transgenerationally (to great grandchildren).
- Development is also a time when improved later health can also be promoted; thus, the term DOHaD should also be used to focus attention on improving health across the life span. Although a bad start lasts a lifetime; a good start also lasts a lifetime. Interventions targeted at improving development by reducing stress, improving nutrition, and reducing environmental chemical exposures could have an important effect in reducing vulnerability to diseases.

Implications of a standard global terminology for DOHaD

Research

Although it is likely that societies, agencies, and individual investigators, at least in the short term, will continue to focus their work on specific environmental factors, over the long term an inclusive global definition should lead to the breakdown of barriers between groups focused on nutrition, stress, and environmental chemicals etc., which will lead to the production of data more useful for improving health. Research goals of an integrated approach to DOHaD include:

- Integration of environmental factors playing a role in DOHaD in both animal and human studies to get a more complete understanding of the role of such factors and their interactions in susceptibility to disease/dysfunctions.
- Promotion of biomedical research including toxicological and biomarker research, prospective cohort studies starting at birth of before, and shorter-term epidemiologic studies of pressing problems such as over-and undernutrition, endocrine disruptors, stress, and other environmental stressors in regard to disease susceptibility across the life span. This research will provide a blueprint for evidence-based prevention and environmental intervention.
- Improved understanding of common outcome pathways and mechanisms for environmental factors (*e.g.,* epigenetic inheritance) leading to susceptibility to disease/dysfunction later in life and thus common interventions against causative factors.
- Development of early life biomarkers of these pathways, such as subclinical changes in blood components and thus of developmental exposure and later risk.
- Uncovering of differences in mechanisms and pathways among the different environmental stressors, (*e.g.,* nutrition and developmental plasticity that can provide an initial fitness advantage followed potentially later in life (postreproductive years) as increased disease susceptibility versus environmental chemicals that cause developmental disruption and lead to disease across the life span) that might shed light on interventions specific to the type of environmental stressor.
- Expansion of the list of diseases/dysfunctions affected by environmental factors during development from the initial focus on obesity, heart disease, and diabetes to cover neurocognitive, reproductive health, and immunologic problems and common childhood and aging diseases/dysfunctions.

Clinical

An important benefit of an integrative terminology for DOHaD is the ability to convey to clinicians, health care personnel, and students the importance of preventing environmental exposures across the life span, with a focus on sensitive windows of development. Elements of messages for clinicians include:

- Evidence in support of the DOHaD concept across the environment is sufficiently robust and repeatable across species, including humans, to support incorporation into clinical practice.
- The life course model underpinning DOHaD means that responses to environmental challenges are affected by previous history, a point not widely appreciated clinically.
- The fact that effects are not apparent at birth does not mean they are not there and will become apparent later in life.
- Environmental effects detected early may seem small but set the trajectory for later disease risk.

- Neurodegenerative diseases, breast cancer, cardiovascular disease, metabolic syndrome, infertility, asthma and atopic diseases, learning disabilities, and childhood cancers have one thing in common: it is likely that they have their origins partly during development as a result of environmental influences, including altered nutrition, stress, drugs, infections and exposure to environmental chemicals. All these diseases share a window of sensitivity that encompasses *in utero* and early childhood. Health care professionals concerned with adolescent health, reproductive health, preconception, pregnancy and newborn and child care can therefore play an important role in preventing these exposures and improving global health.
- The Endocrine Society (24, 25), the American College of Obstetricians (26), the American Society of Reproductive Medicine, and the Royal College of Obstetricians and Gynecologists, the European Society for Pediatric Endocrinology and the United States Pediatric Endocrine Society (27) and other scientific groups (1) have put forward statements calling for action on environmental chemicals due to the sensitivity of developing individuals and the resulting increased disease risk across the life span. These professional clinical societies should expand their focus to include nutrition and stress as well as environmental chemicals when they discuss disease prevention.
- Use of early biomarkers of disease risk may provide both an indication of environmental exposures and also of likely risk trajectory which can be used for disease prevention.
- Clinicians should shift their focus to early prevention, not risk of disease in adults and a focus on just treatment of those affected by disease.
- The adoption of the DOHaD paradigm provides an opportunity for both patients and physicians to take action to prevent diseases many years before such disease is evident. Appropriate action will not only result in healthier lives to current citizens but also enable them to pass on good health to the next and subsequent generations.

Policy

The prevalence of chronic NCDs is increasing dramatically and this is a global problem. As noted above, all countries have populations within them that experience exposures to the range of environmental factors understood to influence developmental plasticity. The integration of all aspects of the environment into DOHaD increases the possibility to:

- Develop global programs and policies to increase awareness of the effect of DOHaD on NCDs across the life course.
- Develop an integrated approach to disease prevention that expands the environmental focus from alcohol, smoking and drugs to encompass improving healthy diet, reducing stress, and reducing exposure to toxic environmental chemicals. Although the parent child setting would be a primary focus for such an integrated approach, interventions could be targeted across the life course for many of these environmental factors.
- Bring together global agencies and societies with disparate missions, such as the United Nations Environment Program, the World Health Organization, UNICEF, the DOHaD Society and its affiliates, the Endocrine Society, and various Nutrition Societies to share information and work together on common objectives to improve health across the globe. The economic and humanitarian benefits of such initiatives will be substantial in both the short-and longer term.

Summary

The DOHaD paradigm must include of all aspects of environment, including nutrition, environmental pollutants, and stress. Each of these types of environmental stressors can alter developmental plasticity independently and are likely also to interact to affect functional capacities and disease risk. To truly understand the role of effects on developmental plasticity in increasing risks of chronic, NCDs, and other conditions, all aspects of the environment should be considered, and when possible, integrated.

DOHaD must include all windows of sensitivity to environmental stressors across the life span, including preconception, pregnancy, early childhood, and others yet to be discovered. It must include diseases/dysfunctions that occur in adulthood as well as those diseases/dysfunctions that occur across the life course, including childhood diseases such as asthma, cancers, and learning disabilities, conditions in adolescence such as reproductive disorders, and aspects of aging.

A focus on DOHaD in the research community allows for integrated, coordinated approaches focusing on multiple environmental stressors that can better inform public health interventions.

A DOHaD focus in the clinic offers the possibility to prevent disease onset and not just treat diseases after the fact.

A focus on DOHaD in the policy sectors offers the possibility to improve human health across the life course and across the globe by enhancing wider social interventions and policy programs focused on prevention of

disease by reduction of environmental stressors at critical stages of development.

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