SPECIAL ARTICLE

Meeting Report on the 3rd International Congress on Developmental Origins of Health and Disease (DOHaD)

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ABSTRACT: Developmental origins of health and disease (DOHaD) focuses on the earliest stages of human development, and provides a novel paradigm to complement other strategies for life-long prevention of common chronic health conditions. The 3rd International Congress on DOHaD, held in 2005, retained the most popular features from the first two biannual Congresses, while adding a number of innovations, including increased emphasis on implications of DOHaD for the developing world; programs for trainees and young investigators; and new perspectives, including developmental plasticity, influences of social hierarchies, effects of prematurity, and populations in transition. Emerging areas of science included, first, the controversial role of infant weight gain in predicting adult obesity, diabetes, and cardiovascular disease. Second, in the era of epidemic obesity, paying attention to the over-nourished fetus is as important as investigating the growth retarded one. Third, environmental toxins appear to have a broad range of long-lasting effects on the developing human. Fourth, epigenetic mechanisms could unite several strands of human and animal observations, and explain how

genetically identical individuals raised in similar postnatal environments can nonetheless develop widely differing phenotypes. Improving the environment to which an individual is exposed during development may be as important as any other public health effort to enhance population health world wide. (*Pediatr Res* 61: 625–629, 2007)

CONGRESS DESCRIPTION

The 3rd International Congress on Developmental Origins of Health and Disease (DOHaD) took place in November 2005 in Toronto, Canada. DOHaD III was the third biannual congress in this area of inquiry, following the 1st and 2nd World Congresses on Fetal Origins of Adult Disease (FOAD) held in Mumbai, India, and Brighton, UK, respectively. The name change from FOAD to DOHaD recognizes the broader scope of developmental cues, extending from the oocyte to the infant and beyond, and the concept that the early life environment has widespread consequences for later health. After the 2nd FOAD Congress, the International Society for DOHaD was formed, with members extending from evolutionary biologists through all branches of the basic and clinical sciences to epidemiologists and public health scientists. The 3rd International Congress was the first to be held under the auspices of the new society.

The 3rd Congress retained the most popular features from the first two Congresses, while adding a number of innovations, including 1) increased emphasis on implications of DOHaD for the developing world; 2) programs for trainees and young investigators; and 3) new perspectives, *e.g.*, evolutionary biology, developmental plasticity, influences of social hierarchies, effects of prematurity, populations in transition, the toxic environment, approaches to data analysis, discussion of controversial areas and policy implications. The

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content was organized around four domains—exposures, outcomes, mechanisms, and interventions—woven in an integrated fashion throughout the program. The format included both plenary and parallel scientific sessions, with additional special sessions, dedicated poster sessions, and opportunities for interdisciplinary discussion.

Hailing from over 50 countries, 691 delegates attended the Congress. This number represented a substantial increase from FOAD I (502) and FOAD II (531), reflecting the growing interest in the field. Approximately 37% of delegates were from Europe, with 36% from North America, 12% from Asia or Middle East, and the remainder from Australasia, Africa, and Central/South America. Overall 15% were from developing countries. Half were female, and 22% were students. Of the nonstudent delegates, most (62%) worked in academia, and the remainder were split among industry, government, and other occupations.

A core planning committee, comprising the authors of this report, was responsible for overall planning and oversight. The core committee had the able assistance of a local organizing committee as well as an at-large planning committee for developing the scientific program, grading abstracts, and moderating sessions. We received over 500 abstract submissions. At the Congress, delegates presented 100 abstracts orally and more than 300 in poster format.

Delegate evaluations ($n = 103$) of the Congress were positive. Particularly well-regarded parallel sessions, which consisted of 2-3 invited talks and 4 oral presentations, were those on (exposures) infant feeding and postnatal growth, developmental disruption, social hierarchies; (mechanisms) genetic/epigenetic influences, endocrine mechanisms, programming of nutrition and physical activity, stress/infection, oxidation/endothelium/vasculature; (outcomes) diabetes and metabolic syndrome, cardiovascular disease and risk factors; and (interventions) animal models, clinical and public health interventions. Among the plenary sessions, a particular favorite was a new feature highlighting controversies in the field of DOHaD. Other popular new features were the breakfast workshops, moderated poster sessions for DOHaD New Investigator Award finalists, and meet-the-professor roundtable luncheons. The mean score for overall content of the program was 4.3 on a 1-5 scale with 5 being "excellent." The most cited concern was inability to attend all sessions of interest, given that 4 to 5 parallel sessions occurred simultaneously.

EMERGING THEMES

In recent years it has become clear that neither genetics alone nor adult lifestyle factors can fully explain rates of common chronic diseases. DOHaD focuses on the earliest stages of human development, and provides a novel paradigm to complement other strategies for lifelong prevention of these conditions (1). It may well be that improving the environment to which an individual is exposed during development is as important as any other public health effort to improve population health world wide. Thus, a better understanding of the DOHaD represents a major area of preventive medicine. We highlight four areas that emerged from DOHaD III.

POSTNATAL INFLUENCES MODULATE INTRAUTERINE PROGRAMMING

At the first plenary session, Honorary Chair David Barker presented recently published results from a Finnish cohort born between the two world wars. In that study, relatively low birth weight combined with poor weight gain until age 2 y followed by increased weight gain during childhood and adolescence predicted development of coronary heart disease as an adult (2). These results are consistent with previously published results from India showing that increasing body mass index through adolescence confers excess risk of impaired glucose tolerance in early adulthood (3).

The particular role of early postnatal growth from birth to 2 y is, however, unresolved. In contrast to the findings from Finland are recent observational studies of term infants and randomized trials of premature infants, summarized by speakers at the Congress. Those studies suggest that accelerated weight gain during infancy, even during the first weeks of life, can result in overweight, insulin resistance, and higher leptin and blood pressure levels one to four decades later (4-6). Some of the discrepancies between studies may result from methodologic considerations or the fact that studies have emanated from different historical eras, but establishing the contemporary situation is of great importance (1).

This issue is critical in developing countries undergoing the epidemiologic transition to chronic diseases (7). In many households, maternal obesity occurs concomitantly with childhood stunting (8,9). In these settings, nutrition programs to achieve increased linear growth must not also cause excess weight gain in childhood (10). Animal studies confirm and extend the epidemiologic observations. In a rat model, maternal energy restriction results in offspring insulin resistance and elevated blood pressure, and these effects are magnified by excess energy intake and weight gain postnatally. However, the prenatally induced effects are not immutable, as administration of leptin at a critical period of hypothalamic development reverses many of the morbid effects (11). Thus, in at least some cases developmental cues may elicit responses that are not programmed in a deterministic way, but are reversible.

Some have used the term "thrifty phenotype" to refer to the observation that babies who are born at lower birth weights (or animal fetuses whose mothers were undernourished), but gain excess weight postnatally, have elevated risks of metabolic and cardiovascular outcomes. More recently, DOHaD scientists have invoked a more all-encompassing term, "predictive adaptive responses," which posits that the degree of mismatch between early developmental and later influences can predispose to poor health (12,13). This perspective fits well with newer concepts of early origins of obesity, reviewed next.

OBESITY AND ITS CONSEQUENCES ARE EPIDEMIC IN DEVELOPING AS WELL AS DEVELOPED WORLD

Given the worldwide epidemic of obesity, now spreading rapidly from developed to developing countries, the program of DOHaD III contained many sessions related to basic, clinical, and population research into causes and consequences

of obesity. While much DOHaD research has focused on “undernutrition” of the fetus (partly determined by maternal diet), there is now an equally important focus on “overnutrition.” Several speakers at the Congress emphasized that while lower birth weight is associated with adverse metabolic outcomes, higher birth weight is associated with higher body mass index in childhood and adulthood, along with an increased risk of obesity and diabetes, (14,15) and animal studies are showing that high-fat or high-energy diets to pregnant mothers can result in similar outcomes (16,17). In addition some studies show that higher birth weight is associated with elevated risks of premenopausal breast cancer, (18) possibly explained by an *in utero* environment with higher levels of estrogen or leptin (19).

These observations have led to a growing number of human studies and animal experiments examining aspects of maternal energy surfeit, excess gestational weight gain, and gestational diabetes. For example, 3 abstracts presented at the Congress found associations between higher weight gain during pregnancy with offspring obesity in developed world populations (20–22). In an Indian population, female 5-y-old offspring of diabetic mothers, but not diabetic fathers, had increased adiposity and insulin levels (23). As in US populations, the offspring of diabetic mothers were fatter at birth and in childhood (5 y of age), but not at 1 y of age. These findings raise the question of whether a fetal influence (hyperinsulinism) must be combined with a “2nd hit” postnatally to produce the offspring phenotype. In a nonhuman primate model, chronic maternal overfeeding leads to fetal oxidative stress in the liver, resulting in fatty liver and disordered lipid handling (24). In a rat model, higher birth weight from maternal diet-induced obesity leads to mammary tumorigenesis (25).

These findings highlight the adverse effects of the maternal obese and/or diabetic intrauterine environment. Interrupting such effects is crucial in the developed world, where obesity and diabetes are already epidemic, and it is becoming ever more important in developing countries undergoing the nutritional and epidemiologic transition, areas of the world that will witness the largest increases in diabetes in the 21st century (26).

RESEARCH IS EMERGING ON DEVELOPMENTAL DISRUPTION BY ENVIRONMENTAL TOXINS

It is possible that long-term consequences of fetal or infant exposure to very low doses of bisphenol A may occur, due to leaching from polycarbonate plastic. Bisphenol A acts as an estrogen-like compound. In animals, bisphenol A alters cellular signaling, fetal development and adult physiology and reproduction at doses far beneath the currently recommended safe exposure level (27). New scientific evidence on adverse effects of low doses of bisphenol A is required to assess its risk-benefit profile.

Several abstracts addressed other harmful effects of maternal exposures on offspring outcomes. For example, maternal smoking during pregnancy may cause reno-vascular changes (28) and elevated blood pressure.(29)Maternal exposure to

endotoxin can result in fetal brain damage in the sheep (30) or altered intestinal growth and barrier function in the rat (31).

Another topic of interest was trans-generational actions of endocrine disruptors on disease development. Fetal exposure to certain endocrine-disrupting compounds, such as the anti-androgenic fungicide vinclozolin, can affect male fertility not only among the offspring, but also in subsequent generations (32). These effects appear to be caused by altered patterns of DNA methylation, which in turn modify transcription and can then induce the development of disease in later life. This is an example of epigenetic inheritance, discussed in the next section.

EPIGENETIC MECHANISMS MAY EXPLAIN OBSERVED PHENOMENA

One of the most exciting emerging themes in the DOHaD field is epigenetics. The notion that a maternal environmental influence such as diet could alter offspring outcomes through epigenetic changes in gene regulation could unite several strands of human and animal observations. Experiments presented at the Congress demonstrated that feeding female Agouti (yellow) mice dietary supplements of vitamin B12, folic acid, betaine and choline just before and throughout their pregnancy can produce graded change in coat color of the offspring, ranging from a yellowish fur from mothers eating a regular diet to brown fur in pups of the supplemented mothers. Furthermore the brown-fur offspring grow up with lower rates of obesity, diabetes and cancer. The epigenetic mechanism associated with this phenomenon involves the switching off the Agouti gene by methyl groups from the supplements (33). Some of these effects appear to be tissue specific and can be induced even in normal rats by maternal dietary manipulation (34). These and similar findings show, in principle, how genetically identical individuals raised in similar postnatal environments, *e.g.*, identical twins, can nonetheless develop widely differing phenotypes.

As noted in the previous section, epigenetic changes in one generation can result in phenotypic changes across many generations. In a broader context, nongenomic trans-generational influences may result from imprinted genes in the embryo and placenta, including epigenetic mechanisms affecting embryonic germ cells, heritable changes to mitochondrial DNA, maternal adaptations to pregnancy and behavioral influences on the newborn, and the range of factors falling under the broad heading of cultural inheritance (35–40). There is now evidence for nongenomic inheritance of many environmentally induced components of risk for later chronic disease (41,42).

OTHER ASPECTS

Several other ramifications of the DOHaD paradigm were in evidence at the Congress. While much attention has focused on the important and common outcomes of obesity, diabetes, and cardiovascular disease, the DOHaD principles apply as well to a range of conditions, including cancer, (25, 43–49) reproductive outcomes, (50,51) mental health and neurologic conditions, (52–57) and respiratory disease, (58–61) as well

as body composition. A separate session reflected the primacy of the placenta not only in nutrient transport, but also as an endocrine organ and an important mediator of environmental cues itself (62–66). In addition, the moderator of the parallel session on data analyses enhanced interaction by placing data sets on the DOHaD website ahead of the meeting, so that attendees could analyze these data before listening to how invited discussants handled them.

THE FUTURE

An inherently interdisciplinary field, developmental origins of health and disease has benefited greatly from the biannual Congresses to date, as they bring together under one roof the many scientists who otherwise would not have the opportunity to share their research with those from other fields. From the 1st to the 3rd Congresses, from preconception to adulthood, and from genes to society, there has been an explosion of new information in DOHaD. It is clear that the influence of population sciences on clinical and basic sciences, and *vice versa*, is catalyzing this growth. The International Society of DOHaD therefore decided to increase the frequency of meetings to annually, with DOHaD IV at the University of Utrecht, Netherlands, in September 2006, and DOHaD V in Perth, Western Australia in November 2007. Details are available at the Society website, www.dohadsoc.org.

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