DOHaD (Developmental Origins of Health and Disease) and Birth Cohort Research

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Summary Epidemiological and animal experimental studies are disclosing that the malnutrition or overnutrition in utero would induce epigenetic changes of fetus, what is the origin of lifestyle-related disease in adult. Representative birth cohorts studies in DOHaD are explained.

Key Words DOHaD (developmental origins of health and disease), malnutrition in utero, epigenetics, birth cohort study, lifestyle-related disease

Lifestyle-related diseases such as type 2 diabetes and cardiovascular disease are the leading cause of death and disability, and show an increasing tendency worldwide. These lifestyle-related diseases are usually combined. For prevention, the development mechanism for the diseases should be evaluated. A lifestyle-related disease has been considered mainly to be induced by the specific disease-susceptibility genes and the lifestyle after birth. Intensive GWAS (Genome wide association study) has been carried out (1). It is difficult to elucidate the steep increase in those lifestyle-related disorders only by specific genes. Now a new theory has been proposed for this medical field, DOHaD (Developmental Origins of Health and Disease) (2). Epidemiological and animal experimental studies have disclosed the intimate links between exposure particularly to malnutrition, in the developmental stage and lifestyle-related chronic diseases in adulthood. Such studies provide the foundation and framework for this new field of life science, DOHaD. Although a great number of studies have been done for elucidating the putative concepts and molecular mechanisms relating specific exposures in early life to the risk of developing chronic diseases in adulthood, a complete picture still remains obscure. Until recently in this field the main research point has been on periconceptional and peri-natal under-nutrition and specific nutrient deficiencies. But now overweight and obesity are increasing. So by the same token, perinatal over-nutrition and specific nutrient excesses should be examined. In addition to nutrition, psychological stress, environmental chemicals and artificial reproductive techniques are other important fields in DOHaD. This theory is historically reviewed and the new research fields are brought in.

FOAD (Fetal Origins of Health and Disease)
The Developmental Origins of Health and Disease (DOHaD) approach evolved from epidemiological studies of infant and adult mortality, Barker first showed us the most influential studies in this field and proposed the fetal origins of adult disease (FOAD) hypothesis called Barker’s Hypothesis (3–5). The studies showed a large positive geographic correlation between standardized rates for infant mortality from 1921 to 1925 and ischemic heart disease from 1968 to 1978 in England and Wales (3). They thought the neonatal death rate was associated with low birth weight due to adverse intrauterine malnutrition. Barker’s team moved to investigate the demographic record of the Hertfordshire area, where accurate surveys of size at birth and weight in infancy had been documented and preserved from 1901 to 1945 (4). They found the adults with the lower birth weight showed higher rates of death from ischemic heart disease, and the standardized death rates decreased with increasing weight at 1 y of age (4). This led them to the hypothesis that poor fetal and infant growth was followed by a high risk for ischemic heart disease and adult disease. They proposed the FOAD hypothesis (5). This integration proposed that malnutrition during gestation would change and reprogram permanently the body’s structure, function and metabolism in a way that increased the risks for coronary heart and adult diseases in later life.

Roseboom et al. (6) investigated the Dutch winter famine cohort exposed to the 1944–1945 famine at the end of World War II and showed that fetal under-nutrition may affect different organs of the body depending on different critical phases of development and those adults demonstrated an increased risk for insulin resistance, impaired glucose tolerance, high serum cholesterol, coronary heart disease and psychological disorders. Members of the Dutch winter famine cohort showed proof of Barker’s theory.

DOHaD (Developmental Origins of Health and Disease)
The FOAD concept has advanced to the DOHaD theory, with the concept that the early life environment has widespread consequences for later health from the oocyte to the infant and adult, exhibiting the broader scope of developmental cues (7). Now the DOHaD concept has expanded to broader fields and themes: the pathways to obesity in childhood and adulthood having the origins in utero and infancy for both over- and under-nutrition.
the evaluation of psychobiological stress during fetal development and later outcomes, and the evaluation of epigenetic modification based on the DOHaD approach. There are many famous birth cohort research projects going on in the world, including those in Japan like the Echo-Chil Cohort Study, Hokkaido Study, Hamamatsu Birth Cohort Study, and Touhoku Mega Bank study. As representative prospective birth cohort projects, I introduce three studies, the Southampton Women’s Survey (SWS), Project VIVA, and the Behavioral Perinatology Research Program.

The Southampton Women’s Survey (SWS)

The University of Southampton has conducted the Southampton Women’s Survey (SWS). The SWS started with interviews of 12,500 young female residents of Southampton to obtain measures of pre-pregnancy characteristics, followed by 3,000 live births, and prospective evaluation in detail of birth phenotypes and outcomes in infancy and childhood (8). They studied the mothers’ nutrient intake, body composition and endocrine profile with fetal growth, placental, and fetal adaptive responses, interactions of maternal and intrauterine factors with genes, and postnatal life style of offspring that influence growth in infancy, looking for pathways leading to poor adult health.

Using Doppler ultrasound, Haugen et al. (9) analyzed blood flow of the fetal ductus venosus, the vessel shunting placental blood directly from the liver to the brain and heart. In the low-risk fetuses, the blood flow was reduced with liver-sparing response, and by contrast in the high-risk group for fetal hypoxia, the flow of ductus venosus shunting increased, a brain-sparing effect.

Harvey et al. (10) studied the neonatal body composition with dual-energy X-ray absorptiometric scanning, and disclosed that total fat mass was related to maternal lifestyle factors, smoking and physical activity. These results suggest to us that these not-ideal maternal lifestyle influences have persisting effects on offspring fat mass and an ideal maternal lifestyle could pave the way to prevent later obesity. This may provide newly improved estimates of the underlying DOHaD-related factors that contribute to risk for lifestyle-related diseases later in life.

Project VIVA

In 1999, Project VIVA was initiated in eight offices of Harvard Vanguard Medical Associates, a large multispecialty group in Massachusetts. In this study, women early in pregnancy were recruited and prospectively assessed twice during pregnancy, and their babies were studied within 3 d of birth, and at 6 mo, and at 1, 2 and 3 y of age (11). The study was then extended to conduct follow-up through 7 y of age. Taveras et al. (12) reported that the ratio of weight gain in the first 6 mo to the birth weight was predictive of the weight at 3 y. This suggests that increases in weight in the first 6 mo may have an additional new programming effect for obesity in early childhood and for later obesity. Although the birth weight has been thought to be a marker of under-nutrition or over-nutrition in utero and a main predictor for permanent and serious later outcomes, Taveras’ group showed that birth weight is not the main predictive factor for postnatal health outcomes. In the Helsinki 1934 to 1944 Birth Cohort, Eriksson and Barker (13, 14) also showed that both the tempo of growth in childhood and birth weight determined adult health and disease. Coronary heart disease was markedly more strongly related to the tempo of childhood body mass index (BMI) gain from ages 2 to 11 y than to BMI itself at any other age.

Behavioral Perinatology Research Program

Early DOHaD research had been mainly related with nutrition and environmental chemicals, but exposure to other factors such as prenatal maternal stress and maternal-placental-fetal biological mediators of stress could not be neglected for fetal development and future health. Drake et al. (15) stressed fetal glucocorticoid overexposure as an alternative factor in adult disorders related to cardiovascular, metabolic, neuroendocrine, and behavioral phenotypes. A multi-investigator research program at the University of California-Irvine was initiated in 1993, the Behavioral Perinatology Research Program (16).

These researchers evaluated young adults born with a normal birth-sized phenotype, whose mothers were exposed to a major stressful life event during pregnancy. Compared with healthy individuals, Entringer et al. (17, 18) showed that maternal stress-exposed offspring exhibited insulin resistance and a lipid profile specific to metabolic syndrome, altered immune function, altered endocrine function, and cognitive dysfunction. These findings suggest that fetal exposure to severe maternal stress may have lifelong negative physiological consequences and may directly influence adult health even without low birth weight. So abuse in childhood, family strife or emotional neglect may have epigenetic effects in neural and endocrine response to stress, and may increase the susceptibility to common disorders in adulthood such as depression, diabetes, heart disease, or obesity.

In Germany, K. M. Radtke and colleagues analyzed the methylation of the GR gene in mothers and their children at 10–19 y old, with maternal exposure to intimate partner violence (IPV) (19). The mothers did not show any change in the GR gene, but the methylation of GR promoter regions was increased in their offspring. These results suggest that sustained epigenetic modifications was established in utero and this may be a plausible mechanism by which prenatal stress may program adult psychosocial function.

Conclusion

In this review, I introduced only a small number of cohort studies. DOHaD is the most important concept for prevention of the expansion and development of lifestyle-related disorders. From the stand point of DOHaD, such research should be urgently promoted for epigenetics, GWAS, environmental chemicals, and stress during the developmental stage. It should also combine...
broad fields, of science, including basic life science, preventive medicine, clinical medicine, economics, social science, pedagogy, politics, and drug discovery.

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