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REVIEW

The developing world of DOHaD

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Since its debut in a ground-breaking report by Barker and Osmond in 1986, the concept of the Developmental Origins of Health and Disease (DOHaD) has been further developed in several aspects. Its methodology and conclusions relating to proposed origins and outcomes of early life events have been developing and spreading internationally. Indeed, the DOHaD concept now seems to have influenced many fields of research. This article aims to briefly review why the DOHaD concept is important in biomedical science, how it has developed, is currently developing, and how it should develop in future.

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Origin of the 'Developmental Origins of Health and Disease' (DOHaD) paradigm

Most researchers working in the life sciences have probably been aware for some time that environmental factors in early fetal life are able to influence the expression of genes, with effects on later health and disease. However, the publication of Barker's ground-breaking epidemiological report in 1986[1] is generally considered as the beginning of 'DOHaD' concept. He demonstrated in his report a positive correlation between standardized mortality for ischaemic heart disease in 1968–78 and neonatal and infant mortality in 1921–25 in England and Wales, and speculated that 'poor nutrition in early life increases susceptibility to the effects of an affluent diet, resulting in increased mortality for coronary heart disease in later life'. This trail-blazing report was followed by more articles by himself and his colleagues on this topic which led to his now famous hypothesis that poor prenatal nutrition in early life increases the adverse effects of an affluent diet in adulthood, resulting in an increased risk of various non-communicable diseases (NCD).[2–6] The so-called 'Barker hypothesis' is now also referred to as the 'fetal origins hypothesis', 'thrifty phenotype hypothesis', and/or 'developmental programming', which is sometimes teleologically described as 'predictive adaptive response'.

The 'DOHaD' paradigm seems to have become well accepted among scientists and researchers in medical and biological sciences. Since its introduction, the DOHaD concept and the fields it covers have been expanding and developing in many ways. The following sections will describe in more detail how the 'DOHaD' theory has become disseminated and how it has developed for the last three decades.

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Understanding development of life (organism)

The 'DOHaD' concept would certainly be one of the most important theories in biological science. The 'gene and environment theory' or simple application of Mendelism and Darwinism has been long a central framework in modern biological science which explains the development and evolution of an organism and determines the resultant phenotype. However, the detailed mechanisms by which a set of genes interacts with the environment to produce various phenotypic expressions have not been known. There are two processes by which cells grow and develop in an organism: differentiation (development of cells into a specific tissue or organ in an organism) and variation (minor differences in tissues or organs between individuals of a given species). Recently, the developing field of epigenetics has the potential to explain some aspects of the mechanisms of differentiation and variation.[7]

Development of DOHaD studies

The range of life periods that the 'DOHaD' hypothesis covers has extended from Barker's original fetal period to the period covering meiosis and gametogenesis to the entire postnatal developmental period until maturation from infancy to adolescence. The resultant health status in adulthood of the first generation may influence the development of gametocytes and their environment of the next generation.[8]

Extension of the range of period when programming can occur has been accompanied by a change in terminology. The 'Barker hypothesis' initiated worldwide interest in this idea of developmental plasticity, which led to the establishment of an worldwide society for DOHaD as well as international congresses which were initially held under a name of 'FOAD' (fetal origins of adult disease); later the term 'DOHaD' was adopted, to indicate a broader perspective period of 'origin' extending not just for the prenatal period but for the entire developmental period.[9]

Studies on the DOHaD hypothesis originally started with epidemiological investigations of links between indices of fetal-infant nutrition (weight at birth and in infancy, infant mortality) and health status in adulthood in regions of the United Kingdom. Those observational facts have been demonstrated later to be able to be explained partly by mechanisms at the molecular and cellular levels, including the process of epigenetic modification of gene expression.[10] Importantly, Barker's original observational studies were followed by those with larger scale covering broader districts and even worldwide. The scope of DOHaD is becoming more and more important for improving public health and well-being. Indeed the DOHaD paradigm is likely to apply to all species over generations.

Understanding of the spectrum of causative factors of DOHaD outcomes has also been developing and expanding since the first appearance of the DOHaD concept. The causative factors originally started with nutritional status during pregnancy as indicated by infant mortality, birth weight and placental weight; they have now evolved to include various external and internal environmental factors affecting the body. These include the physical, chemical and biological environment such as drugs and chemicals including pollutants and medicines, light and other electromagnetic waves, sounds and oscillations, indigenous microbiota in the gut and elsewhere.[11,12] In particular, the microbiome is becoming recognized as an important and influential biological environment in the context of global prevalence of allergic diseases.[13] Mental and physical 'stress' is another influential factor not to be ignored, modulating neuro-endocrine pathways in every stage of development.[14]

Assumed target organs started with the cardiovascular system and then have developed to include the metabolic, endocrine, respiratory, renal, nervous, mental, gastrointestinal, reproductive systems, all of which obviously influence the development and health of the offspring.[12]

The mainstream of DOHaD studies are based on basic life sciences in close relation with molecular biology, developmental biology, human genetics and epidemiology. The DOHaD approach is becoming more common and gaining closer relationship with many research fields of other disciplines. Obstetrics, embryology, neonatology, paediatrics and internal medicine have always been central to DOHaD studies. Nutritional sciences, dietetics, endocrinology, nephrology and cardiology have always been important topics related to DOHaD studies. Neurology and sciences relating to mental health such as psychiatry and psychology have also been among essential topics. DOHaD studies have often dealt with such a variety of subjects as environmental science and ecology, toxicology and pharmacology, agriculture and fishery, community hygienic and preventive medicine. Apparently, the fields that DOHaD studies cover and link to have expanded to many areas of research in the life sciences. However, the DOHaD concept should not dominate all the biological and health sciences: it is rather a concept or a fundamental framework that supports biological and human sciences. DOHaD paradigm should never be an independent and dominant academic kingdom. It should rather act as one of essential basic principles which certainly apply and contribute to many areas of life sciences in various ways.

The methodology of medical research is underpinned by basic biological sciences, including *in vitro* and *in vivo* experimental studies using cells, tissues and whole animals, as well as human clinical studies. Epigenetics is now one of the main basic disciplines of DOHaD. Molecular and biochemical studies are obviously essential parts of DOHaD studies. Animal experiments have a definite advantage over human studies not only because of bioethical reasons but also because of their advantage of shorter life cycles which are beneficial when studying transgenerational effects.

The DOHaD hypothesis was originally based on a retrospective epidemiological study by Barker.[1] Epidemiological cohort studies have been always one of main analytical methods in DOHaD. Nowadays, transgenerational large-scale cohort studies have been carried out in a number of areas in the world and have produced some significant findings. Some of them are plain observational follow-up studies and some have various levels of interventions. For example, the Southampton Women's Survey,[15]the Danish National Birth Cohort[16] and Project VIVA[17] are among early studies that have been producing some outcome results. The docosahexaenoic acid (DHA) to Optimize Mother Infant Outcome (DOMInO) trial is one of the interventional studies which looked at effects of DHA supplementation during pregnancy on outcomes of mothers and their children.[18]

Development of studies on DOHaD in developed and developing countries

The academic development of DOHaD research is unique in the way that its professional society has developed and the locations at which international congresses have been held. The first international FOAD conference was held in Mumbai, India, followed by Brighton, United Kingdom. Interestingly, international congresses on DOHaD have been held mostly in United Kingdom which was the home of Barker, and in the Netherlands which was the location of the well-known 'Dutch famine', and their historical colonial countries (other countries where International DOHaD Congress has been held include Canada in 2005, Australia in 2007, Chile in 2009, United States in 2011, Singapore in 2013 and Republic of South Africa in 2015). Other additional factors contributing to the emergence of some academic hubs of DOHaD seem to be related to the contemporary worldwide problem of obesity and diabetes, especially in middle income countries.[19] Undernutrition is still a major problem in many countries; however, too rapid and often imbalanced changes in life style and environment are also becoming a matter of concern in some 'developing' countries. DOHaD is not only about under or imbalanced nutrition in early life causing an aptitude for NCD in later life, but is also

about all environmental factors that may be linked to NCDs. The global prevalence of NCD is becoming more recognized as an imminent worldwide problem. According to World Health Organization (WHO) 2017, ~70% of the 56 million annual deaths in the world are due to NCDs, of which ~50% occurred before the age of 70 in 2015.[20] Since 2013, members of the United Nations and WHO have gradually been shifting their main targets of global action plan from communicable to non-communicable diseases. DOHaD studies may well play a key role in challenging the common problem of NCD both in developed and developing countries, irrespective of their historical and geographical background.

Development of DOHaD from theory to practice

The DOHaD concept is not just about academic science. It is also about everyday practice for individuals as well as about public health, policy making and education. Its findings contribute to public knowledge and have helped improve the level of human health. It also has a great impact on general consciousness of health and disease and is expected to promote dissemination and education of this important basic idea in life.

The 'First 1000 Days' campaign, proclaiming the importance of nutritional status of infants and nursing mothers in the fetal and neonatal period until 2 years after birth (total of ~1000 days; 280 days before birth + ~730 infantile days after birth), is a good example aiming to enhance worldwide awareness of the DOHaD concept including the general public and professionals in education and health policy.[21]

Recent development of DOHaD studies

The 'DOHaD' field of research is developing rapidly. In the field of epigenetics, the NIH Roadmap programme on the Epigenomics of Human Health and Disease is applying new projects characterizing reference epigenomes and comparing them in disease and non-disease states.

There is no doubt that prospective birth cohort studies (both observational and interventional) will be a mainstream topic in future DOHaD research. A number of large-scale birth cohort studies have already been launched in Europe, North America and Australia, investigating the relationship between measures of antecedent exposures and resultant outcomes. More recently, the Generation R study in the Netherlands involves ~10,000 mothers who gave birth in 2002–2006 period.[22] A very large-scale prospective birth cohort of the National Children's Study in the United States is recruiting 105 sites with ~100,000 children.[23] The Australian Longitudinal Study on Women's Health (ALSWH) or Women's Health of Australia (WHoA) is another large-scale study, examining the health of over 50,000 Australian women.[24] NiPPeR trial (Nutritional intervention Preconception and during Pregnancy to maintain healthy glucosE levels and offspRing health) is another large-scale interventional study looking at effects of nutrients and probiotics before and during pregnancy.[25]

In Japan, the Hokkaido Study on Environment and Children's Health is underway recruiting ~20,000 mother–child pairs.[26] The Tohoku Medical Megabank project is designed for reconstruction of regional healthcare in areas affected by the Great East Japan Earthquake of 2011, aiming for the provision of research infrastructure for the development of personalized genomic medicine.[27] It involves a three-generation cohort project aiming for ~20,000 mothers, their children and parents.

Conclusion

After successful control of major infectious diseases and malnutrition in the last century, NCDs and life-style-related health problems are emerging as a significant burden in this century all over the world. People are becoming more conscious about nutrition and health. Communities and governments have started taking actions aiming for a healthier diet and life-style. In this context, the findings of DOHaD research can provide valuable scientific evidence and leadership to the public. Optimal level of inputs or stimuli from the environment is certainly the key to our health and well-being over generations.[28] As Barker has already shown clearly, both low birth weight and high birth weight were associated with increased risk of death from ischaemic heart disease.[3] The U- or J-shaped response pattern (i.e. opposite directing responsiveness in low *v.* high inputs) seems to be a ubiquitous scheme in living organisms.[29] The DOHaD paradigm, together with its background of epigenetics (based on '*central dogma*' of molecular biology[30]), has certainly become a central concept in medicine and biological science.

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