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DOHaD in Indigenous populations: DOHaD, epigenetics, equity and race

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Editorial

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This themed issue highlights the *Developmental Origins of Health and Disease* (DOHAD) concept in Indigenous populations, who experience disproportionate disadvantage even when living in affluent countries. The disparities in health tend to mirror the disparities in socio-economic conditions. The DOHaD concept provides a framework to both explain these differences and to provide a platform from which to deliver programs to address these.

DOHaD is the study of how the early life environment can impact the risk of chronic diseases from childhood to adulthood and the mechanisms involved.[1,2] Epigenetic modifications such as DNA methylation, histone modifications and non-coding RNAs are involved in mediating how early life environment impacts later health. Development is a plastic process that responds to changes particularly in nutrition (both too little and too much) and also to stress, drugs and environment, such that these adaptations increase the risk of disease in the long term. These diseases are non-communicable diseases (NCDs) and include obesity, diabetes, hypertension and cardiovascular disease, as well as asthma, allergy, immune and autoimmune diseases, neurodevelopmental and neurodegenerative diseases/dysfunctions, changes in timing of puberty, infertility, cancers, depression and psychiatric disorders.[3–5]

Epigenetics not only provides a mechanism to explain developmental programming and the risk of chronic diseases but also provides a basis for understanding gene–environmental interaction and the intergenerational effects of adversity.[6,7] Although the genetic code does not change in response to the environment, the biological switches that turn those genes on and off do. These altered regulatory commands can then be passed from parent to child and thus the altered gene expression patterns that affect the health of a person into adulthood can be passed from one generation to the next generation. The exciting corollary to this notion is that there is the potential to reverse these effects.

The most critical and sensitive time for development is the First Thousand Days from conception (or most accurately, preconception) to about age 2.[8] A double-hit mechanism is one explanation, whereby the first hit sets the scene and the second hit makes manifest the adverse outcome.[9] The first hit in this scenario is the biological embedding and vulnerability created from the experience of previous generations through the first 1000 days post-conception that increase sensitivity to adverse family and community environments encountered later in life. The second hit comes from hostile environments marked by racial and other discrimination, inequality and social disadvantage that creates constant wear and tear on human systems and increases the likelihood that the original vulnerability will transform into later disease.[6] As some of these changes can be transmitted across generations, the 'second hit' of one generation can become the 'first hit' of the next. When these effects are multiplied in large populations that live in conditions that create and sustain high levels of stress, limited access to nutritious food, poor housing and limited educational and employment opportunity, there is an emergence of clusters of chronic disease and social problems.[5] However, this clustering within large populations is not random but influenced by race.

Race has so many negative connotations that it is so often by-passed, or completely ignored, in the discourse on health and social inequities. There are profound scientific and ethical problems of unjustified generalizations in the design and conduct of research, as well as in the interpretation and translation of scientific findings using considerations of race. However, the discourse about social inequities must incorporate race to inform the best policies and hence the best outcomes for the most vulnerable people, which are often the Indigenous populations. This theme is interwoven into these following articles.

McEwan *et al.* provide a narrative review of DOHaD as it applies to Indigenous populations and highlight the paucity of studies that have been conducted in the Indigenous population.[10] One major study is the national longitudinal study of Indigenous children, 'Footprints in time' that describes the health of Australian Indigenous children using a social and cultural lens, with a focus on early development as well as intergenerational effects.[11] The next-generation cohort describes the high risk of diabetes seen in children of First Nations mothers who have diabetes themselves, a large proportion of whom have a unique HNF1α and which is also a significant factor in the increased risk of diabetes in their children.[12] The Indigenous Australian pregnancy-through-to-early childhood cohort showed that the high

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risk of obesity seen in the Indigenous children was associated with being born preterm, large for gestational age or being exposed to an obesogenic intrauterine environment. This study did not show a significant association with low birth weight and later obesity.[13] Mah *et al.*[14] describe the effects of stress on Aboriginal women during pregnancy and beyond from a developmental perspective. The Saskatchewan study reminds us that the both ends of the spectrum of birth weight, high as well as low birth weight, confer a greater degree of risk for development of diabetes in a study of both First Nations and non-First Nations people.[15] The study by Hoy and Nicol demonstrates the association of birth weight and mortality in an Indigenous population showing that both low birth weight and birth weight as a continuum had a strong association with natural deaths.[16] Together, this collection of studies highlight the need for more understanding of the role of DOHAD in the health of Indigenous populations and the selection and implementation of interventions to improve health in the future.

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