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Editorial

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A Canadian perspective on the developmental origins of health and disease: understanding the past as a way forward

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More than two decades ago, David Barker published a landmark paper describing the fetal origins of adult disease hypothesis, which posited that suboptimal conditions during pregnancy 'program' the fetus for the development of chronic diseases in adulthood.[1] The conceptual underpinnings of the fetal programming hypothesis were built on a series of epidemiological studies linking indices of adversity in early life with cardiovascular mortality in later life. In the ensuing decade, this concept stimulated a great deal of interest and work from research groups all around the world, and this global effort culminated in the first World Congress on the Fetal Origins of Adult Disease, convened in 2001 in Mumbai, India. In 2004, following the second World Congress held in Brighton, UK, the society adopted the title of '*Developmental Origins of Health and Disease*' (DOHaD), to 'recognize the broader scope of developmental cues, extending from the oocyte to the infant and beyond, and the concepts that early life environments have widespread consequences for later health.'[2] The first meeting of the DOHaD Society was held in Toronto in 2005, highlighting Canada as a prominent entity in the field. In 2016, DOHaD Canada became a recognized chapter of the International DOHaD Society. The Inaugural Meeting for DOHaD Canada, held in Montebello, Québec in 2017, was a resounding success, attracting leading investigators, clinicians and trainees – a testament to Canada's engagement in the field. Canada continues to uphold its commitment to DOHaD-related research; with a membership of almost 200 investigators and trainees, DOHaD Canada will host its third meeting in Mont-Tremblant, Québec in February of 2019. The meeting will focus on the country's research strengths: epigenetics and omics mechanisms underlying DOHaD, vulnerable populations, and solution-oriented research and policy.

DOHaD Canada's mission is to be a globally connected network focused on creating, translating and communicating the latest knowledge on early development to improve the immediate and long-term health of Canadians, and to promote maternal-child health and well-being on a global platform. The Society engages in social, biological, clinical and economic research focusing on: (i) how environmental factors during the early life period (preconception, childhood and adolescence) interact with development to place individuals on trajectories that impact life-long health, learning and social functioning; and (ii) development of strategies that prevent or reverse negative lifecourse outcomes, promoting health and wellness for all Canadians. Within its broad mandate, DOHaD Canada has made a concerted effort to address the unique health needs borne of its diverse populations, storied cultural heritage, expansive geography and varied climates.

As a country, Canada ranks among the highest in international indices of civil liberties, quality of life, education and government transparency. Canadians take immense pride in the nation's commitment to multilateralism and international citizenship; its embrace of multiculturalism and immigration, and a government committed to gender equality, reconciliation efforts and environmental conservation. In addition, perhaps underscored by our neighbours to the south, access to universal health care constitutes an important facet of Canadians' national identity. Internationally, Canada has played a key role in global initiatives to improve the health of women and children. First, through new commitments in the 2010 Muskoka Initiative,[3,4] Canada raised its contribution to maternal, newborn and child health (MNCH) initiatives to support efforts to reach the millennium development goals (MDGs) 4 and 5 (reducing child mortality and improving maternal health), directing funds to three inter-related paths: strengthening health systems, reducing the burden of illness and improving nutrition.[5] Second, at the 2014 Toronto summit,[6] this commitment was renewed through new funds for MNCH to bridge remaining gaps in the MDGs and move toward achieving the sustainable development goals.

Yet, despite holding these core values dedicated to promoting national and global health and well-being, Canada also has complex and pressing health issues. There are glaring inequities associated with Indigenous health, poverty and crime, attributed to a history of colonization and forced assimilation. With a higher incidence of mental health and chronic

disease, reduced access to health care and exposure to circumstantial health risks (lack of access to safe drinking water), Indigenous health is considered by many to be the nation's biggest health problem. Additionally, Canada, along with the United States, is currently in the midst of a public health crisis from opioid-related deaths and harms. The Canadian opioid crisis has concerned every region of the country, although certain areas (e.g., western provinces and northern territories) have been disproportionately affected.[7] Although Canada has enacted several initiatives to curb the mortality associated with opioid overdose,[8] it remains a pressing concern. Finally, like all countries, Canada is having to cope with potentially devastating health effects related to climate change (e.g., reduction in air and water quality, water and food-borne illnesses, weather-related natural hazards, etc.). As an existential threat, everyone on the planet has a stake in stopping and reversing this tide.

Themed issue: spotlight on DOHaD research in Canada

The goal of this themed issue, initially conceived in the wake of the inaugural DOHaD Canada meeting, is to spotlight Canadian health priorities and interests from a DOHaD perspective. It presents a flavour of the exciting work by Canadian researchers on developmental 'stressors' and their effects on the immediate and long-term health of an individual. In this issue you will read articles under three broad themes: early adversity, environmental conditions and vulnerable populations.

Early adversity

Canada has a high incidence of stress-related illness (e.g. cardiovascular disease, ulcers and nervous disorders) with more than one in four Canadians reporting daily stress levels in the high to severe range.[9] The combination of early onset, chronicity, disabling nature and limited benefits from treatment makes these illnesses some of the most burdensome disorders for individuals, families and society in Canada.[10,11] Indeed, stress-related work impediments cost industry about 10% of its annual profits, and it is estimated to cost the Canadian health system > $14 billion CAD each year.[9,12,13] Given the health, social and economic burdens of stress-related illness, there is a need to predict early in life who will be at risk for developing common physical and mental illness disorders, for timely intervention and prevention of onset.

Emerging research on human development that integrates maternal and child adversity with (epi)genetics, neuroscience, lifecourse epidemiology and developmental psychology has fundamentally altered our understanding of how environment and biology influence health and well-being over the lifecourse. Over the last two decades, developmental molecular (epi)genetics, in particular, has provided significant advances in our understanding of fundamental mechanisms linking early exposures with later phenotypes. From initial studies focused on a single mark, DNA methylation, in the context of fetal and postnatal growth, to present-day databases of hundreds of genome-wide studies, collectively these studies indicate a fundamental role for the (epi)genome and the early environment in the stable development of learning and memory ability, emotional responses to stress and social interactions, along with risk for certain cardiovascular, metabolic and neuropsychiatric disorders. Here, epigenetic biomarkers of exposure to childhood adversity may help identify individuals at risk and to target interventions.

In this themed issue, Sasaki and Matthews[14] first review some of the technical caveats and considerations in the design of studies that examine long-term effects of maternal exposures on adverse health outcomes in offspring – from the selection of target tissues and bioassay precision to the challenges of combining animal models with human studies. However, despite the identification of hundreds of genes as well as interacting (epi)genetic and environmental factors that contribute to disease susceptibility and behaviour, we still lack an understanding of the neurochemistry – the proteins and pathways – that lead from genes to behaviour. Barha *et al.*[15] examined a potential mechanistic link between maternal stress hormone levels early post-conception and levels of DNA methylation and stress-responsivity in their children. Given that maternal anxiety and depression are related to adverse childhood experiences and negatively affect children's behaviour,[16–18] these exposures provide potential pathways between maternal adverse childhood experiences and child psychopathology. Letourneau *et al.*[19] tested the theory of intergenerational transmission of stress and found maternal adverse childhood experiences were predictive of mood and anxiety during pregnancy and postpartum, and externalising problems in the children, especially boys. Aylott *et al.*[20] further confirmed this opposite-sex-specific parent-of-origin effect in the etiology of psychotic symptoms. Together these articles provide key insight into the gene–environment interactions that govern the intergenerational transmission of stress and the emergence of physical and mental illness and their transmission. This research may lead to more effective prophylactic (e.g., social support) and treatment strategies for the > 1 million Canadians who currently suffer from severe mental illness.[21]

Environmental conditions

As the world's second largest country, Canada is relatively sparsely populated owing to its abundance of forests, fresh water lakes and tundra. Canada is among the wealthiest countries in terms of natural resources, which include energy, minerals, timber and fresh water, as well as rich diversity of wildlife. Its vast geography is home to ecosystems in varied climates, ranging from coasts of the maritime provinces and British Columbia to the continental weather of the prairies, and to the arctic landscape of the north.

Despite increasing efforts to transition to sustainable energy resources, climate change is causing widespread environmental issues that pose a threat to our quality of life. These include reduced air quality, water and food-borne contamination, extreme weather phenomena and increasing incidence of natural disasters. Canada is committed to assessing and understanding the effects of climate change on health, with the goal of helping populations adapt to climate change. These initiatives, which build on current health policies and practices, include improved climate change scenarios, climate and infectious health alert and response systems, and regional adaptation work programs.[22] In addition, assessment of key vulnerabilities and health adaptation in northern Inuit communities is also an emphasis,[22] as these communities are particularly vulnerable to the changing climate. The eroding northern landscape and pollution leading to food contaminations, which bio-concentrate and magnify adverse effects, may already be causing irreparable harm.

In this themed issue, two studies are profiled. The article by Olson *et al.*[23] describes efforts to improve resilience, particularly in pregnant women, in the wake of natural disasters. The article provides context for the interpretation of data and outcomes from these trials, and may also provide perspective for those without

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lived experience. The article by Maurice *et al.*[24] describes the effects of environmentally relevant contaminant mixtures on male reproductive capacity and health. The contaminant mixes consist predominantly of organochlorides (e.g., polychlorinated biphenyls and chlorinated pesticides), which persistently contaminate the arctic food chain, and, therefore, may have important health consequences for Inuit populations.

Vulnerable and at-risk populations

The final theme in this issue highlights research on health outcomes in at-risk and vulnerable populations in Canada. Health gaps, disparities and inequities that exist in health research, care (including access) and policy occur globally. These gaps overlook underrepresented and/or underserviced individuals, groups and populations, and often discriminate based on geography, sex and gender, ethnicity and culture, and/or socioeconomic and demographic status. Unfortunately, we do not need to travel beyond Canadian borders to find such health inequities. Indigenous peoples, immigrants to Canada, and individuals with problematic substance use are three groups that are at greater risk for worse health outcomes, or greater declines in health over time, compared to non-Indigenous Canadians,[25,26] the Canadian-born population[27] and those without problematic substance use or substance use disorders (SUDs),[7,28] respectively. What determines health, and health gaps, in these at-risk populations include numerous factors such as, but not limited to, poverty, under and unemployment, lack of access to essential services and health care (including health interventions), food insecurity, low rates of breastfeeding and early child education, climate change and governmental policies.[29–32] Critically, these conditions establish an intergenerational cycle of health disparities, which often disproportionately affect women and children.

Although the degree of health inequity between Indigenous and non-Indigenous populations are no doubt impacted by social determinants[33] including those listed above, more significantly, they are rooted in the historical and present trauma faced by Indigenous peoples. As Phillips-Beck *et al.*[34] and Bombay *et al.*[35] report in this issue, adverse early life experiences shape the health outcomes of Indigenous women, men, children and youth, notably affecting their risk for cardiometabolic diseases and mental health disorders. In their papers, the authors discuss how to bridge health gaps faced by Indigenous peoples in Canada through culturally sensitive and community-specific interventions across the lifecourse, and especially through interventions that are applied in early life. Additionally, they discuss future research, including the need to predict risk and resilience across generations, while considering that the predictive value of these factors may change with age.

Another population facing considerable health disparities in Canada includes individuals with problematic substance use and SUDs. The prevalence of these cases is on the rise in Canada, including the population of individuals who misuse prescription and non-prescription opioids.[7,36] Health outcomes are poorer, and deaths higher, in individuals with problematic use of opioids.[7] Critically, Indigenous peoples are two to four times more likely to have SUDs.[37] Further, while SUDs and problematic substance use are generally lower in women than in men,[7,38] women may be at higher risk of adverse health outcomes related to problematic substance use.[38,39] Preconception and pregnancy are sensitive periods in which substance use, and specifically opioid misuse, have dramatic detrimental effects: women who use opioids during pregnancy have increased rates of preterm birth, and their infants are more likely to be born low birthweight or growth restricted and have neonatal abstinence syndrome, which increases their risk of morbidities in the first year of life including feeding problems, infections, and poor neurologic development and function.[40–42] SUDs often coexist with other social factors that contribute to health disparities in women, such as low socioeconomic and demographic status, high levels of psychological stress,[43] and nutritional insecurity[44–46]; each of these alone are known to program poor pregnancy and infant outcomes. In their paper, Miller *et al.*[47] address the growing opioid misuse crisis in a Canadian population of pregnant women and their infants. They describe the adverse outcomes associated with opioid dependency in pregnancy and highlight the complexities in treating and supporting women with SUDs and opioid dependency. They also discuss how an interdisciplinary approach, integrating social, environmental and biological contexts, is required to improve maternal and neonatal outcomes and narrow health gaps in this vulnerable population.

Beyond the maternal-offspring dyad: making Canadian DOHaD more inclusive

The Canadian perspective on health care, health policy and health research is unique, shaped by the diversity of our peoples, our history, our geography and our values. Through this perspective, we have the potential to continue to make major contributions to improve health outcomes and prevent chronic diseases within our country and on the global stage. This requires substantial and sustained investments by our government in health research, acknowledgment of the inequities that exist within our borders and action to close these gaps, and continued collaboration with international researchers and health partners. This perspective also positions us as a leader in DOHaD research and knowledge: our strength in integrating research on social, environmental and biological determinants of health will grow the DOHaD knowledge base, and expedite the research community's efforts to fill gaps in our understanding of the origins and mechanisms contributing to health and disease states. Through an inclusive approach, we can transform the health of Canadians, Indigenous peoples in Canada, and populations globally – to improve outcomes in the later years of childhood and youth. Our children deserve no less.

This themed issue contains articles written by members of the Canadian DOHaD research community, and brings together major areas of research in the field of developmental origins of disease. In 2021, Canada will once again host the World Congress on Developmental Origins of Health and Disease, which will showcase multidisciplinary DOHaD research from around the world. The meeting will be held in Vancouver, British Columbia, with satellite symposia in Québec and Alberta. We hope you enjoy reading about current DOHaD research from a Canadian perspective, and we look forward to seeing you in Vancouver in 2021!

Kristin Connor, Stephane Bourque and Ian Weaver, Guest Editors of the DOHaD Canada themed issue.

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References

1. Barker D.J. Fetal origins of coronary heart disease. *BMJ*. 1995; 311, 171–174.
2. Gillman M.W, *et al.* Meeting report on the 3rd International Congress on Developmental Origins of Health and Disease (DOHaD). *Pediatr Res*. 2007; 61, 625–629.
3. Leaders of the Group of Eight. Muskoka Declaration: recovery and new beginnings. http://www.g7.utoronto.ca/summit/2010muskoka/communique.html, Muskoka, Canada, 2010.
4. Government of Canada. Formative evaluation of Canada's contribution to the Maternal, Newborn and Child Health (MNCH) Initiative. Devlopment Evaluation Division, https://www.international.gc.ca/gac-amc/publications/evaluation/2016/eval_mnch-smne.aspx?lang=eng#summ Ottawa, ON, 2015.
5. Government of Canada. Audit of the Maternal, Newborn and Child Health commitments. Global Affairs Canada, https://www.international.gc.ca/gac-amc/publications/audits-verification/2016/mnch-smne.aspx?lang=eng#summary, Ottawa, ON, 2016.
6. Government of Canada. Canada's forward strategy saving every woman, every child: within arm's reach. https://www.who.int/pmnch/media/news/2014/canada_strategy.pdf (Office of the Prime Minister of Canada), Toronto, ON, 2014.
7. Belzak L., Halverson J. The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can*. 2018; 38, 224–233.
8. Wood E. Strategies for reducing opioid-overdose deaths – lessons from Canada. *N Engl J Med*. 2018; 378, 1565–1567.
9. Crompton S. What's stressing the stressed? Main sources of stress among workers. Vol. Catalogue no. 11-008 Statistics, Canada, Ottawa, ON, 2011.
10. Smith K. Trillion-dollar brain drain. *Nature*. 2011; 478, 15.
11. Ratnasingham S., Cairney J., Rehm J., Manson H., Kurdyak P.A. Opening eyes, opening minds: the Ontario burden of mental illness and addictions report. Institute for Clinical Evaluative Sciences and Public Health Ontario, Toronto, ON, 2012.
12. Canadian Institute for Health Information. Community mental health and addiction information: A snapshot of data collection and reporting in Canada. CIHI, https://secure.cihi.ca/free_products/CIHI-comm-mental-health-en-web.pdf, Ottawa, ON, 2017.
13. Smetanin P, *et al.* The Life and Economic Impact of Major Mental Illnesses in Canada: 2011 to 2041. RiskAnalytica, on behalf of the Mental Health Commission of Canada 2011, Toronto, ON, 2011.
14. Sasaki A., Matthews S.G. Genome-wide epigenetic signatures of childhood adversity in early life: opportunities and challenges. *J Dev Orig Health Dis*. 2019; 10, 65–72.
15. Barha C.K., *et al.* Early post-conception maternal cortisol, children's HPAA activity and DNA methylation profiles. *J Dev Orig Health Dis*. 2019; 10, 73–87.
16. Huizink A.C., Mulder E.J., Buitelaar J.K. Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? *Psychol Bull*. 2004; 130, 115–142.
17. Rice F., Jones I., Thapar A. The impact of gestational stress and prenatal growth on emotional problems in offspring: a review. *Acta Psychiatr Scand*. 2007; 115, 171–183.
18. Talge N.M., *et al.* Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry*. 2007; 48, 245–261.
19. Letourneau N., *et al.* Intergenerational transmission of adverse childhood experiences via maternal depression and anxiety and moderation by child sex. *J Dev Orig Health Dis*. 2019; 10, 88–99.
20. Aylott A., *et al.* Like father like daughter: sex-specific parent-of-origin effects in the transmission of liability for psychotic symptoms to offspring. *J Dev Orig Health Dis*. 2019; 10, 100–107.
21. Cairney J, Streiner D.L. *Mental Disorders in Canada: An Epidemiological Perspective*. 2010. University of Toronto Press: Toronto/Bufffalo/London.
22. Government of Canada. Climate change and health: health effects. Government of Canada, https://www.canada.ca/en/health-canada/services/climate-change-health.html, Ottawa, ON, 2018.
23. Olson D.M., *et al.* Recent Canadian efforts to develop population-level pregnancy intervention studies to mitigate effects of natural disasters and other tragedies. *J Dev Orig Health Dis*. 2019; 10, 108–114.
24. Maurice C, *et al.* Prenatal exposure to an environmentally relevant mixture of Canadian Arctic contaminants decreases male reproductive function in an aging rat model. *J Dev Orig Health Dis*. 2018; 9, 511–518.
25. Sheppard A.J., *et al.* Birth outcomes among First Nations, Inuit and Metis populations. *Health Rep*. 2017; 28, 11–16.
26. Anderson I., *et al.* Indigenous and tribal peoples' health (The Lancet-Lowitja Institute Global Collaboration): a population study. *Lancet*. 2016; 388, 131–157.
27. Gushulak B.D., *et al.* Migration and health in Canada: health in the global village. *CMAJ*. 2011; 183, E952–958.
28. Tam T. Chief Public Health Officer's report on the state of public health in Canada 2018. Problematic substances use in youth. Public Health Agency of Canada, Ottawa, ON, 2018.
29. CSDH. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. World Health Organization, Geneva, 2008.
30. Rollins N.C., *et al.* Why invest, and what it will take to improve breastfeeding practices? *Lancet*. 2016; 387, 491–504.
31. Campbell F., *et al.* Early childhood investments substantially boost adult health. *Science*. 2014; 343, 1478–1485.
32. Campbell-Lendrum D, Wheeler N, Maiero M, Villalobos Prats E, Neville T. *COP24 Special Report: Health and Climate Change*. 2018. World Health Organisation: Geneva.
33. Martin D., *et al.* Canada's universal health-care system: achieving its potential. *Lancet*. 2018; 391, 1718–1735.
34. Phillips-Beck W., *et al.* Early-life origins of disparities in chronic diseases among Indigenous youth:pathways to recovering health disparities from intergenerational trauma. *J Dev Orig Health Dis*. 2019; 10, 115–122.
35. Bombay A., *et al.* Suicidal thoughts and attempts in First Nations communities: links to parental Indian residential school attendance across development. *J Dev Orig Health Dis*. 2019; 10, 123–131.
36. Fischer B., *et al.* Illicit opioid use in Canada: comparing social, health, and drug use characteristics of untreated users in five cities (OPICAN study). *J Urban Health*. 2005; 82, 250–266.
37. Currie C.L., Wild T.C., Schopflocher D.P., Laing L., Veugelers P. Illicit and prescription drug problems among urban Aboriginal adults in Canada: the role of traditional culture in protection and resilience. *Soc Sci Med*. 2013; 88, 1–9.
38. Special Advisory Committee on the Epidemic of Opioid Overdoses. National Report: Apparent Opioid-related Deaths in Canada (January 2016 to June 2018). Public Health Agency of Canada, 2018.
39. Government of Canada. Background Document: Public Consultation on Strengthening Canada's Approach to Substance Use Issues. Health Canada, Ottawa, ON, 2018.
40. Gouin K., Murphy K., Shah P.S. Knowledge synthesis group on determinants of low birth weight preterm births. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. *Am J Obstet Gynecol*. 2011; 204, e341–312.
41. Patrick S.W., *et al.* Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015; 135, 842–850.
42. Hwang S.S., *et al.* Maternal substance use disorders and infant outcomes in the first year of life among Massachusetts singletons, 2003–2010. *J Pediatr*. 2017; 191, 69–75.
43. Krans E.E., Cochran G., Bogen D.L. Caring for opioid-dependent pregnant women: prenatal and postpartum care considerations. *Clin Obstet Gynecol*. 2015; 58, 370–379.
44. Zador D., Lyons Wall P.M., Webster I. High sugar intake in a group of women on methadone maintenance in south western Sydney, Australia. *Addiction*. 1996; 91, 1053–1061.
45. Tomedi L.E., Bogen D.L., Hanusa B.H., Wisner K.L., Bodnar L.M. A pilot study of the nutritional status of opiate-using pregnant women on methadone maintenance therapy. *Subst Use Misuse*. 2012; 47, 286–295.
46. Shrestha S., *et al.* Dietary intake among opioid- and alcohol-using pregnant women. *Subst Use Misuse*. 2018; 53, 260–269.
47. Miller C., *et al.* Maternal and neonatal characteristics of a Canadian urban cohort receiving treatment for opioid use disorder during pregnancy. *J Dev Orig Health Dis*. 2019; 10, 132–137.

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