NRC Research Press

CURRENT OPINION

# Increasing the quality of life from womb to grave: the importance of pregnancy and birth cohorts

Bonnie J. Kaplan, Brenda M. Leung, Gerald F. Giesbrecht, Catherine J. Field, Francois P. Bernier, Suzanne Tough, Xinjie Cui, Deborah Dewey, and the APrON Study Team



**Abstract:** Epigenetics is revealing how "nature is nurtured", with environmental factors such as nutrition, environmental neurotoxicants, and psychological stress influencing DNA expression. In this current opinion paper, we argue that understanding the dynamic interplay between the genome acquired at conception and environmental exposures throughout life requires pregnancy and birth cohorts, and that greater Canadian national commitment to the infrastructure needed for sustaining such cohorts is warranted. We present a framework that is now being implemented in Alberta.

*Key words:* longitudinal studies, epigenetics, cohort studies, maternal health, child health.

**Résumé :** L'épigénétique révèle la manière dont l'expression de l'ADN subit l'action des facteurs environnementaux tels la nutrition, les neurotoxines environnementales et le stress psychologique. Dans cette opinion courante, nous soutenons la thèse que l'étude de la grossesse et des cohortes de naissance est nécessaire pour comprendre l'interaction dynamique du génome acquis à la conception avec les expositions aux facteurs environnementaux. À cette fin, il faut obtenir un plus grand effort du Canada pour soutenir l'infrastructure requise pour l'étude de ces cohortes. Nous présentons un cadre de travail actuellement mis en œuvre en Alberta. [Traduit par la Rédaction]

*Mots-clés :* études longitudinales, épigénétique, études de cohortes, santé maternelle, santé infantile.

## Introduction

Many recent developments in the study of nutritional effects on maternal and newborn health have been fueled by emerging studies of epigenetics. Findings are leading to a reformulation of the nature–nurture debate toward the investigation of mechanisms through which nature can be nurtured. What is now clear is that environmental exposures make ongoing contributions to human development, likely through changes in gene expression and probably throughout life, with implications for both health and disease (Szyf 2011). In this current opinion paper, we argue that human pregnancy and birth cohorts followed prospectively are essential for understanding these epigenetic effects, which are critically important for understanding and preventing the chronic diseases that are the leading causes of morbidity and mortality. Progress on this topic requires a greater commitment to establishing and supporting pregnancy and birth cohorts for research purposes within the Canadian context. Canada's single payer (universal) health care system, frequently organized in large coordinated regions, creates a unique opportunity for us to follow the trajectory of health that can only be addressed with longitudinal population-based cohorts. The opportunity created by our health system as well as the greater emphasis on longitudinal research outside our borders impels us to make the case for greater national commitment to protect existing longitudinal cohorts: they are scientific resources that have the potential to directly influence health practice and policy in the Canadian context.

For 65 years, longitudinal cohorts have contributed to the world's knowledge of the impact of the environment on health and disease. The first national longitudinal birth cohort was initiated to follow health variables: a group of Britons born in 1 week in March 1946 (Anonymous 2011). Other salient contributors to this field, all from outside Canada, include the United States Framingham Study's contribution to heart health that began in 1948 (http://www.framinghamheartstudy.org), the New Zealand Dunedin Multidisciplinary Health and Development Research Unit cohort established in 1972 (dunedinstudy.otago.ac.nz), the Australian Raine study established in 1989 (www.rainestudy.org.au), the United Kingdom ALSPAC (Avon Longitudinal Study of Parents and Children), which began in 1991 (www.bristol.ac.uk/alspac), and the Generation R Study established in the Netherlands in 1992 (www.generationr.nl).

Canada does not have as long a tradition of longitudinal research, other than periodic national surveys (e.g., the National Longitudinal Study of Children and Youth), though some cohort studies have provided important health information. Examples are the Ottawa Prenatal Prospective Study (OPPS) from the University of Ottawa, which followed mothers and offspring from pregnancy to 27 years of age, the Study of the Impact of Diet and Exercise Activity to Improve Pregnancy Outcomes (IDEA) at the University of Manitoba, which followed mothers and their offspring from second trimester to 18 months (though without the collection of biological samples), and the Quebec Longitudinal Study of Child Development (QLSCD/ELDEQ), which followed children after birth. However, none of these studies has yet provided

Received 25 February 2012. Accepted 18 July 2012.

**B.J. Kaplan.** Behavioural Research Unit, Department of Pediatrics, Alberta Children's Hospital/University of Calgary, 2888 Shaganappi Trail NW, Calgary, AB T3B 6A8, Canada.
**B.M. Leung.** Department of Community Health Sciences, Faculty of Medicine, University of Calgary, 2500 University Drive N.W., Calgary, AB T2N 1N4, Canada.
**G.F. Giesbrecht, F.P. Bernier, S. Tough, and D. Dewey.** Department of Pediatrics, Alberta Children's Hospital, 2888 Shaganappi Trail N.W., Calgary, AB T3B 6A8, Canada.
**C.J. Field.** Alberta Institute for Human Nutrition and Alberta Diabetes Institute, 4-126A Li Ka Shing Health Research Innovation Center, University of Alberta, Edmonton, AB T6G 2E1, Canada.
**X. Cui.** Alberta Centre for Child Family and Community Research, 9925 109 Street, Edmonton, AB T5K 2J8, Canada.
**Corresponding author:** Bonnie J. Kaplan (e-mail: bonnie.kaplan@albertahealthservices.ca).

a thorough examination of the status of the intrauterine environment and its impact on fetal development.

A detailed analysis of the benefits and challenges of longitudinal cohort studies is beyond the scope of this paper (and is available elsewhere (Manolio et al. 2006)). In this paper we highlight several relevant developments in the field, and emphasize some prenatal environmental factors being studied for their impact on gene expression to illustrate why greater Canadian support of longitudinal research is warranted.

## Epigenetics: the interplay of genes and the environment

Epigenetics provides a biological link between the environment and the genome (Szyf, 2011). The term refers to heritable changes in gene expression that do not involve changes in DNA sequence. Although typically mitotically stable, ensuring that epigenetic changes are passed on to daughter cells, the changes may also be passed on to subsequent generations (transgenerational epigenetics). Epigenetics works through a variety of mechanisms whereby the environment of a cell is modified, resulting in localized specific changes to the regulatory status of genetic material, without altering the DNA. Mechanisms by which gene expression is modified include primarily changes in DNA methylation, but histone modifications, histone variants, nucleosome positioning, and others have also been postulated (Berger et al. 2009).

One major category of epigenetic modifiers is nutrition. As Mutch pointed out, “it is our continuous exposure to foods throughout our lifetime that renders diet the most important environmental factor challenging our biological system” (Mutch et al. 2005). It is well established that maternal malnutrition has profound and enduring effects on the organization and function of various biological systems in the fetus. More recently, the role of poor diet on biochemical processes (e.g., methylation) at the DNA level has been investigated. For instance, McKay and Mathers examined the way in which DNA methylation was influenced by the availability of dietary methyl donors (e.g., folate, choline, and methionine) and proposed that these biochemical processes operate not only during cellular differentiation but throughout life (McKay and Mathers 2011). This possibility has profound implications for the modifiability of the expression of an individual's genetic “program” throughout the lifespan. A second example of dietary nutrients in relation to epigenetic processes is Dolinoy's research, which showed that nutritional protective factors can buffer the impact of environmental toxins (Dolinoy et al. 2007). In that study, yellow Agouti mice, for whom in utero or neonatal exposure to bisphenol A resulted in higher body weight and increases in some types of cancer, were then treated with known methyl donors such as folic acid. The investigators showed that the DNA hypomethylating effect of BPA was reversed by treatment with a nutrient that is known to influence methylation. Based on the most recent epigenetic studies, it appears that adequacy of nutrient status throughout life may moderate phenotypic expression (e.g., symptoms) for some disorders with known heritability (Kubota et al. 2010; Lenroot and Giedd 2011). For example, folic acid has been effective in treating the autistic behaviours associated with Rett syndrome in patients with low folic acid levels in their spinal fluid (Kubota et al. 2010).

Longitudinal studies with prospective measures of broad domains of nutrient exposures and outcomes are needed to disentangle the complexity inherent in the investigation of the role of nutrition and how it impacts health via both epigenetic and non-epigenetic mechanisms, especially as they relate to child development (Szyf 2011; Swanson and Wadhwa 2008). It is possible that there is nothing in life that is more variable than human cognition and behaviour, especially when the child is changing because of innate developmental programs, as well as the environment. Longitudinal cohort studies that collect information ranging from genes to the environment are necessary to unravel the critical features of a child's world that determine the level of physical and mental health that a child will enjoy.

## Life in the womb and its impact on adult health

A second field of increasing interest, which also adds weight to the value of longitudinal pregnancy and birth cohorts, is the long-lasting impact of the fetal period on health and longevity. The concept of fetal programming, first introduced by Barker 15 years ago (Barker 1997), evolved from data relating fetal origins (based on birth weight in his studies) to the risk for cardiovascular disease and diabetes later in life (Barker et al. 2002). Barker proposed that this association between fetal events and adult disease may be the consequence of genetic and epigenetic adaptations (possible because of developmental plasticity) made by the fetus to survive in a less-than-optimal intrauterine environment. The result of these adaptations may be that when the child later encounters a different environment (e.g., sedentary lifestyle and adequate food), he or she is at greater risk of illness than an infant from a healthy uterine environment (Barker 2004). However, Barker's theory focused mainly on protein-energy status and the outcomes of birth weight and head circumference, which are not sensitive to prenatal nutrition and energy balance. Thus, more comprehensive measures of the fetal environment and long-term follow-up with cognitive and behavioural measures are required. Longitudinal research that captures information on exposures prior to, or during the early stages of, pregnancy is the ideal setting for the investigation of the developmental origins of health and disease.

The overall picture now evolving is that the nutrient environment is a major contributor to epigenetic effects and fetal programming, and thus contributes to the long-term risk for diseases and disorders. So far, the majority of this research is based on animal models (Symonds 2007), although there are also important studies of select populations, such as the descendants of those who experienced the Dutch Hunger Winter of 1944 (Lumey et al. 2011). But malnutrition in settings involving war and natural disasters tends to consist of deficiencies in both energy and micronutrients, as well as other obvious stressors. Today, the developed world faces the new nutritional challenges of energy excess with both selective micronutrient deficiencies and excesses (via supplementation). Furthermore, we are continuously being exposed to new synthetic chemical compounds as never before in human existence, and the impact of these compounds on health is only starting to emerge. Thus, what is truly needed for understanding the implications of such variables on long-term health is the capacity to prospectively track groups of pregnant women and analyze their exposure to factors such as nutrients, psychological stress, environmental contaminants, and physical activity as well as new, emerging health issues such as obesity. Because of the latent onset of most diseases, the offspring need to be followed to investigate the factors that may be predictive of neurodevelopmental outcomes and adult-onset diseases and disorders.

## Tracking the course of nature and nurture as they unfold

Much of what we currently know about the long-term contributions of environmental exposures to “lifestyle” diseases comes from retrospective longitudinal studies, such as the ones conducted by Barker and colleagues when they developed the concept of fetal origins of adult disease (Barker et al. 2002). But there is reason to believe that epigenetic and other proposed programming mechanisms may operate within the scope of what is considered healthy during much of development, and only manifest as frank disease in adulthood. An example of this possibility is the prospective study of children in Adelaide, Australia, where associations between blood pressure and fetal adversity were not ap-

parent at 8 years of age but emerged at 20 years of age (Moore et al. 1999), suggesting that epigenetic changes associated with early adversity may be expressed only with additional environmental exposures. Such findings also emphasize the need to track epigenetic changes across the lifespan to determine how early exposure may be expressed later in life.

Our position is that longitudinal research is the best method for providing real life temporal estimation of possible causal events that lead to variation in health outcomes. Longitudinal studies, however, are costly and time-consuming for individual teams of researchers. Clearly, the value of this type of work is greatly enhanced by collaboration among cohort studies. Initiatives such as the inventory of European birth cohorts (Birthcohorts.net) help to facilitate such collaborations. In 2006, the Maternal, Infant, Child and Youth Research Network (MICYRN; www.micyrn.ca) was established in Canada as a collaborative national initiative to build capacity for Canadian researchers with existing cohorts. Such organizations, given the appropriate support, have the potential to facilitate collaborations among cohort studies to maximize investments made in each study.

Assessing the complex interaction of multiple exposures on development is the overriding goal of a pregnancy cohort study currently underway in Alberta, Canada. In the spring of 2009, the Alberta Pregnancy Outcomes and Nutrition (APrON) study began recruiting pregnant women in their first or second trimester to establish a pregnancy cohort (www.ApronStudy.ca). The primary aims of the APrON study are to determine the relationships between maternal nutrient intake and status before, during, and after gestation, as well as (*i*) maternal mood, (*ii*) birth and obstetric outcomes, and (*iii*) infant neurodevelopment. APrON has the potential to encompass various areas of fetal programming, but for now is focused on nutrition, environmental neurotoxicants, and psychophysiology of stress. Blood samples from mother and baby are assayed for nutrient status. DNA from parents and baby is banked for future studies. Urine samples from the mothers will be analyzed for thyroid hormones. Further details on APrON′s study methodology will be published elsewhere; for the purpose of the present paper, we address briefly the advantages of such a resource for the evaluation of some key epigenetic influences on disease susceptibility:

- *Nutrition*. APrON is carrying out the most detailed evaluation of nutrition in a pregnancy cohort yet reported, particularly because of the repeated measures during gestation. Nutrient data include maternal *dietary intake for 12 months prior to pregnancy*, which is necessarily retrospective using a food frequency questionnaire, as well as prospective evaluation of *nutrient intake* (from 24-h recalls) and *nutrient status* (from blood samples) during pregnancy and at 3 months postpartum.
- *Environmental Neurotoxicants*. We have recently been funded to examine the associations between children's perinatal exposure to bisphenol A and phthalates and neurodevelopment assessed at 2 years of age, while considering the possible moderating effects of nutrient status, and the possible antagonizing effects of exposure to lead and methylmercury.
- *Stress*. In a series of substudies examining the effects of antenatal maternal stress on infant stress reactivity, ambulatory heart rate and actigraphy and diurnal suites of saliva are collected in combination with maternal self-report of stress. Postnatal mother–infant interaction is also assessed to determine the extent to which the postnatal environment may "reprogram" infant stress reactivity. These studies (Giesbrecht et al. 2012*a*, 2012*b*) have focused on the mechanisms whereby the maternal stress signal is conveyed to the infant. Future work will also incorporate the role of nutrition in moderating the effects of the psychophysiology of maternal stress on infant development.

In addition to these factors, important moderator variables are being evaluated: for example, sociodemographic information, repeated measures of maternal mental and physical health, birth record data, maternal report of physical activity, stressful life events, perceived social support, and maternal–child interaction. Long-term follow-up of behavioural and cognitive development into early and later childhood is planned to determine the influences of nutrition, neurotoxicant exposure, and stress.

## The value of sustaining cohort studies across Canada

Once established, longitudinal cohorts need to be seen as assets for all of Canadian society; however, one of the most significant challenges facing such studies is that limited funding is available to maintain the cohorts beyond the initial 3–5 years of funding. It is necessary to sustain study personnel and participants beyond that time to prevent the loss in value of the initial investment required to establish and evaluate the cohort. Additional cooperation among various national and provincial funding agencies, academic institutions, and foundations should be encouraged to maintain cohorts beyond the first few years of the child's life, as the cohorts represent a tremendous resource for contributions of future researchers to Canadian health care knowledge. Sustained long-term funding could also foster improved collaborations among cohort projects, which would enhance their value.

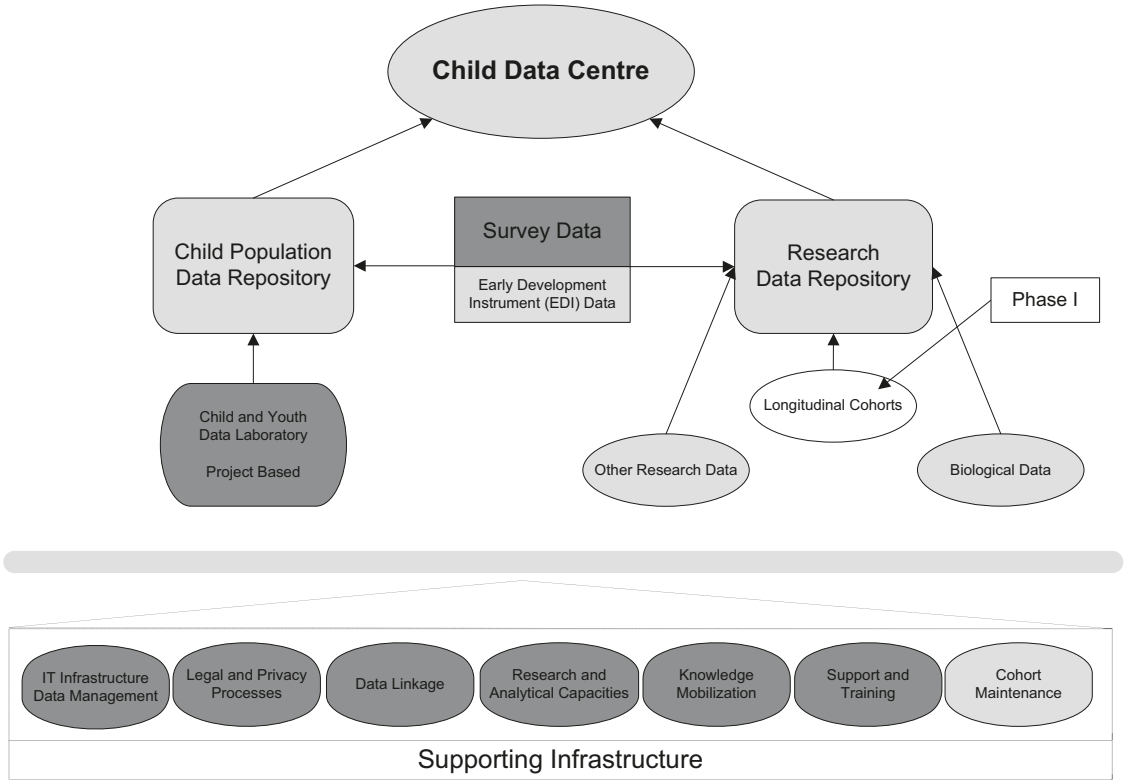
A national strategy could help foster improved support and infrastructure for Canadian longitudinal research to increase awareness of existing cohort studies in the country, assist in harmonizing the methodologies and health-related questions addressed, shed light on topics where knowledge is lacking, and encourage free and open access to data by all qualified investigators. We note that the value of longitudinal cohorts is better recognized by governments in other countries, where millions of dollars are spent establishing and tracking pregnancy and birth cohorts (e.g., the US National Children's Study; http://www.nationalchildrensstudy.gov/Pages/default.aspx).

## Implementation of a method to sustain cohorts

A new resource for addressing issues of cohort maintenance and optimal data use is currently being developed in Alberta, and is called the Child Data Centre (CDC). The CDC is a data and research facility where government administrative data, survey data, and research data related to child well-being is securely stored, cleaned, catalogued, enhanced, managed, and linked (where and when appropriate) (Fig. 1). Secure access and appropriate use of the data for research by external research communities will be managed and supported through this facility. Capacities and processes for cohort maintenance will be developed as well.

One component of the CDC, the Child and Youth Data Lab (CYDL), uses linked anonymous administrative data from multiple provincial government ministries (e.g., Health, Education, Human Services, and Justice) to conduct policy-relevant research. The CYDL has been in operation for more than 5 years and established its technical infrastructure, developed research and legal–privacy processes, and has built strong relationships and trust with the partnering ministries. Much of this work will expedite implementation of the Research Data Repository component of the CDC. This part of the implementation of the CDC is now supported both in principle and, importantly, financially by the provincial government and the 2 Alberta research institutes focused on child and maternal health: Alberta Children's Hospital Research Institute at the University of Calgary (Alberta, Canada) and the Women and Children's Health Research Institute located at the University of Alberta in Edmonton (Alberta, Canada). The implementation is taking a phased approach. The work plan for Phase I has been defined, the funding is in place, and a scientist has been hired to operationalize key functions of the Research

**Fig 1.** Structure and function of the child data centre.




The broad functions of the CDC include:

- Data acquisition
- Data management, such as:
  - Data standardization
  - Metadata development
  - Documentation
- Data access control and management
- Data content and analysis support
- Research output review and release
- Research and research collaboration
- Knowledge mobilization
- Training and marketing

Data Repository of the CDC, develop a plan for data harmonization and maintenance, and to work with other regional and national initiatives (including MICYRN). Policies and guidelines established for data sharing within the CYDL mandate will guide the development of similar issues within the Research Data Repository of the CDC. The use of administrative data, survey data, and research data, including more detailed information obtained through longitudinal cohort studies by the CDC, can address more complex questions.

The CDC will address the needs of the academic and research communities in the following ways:

- Scientists working in the area of child-related research want to secure the data that they have collected through their research initiatives and to ensure that the longitudinal aspect is not lost.
- Greater access to content expertise and data capabilities related to the analysis of longitudinal data available through the CDC will enhance understanding of life-course influences on health.
- The design of the CDC includes enhanced trainee opportunities to engage in policy-relevant research to understand decision-making processes and engage in knowledge exchange.

As is being recognized in many provinces, there are many opportunities for enhanced understanding of health that can be gained by life-course and longitudinal analysis, shared infrastructure, and linkage capabilities. The focus of the CDC will be to gather together data from individual research studies, administrative and census data, and make those data available to the broader research community so that new knowledge can be discovered more effectively and then translated into action in a timely way to make a difference for future generations.

In summary, investigators clearly see the need for birth cohort research groups to work together to maximize outcome and fi-

nancial resources, which is the reason national and international networks have developed. The structure for connecting and communicating amongst cohort studies in Canada exists in MICYRN, but more secure infrastructure is required to attend to long-term needs for administrative personnel, data repositories, stakeholder engagement, and knowledge translation for policy development. If provided the infrastructure and long-term support, longitudinal cohort research will facilitate finding answers to critical questions relevant to health and development, which will inform prevention, policy, program decisions, and professional practice.

## Acknowledgements

We thank Alberta Innovates – Health Solutions for their support of APrON, the Alberta Children's Hospital Research Institute (ACHRI), the University of Calgary, and the University of Alberta for their ongoing support.

## References

Anonymous. 2011. The generation game. Nature, **471**(7336): 5. doi:10.1038/471005a. PMID:21368779.

Barker, D.J. 1997. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition, **13**(9): 807–813.: doi:10.1016/S0899-9007(97)00193-7. PMID:9290095.

Barker, D.J. 2004. The developmental origins of adult disease. J. Am. Coll. Nutr. **23**(6 Suppl): 588S–595S. PMID:15640511.

Barker, D.J., Eriksson, J.G., Forsen, T., and Osmond, C. 2002. Fetal origins of adult disease: strength of effects and biological basis. Int. J. Epidemiol. **31**(6): 1235–1239. doi:10.1093/ije/31.6.1235. PMID:12540728.

Berger, S.L., Kouzarides, T., Shiekhattar, R., and Shilatifard, A. 2009. An operational definition of epigenetics. Genes and Development, **23**(7): 781–783. doi:10.1101/gad.1787609. PMID:19339683.

Dolinoy, D.C., Huang, D., and Jirtle, R.L. 2007. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc. Natl. Acad. Sci. U.S.A. **104**(32): 13056–13061. doi:10.1073/pnas.0703739104. PMID:17670942.

Giesbrecht, G.F., Granger, D., Campbell, T., and Kaplan, B.J.; the APrON Study Team. 2012*a*. Salivary alpha-amylase during pregnancy: Diurnal course and associations with obstetric history, maternal characteristics and mood. Dev. Psychobiol. [Epub ahead of print.] doi:10.1002/dev.21008. PMID:22315130.

Giesbrecht, G.F., Campbell, T., Letourneau, N., Kooistra, L., and Kaplan, B.J.; the APrON Study Team. 2012*b*. Psychological distress and salivary cortisol covary within persons during pregnancy. Psychoneuroendocrinology, **37**(2): 270–279. doi:10.1016/j.psyneuen.2011.06.011. PMID:21752548.

Kubota, T., Miyake, K., Hirasawa, T., Nagai, K., and Koide, T. 2010. Novel etiological and therapeutic strategies for neurodiseases: epigenetic understanding of gene-environment interactions. J. Pharmacol. Sci. **113**(1): 3–8. doi:10.1254/jphs.09R20FM. PMID:20424390.

Lenroot, R.K., and Giedd, J.N. 2011. Annual Research Review: Developmental considerations of gene by environment interactions. J. Child Psychol. Psychiatry, **52**(4): 429–441. doi:10.1111/j.1469-7610.2011.02381.x.

Lumey, L.H., Stein, A.D., and Susser, E. 2011. Prenatal famine and adult health. Ann. Rev. Public Health, **32**: 237–262. doi:10.1146/annurev-publhealth-031210-101230.

Manolio, T.A., Bailey-Wilson, J.E., and Collins, F.S. 2006. Genes, environment and the value of prospective cohort studies. Nat. Rev. Genet. **7**(10): 812–820. doi:10.1038/nrg1919. PMID:16983377.

McKay, J.A., and Mathers, J.C. 2011. Diet induced epigenetic changes and their implications for health. Acta Physiologica (Oxford, England), **202**(2): 103–118. doi:10.1111/j.1748-1716.2011.02278.x. PMID:21401888.

Moore, V.M., Cockington, R.A., Ryan, P., and Robinson, J.S. 1999. The relationship between birth weight and blood pressure amplifies from childhood to adulthood. J. Hypertens. **17**(7): 883–888. doi:10.1097/00004872-199917070-00003. PMID:10419060.

Mutch, D.M., Wahli, W., and Williamson, G. 2005. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. FASEB J. **19**(12): 1602–1616. doi:10.1096/fj.05-3911rev. PMID:16195369.

Swanson, J.D., and Wadhwa, P.M. 2008. Developmental origins of child mental health disorders. J. Child Psychol. Psychiatry, **49**: 1009–1019. doi:10.1111/j.1469-7610.2008.02014.x.

Symonds, M.E. 2007. Integration of physiological and molecular mechanisms of the developmental origins of adult disease: new concepts and insights. Proc. Nutr. Soc. **66**(3): 442–450. doi:10.1017/S002966510700571X. PMID:17637097.

Szyf, M. 2011. DNA methylation, the early-life social environment and behavioral disorders. J. Neurodev Disord. **3**(3): 238–249. doi:10.1007/s11689-011-9079-2. PMID:21484196.