

The early life origins of health and disease

Prof Jeffrey Robinson
FRANZCOG

Extensive epidemiological and experimental findings show that factors which alter development or growth before birth can have long term consequences on an individual's health and risk of common diseases.

Dr Julie Owens
University of Adelaide

In the 1980s, David Barker and his colleagues set a new agenda for research into the causes of common

diseases, including coronary heart disease, type 2 diabetes, obesity, hypertension and that of the contribution of conditions in early life. This impetus came out of studies where Barker and his colleagues attempted to explain the variation in early deaths from these conditions in England and Wales. Barker and his colleagues were able to undertake these studies of events, separated by decades, because of remarkable health records kept from the early years of the 20th century. In particular, a midwife, Ethel Margaret Burnside, Chief Health Visitor and Lady Inspector of Midwives, had been responsible for collection of data on the size of infants at birth and into childhood in Hertfordshire (Barker 1998).¹ These records and similar ones from Preston and Sheffield, further north in England, were available to Prof Barker and his colleagues, who traced survivors and sought causes of early death from death certificates. Initially, they traced males because they rarely changed their names and were able to examine the relationships between birth size in males and their subsequent risks of death from cardiovascular disease. Later, the findings in men were shown to hold for women, too. Since that time, there have been numerous papers describing the relationships between birth size as a summative measure of fetal growth and common adult diseases. While the vast majority of these support the original conclusions reached by Barker and his colleagues, there have been a few dissenting voices.

The purpose of this article is to provide a brief summary of the main conclusions that have been reached on early life contributions to health and disease. See the list of references for articles offering more in-depth descriptions of findings.^{1,2,3,4,5}

Human epidemiological studies

Ischaemic heart disease

In their now classic paper, Barker and his colleagues showed that the standardised mortality ratio for death from ischaemic heart disease decreased with increasing birthweight and across the normal range of birthweight. There was also a small increase in the standardised mortality ratio at the highest birthweight (over 10lbs). Growth in the first year of life modified this relationship with lower relative risks for ischaemic heart disease in those with heavier weights at one year of age. However, increase in weight during childhood, which leads to an upward path across centiles for weight or accelerated weight gain, had the opposite effect on later cardiovascular mortality.

Recently, Huxley and her colleagues (2007) completed a meta-analysis of 17 studies of the relationship between birthweight and ischaemic heart disease. They concluded that a 1kg increase in birthweight is associated with a 10 to 20 per cent lower risk for later ischaemic heart disease. Importantly, adjustments for socio-economic status did not alter this conclusion.

Hypertension

Because development of ischemic heart disease requires many years, researchers have instead used risk factors for heart disease such as hypertension, as surrogates to examine its relationship to size at birth and early life events, particularly in more contemporary cohorts, in Australia and elsewhere. Barker and his colleagues reported that there was an increase in blood pressure with decreasing birthweight and, like ischaemic heart disease, this relationship is a continuous one that extends across the normal range of birthweights. This relationship has been the subject of several systematic reviews, with all but one supporting the original findings that mean blood pressure in men and women increases by up to 2 to 4 mm Hg for each kilogram increase in birthweight. In our study in Adelaide, systolic blood pressure increased by 2.6 mm Hg per kilogram birthweight in men and 4.6 mm Hg per kilogram in women and the rise in blood pressure with age was greater in those who were lighter at birth. Again, this was independent of socio-economic class and occurred within each strata of socio-economic status.

Type 2 diabetes mellitus

There is a rapidly emerging epidemic of type 2 diabetes, particularly in the developing world. Part of this has been ascribed to the changes in nutrition, physical activity and obesity as societies move from subsistence economies with marginal nutrition to increasing westernisation and affluence. However, there is also evidence that conditions within the uterus 'program' increase the subsequent risk for obesity and type 2 diabetes. In their original paper, Hales *et al* (1991)⁶ showed that the percentage of men with insulin resistance and syndrome X (the metabolic or insulin resistance syndrome) decreased in 64-year-olds from 30 per cent in those who had weighed less than 5.5 lbs at birth to 6 per cent in those with birthweights of 9.5lb or more. The adjusted odds ratio of 18 was found for those who weighed less than 5.5lbs at birth compared with those weighing more than 9lbs.

In a recent systematic review of 48 studies, most studies demonstrate an inverse relationship between birthweight and measures of reduced glucose tolerance and insulin resistance. There was no consistent relationship between insulin secretion and birthweight. An updated systematic review demonstrates that the relationship between birthweight and subsequent type 2 diabetes is U-shaped⁷ with both low and high birthweight substantially increasing the risk of developing type 2 diabetes in later life.

Hales and Barker⁸ proposed the 'thrifty' phenotype to account for this phenomenon and in contrast to the Needs proposal of a 'thrifty' genotype. Since then, debate continues about the relatively important contribution of the environment and the genome to fetal growth and the subsequent risk for abnormal glucose tolerance and type 2 diabetes. Importantly, a recent study found that low birthweight could account for 18 per cent of the population prevalence of type 2 diabetes, establishing early life factors as a major contributor to the overall burden of this disease.

Experimental induction of components of the metabolic syndrome

The original observations of the epidemiologists spurred the experimentalists to devise ways of directly testing if restriction of fetal growth would induce components of the metabolic syndrome. It has been remarkably easy for the experimentalists to induce part or all of the metabolic syndrome in non-human species.^{3,5} Manipulation of maternal dietary intake and composition, induction of anaemia in the mother, restriction of placental growth by ligation of uterine arteries, embolisation of the placental circulation or pre-pregnancy reduction in the number of placental attachment sites have all been used in various species including rats, mice, rabbits, guinea pigs, pigs, sheep and primates. Exposures have been for all of pregnancy or restricted to part of gestation. Brief periods of altered nutrition in pregnancy and in the pre-implantation period are sufficient to induce life-long changes in the physiology of the animal after birth. Administration of glucocorticoids during pregnancy, which is a common exposure in human pregnancy, typically causes fetal growth restriction in rats, guinea pigs and sheep, and the long term consequences have also been investigated extensively. Maternal glucocorticoids do program a range of physiological systems and functions in non-human species, but whether this can occur independently and in the absence of an impact on fetal growth is unclear.

Studies in non-human species also facilitated the elucidation of the underlying mechanisms whereby disturbance of the environment in early life, at critical stages of development of regulatory systems and their target tissues, could alter functional development, impairing functional capacity and predisposing to disease in later life. The options include alterations in cell numbers, type and proportions and tissue structure including vascularity and alterations in intrinsic cell functional capacity, via altered gene expression. The mechanisms proposed, and for which there is some evidence, include altered cell kinetics, clonal selection and modifications to the epigenome in the developing embryo, fetus and neonate.⁵ Epigenetic changes to DNA are covalent modifications such as methylation of cytosines in CpG islands, usually in promoter regions or other regulatory control regions that therefore alter expression of genes with the potential for functional consequences. These epigenetic modifications are relatively stable and heritable and can therefore persist once induced.

'The maternal environment is a crucial factor which can alter growth and development of the fetus.'

Conditions immediately prior to or around conception as well as later in gestation can impact significantly on later health of offspring. Brief exposure of rat embryos during the pre-implantation period to a maternal diet low in protein is sufficient to alter cardiovascular function when the offspring are assessed as adults. A later study showed that this challenge also altered imprinting of the H19 and Igf 2 genes at day 20 of gestation. This suggests that perturbation around the time of fertilisation and early embryonic development, when major changes in DNA methylation and epigenetic state occur, can persistently alter epigenetic state and gene expression at least up to near term. A brief period of undernutrition confined to the beginning of pregnancy in sheep has also been shown to significantly alter the length of gestation and activity of the fetal hypothalamo-pituitary adrenal axis.

The evolutionary biologists and ecologists view that there is plasticity during development and that different phenotypes can

be expressed by the same genotype under different environmental conditions.⁹ This is considered to provide a mechanism for more rapid adaptation by species in response to environmental change than is possible through classical genetic processes. Some of the first evidence for efficacy of interventions to prevent or ameliorate early life programming of later function has emerged from studies in non-human species. In a series of studies of maternal protein restriction during pregnancy in the rat, it has been demonstrated that a reduced dietary intake of up to 8 per cent protein compared to 18 per cent in a controlled diet led to reduced fetal growth and later, an increase in blood pressure in adult offspring. This led to the first experimental prevention of the emergence of high blood pressure following maternal protein restriction when captopril was given to young offspring. Later studies showed that supplementing the maternal low protein diet with a single amino acid could prevent the emergence of hypertension in offspring.

Other studies have gone on to determine if it is possible to also prevent the development of the adverse metabolic phenotype seen following prenatal challenge. Two recent experiments have addressed this question. In the first, Peter Gluckman and his colleagues severely restricted the dietary intake of pregnant rats. The offspring had low muscle mass, abnormalities of insulin secretion and action, hyperphagia, reduced activity and obesity. Postnatally, when the offspring were given high-fat diets, these components of the metabolic syndrome were exaggerated. Administration of leptin to the neonatal offspring from undernourished mothers prevented the emergence of this phenotype. Gluckman and his colleagues proposed that neonatal exposure to elevated leptin provided a false cue during a sensitive developmental period, signalling to the pups that they were obese when they were actually thin after the exposure to maternal undernutrition. This led to a life-long setting of metabolism to anticipate a high plane of nutrition. Further evidence for the involvement of epigenetic mechanisms in early life programming of metabolic phenotype, as well as its modulation by postnatal exposures, was also obtained in this paradigm. Administration of leptin to the neonatal rat altered expression and methylation of some genes and phenotype in adulthood, in different directions, depending on the maternal diet in pregnancy.¹⁰

The mouse has been used to explore the epigenetic consequences of offspring of altered maternal nutrition during pregnancy using the Agouti locus and its methylation as a marker. This gene has a retrotransposon inserted into it, which is a retroviral particle that can change expression of the gene. To prevent this, the retrotransposon is methylated during development. The extent of this methylation can be manipulated, however, by altering maternal dietary intake of folate and methyl donors such as methionine. Increased folate and methionine in the diet results in normal coat colour and healthy adult phenotype. In a recent paper, these authors expanded their studies to include another gene. They also examined the effects of maternal exposure to an environmental toxin, bisphenol, which prevents DNA methylation.

Future directions

Extensive epidemiological and non-human species based studies have clearly demonstrated that environmental conditions in early life, including maternal nutrition, can affect fetal development and have effects on long-term function, including accelerating the age of onset of common adult diseases. Although the early observations of this link relied on measures such as birthweight and other summary measures of fetal growth and later disease, an alteration in birth size is not essential in early life programming. This is clearly obvious in experimental manipulation of conditions in early pregnancy in non-human species that have long-term effects on function without changes in birth size. Investigations in humans of the long-term

consequences of common exposures that do not alter size at birth, to assess whether they have longer term effects on health, may reveal new risk factors and targets for intervention or prevention.

We also need to further investigate interventions during pregnancy for common complications and conditions that have themselves altered fetal growth or function, to see if these are accompanied by long-term changes in function and health, which might be beneficial or harmful. One obvious route is to follow up the offspring of randomised clinical trials. Excellent examples of this already exist, including the 30-year follow-up of the original Liggins and Howie's trial of a single course of corticosteroids before potential pre-term birth. Apart from a small increase in circulating insulin after a glucose load, there were no differences in blood pressure, cortisol, diabetes or cardiovascular disease in offspring from such pregnancies compared to those given placebo.¹² A subsequent analysis showed that pre-term delivery was an important influence on adult blood pressure and insulin resistance independent of glucocorticoids.¹² Our recent follow-up study of infants from single versus repeat doses of corticosteroids in pregnancy provides early support for safety of these regimens (Crowther *et al* 2007). However, longer term follow-up of maternal glucocorticoid administration including assessment of metabolism and endocrine function in offspring is essential.

'There is great scope to reduce the overall burden of cardiovascular and metabolic disease through early life interventions...'

It is just as important to identify what is optimal in terms of maternal diet for the long-term health of offspring. We are only just beginning to explore the effects of variations in maternal diet in contemporary populations, their behavioural and other determinants, and how these may effect subsequent function in children or young adults. Cohort studies will be informative, but we will consider randomised clinical trials of further variations in macro and micronutrient composition of maternal diet and with long-term follow-up of both mother and child.

Conclusions

Extensive epidemiological and experimental findings show that factors which alter development or growth before birth can have long term consequences on an individual's health and risk of common diseases. This is hardly a surprising conclusion for an obstetrician to accept. The maternal environment is a crucial factor which can alter growth and development of the fetus. While it has not been discussed here, gene polymorphisms in the mother and/or the fetus may lead to a greater or lesser susceptibility to changes in the environment. The experimental evidence favours a significant role for altered epigenetic state of labile and imprinted genes that cause later alterations in function. It is also clear that relatively simple interventions such as altering the maternal intake of folate can act through this mechanism, to modify the long-term consequences for the offspring. There is great scope to reduce the overall burden of cardiovascular and metabolic disease through early life interventions, and to also identify, then promote, the optimal early life environment to enhance life long health of individuals and populations.

The implications for obstetricians that can be drawn at this level of our knowledge include caution when introducing new and seemingly minor interventions such as dietary changes and to ensure that we have follow-up programs that enable us to determine

if there are long-term consequences. However, advice for women to maintain a balanced diet, take folate-fortified supplements, begin pregnancy with a normal body mass index and stop smoking all have implications for early origins of health and disease in later life.

Acknowledgements

We thank the National Health and Medical Research Centre (NHMRC), Channel Seven, the Women's and Children's Foundation and Diabetes Australia for grants that made our studies possible.

Selected References

1. Barker DJP. Mothers, Babies and Health in Later Life. 1998. Churchill Livingstone, London.
2. Robinson JS and Owens JA. *The developmental origins of health and adult disease*. 2004. 36th International Symposium on GH and Growth Factors in Endocrinology and Metabolism Geneva, May; pp21-25.
3. McMillen IC and Robinson JS. The physiological basis for the early origins of adult diseases. 2005. *Physiological Reviews*; 85, 571-633.
4. Gluckman P and Hanson M. *The Fetal Matrix: Evolution, Development and Disease*. 2005. Cambridge University Press, Cambridge, England.
5. Wintour EM and Owens JA (eds). Early Life Origins of Health and Disease. 2006. *Advances in Experimental Medicine and Biology*, Vol 573.
6. Hales CN, Barker DJP, Clark PMS. Fetal and infant growth and impaired glucose tolerance at age 64. 1991. *BMJ* 303, 1019-1022.
7. Harder T, Rodekamp E, Schellong K, Duderhausen JW, Plagemann A. Birthweight and the subsequent risk of type 2 diabetes" a meta-analysis. 2007. *American Journal of Epidemiology*; 165, 849-857.
8. Hales CN and Barker DJP. Type 2 (non-insulin dependent) diabetes mellitus : the thrifty phenotype hypothesis. 1992. *Diabetologia* 35, 595-601.
9. Bateson P. (2007) Developmental plasticity and evolutionary biology. *Journal of Nutrition*; 137, 1060-1062.
10. Gluckman PD, Lillycrop KA, Vickers MH, Pleasants AB, Phillips ES, Beedle AS, Burdge GC, Hanson MA. Metabolically plasticity during mammalian development is directionally dependent on early nutritional status. 2007. *PNAS* 104, 12796-127800.
11. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol hypomethylation in early development. 2007. *PNAS*; 104, 13056-13061.
12. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, Harding JE. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. 2005. *Lancet*; 365, 1857-1862.
13. Barker DJP, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. 1989. *Lancet* ; 2, 577-580.

A full reference list is available from the authors on request.

CPD verification

Are you a RANZCOG-approved training supervisor in the Integrated Training Program? Or a RANZCOG-approved assessor of In-Hospital Clinical Assessment modules?

Did you know you can claim CPD points for it?

Download your verification form from the College website at:
http://www.ranzcog.edu.au/fellows/cpdverification.shtml

