

Gene-environment interactions and the developmental origins of health and disease

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Recent studies have clearly established an inverse relationship between suboptimal antenatal and postnatal environments and the development of adult diseases, including the metabolic syndrome (obesity, atherogenic dyslipidemia, hypertension, insulin resistance); type 2 diabetes; cardiovascular disease; neurologic disorders; and mental illness.^{1,2,3,4}

These observations have been confirmed in multiple human populations^{1,5} and in numerous animal studies across multiple species^{4,6,7,8}. It is thus clear that the environment of mother, baby and child is a key contributor to diseases and conditions that account for approximately one third of the global burden of disease, affecting both developed and developing countries. Although adverse antenatal and postnatal environments increase the risk of particular adult diseases, not all individuals exposed to these environments develop these conditions suggesting that an individual's genotype may contribute to the eventual outcome.^{9,10,11,12} It has therefore been hypothesised that interactions between an individual's genotype and the environment underlie the developmental origins of health and disease (DOHaD). See Figure 1.

In 1988, retrospective epidemiological studies in British cohorts reported an inverse relationship between birth size and rates of mortality from coronary heart disease across the normal birth weight range.^{2,3} Subsequently, similar relationships were discovered for other components of the metabolic syndrome, including hypertension, stroke, insulin resistance, type 2 diabetes and dyslipidemia.⁴ Over the next decade, numerous studies were performed in different populations, both in the developed and developing world, confirming this relationship.^{1,5} These studies led to the 'fetal origins' hypothesis that suggested that events in utero which reduced fetal growth permanently altered the structure and

physiology of the offspring such that the risk of heart disease and diabetes in later life was increased.

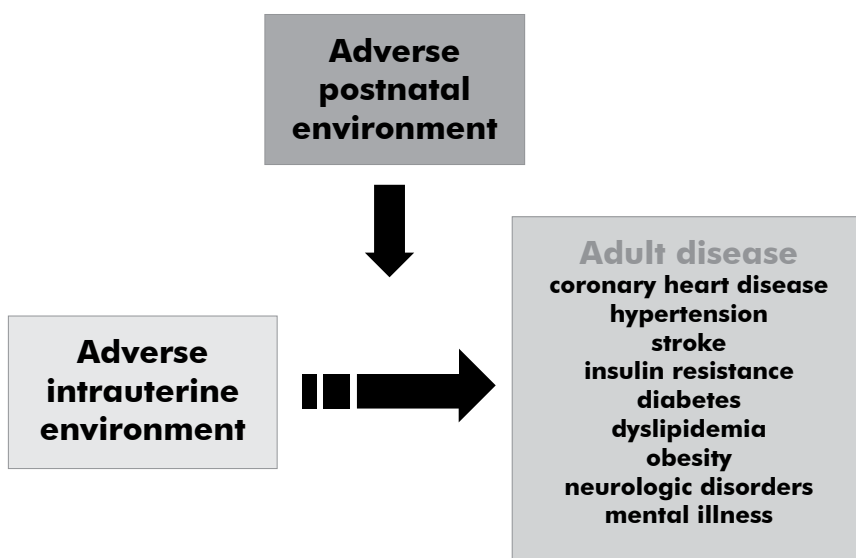
Animal models have provided the most direct evidence to support the DOHaD thesis.⁴ Programming has been demonstrated in sheep¹³, guinea pigs⁶, pigs, mice and rats^{7,14} and can be induced by: 1) prenatal under-nutrition (in total caloric or protein dietary content); 2) unbalanced nutrition (for example, maternal high-lard diet); 3) impairing utero-placental perfusion; or 4) maternal exposure to synthetic glucocorticoids.⁴ Animal studies have demonstrated another important concept, namely, that the fetus need not be manipulated for the relationships between birth size and cardiovascular and metabolic outcomes to be observed.^{4,15,16} The environmental cue can occur in early or late pregnancy, or within the peri-conceptual period.¹⁷ Thus, the term 'fetal origins' has now been replaced by 'developmental origins'.

The most frequent misunderstanding in the DOHaD hypothesis has been the role of birth size. Birth size is simply a crude surrogate reflecting the interactions between the fetal environment and the fetal genome.⁴ There is a growing body of evidence from both animal^{7,18-22} and human studies^{4,23,24} that environmental cues during pregnancy need not alter birth weight to alter long-term outcomes. For example, in the Dutch winter famine, women who ate less than 800 calories a day during the first trimester gave birth to normal-sized infants who later became obese.^{23,24} Programming is not a

process confined to the extremes in fetal growth, but rather one that accompanies the adaptations that every fetus makes to its environment, including subtle variations in growth.⁴ Indeed, these relationships exist across the normal birth weight range. Whilst initial studies of the DOHaD focused on events that occurred before birth, more detailed analysis of human cohorts^{25,26,27} and animal studies⁷ have demonstrated interactions between antenatal and postnatal environment. Those who had the most adverse intrauterine environment and the fastest weight gain after birth were shown to be at greatest risk for programming of the metabolic syndrome. Further, human and animal studies have shown clear differences between males and females, not only in the response to adverse antenatal and postnatal environments, but also in the mechanisms that underlie programming.^{28,29,30}

Although a clear relationship exists between adverse antenatal and postnatal environments and the risk of adult disease, there is growing

Figure 1.



evidence that genetic polymorphisms modulate this relationship. This is illustrated by the influence of polymorphisms in the peroxisome proliferator-activated receptor (PPAR)- γ 2 gene on the relationship between size at birth and adult diseases including: 1) insulin sensitivity and metabolism^{9,31}; 2) hypertension¹²; 3) obesity¹¹ and 4) dyslipidemia¹⁰. The well-known association between small body size at birth and insulin resistance⁹ and/or hypertension¹² was seen only in individuals with the high-risk Pro12Pro allele. Similarly, polymorphisms in the glucocorticoid receptor (GR), a key control element in the hypothalamic pituitary adrenal axis, have been implicated in determining obesity^{32,33,34}, hypertension³⁵, hypercholesterolemia³⁵ and responses to psychosocial stress in adults³³. Thus complex interactions between genes and the environment modulate developmental programming of adult disease.

Over the last 18 months, in conjunction with international collaborators, we have completed the first analyses investigating the association of the fat mass and obesity (FTO) gene with antenatal and postnatal growth trajectories. We have shown that the AA genotype of the SNP rs9939609 in the FTO gene (which has been found to predispose to diabetes through an effect on BMI in adults) was associated with symmetric intrauterine growth restriction beginning as early as 28 weeks gestation. The same polymorphism in FTO was independently associated with increased body mass index (BMI) in males (but not females) at eight, 14 and 17 years of age in multivariate analyses adjusted for birth weight, smoking, socio-economic status, nutrition and activity. Breastfeeding was associated with reduced BMI in childhood/adolescence, in males but not females, independent of FTO genotype. In both sexes, increased weight gain over the first year was associated with higher BMI in adolescence. The obesogenic allele (AA) in FTO was also associated with greater weight gain in the first year compared to non-obesogenic allele (TT). Gene-environment interactions were identified between FTO and measures of nutrition. The impact of weight gain in the first year of life on BMI at eight, 14 and 17 years of age was greater in AA than TT genotypes. Further, the reduction in BMI at 8 and 14 years of age in males associated with breastfeeding was greater in AA than TT genotypes. There was a significant interaction between FTO genotype and diet at 17 years of age in females, with an even greater reduction in BMI seen in AA than TT genotypes in those with a prudent/healthy diet. We have found evidence of gene-environment interactions between childhood nutrition and the FTO gene acting on measures of childhood obesity. These findings highlight the complex pathways underlying the development of obesity and raise the possibility of reducing the prevalence of this condition by targeted interventions in those at greatest genetic risk.

We have also identified a number of SNPs within key candidate genes (leptin, leptin receptor, adiponectin, CRP, IGF-2BP, insulin receptor, mineralocorticoid receptor and others) with associations with antenatal growth trajectories, biometric measures at birth, postnatal growth trajectories, insulin resistance at 14 years of age and non-alcoholic fatty liver disease at 16 years of age. Moreover, we have identified a number of gene-environment interactions between some of these SNPs and measures of nutrition (breastfeeding, healthy/prudent dietary pattern) suggesting the possibility of potential interventions to limit the impact of some of the SNPs associated with increased risk of obesity, insulin resistance and non-alcoholic fatty liver disease.

Epigenetics refers to covalent modification of DNA and core histones that regulate gene activity without altering the nucleotide sequence of DNA. There is growing evidence that the methylation status of genomically imprinted genes can be altered with consequences for subsequent organ growth and function.^{36,37}

Importantly, the epigenetic lability of imprinted genes is not limited to the pre-implantation period and includes the early postnatal period. Recent studies have demonstrated that retrotransposons are elements within the genome that may also be epigenetically labile to early nutrition.^{38,39} The application of epigenetic approaches and the determination of imprinted or non-imprinted genes and transposon insertion sites that are targets for early nutritional effects on epigenetic gene regulation are important new areas of investigation⁴⁰ which have great potential to uncover important mechanisms underlying DOHaD.

Identification at birth of genetic signatures that enhance the risk of coronary heart disease, stroke, diabetes, obesity, neurologic disorders or mental illness will provide opportunities to develop lifestyle or medical intervention strategies aimed at preventing these adverse outcomes. The potential to impact on global disease burden and the opportunity to establish healthy life-long trajectories for children is immense.

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