What a general paediatrician needs to know about early life programming

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ABSTRACT
The process whereby early exposure to an adverse environment has an influence on later life outcomes has been called ‘early life programming’. While epidemiological evidence for this has been available for decades, only in recent years have the mechanisms, in particular epigenetic modifications, for this process begun to be elucidated. We discuss the evidence for early life programming, the possible mechanisms, how effects may be transmitted across generations, and conclude by looking at some examples relevant to general paediatrics.

CHILDHOOD AND LATER DISEASE RISK
The fact that early exposures might have an influence on health outcomes later in life has been recognised since the first half of the 20th century. In 1933 Kermack et al.1 analysed historic death rates data for England, Scotland and Sweden and noted “the figures behave as if the expectation of life was determined by the conditions which existed during the child’s earlier years”. They further speculated that “improvement in infantile mortality is dependent in large measure on improvement in maternal health”. In 1977 Forsdahl2 correlated higher infant mortality in Norway with a later increased risk of death from cardiovascular causes. He proposed poverty in childhood and adolescence followed by prosperity as a risk factor for cardiovascular disease (CVD), and hypothesised that “some form of permanent damage caused by a nutritional deficit” might be involved.

THE BARKER HYPOTHESIS
Ongoing epidemiological work continued to show an association between low birth weight and a higher risk of CVD, stroke, the metabolic syndrome and osteoporosis in later life. Barker and colleagues,3 in a series of papers argued that a fetus faced with undernutrition slows its growth rate to reduce its nutritional requirements, but this period of undernutrition might also lead to reduced function in key organs, altered metabolic and endocrine feedback loops, and an increased vulnerability to adverse environmental stressors. Over time these ideas have developed into the Developmental Origins of Health and Disease concept, whereby early life exposures are thought to lead to ‘programming’ of cardiovascular, neuroendocrine and metabolic systems, predisposing the individual to later life non-communicable diseases (NCDs).

Some authors have put this concept of programming within an evolutionary paradigm with the idea of the ‘predictive adaptive response’.4 They argue that these stereotyped responses to an adverse early life environment are adaptive in the short term, and particularly when individuals continue to live in a resource-poor environment, represent the best way to guarantee they reach reproductive age themselves. However, in a resource-rich postnatal environment such as that of the developed world, these programmed changes might have the (unanticipated) effect of predisposing affected individuals to an increased risk of NCDs in adulthood (figure 1). Regardless of the validity of the idea of a ‘predictive adaptive response’, in recent years focus has shifted from extremes of birth weight to how programming might occur across all pregnancies and in individuals with birth weights within the normal range.

ADVERSE ENVIRONMENTS IN UTERO
A large number of human cohort studies have demonstrated a link between lower birth weight (suggesting in utero exposure to an adverse environment) and a higher risk of CVD, stroke, insulin resistance and type 2 diabetes in adulthood, in a variety of settings in the developed and developing world,4 and these findings have been replicated extensively in animal studies.5 In addition to cardiometabolic sequelae, low birth weight has also been related to increased risk of death from infectious causes,6 altered immune function, an increased risk of asthma and atopic dermatitis,7 and neurodevelopmental disorders such as attention deficit hyperactivity disorder and schizophrenia.8 The importance of the early life environment in influencing later disease risk has been highlighted by a recent analysis showing that the greater the number of adverse early life risk factors an individual is exposed to, the greater the risk of overweight and obesity in childhood.10

Although many of the original studies focused on poor maternal nutrition as a major contributor to low birth weight, a wide variety of endogenous and exogenous factors are now recognised to influence cardiovascular, respiratory, metabolic and neurodevelopmental outcomes in offspring. Animal models using uterine artery ligation to create in utero hypoxia have shown that offspring are at risk of cardiovascular and metabolic complications.11 Similarly, human studies suggest that maternal hypertension12 and cigarette smoking,13 which lead to in utero hypoxia, also increase the risk of CVD. Although the original epidemiological studies did not distinguish between intrauterine growth restriction (IUGR) and prematurity as a cause of low birth weight, it is increasingly realised that prematurity itself is a major risk factor for the development of NCDs (reviewed in refs. 13 and 14).
Interestingly, maternal obesity/overnutrition during pregnancy, which commonly leads to increased birth weight, also associates with adverse offspring health outcomes which, perhaps surprisingly, are similar to those seen with undernutrition. In animal and human studies maternal overnutrition is linked with an increased predisposition to obesity, hypertension, hyperinsulinaemia, hyperglycaemia, and increased plasma triglycerides, cholesterol and leptin in offspring. In humans, maternal obesity has also been linked to an increased risk of attention deficit hyperactivity disorder and problems with emotional regulation and with premature mortality from cardiovascular events.

Prenatal glucocorticoid overexposure is also associated with programmed effects. Epidemiological studies show that pregnant mothers exposed to a significant life event (death of a loved one, exposure to terrorism or a natural disaster) give birth to infants with a lower birth weight, who have an increased risk of impaired cognition. Maternal stress is also associated with effects on neurodevelopment in neonates, manifesting as lower scores on neonatal assessment, behavioural and emotional problems at the age of 4 years, decreased grey matter density and lower cognitive and language abilities in childhood. The children of mothers treated with glucocorticoids because of a risk that the unborn child has congenital adrenal hyperplasia appear to be at risk of worse cognitive function than controls. Studies in rodent, sheep and non-human primate models show an association between antenatal glucocorticoid exposure (exogenous and endogenous), raised blood pressure (BP) and altered glucose-insulin homeostasis, neuroendocrine function and behaviour.

Finally, a variety of other adverse environmental factors have been shown to impact on neurodevelopmental outcomes: maternal infection, alcohol consumption, recreational drug use, treatment with certain medications (eg, sodium valproate) and prenatal exposure to toxins such as arsenic and lead have all been associated with an increased risk of adverse neurodevelopmental outcomes including schizophrenia and autism (reviewed in ref. 25).

**POSTNATAL FACTORS WHICH INFLUENCE THE RISK OF DEVELOPING NCD**

The long-term consequences of early exposures are modulated by the postnatal environment. Early postnatal growth patterns influence disease risk, for example, in a trial involving a cohort of small for gestational age (SGA) infants, those randomised to a high protein formula who had greater weight gain had significantly higher BP at 6–8 years, and conditional gains in abdominal circumference also associate with higher childhood BP. Three large cohort studies have shown that excessive weight gain in infancy is associated with an increased risk of greater total fat mass and percentage body fat, lower insulin sensitivity and higher systolic BP in childhood. These relationships are complex; however, extensive data from the Helsinki birth cohort study and the Hertfordshire cohort show that low weight at 1 year of age but an early ‘adiposity rebound’ associates with a higher risk of CVD and type 2 diabetes and that boys who were born small but were tall at school entry had a 6-year reduction in life span. These data are supported by animal studies, for example, in mice, poor fetal growth resulting from maternal protein restriction, followed by rapid postnatal growth results in reduced life span.

Because of phenotypical similarities between adults born SGA and prematurely, some researchers have postulated that while in low birthweight infants the adverse environment is experienced in utero, in preterm infants these environmental challenges occur postnatally. Preterm birth, regardless of birth weight relative to gestation (ie, without evidence of in utero growth restriction), has in itself been associated with a reduction in insulin sensitivity and changes in the endocrine regulation of childhood growth and increased adiposity. Similar to SGA infants, rapid early weight gain may also be detrimental for preterm babies: in a randomised controlled trial which allocated preterm infants to high or lower nutrient diets, those with the most rapid weight gain in the first 2 weeks of life showed evidence of insulin resistance in adolescence and other studies report that upward centile crossing for weight in infancy and childhood are associated with insulin resistance and higher BP.

However, low birth weight and preterm infants are susceptible to the influences of postnatal diet, and maternal obesity and overnutrition are risk factors for childhood obesity, which is exacerbated by a high energy diet in infancy. In rodent models of maternal overfeeding, offspring are predisposed to obesity and metabolic abnormalities, and this effect is amplified when the offspring are exposed to high-fat diets following...
expression of the insulin-like growth factor 2 (IGF2), a key mediator of cell differentiation, genomic imprinting and X chromosome inactivation. DNA methylation, histone marks and small, non-coding RNAs contribute to epigenetic changes that have the potential to be altered/disrupted by environmental cues. Epigenetic modifications include DNA methylation, histone marks and small, non-coding RNAs. DNA methylation is crucial for normal development and is involved in cell differentiation, genomic imprinting and X chromosome silencing. A growing number of studies have described alterations in DNA methylation and gene expression in association with early life exposures. Adults exposed in utero to severe calorie restriction during the Dutch Hunger Winter of 1944/1945 have reduced methylation at regions controlling the expression of the insulin-like growth factor 2 (IGF2), a key regulator of insulin resistance. Antenatal glucocorticoids affect the development of key glucocorticoid responsive organs such as the kidneys, adipose tissue and pancreas, linking structural and hormonal changes in the programming of later life disease.

There has been much interest in recent years in the role of epigenetic modifications in early life programming. Epigenetic modifications lead to changes in gene expression that are not explained by changes in DNA sequence, and during normal development, key developmental stages are characterised by epigenetic modifications that have the potential to be altered/disrupted by environmental cues. Epigenetic modifications include DNA methylation, histone marks and small, non-coding RNAs. DNA methylation is crucial for normal development and is involved in cell differentiation, genomic imprinting and X chromosome silencing. A growing number of studies have described alterations in DNA methylation and gene expression in association with early life exposures.

Programming may involve both long-term effects and changes in gene expression that are not passed on to offspring. In rodents, prenatal glucocorticoid exposure leads to reduced nephron number and changes in cardiac noradrenergic innervation together with a reduction in pancreatic β-cell growth, a risk factor for type 2 diabetes. Maternal obesity impacts on offspring body fat and muscle composition, which may contribute towards the development of insulin resistance. Antenatal glucocorticoids affect hippocampal growth, and associate with delayed maturation of neurons, myelination, glia and vasculature.

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persisting health disparities among disadvantaged populations, potentially through effects on the HPA axis.65 66

**SIGNIFICANCE FOR PAEDIATRICIANS**

An understanding of early life programming and its consequences is of clear importance for paediatricians who are ideally placed to identify those most at risk of later disease and to facilitate the development and implementation of interventions. Given that adverse early life environments may affect children’s later life outcomes, and that of their own offspring, a paediatrician’s role takes on important public health aspects.

First, we can influence care from the beginning of life by emphasising the importance of good maternal health and antenatal care in optimising child and adult health. Addressing modifiable risk factors, including maternal obesity, excess gestational weight gain, maternal smoking and vitamin D levels and breastfeeding duration could make a significant contribution to child health, and by implication, improve adult health. Indeed, paediatricians have been involved in the development of the National Institute for Health and Care Excellence evidence-based guidelines for the antenatal and postnatal care of women and babies (http://www.nice.org.uk) and these have been endorsed by the Royal College of Paediatrics and Child Health.

Since any effects of the in utero environment may be amplified as a consequence of early growth patterns, optimising early nutrition may be a key way in which paediatricians can influence later health. In preterm babies, studies are ongoing to develop nutritional strategies which optimise neurodevelopment and prevent extrauterine growth restriction without promoting the development of longer-term metabolic complications, however there is much less evidence for the optimal nutritional management of the SGA infant born at, or near term, or in the management of the offspring of obese women. Overweight and obese women are less likely than lean women to exclusively breastfeed at 2 months of age and are more likely to introduce early weaning foods. Breast feeding may be protective against childhood obesity as a consequence of reduced protein content compared with formula, the presence of active hormones such

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**Figure 2** Potential mechanisms accounting for the transgenerational transmission of disease risk. (A) Persistence of an adverse environment leads to the reinduction of programmed effects in each subsequent generation. (B) Maternal effects: the induction of programmed effects in the F1 offspring following in utero exposure lead to the induction of programmed effects on the developing F2 fetus and so on. (C) Exposure to an adverse environment affects the developing F1 fetus and has direct effects on the germ cells which will form the F2 generation and these changes are maintained in the germ cells for a number of subsequent generations.

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as leptin, ghrelin and adiponectin which may influence appetite control, and poorer regulation of satiety with bottle feeding. 39 Thus, the provision of additional support for breast feeding and improving the food choices of these women has the potential to reduce childhood overweight and obesity, with obvious consequences for the next generation. 69

There is ongoing research (at present mainly in animal models) investigating therapeutic options to reverse or prevent the effects of in utero programming. Studies are ongoing to evaluate strategies for the prevention of CVD in individuals born with IUGR. 70 In animal studies, therapies which have been examined include micronutrient supplementation (eg, folate, glycine and choline) given during pregnancy to mitigate the effects of undernutrition, or statins for hypercholesterolaemia in pregnancy which may protect offspring against the conditioning effect of a high fat diet. 9 Similarly, there may be a role for leptin and statin therapy in those born SGA to modify the long-term hormonal and cardiovascular effects of an adverse antenatal environment. 1

Since programming effects may also occur as a consequence of experiences in infancy and childhood, targeted interventions during infancy and childhood may improve later health. For example a randomised controlled trial of the effects of additional support for single, poor, deprived mothers during pregnancy and during infancy and childhood may improve later health. For example a randomised controlled trial of the effects of additional support for breast feeding and in designing and implementing interventions at many points during the life-cycle. ADHD, attention deficit hyperactivity disorder; HPA axis, hypothalamic-pituitary-adrenal axis; NCD, non-communicable disease.

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