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INVITED REVIEW

# Nutrition in early life and the programming of adult disease: a review

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## Abstract

Foetal development and infancy are life stages that are characterised by rapid growth, development and maturation of organs and systems. Variation in the quality or quantity of nutrients consumed by mothers during pregnancy, or infants during the first year of life, can exert permanent and powerful effects upon developing tissues. These effects are termed 'programming' and represent an important risk factor for noncommunicable diseases of adulthood, including the metabolic syndrome and coronary heart disease. This narrative review provides an overview of the evidence-base showing that indicators of nutritional deficit in pregnancy are associated with a greater risk of type-2 diabetes and cardiovascular mortality. There is also a limited evidence-base that suggests some relationship between breastfeeding and the timing and type of foods used in weaning, and disease in later life. Many of the associations reported between indicators of early growth and adult disease appear to interact with specific genotypes. This supports the idea that programming is one of several cumulative influences upon health and disease acting across the lifespan. Experimental studies have provided important clues to the mechanisms that link nutritional challenges in early life to disease in adulthood. It is suggested that nutritional programming is a product of the altered expression of genes that regulate the cell cycle, resulting in effective remodelling of tissue structure and functionality. The observation that traits programmed by nutritional exposures in foetal life can be transmitted to further generations adds weight the argument that heritable epigenetic modifications play a critical role in nutritional programming.

## Introduction

Research over a period of several decades has identified associations between anthropometric measurements at birth and disease in later life (Barker, 2006; Langley-Evans & McMullen, 2010; Gluckman *et al.*, 2011). The epidemiological studies describing such associations have led to the assertion that factors in the maternal environment influencing growth and development can also alter tissue function, such that adult physiology reflects the early-life experience. Work with experimental models has confirmed that nutrition in early life has the capacity to permanently establish physiological and metabolic states that effectively determine the risk of diseases that occur with ageing (Langley-Evans & McMullen, 2010).

The evidence linking nutrition in early life to health in adulthood now forms a cornerstone of health promotion and public health nutrition programmes globally. A 2009 report recognised and promoted the importance of foetal and early-life nutrition and its relationship with lifelong health. This report found compelling evidence for a role of early-life nutrition in setting the risk of conditions including coronary heart disease, type-2 diabetes, osteoporosis, asthma, lung disease and some forms of cancer (British Medical Association, 2009). These findings were further backed by the 2011 report of the UK Scientific Advisory Committee on Nutrition, which recommended

a strategy to promote, protect and support breastfeeding and to optimise the diets and body composition of young women (Scientific Advisory Committee on Nutrition, 2011). In 2012, the WHO published global targets and recommendations for the nutrition of mothers, infants and young children with the aim of reducing the prevalence of low birth weight (World Health Organization, 2012).

## The concept of early-life programming

The term 'programming', originally coined by Lucas (1991), is used to describe the process by which exposure to specific environmental stimuli or insults, during critical phases of development, can trigger adaptations that result in permanent changes to the physiology of the organism (Gluckman & Hanson, 2004; Gluckman *et al.*, 2011). In other words, when a developing foetus or infant is subject to external challenge, the physiological adaptations that occur to ensure survival may leave behind a permanent memory of that exposure.

Programming is a consequence of the plasticity of cells and tissues during development, which permits the developing embryo or foetus to respond to their current environment. For most types of cell, plasticity is a short-lived characteristic that is a feature only of the embryonic and foetal stages. In some cell types, the adaptive capacity remains present throughout life. For example, the human immune system can respond to infection by a previously unencountered pathogen and the B-lymphocytes that differentiate during that response remain available to combat any subsequent infection by that organism (Gluckman *et al.*, 2011). The majority of tissues retain plasticity only during the periods of embryonic and foetal development. As a result, these are considered to be the critical developmental phases during which perturbation of normal processes and hence programming of human health and disease by nutrition may occur.

A key process through which the environment encountered during early life may determine lifelong physiological and metabolic function, and hence disease risk, is likely to be through the remodelling of organs and tissues (Langley-Evans, 2009). All tissues have a structure that relates to their function, with functional units that are required to mediate physiological function. For example, in the pancreas, the functional unit required for maintenance of insulin synthesis and secretion is the islet. Similar to most human systems, the pancreas is fully formed by the time of birth and the number of islets is set *in utero* (Snoeck *et al.*, 1990). Subtle developmental exposures that result in fewer islets being formed may have no immediate impact upon pancreatic function but make an age-related decline in metabolic regulation more likely. As described below, the same principle applies to other organs and tissues (Langley-Evans *et al.*, 1999) and, hence, factors that determine the quality of the intrauterine environment can modify tissue structure and are effectively risk factors for noncommunicable diseases of adulthood.

A diverse range of different stimuli operating during development may have a programming effect. This review describes the programming effects of the nutritional environment encountered in early life. In addition, any environmental factor that might impact upon foetal growth should be regarded as a potential programming influence, including smoking, severe psychological trauma, maternal infection or pharmacological agents (Seckl & Meaney, 2004; Yehuda *et al.*, 2005; Salmasi *et al.*, 2010; Schmiegelow *et al.*, 2013).

The timing of exposure to potential programming stimuli may be critical in determining the outcome of the event. Greatest sensitivity will occur during the periods of most rapid growth and maturation. For example, the kidney may be most vulnerable during the phase of nephrogenesis (Langley-Evans *et al.*, 1999). The brain, which has a critical period of development early in human gestation, may remain vulnerable for much longer because extensive growth and development of neural pathways and linkages extends well into childhood (Plagemann *et al.*, 2000). Longer periods of exposure may be expected to have an impact upon a greater range of organs and systems.

## Nutritional programming during foetal development

Some of the earliest indications of a relationship between the intrauterine environment and later health were provided by ecological studies that showed simple correlations between place of birth and the risk of death from coronary heart disease and between the risk of death in infancy and coronary heart disease mortality (Barker & Osmond, 1987; Osmond *et al.*, 1990). These early indications were given extra weight through retrospective cohort studies based upon a population from Hertfordshire, UK. Records from 16 000 men and women born in Hertfordshire between 1911 and 1930 included weight at birth and weight at age 1 year. It was found that, although mortality rates for all causes were unrelated to size at birth or in infancy, lower birthweight was associated with increased coronary mortality (Barker *et al.*, 1989). Follow-ups of men aged 64–75 years in this cohort indicated inverse associations between weight at birth and blood pressure (Barker *et al.*, 1990), type-2 diabetes (Hales *et al.*, 1991) and the insulin resistance syndrome (Barker *et al.*, 1993). A number of similar studies indicated inverse relationships between lower birthweight

(but within the normal population range) and disease outcomes. In one of the largest of these studies, the US Nurses Health Study, Curhan *et al.* (1996) collected data on birthweight from 70 297 women and found that, among full-term singletons, and after adjustment for adult body mass index, the risks of coronary heart disease and stroke were both related to weight at birth (relative risk estimate 0.85 per kg increase in birth weight). A lower weight at birth was also associated with higher blood pressure in adult life. In addition to studies showing relationships between birthweight and disease risk in adults, a number of reports indicated that disease markers are elevated in young children subsequent to low birthweight (Bavdekar *et al.*, 1999).

Birthweight is not the only measureable feature at birth that is related to later health and disease. Thinness at birth (measured as ponderal index; weight/length$^3$) has been found to be inversely related to risk of type-2 diabetes and glucose intolerance. Eriksson *et al.* (1999, 2001) have reported extensively upon two populations born in Helsinki, Finland (1924–33 and 1933–44). Follow-ups of these cohorts confirmed that stroke and coronary heart disease mortality were greater with low birthweight. Thinness at birth was also related to risk of coronary heart disease death type-2 diabetes and metabolic syndrome if body mass index was high in later childhood (Eriksson *et al.*, 1999, 2001). Large head circumference in proportion to body length is also a potential disease marker (Carrington & Langley-Evans, 2006) and, together, these observations suggest that factors constraining truncal growth *in utero* also bring about a programming effect upon the developing organs, which permanently perturbs function and redundancy of systems in the face of ageing.

Observations that intrauterine factors were related to disease in adulthood were explained by the initiators of the programming hypothesis in terms of deficits in maternal nutrition. It was argued that, in the early part of the 20th Century when the Hertfordshire and Helsinki cohorts were born, the main drivers of poor pregnancy outcome were poverty and associated undernutrition and infectious disease among young women. This argument received some weight with the observation that placental size was also related to disease outcomes. In children, blood pressure was positively associated with placental weight (Moore *et al.*, 1996) and follow-ups of a cohort of 50-year-old men and women found that highest blood pressure was associated with lower birthweight and a larger placenta (Barker *et al.*, 1990). Because the placenta is the primary determinant of nutritional supply to the foetus, it was reasoned that nutritional deficit or excess could alter the foetal : placental ratio with irreversible consequences for organ structure (Godfrey *et al.*, 1991). Animal studies also indicated that lower birthweight was a frequent outcome of maternal undernutrition (Woodall *et al.*, 1996). In sheep, maternal undernutrition also results in placental enlargement, a response that is interpreted as an adaptation to maximise transfer of nutrients from mother to foetus (McCrabb *et al.*, 1991).

To some extent, this argument remains accepted within the field, although it has to be recognised that measures of infant anthropometry at birth or placental size are only crude proxies for nutritional exposure during pregnancy. However, there are very few studies that have the capacity to offer more meaningful measures in the context of long-term health. Where such information is available, the effects are often small or difficult to interpret. In the winter of 1944–1945, western Holland was subject to a famine of approximately 6 months in duration [at the height of the famine, the adult ration was 2.09–2.51 MJ day$^{-1}$ (500–600 kcal day$^{-1}$)] because of the blockade of food supplies by Nazi forces (Roseboom *et al.*, 2001, 2011). As a result of the duration of the famine, some pregnant women were affected over the final stages of pregnancy, whereas others were undernourished in early pregnancy. Birth weights among babies affected by famine in late gestation were approximately 250 g lower than those of babies born before or conceived after the famine (Lumey, 1992; Roseboom *et al.*, 2001).

For mothers who experienced the famine in the first trimester of gestation, the babies were heavier at birth than the norm for the population. Over a number of follow-ups considering health outcomes for the famine babies compared to contemporaries born before or after the famine, it was shown that exposure to famine in early gestation was associated with a greater prevalence of coronary heart disease and raised circulating lipids, as well as with raised concentrations of blood clotting factors and more obesity compared to those not exposed to the famine (Ravelli *et al.*, 1976, 1999, 2000; Roseboom *et al.*, 2001). Individuals who had suffered exposure to the famine during mid-gestation were more likely to exhibit impaired renal function as adults (Painter *et al.*, 2005) and exposure to famine during late gestation was associated with glucose intolerance and type-2 diabetes (de Rooij *et al.*, 2006a; de Rooij *et al.*, 2007).

A study conducted in a small number of children demonstrated a relationship between maternal iron status and adiposity and offspring blood pressure (Godfrey *et al.*, 1994). Blood pressure was also an outcome reported by Project Viva, a US prospective cohort study following the children of women whose nutritional status had been measured in detail in the period before and during pregnancy. Gillman *et al.* (2003) reported that maternal calcium supplementation during pregnancy reduced blood pressure in 6-month-old infants. Project Viva also identified an association between higher maternal vitamin D

 

intake and lower risk of childhood asthma among 3-year-old children (Camargo *et al.*, 2007). The same cohort showed that babies born to women who gained excessive weight in pregnancy were more likely to be obese in childhood (Oken *et al.*, 2009). Normia *et al.* (2013) reported that, in a small cohort of mother–child (4-year-old) pairs, higher maternal carbohydrate intake was associated with higher childhood systolic blood pressure and higher childhood systolic blood pressure was noted in offspring exposed to lowest or highest tertiles of maternal fat intake during pregnancy. A longer-term follow up of Scots aged in their 40s for whom maternal food intake data were available also provided evidence that maternal intake could be a driver of intrauterine programming (Campbell *et al.*, 1996). Adult blood pressure was associated with maternal intakes of animal protein and sugars, although the relationship was complex and nonlinear.

The epidemiological approaches to investigating the relationships between events in foetal life and outcomes 60–70 years later are inevitably subject to criticism. Clearly, there is no scope for a randomised controlled trial in this area and, although there are a number of ongoing prospective cohort studies, it is inevitable that the literature relies upon retrospective cohorts and case–control studies. These are prone to unadjusted confounding and generally are reliant on poor proxy markers of nutrition in pregnancy. A single measure of weight at birth reveals little about the experience of the foetus *in utero* and cannot provide any indication of whether growth was constrained, or what factors were limiting. As demonstrated by the Dutch Hunger Winter studies, undernutrition at different stages of gestation may have varying effects upon final birthweight, including an increased size at birth (Lumey, 1992; Roseboom *et al.*, 2001). Moreover, among populations in developed countries, the correlation between maternal intake and birth weight is poor (Godfrey *et al.*, 1996; Langley-Evans & Langley-Evans, 2003). The actual nutritional environment encountered by the foetus is far more complex, reflecting maternal intake, stores, maternal activity, placental function and rate of foetal growth. A meta-analysis by Huxley *et al.* (2002) identified a high influence of measurement and publication bias in the literature linking foetal growth to cardiovascular disease but, importantly, other robust systematic reviews and meta-analyses have confirmed relationships between birth anthropometry and the risk of type-2 diabetes and chronic kidney disease (Whincup *et al.*, 2008; White *et al.*, 2009).

Given the unavoidable issues with epidemiology in this area, much of the research designed to investigate the mechanistic basis of programming, and to confirm the association between physiological and metabolic function in adulthood and nutrition during foetal life, has been reliant on experimental animal studies. It is most striking that, across a diverse range of species, including rodents, sheep and nonhuman primates, there are solid relationships between maternal nutritional status and blood pressure, feeding behaviour, adiposity and glucose homeostasis (Langley-Evans, 2013). The animal evidence suggests that apparently very different nutritional insults during pregnancy (e.g. iron deficiency and maternal overfeeding) can elicit essentially the same outcomes in the resulting adult offspring (Langley-Evans *et al.*, 1996; Gambling *et al.*, 2003; Samuelsson *et al.*, 2008). Not only does this confirm the biological plausibility of the programming hypothesis, but it also suggests that a limited number of common mechanisms may link nutritional 'stressors' to development changes that result in later disease.

## Nutritional programming during infancy

The early studies of nutritional programming identified growth over the first year of life as an indicator of disease in adulthood. For example, Hales *et al.* (1991) reported that, in addition to birthweight, weight at 1 year was significantly related to glucose intolerance and beta-cell dysfunction in 64-year-old men. Such studies have not been longitudinal in nature and so, in that study, it was not clear whether the smaller 1-year-olds were also the small newborns, or whether they represented a group who had failed to thrive after birth. However, data of this nature have been regarded as generally supportive of nutritional programming occurring during early infancy. Other studies argue that the key driver of programmed disease is the combination of poor early growth with rapid catch-up growth in infancy and childhood (Eriksson *et al.*, 1999, 2001; Forsen *et al.*, 1999).

Nutrition in the earliest stage of infancy is provided solely as milk, which may be human milk delivered by breastfeeding or formula milk from bottle feeding. There is a large amount of literature available describing the longer-term health benefits of breastfeeding, providing evidence suggesting that disease risk is programmed during this period (if we accept that human milk is optimal for growth and development and formula milk is not). A positive effect of breast-feeding on cognitive function is widely reported (Evenhouse & Reilly, 2005) and breastfeeding appears likely to protect against some immune-related diseases later in life, such as type-1 diabetes (EURODIAB, 2002) and inflammatory bowel disease (Klement *et al.*, 2004). There is significant literature detailing the benefits of breastfeeding in preventing atopic disease in children with a family history (Gdalevich *et al.*, 2001). However, the literature on breastfeeding and later health is plagued by methodological difficulties, being heavily

dependent upon observational studies with self-report of breastfeeding behaviour, and subject to the effects of confounding factors (Schack-Nielsen & Michaelsen, 2007).

There is limited convincing evidence that the window for nutritional programming extends any further into infancy. The World Health Organization recommends exclusive breastfeeding until 6 months of age and continued breastfeeding until 2 years of age or beyond. After 6 months, appropriate complementary foods should be introduced, although some argue that this is too late for infants in developed countries where the risk of water- or food-borne infection is low (Fewtrell, 2011). In developing countries, early or inappropriate complementary feeding may lead to malnutrition and poor growth but, in countries where obesity is a greater public health concern than malnutrition, the relationship between mode of feeding, growth and longer-term health is unclear.

A systematic review of the literature (Pearce *et al.*, 2013) investigating the relationship between the timing of the introduction of complementary feeding and obesity or being overweight during childhood found that introducing complementary foods at ≤4 months was associated with a higher body mass index (BMI) in childhood. However, this was largely reflected in lean mass and there was no strong evidence of earlier weaning being associated with greater adiposity. It is possible that effects of complementary food may interact with earlier nutritional experience. The responses of formula-fed infants to early weaning may differ from those of breastfed babies (Przyrembel, 2012). There is evidence that the mode of feeding before weaning influences flavour preferences in infants. These effects of exposure to either breast milk (and the exposure to flavours in the maternal diet) or formula may affect food choices and health in later life. (Trabulsi & Mennella, 2012).

In addition to the timing of introduction of complementary feeding, the nature of the foods used in weaning have been considered as potential determinants of childhood obesity or being overweight. The systematic review of Pearce & Langley-Evans (2013) found some evidence of an association between high protein intakes at 2–12 months of age and higher BMI or body fatness in childhood. Higher energy intake during complementary feeding was also associated with a higher BMI in childhood. Adherence to dietary guidelines during weaning was associated with a higher lean mass, although consuming specific foods or food groups made no difference to childhood BMI.

Although the early nutritional environment may have some limited effects on adiposity in childhood, the longer-term relationship to health in adulthood is unclear. There is strong evidence indicating that a degree of the risk of adult obesity and being overweight is related to being overweight in childhood, a phenomenon known as tracking (Freedman *et al.*, 2001). It is likely that the strongest determinant of weight and fat mass tracking is genetics rather than diet, however, and it is also apparent that childhood obesity has no strong independent effect upon risk of either cardiovascular disease or metabolic disorders (Lloyd *et al.*, 2010, 2012). These are heavily influenced only by adult adiposity.

Data from robust longitudinal cohort studies suggest that there is no strong relationship between breastfeeding and the risk of coronary heart disease in adulthood (Martin *et al.*, 2004; Rich-Edwards *et al.*, 2004). In the Caerphilly study of more than 2500 middle-aged men, Martin *et al.* (2005) reported that breastfeeding was associated with an increased risk of coronary heart disease mortality. This was not coinsidered to be causal because there was no relationship between mortality and the duration of breastfeeding. Although mortality from heart disease is not explained by feeding in infancy, there are weak but significant associations between breastfeeding and risk factors for heart disease. Adults who were breastfed have lower blood pressure and lower total cholesterol than those who were formula fed (Owen *et al.*, 2002, 2003). The systematic review of Arenz *et al.* (2004) suggested that breastfeeding was protective against obesity in childhood, with a longer duration of breastfeeding having a greater effect. A further review by Owen *et al.* (2005), however, concluded that the protective effect was likely to be heavily confounded and did not persist into adulthood.

## Disease risk across the lifespan

The most robust research linking early-life nutrition to disease in adulthood demonstrates associations between diet during pregnancy and the risk of cardiovascular disease, the metabolic syndrome and type-2 diabetes. These are conditions that develop with ageing, typically manifesting in the fifth decade of life. The determinants of risk at any stage of life are not simple interactions of the individual with his/her environment at that particular point in time. They are in fact the products of cumulative exposures across the whole lifespan. The environment encountered at each stage of life, from the periconceptual period through to senescence, modifies the individual response to nutrients and other challenges at successive stages.

Primarily, the risk of most noncommunicable disease is determined by genetic factors, with numerous single nucleotide polymorphisms (SNPs) accounting for significant risk of coronary heart disease, obesity, type-2 diabetes and cancer (Norheim *et al.*, 2012). For example, the C677T polymorphism of methyl-tetrahydrofolate reductase

 

(MTHFR) is associated with the risk of cardiovascular disease (McNulty *et al.*, 2012) and colorectal cancer (Sohn *et al.*, 2009) and the apo E4 variant of apolipoprotein E is associated with atherosclerosis and Alzheimer's disease (Kofler *et al.*, 2012; Hauser & Ryan, 2013). These gene variants rarely provide a simple predisposition to disease. This is largely because most disease states are not monogenic in origin, as well as there being a degree of gene–environment or gene–nutrient interactions in the aetiology of disease. Again, taking the C677T polymorphism of MTHFR, it is clear that, with an adequate folate status, any association of the TT variant with cardiovascular disease is removed and that, for colorectal cancer, a positive folate balance decreases risk with respect to the TT genotype (Homocysteine Studies Collaboration, 2002; Kim *et al.*, 2012). Abarin *et al.* (2012) reported that, among girls carrying a SNP of FTO, which is normally associated with higher BMI in adolescence, exclusive breastfeeding negated the effect of the high-risk allele.

Throughout life, the pathways that lead from any given genetic predisposition will be modified by both nutrition-related and non-nutritional factors. The effects of multiple protective or harmful SNPs are also modified by their interactions with each other and by epigenetic factors that ultimately control the expression of these 'disease' genes; for example, silencing their expression through DNA methylation (Jaenisch & Bird, 2003). At any given life stage, the expression of the genotype is dependent upon nutritional-signals that play a regulatory role. At the epigenetic level, this essentially comprises the B vitamins, although nutritional status also influences gene expression via transcription factors such as the peroxisome proliferator activated receptors (PPARs) or nuclear receptors.

Although nutritional exposures at all stages of life can modify the disease pathway, the fact that early-life programming can alter tissue function and responsiveness to environmental cues means that nutritional exposures occurring early in life are able to determine how an individual will respond to nutritional signals that come later in life (Fig. 1). To some extent, this is demonstrated by some of the epidemiology that describes the association between foetal growth and adult disease. Studies by Phillips and colleagues showed that, although insulin resistance was greater in 50-year-olds who had been relatively thin at birth, the influence of this marker of early growth was greater in individuals who were overweight or obese in adulthood (Phillips *et al.*, 1994). Similarly, the studies of the Helsinki cohort showed that women who developed coronary heart disease had been born small but had gained weight and increased BMI more rapidly in childhood (Forsen *et al.*, 1999). Overall, their increased disease risk was the product of cumulative nutritional factors at different life stages.

Underpinning all of the interactions between nutritional or non-nutritional exposures across the lifespan is the influence of genotype upon disease risk. A body of evidence favours the concept that nutritional programming provides a layer of risk-modification between the genotype and later lifestyle behaviours (Fig. 1). A range of studies have reported that birthweight modulates the normally observed relationships between specific gene polymorphisms and disease. The PP variant of the Pro12Ala SNP of the PPAR-gamma2 gene is associated with an increased risk of type-2 diabetes. Eriksson *et al.* (2002) reported that this association was present only in individuals who had been of lower weight at birth, showing that an interaction exists between programming influences and the genotype. This may be regarded in two ways, with the inferences that programming only occurs in individuals with a susceptible genotype (i.e. because birthweight did not predict diabetes in individuals without the PP variant) or that the effect of genotype is only expressed in individuals subject to adverse programming, with both being equally valid. de Rooij *et al.* (2006b) followed up individuals from the Dutch Hunger Winter cohort and found that the effects of the Pro12Ala SNP on glucose homeostasis varied with the timing of exposure to famine *in utero*. However, in contrast to the work of Eriksson *et al.* (2002), it was the Ala variant that increased the risk of type-2 diabetes, although only in those exposed to famine during mid-gestation.

There are other examples of interactions between early life factors and genotype. The K121Q SNP of plasma cell glycoprotein 1 is implicated in development of type-2 diabetes, with the Q allele increasing insulin resistance. In the study by Kubaszek *et al.* (2004), 121Q increased the risk of hypertension, type-2 diabetes and insulin resistance, although only in adults who had been of lower weight at birth. Lips *et al.* (2007) followed up individuals from the Hertfordshire cohort to examine the relationship between early growth, genotype and bone health. Their study found that, among women, the 11 genotype of the calcium-sensing receptor CASRV3 polymorphism was associated with higher lumbar spine bone mineral density within the lowest birthweight tertile. The opposite was observed among individuals in the highest birthweight tertile.

Given that the risk of developing cardiovascular disease or the metabolic syndrome in adulthood is determined by factors interacting across the lifespan, including powerful effects of genotype and dietary exposures at all stages of life, the fact that it is possible to detect any influence of foetal growth-related factors at all is remarkable. The persistence of early-life events as influences upon the response to nutritional challenges in adulthood is a testament to the likely strength of early-life programming effects upon the development of organs and systems.

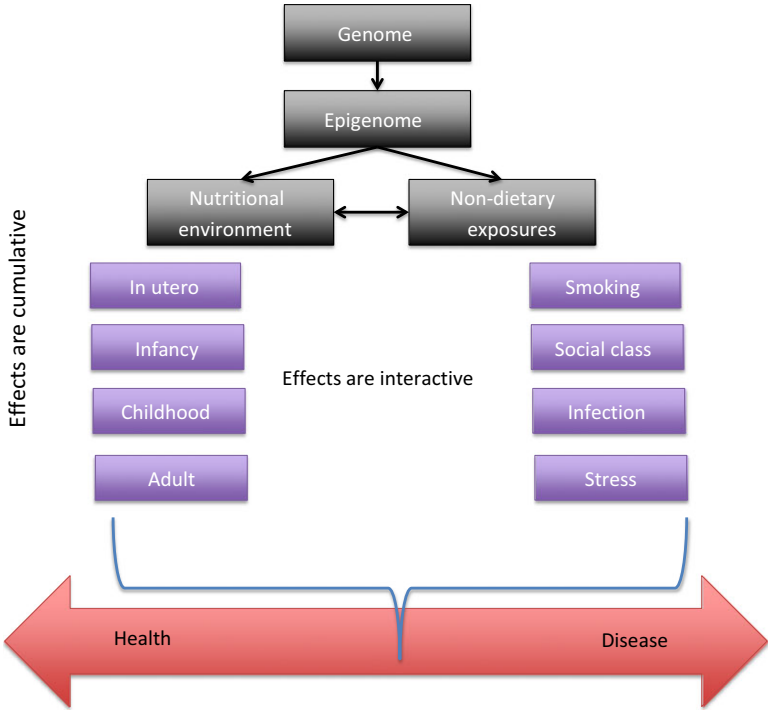


**Figure 1** Disease risk is the product of cumulative risk factors across the lifecourse. Primarily, the risk of most noncommunicable disease is determined by genetic factors, with numerous polymorphisms accounting for significant risk of coronary heart disease, obesity, type-2 diabetes and cancer. The effects of protective or harmful polymorphisms may be modified by their interactions with each other and epigenetic factors that control the expression of these 'disease' genes. Throughout life, the pathways which lead from any given genetic predisposition will be modified by non-nutritional factors. Nutritional exposures at all stages of life also modify the disease pathway. Exposures that occur early in life are able, through programming, to determine how an individual will respond to nutritional signals in later life.

## Transgenerational effects of nutrition in pregnancy

Current thinking in the developmental programming area is that disease arises as a result of a mismatch between the prenatal and postnatal environment. This is supported by evidence demonstrating that rapid catch-up growth following prenatal growth restriction is the strongest predictor of the metabolic syndrome. In populations undergoing economic and nutritional transition from poor to relatively affluent status (e.g. India, China, South Africa), an explosion of obesity, type-2 diabetes and cardiovascular disease is expected as a result of such a mismatch. Although rapid improvements in maternal nutrition in such countries may be expected to lessen the importance of nutritional programming as a contributor to the overall disease burden, it is argued that transgenerational effects may occur, whereby the consequences of deficits in maternal nutrition in pregnancy are ultimately transmitted to grandchildren. This means that, across the globe, nutritional/economic transition may represent a sharp decline in malnutrition-related disease, to be followed by half a century of unavoidable metabolic disease.

Pembrey (1996) proposed that an transgenerational feed-forward control loop exists, linking the growth and health of an individual with the nutrition of their grandparents. This form of control would be likely to involve some genomic imprinting of genes, which are then passed on to subsequent generations. The outcome of such imprinting would be very long-term health consequences for populations that are exposed to either undernutrition or over-nutrition at some stage in their history. The complexity of the epidemiological studies that would be necessary to investigate transgenerational programming in human populations largely precludes such work.

Studies of individuals exposed to the Dutch famine indicate that undernutrition of women during pregnancy influenced the nutrition of their daughters and subsequently had an impact upon the birthweight of their grandchildren. Veenendaal *et al.* (2013) reported that the grandchildren of women who were pregnant during the famine had greater neonatal adiposity and poor health in later life. Women who were exposed to famine *in utero* were themselves more likely to give birth to low birth weight children (Lumey, 1992), which suggests a grandmaternal influence upon foetal growth and development.

Transgenerational effects are not necessarily the product of deficits only in maternal nutrition. Bygren *et al.* (2001) have reported that the grandchildren of men who were overfed in the prepubertal growth period had a significantly shorter lifespan. Davis *et al.* (2008) reported that childhood BMI correlated strongly with grandparental BMI, irrespective of parental BMI. This has been interpreted as the transgenerational transmission of obesity, although BMI also reflects lean mass and any relationships could reflect family behaviours as much as a biological transmission.

Transgenerational programming, the physiological response of offspring across two or more generations, has been previously noted in studies of animals. Beach & Hurley (1982)assessed immune function in the offspring of mice fed a zinc deficient diet in pregnancy. Immunosuppression was severe and persisted into a third generation following the initial nutritional insult before resolving. More recently, Drake *et al.* (2005) have reported that the treatment of pregnant rats with dexamethasone in pregnancy, an intervention known to retard foetal growth and programme hypertension and glucose intolerance in the offspring, produces effects on glucose homeostasis that persist for two generations. Maternal high fat feeding elicited a sex-specific insulin resistant phenotype in second- and third-generation mice offspring (Zambrano *et al.*, 2005).

At the present time, it is likely that the observed programming of physiology, metabolism, health and disease is in part a product of the maternal environment signalling to the foetal epigenome. This is an issue of major significance because epigenetic marks, although sensitive to environment and ageing, may be stably inherited by any future offspring. This allows potential for a nutritional insult in one pregnancy to have effects over several generations. Feeding a low-protein diet to rats during pregnancy programmed blood pressure and nephron number over two generations. Importantly, transmission occurred via the male as well as the female line, which is strongly suggestive of an influence of the epigenome (Harrison & Langley-Evans, 2009). This opens up the possibility that paternal, as well as maternal, nutritional status may be an important determinant of disease risk. This would radically change the way that we think about optimising nutritional status in the peri-conceptual period.

## Mechanistic considerations

The evidence to link early-life nutrition (in particular maternal nutritional status in pregnancy) with disease in later life is overwhelming. The challenge is to utilise this information for the development of novel approaches to public health, or other interventions, to prevent and treat disease. To be able to even put in place simple measures such as advice for optimising nutrition in the peri-conceptual period requires an understanding of the mechanisms that explain how nutritional programming occurs. The animal experiments suggesting that even relatively mild perturbations of dietary quality during can bring about altered function in the ageing offspring are a cause for caution. Any ill-considered intervention in humans could have far-reaching, transgenerational consequences.

As described above, the most likely mechanism that allows a possibly transient nutritional insult, acting during early life, to exert a lasting effect upon physiological function, decades later, involves changes to the structure of organs and tissues during their phases of growth, differentiation and maturation (Fig. 2). This tissue remodelling is typified by observations of the effects of undernutrition and growth restraint upon the kidney in both animals and humans. Nephrons are the functional units of the kidney, being the sites of blood filtration and urine formation. In the human kidney, nephron number is determined before birth and is hypervariable between individuals, ranging between 300 000 and 10 00 000 nephrons per kidney (Mackenzie & Brenner, 1995). Nephron number is an important marker of the likelihood of chronic kidney disease because nephrons are progressively lost with ageing. It is argued that a lower starting number is associated with an earlier loss of functional capacity.

Autopsy studies strongly suggest an association between nephron number and birthweight (Hughson *et al.*, 2003) and investigations of Australian aboriginal populations suggest that poverty is a driver of lower nephron number and disease (Singh & Hoy, 2004). Animal studies confirm that nephron number is extremely sensitive to maternal undernutrition and can be constrained by food restriction, protein restriction or iron deficiency during nephrogenesis (Langley-Evans *et al.*, 1999; Swali *et al.*, 2011). There is also evidence of remodelling being associated with maternal nutritional insults in the brain (Plagemann *et al.*, 2000) and pancreas (Snoeck *et al.*, 1990) but only in animals.

The conditions that appear to be programmed *in utero* are exclusively diseases that have their onset in middle-age or the later years. This suggests that key features of tissue remodelling are the depletion of functional reserve, as illustrated in the case of the kidney above, and a susceptibility to more rapid loss of functional units. There are numerous examples in animal studies that suggest a greater susceptibility to oxidative injury and senescence in the offspring of mothers that were undernourished in pregnancy (Jennings *et al.*, 2000; Langley-Evans & Sculley, 2005, 2006; Tarry-Adkins *et al.*, 2013).

Remodelling of tissues is not a simple response to a lack of substrate, or endocrine signals from mother to

 

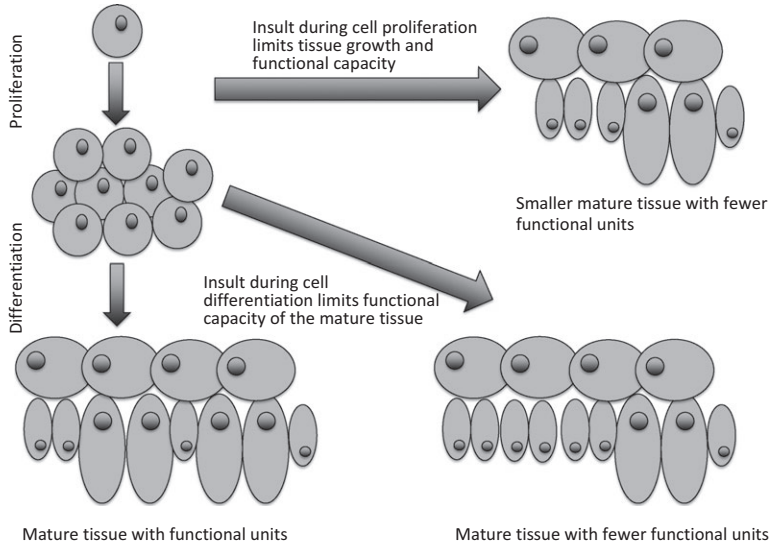


**Figure 2** The basis of tissue remodelling. The development of tissues depends on an ordered pattern of cell proliferation from early progenitor cells, with later differentiation of the tissue precursors to form the specialised cell types and functional units responsible for tissue function. Tissue development is therefore associated with waves of cell division, apoptosis and differentiation to achieve the mature structure. Remodelling of tissues will occur if environmental factors, including signals of less than optimal nutrition, impact upon the proliferation and differentiation phases, resulting in tissues that are smaller (or of normal size) but with fewer functional structures and hence limited capacity to withstand age-related degeneration.

foetus indicating a sub-optimal environment. The process inevitably involves changes in these signals, eliciting changes in gene expression that impact upon tissue development. The programming literature now contains innumerable reports of long-term gene expression changes in response to an early-life insult; for example, altered expression of the genes involved in hepatic glucose handling following intrauterine exposure to maternal overfeeding in the rat (Erhuma *et al.*, 2007; Bayol *et al.*, 2010). In humans, there are fewer such reports and, in most cases, it is impossible to ascribe causal relationships between gene expression and outcome. For example, Díaz *et al.* (2013) reported that placental expression of pre-adipocyte factor 1 was inversely correlated with infant fat mass at age 1 year. Similarly Lewis *et al.* (2012) reported that placental expression of Pleckstrin homology-like domain family A2 was related to bone mass in 4-year-old children. These studies provide potentially useful predictive biomarkers for disease but do not cast significant light on how maternal nutritional status elicits programming responses. The state of research in humans in this context is far less advanced and convincing than the environment–polymorphism interactions described above.

Although of interest in terms of exploring how longer-term disease states are driven by early-life nutrition, these reports do not provide a strong basis for determining the initial drivers of programming. It is likely that, in the face of intrauterine nutrient excess or deficit, a number of changes occur in gene expression that are very short-term but sufficient to perturb tissue development irreversibly. There is emerging evidence to suggest that genes controlling the cell cycle and DNA replication (hence the proliferation phases of organ development) may be particularly susceptible to influences of maternal undernutrition (Fig. 2) (Swali *et al.*, 2011, 2012).

Although other potential mechanisms cannot be ignored, influences of epigenetic factors (e.g. DNA methylation and histone modifications) are considered to play an important role in developmental programming of disease (Burdge *et al.*, 2007). DNA methylation provides an important mechanism for gene silencing, whereas modifications of histone proteins can either allow gene transcription or silence expression (Jaenisch & Bird, 2003). Environmental challenges in early life, including under- or over-nutrition, are likely to affect DNA methylation significantly because, during the very early phases of embryo development, DNA methylation is extensively reprogrammed. Differences in methylation were found at the IGF2 locus between individuals exposed to the Dutch famine and their unexposed siblings (Heijmans *et al.*, 2008). A rapidly increasing body of evidence from both animal and human studies show that the epigenome is sensitive to nutrition during foetal and adult life (Sharif *et al.*, 2007; Sinclair *et al.*, 2007; Lillycrop *et al.*, 2008; Bogdarina *et al.*, 2010).

Effects of early nutrition upon the epigenome are likely to have a number of significant effects upon later health and wellbeing. First, epigenetic marks control gene expression and this means that even transient nutritional

 

exposures could leave an epigenetic memory within cells, which will then govern how genes are expressed in response to further environmental cues. Second, the state of the epigenome is not entirely stable throughout life. As epigenetic drift occurs, patterns of gene expression within tissues can change and this has been linked to certain cancers and Alzheimer's disease (Fraga & Esteller, 2007; Wang *et al.*, 2008). The nature of age-related drift may be partly mediated by early-life events and the state of the epigenome in infancy. Finally, it is assumed that changes to the epigenome may be heritable and this could explain why programming effects of nutrition can persist over several generations and be passed down the male line.

## Conclusions

Although heavily reliant on findings from retrospective cohort studies and experiments with animals, there is an overwhelming body of evidence to demonstrate that nutritional influences encountered during early life have a lasting impact upon health and well-being. The potential impact of these findings for public health is huge because pregnancy and early infancy represent windows of opportunity during which parents are most willing to adopt lifestyle changes that could have health implications across multiple generations. There is a need for greater understanding of the processes involved in early-life programming to refine advice given to women who are pregnant or planning a pregnancy and mothers with young children. The recognition that lifestyle factors impacting upon health are operant from the moment of conception has profound implications for the way in which we regard the aetiology of disease and should be a factor incorporated into any future use of genomic or epigenomic information as a basis for personalised nutritional advice.

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