

Metabolic Disease: Evolutionary, Developmental and Transgenerational Influences

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Introduction

There is a rising incidence of metabolic syndrome (non-insulin-dependent or type-2 diabetes, obesity and cardiovascular disease) in both the developed and developing worlds. It is generally assumed that this rapid increase is simply a reflection of the marked change in dietary and exercise behaviors of children, adolescents and adults. These factors play a dominant role, but other factors must be involved to explain the changing pattern of disease. This chapter reviews the growing evidence that the developmental and environmental history of both the individual and his/her population are important factors.

The first suggestion that there may be early life determinants of later disease came from Forsdahl [1] who reported that the risk of arteriosclerotic heart disease was enhanced in those who had experienced a poorer environment as infants. However, it was the retrospective epidemiological studies of Barker [2] and his colleagues that suggested that the intrauterine and infant environments might have major influences on the later risk of disease. They proposed that certain events in prenatal life ‘programmed’ postnatal physiology in such a way that adult type-2 diabetes (T2D), cardiovascular heart disease, and central obesity were more likely. This conclusion generated controversy, but subsequent work has confirmed many elements of the original hypothesis. We now view the processes of developmental plasticity as underlying a set of responses that generally operate to enhance the organism’s adaptive potential. This chapter will review the background and place this concept within its clinical context.

Developmental Processes and Disease Risk

While the pattern of development is genomically determined, a range of phenotypes can develop from one genotype. Environmental stimuli induce changes in the body's structure and function at critical stages during development. For example, in the spade toad, metamorphosis from a tadpole can be accelerated as pond levels decrease [3]; this may assist survival, but can have a later cost in terms of reproductive fitness – this is an example of a biological ‘trade-off’ arising from a developmental choice.

The Embryonic and Fetal Period

In mammals, the pre-embryo, embryo and fetus all have the potential to sense aspects of their environment and respond to it. For example, ruminant embryos maintained *in vitro* develop a different allocation of cells to inner cell mass and trophectoderm when compared to allocation *in vivo*, leading to the large offspring syndrome [4]. The many homeostatic physiological responses of the developing fetus are well described – for example the reduction in visceral blood flow in response to asphyxia to protect the heart and brain, even though if prolonged it is associated with asymmetrical intrauterine growth retardation.

Some developmental plastic responses are probably similarly adaptive *in utero*. For example, the reduction in nephron number in fetuses exposed to maternal undernutrition reduces energy investment in nephron differentiation at a time when nephron development has no immediate advantage [5]. On the other hand, it may simply be that the environmental effect is disruptive and teratogenic and has no adaptive value. However, other fetal responses, while having less obvious immediate adaptive value, may confer advantage later in life – these are predictive adaptive responses which will be discussed further later [6].

A fetus in late gestation responds to a deprived environment by reducing its growth, or if the insult is very severe, by initiating premature labor. As fetal energy provision is entirely dependent on maternal and placental physiology, the fetus must reduce anabolism and, under some circumstances, increase catabolism [7]. Prolonged fetal undernutrition may be associated with permanent changes in fetal growth capacity, whereas short-term growth impairment is followed by catch-up growth. In addition, periconceptual changes in nutrition may alter the late gestational growth rate of the fetus and its sensitivity to later nutritional challenges [7]. The implications of this recent finding are important – in late gestation fetal growth rates may reflect past experience, not just the current environment.

Birth size is the consequence of a complex series of interactions between the fetal genome and the fetal environment. In turn, the fetal environment is largely generated by maternal factors (both genomic and environmental) and by placental function. From their cross-breeding experiments, Walton and

Hammond [8] were the first to suggest that maternal, rather than paternal, factors determined birth size and subsequent embryo transfer experiments have shown that maternal effects are not genetic in origin. Morton [9] and others have shown that there is a greater correlation between birth weights of half-sibs with a common mother, than half-sibs with a common father, and recent studies on infants born after oocyte donation similarly suggest the importance of maternal phenotype [10]. There is a strong correlation between maternal and offspring birth weights, which may be due to effects mediated by the size of the mother's reproductive tract, as well as by genetic influences. In general, estimates suggest a higher environmental than genomic contribution to birth weight variation [11].

Evaluation of the epidemiological evidence linking birth weight and the risks of subsequent T2D can be evaluated against this background. The original studies of Barker [2] showed an inverse relationship between birth size and the subsequent risks of developing insulin resistance (IR) or T2D [12]. Such observations have now been extensively replicated, although few studies use the end-point of clinical disease. Where the end points were a surrogate measure of disease (e.g., systolic blood pressure), the relationships have been weaker; failure to recognize this point has led to unnecessary controversy [13]. More recent studies show a U-shaped relationship between birth weight and metabolic disease [2, 14, 15], presumably reflecting the impact of gestational diabetes in the upper birth weight cohort.

These studies also show relationships with other measures of the metabolic syndrome, including hypertension, cardiovascular disease, hyperlipidemia and, of particular interest, truncal obesity. There is an increased incidence of central or truncal obesity in those born of smaller birth size [16, 17]. Interestingly, first-born children tend to be smaller at birth due to increased maternal constraint (see below) – and first-borns become relatively obese compared to siblings [18]. Both monozygotic and dizygotic twins have a greater risk of IR in childhood. Both twins in a pair are similarly affected independent of birth size, reflecting increased maternal constraint in both [19].

Postnatal Factors

There is an interaction between prenatal exposure and the postnatal environment in creating disease risk. Whether these are independent or interdependent effects are not clear. Studies in Finland and India suggest T2D/IR is most likely in children born small who gain weight rapidly and early in mid-childhood [20, 21]. This relationship is clearly shown in experimental studies. Rats undernourished in utero and then placed on a high fat diet post-weaning show clear evidence of synergism between the effects of prenatal undernutrition and the postnatal high fat diet in determining adult insulin sensitivity, fat deposition (fig. 1) [22] associated with reduced muscle mass, impaired voluntary exercise and increased lethargy [23].

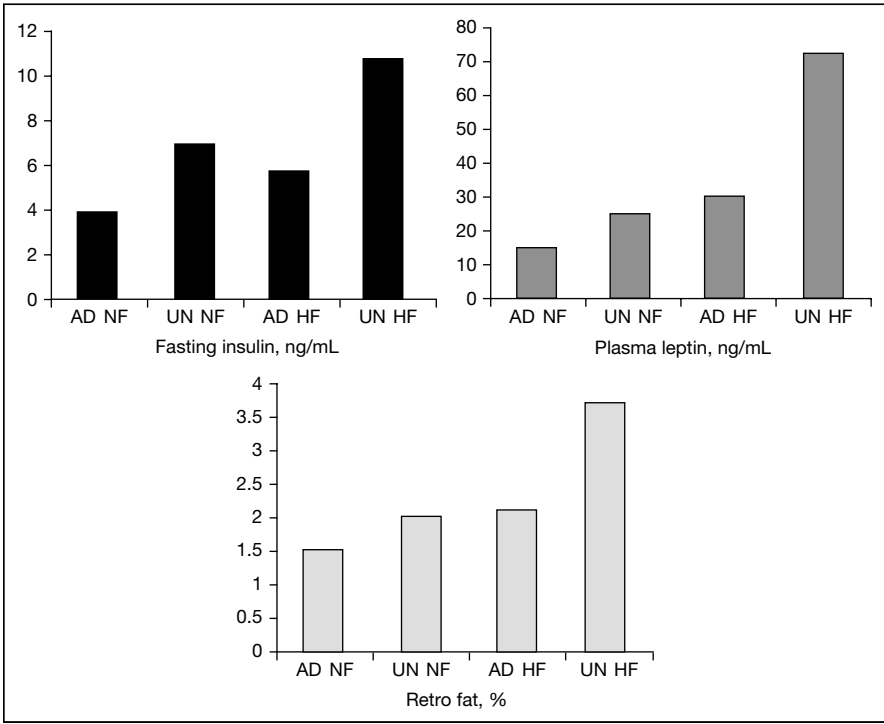


Fig. 1. Evidence that the prenatal gene–environmental interaction determines the impact of postnatal nutrition. Pregnant rats were fed ad libitum (AD) or undernourished throughout pregnancy (UN; 30% of an ad libitum diet). At birth, their pups were cross-fostered to ad libitum (‘normal’) rats until weaning, at which time the pups were placed on normal (NF) or high fat (HF) diets. Fasting insulin, leptin levels, and retroperitoneal fat pads were measured on day 125. Both prenatal undernutrition and postnatal high fat diets have independent effects on all three measures ($p < 0.001$), and for each there is a marked interaction between the prenatal and postnatal diet demonstrating a synergistic effect ($p < 0.001$). Data from Vickers et al. [22].

The period immediately after birth may be a further period in which ‘programming’ might occur – indeed the term was introduced by Lucas [24] following studies on the long-term consequences of different forms of infant feeding. Follow-up of these infants suggests that higher nutritional intake in preterm infants, which may benefit brain development, may also lead to a greater risk of IR [25].

Underlying Mechanisms

The phenomenon is easy to induce in a range of experimental animals by either manipulating maternal nutrition [22] even prior to conception [26] or

administering glucocorticoids to the mother [27]. In rodents, the progeny develop obesity with abnormalities of appetite regulation, hyperphagia, central obesity, reduced muscle mass, diminished exercise willingness and increased lethargy [22, 23].

It has been known for many years that growth-retarded fetuses have abnormalities of both insulin secretion and insulin action, and insulin is both a direct and indirect (through controlling the release of IGF-1) mediator of fetal growth [28]. Some of the mechanisms described include increased apoptosis of pancreatic β -cells, decreased expression of the pancreatic transcription factor *Pax*, and multiple abnormalities of components of the signal transduction pathway by which insulin affects GLUT-4 action [29]. Other factors may include reduced skeletal muscle mass [21], and changes in the ratio of gluconeogenic to glycolytic enzyme activity in the liver associated with altered hepatic zonation [30].

Attention is now focusing on nutritionally or hormonally induced epigenetic change as the basis of these changes. Both imprinted and non-imprinted genes can be affected. As the most common pathway for epigenetic change involves altered methylation of DNA [31], it is not surprising that preliminary evidence points to a possible role of folate and glycine intake (which influence methyl group provision) in mediating developmental nutritional influences [32, 33]. This is a currently an area of active enquiry.

The nature of the effector mechanism may well be affected by the timing of any insult depending on critical developmental windows. Both the pre-implantation embryo [34] and perhaps the pre-ovulatory oocyte are targets for developmental epigenesis, but the long-term effects will depend on the critical window of development in which the exposure takes place.

Transgenerational Effects

IR and T2D are known to cluster in families and populations – this does not inevitably mean that they are purely genetic effects. Maternal effects on the offspring are well described in the comparative literature [35, 36]. Following the Dutch famine, the grandchildren of women exposed to the famine were also born smaller, suggesting that transgenerational environmental influences act in humans [37]. This aligns with comparable data in the rodent experimentally undernourished in utero [38]. There are two possible mechanisms – that of epigenetic change or effects on the reproductive tract of the F1 generation which in turn impacts of the growth of the fetal F2 generation. There are clinical data supporting the latter – the reproductive tracts of girls born small are growth impaired [39]. Thus, a cycle can be set up by which a fetus born small in one generation will, regardless of their postnatal growth, give birth to offspring exposed to a restricted fetal environment (fig. 2).

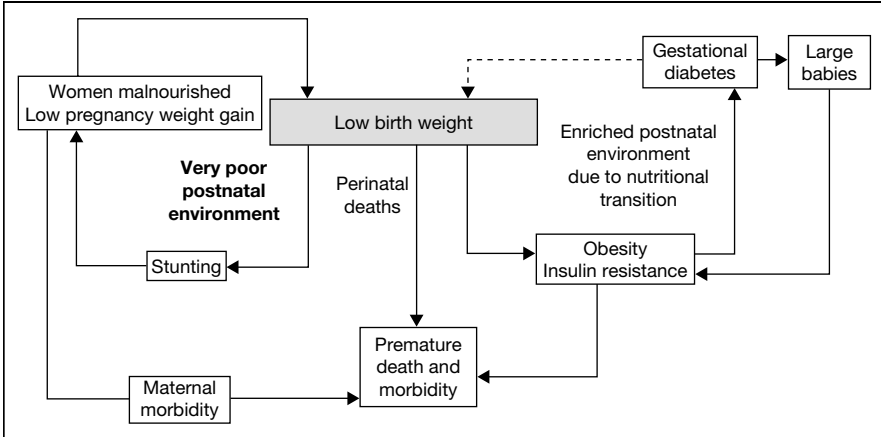


Fig. 2. The consequence of low birth weight on the life course is dependent on the postnatal environment. The left hand cycle shows the repetitive cycling of low birth weight between generations in very deprived populations; the right hand cycle shows the problems that arise with rapid nutritional transitions that lead to insulin resistance and obesity and its consequences in adulthood.

An Evolutionary Perspective

In assessing the importance of this phenomenon it is useful to consider why it has persisted through evolution of the modern human despite conferring disadvantages in later life. The thrifty genotype hypothesis developed by Neel [40], and later extended to explain the incidence of T2D in modern society, suggested that in the Neolithic period genes were selected that enabled our ancestors to cope with the hunter-gatherer life style and its phases of feast and famine, in one way by conferring a tendency to lay down truncal fat. Others had suggested that genetic drift and the bottlenecks formed during human migration further assisted the selection of genes favoring IR [41]. It was suggested that these genes favoring IR could act in utero to limit fetal growth and independently affect the postnatal risk of disease [42]. Whilst undoubtedly true in some cases (e.g., studies of glucokinase polymorphisms), such explanations cannot explain the extensive experimental findings in animals or those made following the Dutch famine. Moreover, the studies by Eriksson et al. [43], on individuals with the PPAR γ 2 polymorphism which predisposes to T2D, demonstrate that its effect is restricted to those born small and has no effect in those of normal birth size, essentially arguing against the thrifty genotype hypothesis. Hales and Barker [44] developed the alternate ‘thrifty phenotype’ hypothesis to argue that the responses made by the fetus to a deprived environment (e.g., growth retardation, IR) would have advantage in a deprived postnatal environment.

The predictive adaptive response (PAR) model is a synthesis of these two concepts in a more general framework [45]. While some components of postnatal ‘programming’ may be the capricious outcome of developmental trade-offs having an adaptive advantage in utero, the primary reason for the persistence of the phenomenon through evolution has been due to the postnatal adaptive value of PARs [45]. These are responses made by the embryo and fetus that need not have any immediate value, but create long-term advantage. One example is the altered stress response of the arctic snowshoe hare born to a mother in a stressed environment where there is a high predator density [46]. The leverets are born with a similarly enhanced stress response, which confers no intrauterine advantage, but makes them more vigilant as adolescents, aiding survival.

We propose that the fetus is constantly sensing maternal signals transduced by the placenta that inform it about the external environment. From this, it predicts its postnatal environment and makes adjustments to its physiological set points accordingly. These adjustments occur through the processes of epigenetic mechanisms and developmental plasticity, and are essentially irreversible. As a result, the fetus establishes its physiology for a range of predicted postnatal environments. If the actual postnatal environment does not match that predicted, then the risk of disease is enhanced because the pre-set physiological homeostasis is inappropriate. While PARs operate in many physiological systems, including thermal [47] and osmolar regulation [48], those of particular interest relate to nutritional, metabolic, and cardiovascular homeostasis.

Nutritional and/or hormonal signals inform the developing fetus of its likely postnatal nutritional environment. If it predicts a more constrained environment postnatally, then the appropriate adaptive responses are to invest in mechanisms that might promote fat storage and reduce metabolism and growth. If the postnatal environment is indeed poor, the organism will cope and have a greater likelihood of surviving to reproduce. If in fact the postnatal environment is relatively enriched then, with these adaptations, the organism may become obese, IR, and may have a lower chance of reproductive success. Such mechanisms are non-directional and evolved to allow a diversity of genotypes within a population to survive transient environmental change [45].

In the modern human, fetal growth is still constrained because uterine environmental factors are the dominant determinants of birth size. However, the postnatal environment is dramatically different from that in which hominids evolved and thus there is more likely to be a discrepancy between the predicted and actual postnatal environments. Such a discrepancy will be enhanced if fetal growth is impaired by maternal or placental disease or by excess constraint; it will also be enhanced if the postnatal environment is particularly energy-rich due to high energy food availability and lower energy expenditure. Therefore, the constrained environment of the human fetus

makes it inevitable that as the postnatal environment becomes richer, there will be a rapid rise in metabolic disease.

Gestational Hyperglycemia and Maternal Diabetes

Gestational diabetes also has fetal effects. In this situation maternal hyperglycemia leads to fetal hyperglycemia, hyperinsulinemia, and increased adipogenesis. The increased fat mass puts the progeny, in turn, at greater risk. In the neonatal rat fed a high carbohydrate formula, the islets develop with a relative deficiency of α -cells, increased apoptosis, and decreased IGF-2 expression [49]. This might suggest that perinatal hyperglycemia has direct developmental effects on the pancreatic islet with long-term effects due to the ensuing developmental disruption. Experimentally induced maternal diabetes also leads to progeny with peripheral IR [50].

In populations such as India, the combination of maternal constraint (due to small maternal size) and the legacy of programming, which occurred when the mother herself was growth-restricted as a fetus, may put the offspring in the situation of being both relatively small and yet hyperinsulinemic [21]. This manifests as relative fatness in the otherwise small infant. Both factors put the infant at particular risk of subsequently developing IR and early adiposity.

Implications of the Developmental Origins of Disease Concept

These considerations may provide an explanation for the rapid explosion of metabolic disease in young adults in societies undergoing rapid nutritional transition – for example in migrant populations or in those moving from rural to urban environments. If maternal constraint is a further factor, as suggested above, then the situation in China may be of increasing concern given the large number of single-child families. In such populations, there is the combination of increased maternal constraint due to primiparous pregnancy and a tendency for parental over-investment in the offspring.

The PAR model relates to relative rather than absolute levels of nutrition. Thus, these considerations apply equally in developed societies. A mismatch between the fetal prediction and the actual postnatal environmental mismatch can occur at any level of intrauterine nutrition if the postnatal environment is sufficiently enriched. Experimental data support such a conclusion [22, 23, 51].

While attention to appropriate postnatal physical exercise levels and diet are clearly essential in reducing the global burden of metabolic disease, a developmental view is valuable in placing various strategies in perspective. Clearly four elements are important in determining an individual's risk of developing metabolic disease: genotype, developmental events, postnatal environment and behavior, and the population history.

A key understanding from this modeling is that it is not the absolute levels of dietary intake and energy expenditure that determine risk, but rather how consistent these are with the developmental prediction. Additionally, it would appear that individual risk is influenced by the nature and speed of the nutritional transition that has taken place over recent generations in the individual's population.

The PAR theory also has broader implications. On one hand, it may be that epigenetic, rather than genetic, inheritance explains the apparent clustering of metabolic disease in populations and family linkages. On the other, it implies that rapid correction of this cycle of low birth weight is not possible; indeed, a rapid transition to a postnatal environment of excess is associated with exacerbation of disease risk in the short term (fig. 2). Whether or not it is feasible to intervene with the PAR processes after they have been induced is not known; experimental studies are only starting to address this now. Progress may depend on gaining a better understanding of the triggering processes operating in early pregnancy. While these are yet to be proven, there is much interest in the role of micronutrients influencing methylation and clinical trials of periconceptional supplementation are now starting. Although the history of micronutrient supplementation in established pregnancy has been disappointing, the rationale for periconceptional intervention is compelling, even if it will be difficult to design the optimal intervention.

Final Comments

There has been controversy about the biological plausibility and relative importance of the developmental origins of disease theory as an explanation of the rising incidence of T2D and related metabolic disorders. However, the weight of experimental data adds enormously to the compelling epidemiological data. Studies of developmental plasticity and epigenetic inheritance provide a possible mechanistic basis for future work. Evolutionary theory provides general biological plausibility. The relative importance of the prenatal environmental exposure relative to postnatal life style events is still unclear, but the animal data suggest that the prenatal environment is a major determinant of the strength of the postnatal environmental interaction. It is safe to conclude that prevention of T2D, obesity and IR in both developed and developing countries will need to extend to consideration of the health of women of reproductive age and to their unborn and newborn children.

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