Developmental Mismatch – consequences for later cardio-respiratory health

Running title: Developmental mismatch & cardio-respiratory health

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Abstract

Clinical and epidemiological studies have established that people who were small at birth and had poor infant growth have an increased risk of adult cardiovascular and respiratory disease, particularly if their restricted early growth is followed by accelerated childhood weight gain. This relationship extends across the normal range of infant size in a graded manner. The 'mismatch hypothesis', proposes that ill health in later life originates through developmental plastic responses made by the fetus and infant; these responses increase the risk of adult disease if the environment in childhood and adult life differs from that predicted during early development.

Introduction

There is now substantial epidemiological evidence that environmental influences acting during development can induce plastic responses in the fetus and infant, predisposing to disease and ill health in later life. In this review we outline some of the evidence that ill health in adulthood originates from a mismatch between the developmental and later environments. We discuss common mechanisms by which maternal diet, body composition and lifestyle may affect cardiovascular and respiratory function. Finally, we consider the possibility of developing therapeutic interventions based upon the mismatch hypothesis.

The 'developmental origins of health and disease' hypothesis originated from the observation that regions in the UK that had high infant mortality in the early twentieth century also had high death rates from coronary heart disease and respiratory disease sixty or so years later[1]. Follow up of individuals whose weight had been documented at birth led to the discovery of associations between lower birthweight and increased rates of cardiovascular and respiratory disease in adulthood[2,3]. These findingshave been extensively replicated worldwide[4]. Moreover, early life developmental processes are now held to contribute to other causes of chronic ill health, including type 2 diabetes, osteoporosis[5], affective disorders[6] and some forms of cancer[7].

The original association between lower birthweight and cardio-respiratory disease was graded across the normal range of birthweights and did not simply depend on infants born prematurely or those with intrauterine growth restriction[2,3,8]. Studies in laboratory and farm animals have provided clear evidence that the intrauterine environment influences the biology of the offspring and have advanced our understanding of the mechanisms underlying these phenomena[9]. The process

whereby an early environmental influence induces metabolic or endocrine changes in later life is sometimes referred to as 'programming' or 'developmental induction'.

While initial work concentrated on fetal life, subsequent studies demonstrated that the sensitive periods during which the early environment can have long lasting effects on the offspring encompass the time from conception, through gestation and into postnatal life. People at particular risk of cardiovascular and metabolic disease in adult life are those in whom restricted fetal and infant growth was followed by accelerated childhood weight gain and upward crossing of weight centile lines[10].

Confounding influences and the size of the mismatch effect

An early criticism of the developmental origins hypothesis was that the link between birthweight and adult disease could be explained by continuation into adulthood of the adverse events that had caused growth restriction. However, there is now strong evidence against this argument. In several studies, data on adult lifestyle factors, notably smoking, employment, diet, alcohol consumption and exercise were collected; allowing for these lifestyle factors had little effect on the association between birthweight and coronary heart disease[11]. It has also been argued that the associations between size at birth and later disease could primarily reflect genetic influences. However, birth size is principally determined by the quality of the intrauterine environment[12]. Finally, the strength of the relationship between birthweight and outcomes such as childhood blood pressure has been questioned; associations are, however, stronger for adult hypertension than they are for childhood blood pressure.[13] Moreover, epidemiological and experimental evidence suggests that the factors that affect developmental plastic responses in utero include maternal diet, body composition and endocrine status, and birthweight is a crude proxy for these exposures. . There is increasing

evidence for transgenerational effects, whereby the mother's own birthweight may influence the long-term health of her offspring[14].

Conceptual Basis

The consistency of the long-term effects of developmental plastic responses across species and within the normal range of fetal growth suggests a physiological rather than a pathological basis to the developmental origins phenomenon. It has been proposed that the link between early life environment and adult disease may have an underlying evolutionary explanation. The predictive adaptive responses (PAR) hypothesis suggests that there is an evolutionary advantage if the developing organism can predict conditions in the postnatal environment and can then alter its development to optimise its survival in the predicted environment[15]. This approach may increase the chance of survival to reproductive age, even if there are adverse long-term health consequences. Data on human reproductive function support the PAR theory[16].

The PAR theory suggests that the long-term consequences may be especially harmful if there is a 'mismatch' and the postnatal environment differs from that predicted (Figure 1). 'Mismatch' is a conceptually important link between maternal influences upon developmental plastic responses and the long-term health consequences for the fetus[17]. This may be a particular problem in societies where there is a rapid economic or social change. Inappropriate developmental adjustments may manifest following a rural to urban transition, for example, if there is a rapid change from a high exercise, low nutrition environment to one with low exercise and high nutrition8. Similarly, maternal disease or impaired placental function could lead the fetus to adjust its development inappropriately[19,20]. 'Mismatch' may occur between the fetal nutrient demand, largely determined by the early fetal growth trajectory, and the materno-placental capacity to meet this

demand. Moreover, maternal influences may act via alterations in the fetal endocrine milieu or the placental vasculature, to effect developmental plastic responses, which effectively 'mismatch' the fetus to its adult environment.

A fundamental tenet of the concept is that developmental mismatch will affect the responses of the offspring to a subsequent environmental challenge. This has been demonstrated in studies of sheep, in which poor antenatal nutrition induced a phenotype best suited to similar poor postnatal nutrition, suggesting that there was a prenatal "prediction" of the postnatal environment;[21] if the antenatal prediction was not reflected in the postnatal environment, left ventricular hypertrophy and increased coronary artery vascular reactivity were induced in adult life.[21] it is thought that fetal responses to changes in maternal nutrition may be of immediate benefit to the fetus, but the long-term effects of these adaptations may prove detrimental if nutrition in postnatal life does not match that predicted by the fetus on the basis of its intrauterine environment.

Mechanisms

The mechanisms underlying the developmental mismatch hypothesis have been investigated using a variety of animal species. The advantages of animal experimentation are that a defined antenatal challenge can be administered and the offspring can be studied in utero or at various postnatal ages. The challenges used have largely been unbalanced maternal nutrition or glucocorticoid administration. The phenotypic outcomes resemble those reported in humans from epidemiological studies. These studies suggest that significant developmental mechanisms act at four broad levels: 1) epigenetic processes, 2) mitochondrial function, 3) changes in the development of specific organs or tissues and 4) effects on homeostatic control systems.

Epigenetic processes

An epigenetic modification is one that does not alter the heritable DNA sequence but does affect gene expression. DNA methylation is the best understood epigenetic modification and maternal diet has been shown to cause specific changes in DNA methylation in the offspring. Maternal protein restriction in the rat alters DNA methylation of the glucocorticoid receptor and peroxisomal proliferator-activated receptor alpha (PPARα) genes in the offspring, changing their expression, and altering the expression of other genes controlled by these transcription factors (Figure 2)[22]. These genes are of particular interest because alteration of their expression is associated with perturbation of cardiovascular and metabolic control.[23] The methylation changes are accompanied by alterations in histone methylation and acetylation, which similarly change gene expression. Maternal dietary folate supplementation prevents the epigenetic modification associated with maternal protein restriction in these rats[22].

During gametogenesis, and in the preimplantation embryo, there is considerable de-methylation and re-methylation, and these may be critical windows for the establishment of epigenetic modification. Furthermore, there are graded changes in the epigenetic control of some genes during development, providing the opportunity for environmental influences to act via them[24]. The DNA methylation and histone acetylation processes underlying epigenetic control of gene expression require the folate-dependent the transfer of one-carbon groups, predominantly from glycine, a non-essential amino acid but one for which the fetal requirements are very large in late gestation. In pregnant rats fed a low protein diet, supplementation of the dam with glycine prevents hypertension and endothelial dysfunction in the offspring[25].

One of the most striking phenomena in this field is that phenotypic effects can be induced by nutritional and other environmental challenges in early gestation in a range of species[26-29]. Such effects underline the possible influence of epigenetic processes in the embryo, and also raise issues about the long-term consequences of assisted reproductive therapies in which a period of embryo culture in exogenous media occurs.

Altered mitochondrial function

Mitochondria are central to metabolic control and hence it is not surprising that mitochondrial function may be set to match the predicted later metabolic demands. Mitochondrial DNA is susceptible to environmental effects, which could produce changes in mitochondrial copy number. Such epigenetic effects may occur as a consequence of changes in mitochondrial DNA methylation, by the effects of pro-inflammatory cytokines, or via the effects of reactive oxygen species. Changes in mitochondrial DNA are passed via the female line to future generations, thereby offering the possibility of a trans-generational process for induction of phenotype. Support for this has recently been gained via studies in which animals were bred over 11 generations to select for reduced exercise tolerance. The animals then showed all the components of the human metabolic syndrome and underlying defects in mitochondrial function[30]. Impaired mitochondrial function in the offspring of rats fed a high fat diet during pregnancy is coupled with insulin and leptin resistance and relative insulin depletion of the pancreatic islets[31].

Organ structure and composition

A range of experimental studies and human observations has shown that a severe reduction in nutrient and oxygen supply differentially affects the growth and development of organs and tissues. This may occur because those not essential to fetal survival are sacrificed. Organs affected

include the lungs, kidney, gut and liver[32]. However, in the face of a milder challenge changes in fetal tissue or organ development may occur as part of a strategy to tune phenotype to the predicted post-natal environment, based on nutritional and endocrine cues from the mother. Examples for which there is strong experimental and preliminary human evidence include reductions in capillary density, skeletal muscle growth and nephron number which would reduce nutrient demands postnatally[17]. The fetal strategy may include promoting the growth of other tissues, such as adipose tissue, to buffer anticipated nutrient scarcity[33].

Resetting of homeostatic control

Clinical and experimental studies provide evidence for developmental changes in the homeostatic set-points for many hormones and for alterations in tissue sensitivity to these hormones. An example of resetting of homeostatic control with direct relevance to the developmental origins of cardiovascular disease is the influence of nutrition and stress on placental 11-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity. This enzyme plays an important role in protecting the fetus from high levels of circulating glucocorticoids in the mother. Mothers who report dieting before pregnancy have decreased placental 11β-HSD2 activity at term[34]. In rats, reduced placental 11β-HSD2 activity is associated with increased blood pressure in the offspring during adult life[20]. In the rat, low placental 11β-HSD2 activity may lead to premature activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis. If a similar mechanism operates in human pregnancy, this could explain the relationship between maternal influences and alterations of adrenocortical function in the offspring.

Alterations of the fetal HPA axis and sympathoadrenal responses are likely to be an important mechanism by which developmental exposures affect the subsequent responses of the offspring to

stressful challenges. Lower birthweight has been linked with increased fasting cortisol concentrations in later adult life[35]. Moreover, studies of children whose antenatal growth was restricted demonstrate alteration of adrenocortical responses to stress in boys and basal adrenocortical activity in girls[36]. Similar gender differences in HPA responses have been reported in animals. Given the known associations between small alterations in adrenocortical activity and features of the metabolic syndrome, these effects may have important health implications. The maternal influences underlying developmental effects on HPA and sympathoadrenal responsiveness remained to be defined, but there is evidence that both maternal diet (Figure 3) and stress in pregnancy may be important.[37, 38]

Developmental origins of respiratory disease

It has been hypothesised that subtle influences on fetal lung and immune development could have an important impact on the risk of asthma and chronic obstructive airways disease throughout life. Epidemiological studies provide strong evidence that a suboptimal intrauterine environment can affect postnatal respiratory health. Indeed chronic obstructive airways disease was one of the original disorders for which such studies suggested an important developmental influence[3,7]. Although difficult to separate from antenatal effects, adverse factors in the early postnatal environment, such as tobacco smoke, could additionally lead to persisting alterations in lung structure and function[39, 40].

Lung function

It has been suggested that maternal smoking during pregnancy may cause impaired infant lung function[41]. There is reason to suspect that maternal diet and nutrition before and during pregnancy may also affect fetal lung development[3]. Independently of maternal smoking, children and adults

who were small at birth tend to have reduced lung function and an increased risk of respiratory morbidity and mortality. Clinical studies have found that, independently of their current weight, infants who had a lower birthweight tend to have impaired lung function[42]. Moreover, greater postnatal weight gain is also associated with impaired infant lung function (Figure 4). Accelerated postnatal weight gain following lower birthweight may well translate into later obesity and explain the relationship between obesity and asthma.

The mechanisms by which poor fetal growth affects lung function are open to conjecture, however, animal and human studies suggest that micronutrients may be important in airway development during fetal life and childhood. It is recommended that pregnant women avoid foods rich in vitamin A because of concerns about teratogenicity. However, this vitamin is involved in normal embryonic lung development, including alveolisation[43, 44], and in maintenance of lung function[45]. Additionally, rats deficient in vitamin A develop respiratory problems in early life[46]. A reduction of between 30 and 60 percent of blood retinol levels in rats leads to reduced surfactant phospholipid production[47]. This effect is thought to be due to impairment of surfactant protein gene expression[48]. Surfactant proteins serve to increase lung compliance and have an additional role in immune defence of the airway. If these roles also occur in humans then vitamin A deficiency may contribute to both respiratory distress syndrome and to an increased susceptibility to infection. Additionally, data from the ALSPAC birth cohort have suggested an association between low selenium status in utero and persistent wheeze in childhood[49].

Lung structure

Although the mechanisms linking early lung development with lung function in later life are unknown, impaired airway and alveolar growth may be important. Airway branching is complete by

16 weeks gestation, and alveolar formation begins before birth. Between birth and 18 months of age there is a rapid increase in alveolar number and size, whilst airway diameter continues to grow. Environmental influences during both antenatal and early postnatal life therefore have the potential to affect lung development.

Atopy and asthma

Normal pregnancy is characterised by a suppression of maternal cell-mediated responses to feto-paternal antigens. This is predominantly effected by a switch to a dominant humoral immune response. Tissues of the feto-placental unit secrete cytokines similar to those associated with a T-helper-2 (Th2) response. These cytokines promote ongoing pregnancy and are also thought to have additional properties in terms of promoting fetal growth[50]. Several studies have suggested that high rates of fetal growth are associated with the development of atopy[51, 52], and a larger head circumference at birth and higher birthweight have been linked with elevated serum total IgE in adulthood[53]. It is possible that aspects of a woman's nutrition, such as high fat mass and high vitamin D status, may alter fetal concentrations of growth factors, such IGFs, TGF-β and EGF, so promoting both fetal growth and the development of atopy[54]. Many immune cells possess receptors for vitamin D and vitamin D biases the immune system towards a Th2 phenotype[55]. Moreover, polymorphisms in the vitamin D receptor gene have now been linked to asthma in two separate studies[56,57]. Preliminary evidence has also linked low maternal intake of the antioxidant vitamin E with elevated responsiveness of cord blood mononuclear cells to allergens[58] and with both wheeze and eczema in the first two years of life[59].

Infants born to atopic mothers are much more likely to develop early onset atopic disease than those born to atopic fathers[60]. This effect could represent a predominantly epigenetic mechanism and there is strong evidence that the intrauterine environment of atopic mothers influences fetal immune development. It is known, for example, that the amniotic fluid of atopic mothers has higher levels of both IgE and the allergy associated cytokine IL10 than that of non-atopic mothers[61].

The past decade has seen the development of the 'hygiene hypothesis'; this hypothesis explains asthma pathogenesis, and that of other atopic disorders, by attributing central importance to developmental processes. It provides another example of the mismatch concept by suggesting that a lack of exposure to infections and microbial products early in life changes the environment in which the immune system responds optimally, biasing it towards an IgE mediated response and thus predisposing to atopy[62].

Maternal influences

Research to date has linked particular maternal influences with the later health of the offspring, notably transgenerational effects of the mother's own intrauterine experience, and her body composition, dietary balance and endocrine status before and during pregnancy. Understanding maternal and early environmental influences on the offspring's developmental plastic responses may allow the design of new interventions to optimise early development and thereby improve health throughout life. While it is too early to make specific recommendations, new public health interventions may arise from further studies examining maternal diet and lifestyle in relation to the offspring's long-term health.

High maternal weight and adiposity are associated with cardiovascular and metabolic disease in the offspring (Figure 5)[8]. There is also strong evidence that the children of mothers with a low body mass index are predisposed to insulin resistance in adult life[63, 64]. While body composition is something that is not easily changed, measurement of body composition may allow us to identify pregnancies that are at greater risk and raises the possibility of targeted interventions.

There is increasing evidence that fetal development can be affected by nutritional variation even within the normal range of western diets, and the problem is compounded because many women constrain their weight by dieting or eat unbalanced diets. Evidence for long-term detrimental effects of an unbalanced high-protein, low-carbohydrate maternal diet has come from Motherwell, UK; as adults, the offspring have elevated blood pressure and heightened cortisol responses to a stress challenge[65]. Apart from diet, there is evidence that maternal exercise, smoking and alcohol intake can have effects on both placental function and fetal development. In one controlled study, women who exercised in early but not late pregnancy had larger babies and elevated placental volume at mid-gestation and term[66]. In women who exercise heavily, the placenta may be able to sense maternal activity levels and adjust its growth to allow it to better compete for nutrients. Maternal smoking is well known to reduce fetal growth and has been shown to affect placental structure[67]. Maternal smoking also has adverse structural and functional effects on the developing fetus with important examples being bone density[68] and lung function[41].

Medical interventions

Where an adverse in utero environment cannot be prevented, it could be possible to treat children from high-risk pregnancies to ameliorate or prevent the long-term effects of such an environment. Rats whose mothers were undernourished during pregnancy have altered appetite regulation and

became obese, an effect which disappears after a single postnatal treatment with leptin, even when the offspring are fed a high fat diet postnatally[69]. Importantly, the effects of leptin treatment on the epigenetic control of genes such as 11β-HSD2 and PPARα are dependent on the antenatal nutrition of the animals[70], demonstrating how the phenotypic responses of the offspring are set in antenatal life. This experiment demonstrates the potential for identifying and treating infants whose in utero environment was suboptimal. Although pharmacological intervention may be possible, it is hard to imagine how the safety of such an intervention could be demonstrated in humans and attention should be focused on lifestyle preventive strategies, allowing the development of public health interventions.

We should also bear in mind that treatments currently in use could have unintended consequences in later life. In particular, there is evidence that antenatal steroids and assisted reproductive technologies have the potential to adversely affect the offspring. Antenatal steroids have obvious and immediate benefits in premature labor where the benefits outweigh concerns about possible increased risk of disease 60 years later. However, given that a single dose of antenatal steroids has been shown to affect glucose tolerance 30 years later, the potential risks of multiple doses of steroids should be kept in mind[71, 72]. Similarly, although the majority opinion is that assisted reproduction in humans is generally safe, not all are on agreement on this point and long-term follow up studies of the offspring should be undertaken.

Practice points

Strategies to improve the development of infants and young children may give the most immediate benefit but improving the intrauterine environment is an important long-term goal. We need to identify public health measures to improve women's body composition before pregnancy, with

avoidance of excessive thinness or overweight. Animal studies suggest that measures to improve maternal nutrition before and during pregnancy can improve the development of the offspring[25], but as yet there is no compelling evidence of benefit from trials in human pregnancy. In infants we need to protect growth in weight, length and head circumference during the first year after birth by good infant feeding practices, avoidance of recurrent infections, and cognitive stimulation. We need to prevent accelerated weight gain among children especially those who were small or thin at birth or at one year. Such an approach may allow us to reduce the prevalence of major chronic diseases and diminish social inequalities in health.

* Fetal growth restriction is a risk factor for cardiovascular and respiratory disease. The risk is graded across the whole range of normal birthweight. Growth restriction is also a risk factor for hypertension, type 2 diabetes, affective disorders, osteoporosis and some cancers in later life.

* Accelerated childhood weight gain and adult obesity exacerbate this risk.

* A woman's diet and lifestyle may have significant long-term effects on the development and health of her offspring. These influences can operate before conception and in very early pregnancy, not just during the major period of growth in late gestation.

* Before birth and during infancy the offspring alters its development in prediction of the environment it will face in later life. If the prediction is accurate it is more likely to remain healthy; if not, risk of disease increases.

* Risk of cardiovascular and respiratory disease increases with a greater mismatch between the early and later life environments. Thus, it is greater in societies in rapid economic transition.

* Animal studies have revealed mechanisms linking unbalanced maternal nutrition, body condition or stress to developmental plastic responses in the offspring. They also show how early interventions can prevent later pathophysiological changes.

* Translating the mismatch concept into initiatives to both promote the health of women of reproductive age and the development of children, has the potential to have an enormous impact on the incidence of chronic non-communicable disease, in both developed and developing societies.

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Figure caption list

Figure 1. Impaired cardiovascular structure and function result in the offspring if the post-natal environment is mismatched to the phenotype induced in development, involving epigenetic modification of gene expression informed by cues from the mother's body composition and diet.

Figure 2. Compared with controls (C), rats whose mothers were fed a protein-restricted diet (R) had lower PPARα gene promoter methylation, associated with higher hepatic PPARα gene expression, and increased expression of Acyl CoA Oxidase, for which PPARα is a transcription factor (derived from reference 22).

Figure 3. Men and women age 30 years have greater salivary cortisol responses to the Trier Social Stress Test if their mother's consumed more meat and fish in late pregnancy (derived from reference 36a)

Figure 4. At age 4-8 weeks, forced expiratory volume in 0.4 sec ($FEV_{0.4}$) is diminished in healthy infants that were smaller at birth and forced expiratory flow at functional residual capacity ($Vmax_{FRC}$) is diminished in infants that had greater postnatal weight gain (n=131 Southampton Women's Survey infants born at term) (derived from reference 39).

Figure 5. Standardised mortality ratios (SMR) for coronary heart disease in offspring of mothers of below average height (n= 1690 men born in Helsinki University Central Hospital during 1924-33 whose mothers were weighed on admission in labour)(derived from reference 8).