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Programming of cardiovascular disease across the life-course

Dr Heather L Blackmore and Professor Susan E Ozanne

University of Cambridge, Metabolic Research Laboratories and MRC Metabolic Diseases Unit, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrookes Hospital, Cambridge CB2 0QQ, United Kingdom.

Corresponding author contact information:

Heather L Blackmore, PhD

University of Cambridge, Metabolic Research Laboratories and MRC Metabolic Diseases Unit, Wellcome-Trust MRC Institute of Metabolic Science, Level 4, Box 289, Addenbrookes Treatment Centre, Addenbrookes Hospital, Cambridge CB2 0QQ, United Kingdom.

Phone: +441223 336787

Fax: +441223 330598

Email: hlb46@cam.ac.uk

Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, affecting both developed and developing countries. Whilst it is well recognized that our risk of CVD can be determined by the interaction between our genetics and lifestyle, this only partly explains the variability at the population level. Based on these well-known risk factors, for many years intervention and primary prevention strategies have focused on modifying lifestyle factors in adulthood. However, research shows that our risk of CVD can be pre-determined by our early life environment and this area of research is known as the Developmental Origins of Health and Disease. The aim of this review is to evaluate our current understanding of mechanisms underlying the programming of CVD.

Ageing and cardiovascular disease

Life expectancy is increasing worldwide. World Health Organization statistics state that by 2050, 2 billion people will be older than 60 years of age [1]. This increase in lifespan brings about a rise in age-associated conditions such as type 2 diabetes, cancer and cardiovascular disease (CVD). As CVD has a long pre-clinical phase resulting in diagnosis in old age, the identification of biomarkers that precede the clinical state is critical in defining an individual's risk in later life. Left unresolved sub-clinical conditions manifest into diseases such as atherosclerosis, myocardial infarction, stroke and heart failure. Although adverse lifestyle choices in adulthood (poor diet and lack of exercise) are known to prematurely cluster these risk factors in individuals, evidence from the field of Developmental Origins of Health and Disease (DOHaD) shows that a suboptimal early life environment leads to the premature presentation of these pre-clinical conditions. Consequently, such programming effects are associated with higher incidence of cardiovascular conditions and premature mortality in these individuals.

The importance of the early life environment in shaping our vulnerability to disease

The DOHaD hypothesis emphasizes the concept that during early life, insults that occur during critical periods of development can alter offspring structure, function and/or molecular phenotypes that persist into adulthood. Specifically, exposure to adverse conditions *in utero* leads to the sparing of vital organs (such as the brain) at the expense of considered less-essential organs such as the pancreas, resulting in asymmetric growth and altered function [2]. Whilst these adaptations may initially prove beneficial for survival in the short-term, they ultimately lead to increased disease susceptibility. According to the theory of the Predictive Adaptive Response proposed by Mark Hanson and Peter Gluckman [3], the propensity for disease in adult life is reduced if the postnatal environment matches the intrauterine "prediction". In contrast, if the pre- and postnatal environments differ, adaptations made *in utero* no longer prove advantageous and therefore manifest in increased adulthood diseases.

Much research has highlighted the importance of the early life environment beginning before conception, spanning across pregnancy, lactation and into the postnatal period. Epidemiological studies have shown that individuals born low birth weight have aortic wall thickening at birth and elevated blood pressure and impaired endothelial function in adulthood [4-6]. Notably, these individuals also showed the greatest risk of atherosclerosis, coronary heart disease, myocardial infarction, stroke and premature mortality from ischemic heart disease [7-11]. In

addition to low birth weight, other *proxy* markers of an adverse intrauterine environment, including ponderal index and placental weight, have also been associated with adverse cardiovascular outcomes in adulthood [12, 13]. Whilst such *proxy* markers are useful tools in assessing the quality of the intrauterine environment, they are indirect measures and therefore have limited predictive ability. For instance, there is evidence to suggest that fetal growth does not need to be impaired to have a long-term influence on offspring disease susceptibility [14]. Furthermore, in addition to low birth weight there is evidence to suggest that offspring born high birth weight (greater than 4kg) also have an increased propensity for metabolic diseases in adult life [15]. Therefore, assessing the quality of the intrauterine environment requires elaborate study designs. However, through unusual circumstances such as famine (macronutrient deficiency), researchers have been able to assess the direct impact of nutritional deprivation in early life on risk of CVD.

Maternal macronutrient deficiency

Epidemiological evidence – The Dutch Hunger Winter was a famine that occurred in 1944-45 due to a German blockade that prevented delivery of food and fuel to the western region of the Netherlands. The famine affected individuals of all social classes and led to nutritional deprivation of between 400-800 calories per day. Offspring exposed to the famine in early gestation were at greater risk for the development of obesity, increased systolic (SBP) and diastolic blood pressure (DBP) in response to stress and premature presentation of coronary artery and heart disease [16-19]. Whilst a difference was observed in blood pressure following a stressor response, no differences were observed in relation to basal blood pressure between individuals exposed or un-exposed to the famine in utero. However, an inverse relationship between birth weight and blood pressure was identified, with those born low birth weight having a higher blood pressure [20]. Interestingly, offspring exposed in late gestation were more likely to develop metabolic abnormalities such as impaired glucose tolerance [21]. These studies highlighted that the organs and/or systems affected in adulthood often reflected the period at which the insult occurred during development [22].

The Leningrad famine (1941-1944) was a more severe famine in an area now known as St Petersburg, with an average ration during the 'Hunger Winter' period (November 1941 – February 1942) of 300 calories per day, mostly consisting of carbohydrate [23]. Unlike the Dutch Hunger Winter, nutritional deprivation was lower both prior to and following the famine. Offspring exposed to the Leningrad famine during gestation showed no increase in blood pressure, atherogenic lipid profile or impaired glucose tolerance. However, exposed offspring showed evidence of endothelial

dysfunction and raised von Willebrand factor [23]. These variations in outcomes could be attributed to the fact that individuals from the Dutch Hunger Winter were well nourished prior to and after the famine, therefore helping to drive catch-up growth which is associated with an increased propensity for both metabolic and CVD [22]. In contrast, following the end of the Leningrad famine, food still remained scarce and therefore offspring exposed to the famine were born into a nutritional deprived environment that matched their experiences in utero. Thereby supporting the role of the Predictive Adaptive Response [22].

The Dutch Hunger Winter was based on a population not previously malnourished prior to the famine. Consequently, this data cannot be generalized to individuals from nations who live on a malnourished background. Therefore, the Biafran and Chinese famines have proved critical in our understanding of the long-term impact to these individuals. The Biafran famine occurred as a result of the start of the Nigerian Civil War that broke out in July 1967 and ended in January 1970. Offspring exposed to the Biafran famine in early life (fetal-infant exposure) had elevated SBP, DBP and impaired glucose tolerance measured at approximately 40 years of age [24]. The Chinese famine affected the whole country following a decline in grain production. Unlike famines that had a more defined period, the Chinese famine was prolonged with debate as to its beginning and end, making it more difficult to distinguish individuals' true famine exposure. The famine significantly affected rural but not urban populations. Exposure to the famine in early postnatal life led to development of hypertension in rural populations only [25].

Animal models – Whilst human studies provide us with information on the associations between the early life environment and later disease risk in the offspring, they are unable to address causality. Animal models have proved to be an invaluable resource for evaluating the underlying mechanisms. The power of these models stems from the opportunity for direct manipulation of exposure variables whilst controlling for confounders. Moreover, due to the short lifespan of many laboratory animals, in particular rodents, long-term effects on the cardiovascular system spanning from markers of CVD risk to clinical cardiovascular conditions can be addressed in the same animal longitudinally, using invasive and non-invasive techniques. Such experiments would be difficult to perform in a human setting due to a significantly longer lifespan.

The importance of nutrient access prior to conception has been highlighted by a number of studies that have addressed the impact of periconceptional undernutrition on fetal and adult phenotypes. In an ovine model of preconceptional undernutrition 60 days prior to conception (70% of control food allowance), fetal arterial blood pressure was significantly increased and this was independent of activation of the renin-angiotensin system (RAS) [26]. Another study used a more

severe nutrient restriction model (50% of control food allowance) to study both preconceptional (30 days prior to conception) and periconceptional (15 days either side of conception) undernutrition. Adult female offspring of both exposures had impaired vasorelaxation and enhanced vasoconstriction of femoral and coronary arteries, respectively [27]. There is also evidence that periconceptional undernutrition accelerates development of the hypothalamic pituitary axis, increasing risk of premature delivery and altered physiology with a predisposition to CVD in later life [28].

Maternal calorie restriction is an example of a model used to study the long-term effects of maternal global undernutrition. The extent of calorie restriction varies from as little as 30% to 70% of the daily-recommended intake [29, 30]. One of the most consistent offspring phenotypes following maternal caloric restriction during pregnancy is an increased SBP. This observation has been noted in a range of species, including mice, rats, sheep and cows [29, 31-33]. Whilst in two studies offspring were growth restricted at birth [34, 35], not all studies showed a difference in birth weight [33]. In addition to a raised blood pressure, offspring exposed to maternal caloric restriction showed signs of vascular dysfunction and fibrosis [30, 32]. In terms of the cardiac tissue, offspring developed cardiomegaly, associated with an increase in cardiomyocyte size [30].

Maternal protein restriction is one of the most widely studied models of maternal undernutrition and similarly to global caloric restriction, offspring of protein-restricted dams have been shown to have high blood pressure in adulthood [36-39]. However, not all models of maternal protein restriction show evidence of hypertension or an adverse cardiovascular phenotype [40]. The differences between offspring outcomes have been attributed to the dietary composition of the maternal diet rather than the protein restriction per se. This has been reviewed in detail by Langely-Evans (2001) who compared the dietary composition of two low protein diets with differing offspring cardiovascular outcomes. Key differences were noted in both the fat and carbohydrate composition [41]. This hypothesis was supported by replication of the offspring phenotype on a diet enriched for fat [42]. In addition to changes in blood pressure, maternal protein restriction in rodents has been shown to lead to other offspring phenotypes including, accelerated atherosclerotic lesion progression, hypercholesterolemia, accelerated growth of the heart, delayed formation of the coronary artery, cardiomyocyte cell loss and cardiac dysfunction coupled with an attenuated β-adrenergic responsiveness as a consequence of both impaired adrenergic and insulin signaling [38, 43-46].

Evidence from humans supports that poor fetal growth (i.e. low birth weight), followed by rapid postnatal growth (catch-up growth) is associated with increased risk of CVD [47, 48]. The

recuperated animal model is used to study the effects of undernutrition during pregnancy followed by rapid catch-up growth. Catch-up growth is achieved by cross-fostering offspring from undernourished dams to control females (fed 20% protein) during lactation. Offspring from this model have a shorter lifespan, metabolic abnormalities and age-associated changes in the kidney [49, 50].

For many years research in the field has focused on the long-term impact of maternal undernutrition on offspring cardiovascular health. However, due to rising levels of obesity across the globe, in particular in women of childbearing age [51, 52], the research focus is shifting to studying the long-term cardiovascular consequences of early life exposure to maternal overnutrition and/or obesity.

Maternal overnutrition and obesity

Epidemiological evidence **–** There have been a handful of studies performed to date that have addressed the impact of early life exposure to maternal obesity on long-term clinical CVD and mortality. Data from a cohort of individuals recruited in Helsinki at birth and followed up across their life-course, has shown that offspring whose mothers had a high BMI during pregnancy, and were thin at birth, had increased risk of dying from coronary heart disease [53]. A more recent study showed a correlation between maternal BMI and offspring incidence and mortality from CVD [54]. Specifically, males at the greatest risk of death from CVD had a low ponderal index and were born to mothers with a high BMI. Similarly, data from a British cohort based in Aberdeen showed premature mortality from all causes in offspring of obese mothers [55]. Furthermore, these individuals were more likely to be admitted to hospital for cardiovascular events.

Maternal obesity in humans has been shown to impair diastolic function during fetal life [56]. In terms of cardiac structure, weight gain until late pregnancy has been associated with an increase in left ventricular mass of offspring at 6 weeks and 6 months of age [57], highlighting the persistent alteration of cardiac structure, even when removed from the maternal environment. Studies have also consistently shown a positive association between maternal BMI and clustering of CVD risk factors in children, adolescents and adults. Risk factors include a raised SBP, lower high-density lipoprotein and a high BMI [58-60]. There is evidence to suggest that the clustering of such risk factors may be driven through an increase in offspring adiposity [59]. In addition to maternal obesity, increased gestational weight gain has also been associated with an adverse cardiometabolic profile in the offspring [59, 61].

Whilst a handful of studies have assessed the impact of early life exposure to maternal obesity on end-point CVD and mortality, the majority of human studies in this area have investigated the prevalence of CVD risk factors in the offspring during childhood or young adult life. The study of cardiovascular risk factors in children and young adults is critical, as blood pressure, BMI and lipid levels measured in childhood track into adult life and therefore predispose individuals to premature cardiovascular conditions [62-65].

In human population studies, the genetic heritability of obesity is often a confounding factor when investigating the association between maternal and offspring obesity. Understanding this is important, as offspring obesity may be a key player in the clustering of CVD risk factors following exposure to maternal obesity. Intervention studies in siblings born before and after bariatric surgery have proved critical in disentangling individual contributions of both the genes and environment in offspring exposed to maternal obesity. Siblings born after bariatric surgery had an improved lipid profile, lower prevalence of obesity, reduced C-reactive protein and leptin relative to their sibling born before weight loss [66, 67]. An improvement in the offspring's cardiometabolic phenotype post-surgery has further been associated with alterations of both the transcriptome and methylome, in particular genes important for improving cardiometabolic disease risk [68]. Accordingly, epigenetic modifications in key offspring genes in response to changes in the maternal environment have been hypothesized to be one of the mechanisms by which disease risk is transferred following adverse conditions *in utero.*

Animal models – Studying the mechanisms by which early life exposure to maternal obesity impacts on long-term offspring health is complex. Maternal obesity itself is often complicated by the presence of other co-morbidities that include pre-existing conditions such as type 2 diabetes, hypertension and hypercholesterolemia. Furthermore, obese women are at higher risk of developing complications during pregnancy, including gestational diabetes mellitus and preeclampsia. In addition to understanding the contribution of these co-morbidities, dissecting out the role of the maternal diet becomes almost impossible when addressing such questions in a human setting. As a consequence, there is a large range of animal models that include overnutrition in the presence or absence of obesity, dietary manipulations such as high-fat only or high-fat supplemented with a sugar component and studies assessing different windows of exposure across the early life period (pre-conception, gestation, lactation, post-weaning).

There are a number of studies from ovine models of maternal overnutrition where offspring showed evidence of impaired cardiac development in fetal life. Overfeeding of ewes prior to conception and throughout gestation increased heart weight, collagen deposition, led to the

activation of hypertrophic and stress signaling pathways and impaired ventricular contractility in response to elevated workload stress [69-71]. A change in diet at conception was sufficient to increase fetal heart weight [72]. In nonhuman primate offspring exposed to mothers fed a high-fat diet (HFD) long-term prior to conception, developed vascular wall thickening and impaired vasorelaxation in the abdominal aorta, when they themselves were weaned onto a HFD [73]. Although this provides evidence of the negative long-term effects of maternal obesity and overnutrition in large animals, the majority of research in this area has focused on small rodent models.

Consistent with the larger animal models of maternal overfeeding, exposure to a HFD prior to conception and maintained throughout pregnancy and lactation in rodents led to vascular dysfunction, hypertension and dyslipidaemia in adult offspring [74-78]. It has also been shown that exposure to a maternal HFD during either the pregnancy or suckling period separately was sufficient to program hypertension in the offspring [79]. With the aim of better modeling a human Western diet, researchers began to study the long-term effects of a maternal high-fat high-sugar diet on the cardiovascular health of the offspring. Females exposed to this diet for 6 weeks prior to mating become obese by the time of conception and offspring from these dams developed cardiac hypertrophy as early as 3 weeks of age. Furthermore, these offspring showed pathological re-expression of cardiac fetal genes and increased oxidative stress by young adolescence [80, 81]. By young adulthood and independent of their current body weight, offspring had impaired baseline left ventricular contractility, stiffening and sympathetic dominance, with the latter being a pre-eminent marker of cardiac failure [80]. At the vascular level, offspring developed resistance artery dysfunction at 12 weeks of age and hypertension by 6 months [82]. A similar phenotype has been observed in a rat model of maternal diet-induced obesity, whereby offspring displayed an increase in mean arterial pressure associated with increased sympathetic responsiveness, prior to the onset of obesity [83].

Animal models of genetic obesity are instrumental in understanding the importance of obesity susceptibility genes independent of the maternal diet. In an example of such a model, offspring exposed to obese dams with the agouti yellow (A^y) mutation had increased susceptibility to cardiac injury following ischemia-reperfusion, by occlusion of the left coronary artery [84].

Impact on the heart in early life

If the early life environment were to play a critical role in influencing future cardiac structure and function that persists into adult life, the expectation is that there should be signs of potential dysfunction as early as fetal life. A study into the cardiac function of human fetuses exposed to maternal obesity, showed evidence of impaired cardiac function [56]. Assessment of offspring by echocardiography born small for gestational age, showed signs of both systolic and diastolic dysfunction with impaired ventricular relaxability and a higher blood pressure [85].

Animal models have proved useful in establishing the effect on the fetal cardiovascular system following a variety of insults including maternal overfeeding and growth restriction. In multiple studies using ovine models of maternal overnutrition, fetal heart weight and collagen deposition was increased [69, 72], with other models showing left and right ventricular wall thickening, altered myofiber organisation, inflammation and lipid deposition [86]. In addition to structural changes, fetal hearts exposed to maternal overfeeding showed dysregulation of key signaling pathways including over activation of the JNK-IRS-1 pathway and down regulation of cardioprotective proteins such as AMPK [70]. An increased fetal heart weight, coupled with cardiomyocyte hypertrophy was associated with molecular changes, specifically an increase in hypertrophic proteins, mTOR, NFATc3 and Calcineurin A [71]. In a rabbit model of surgery induced intrauterine growth restriction, echocardiography revealed a globular shaped heart, with no difference to controls in terms of wall thickness. Whilst there was no difference in ejection fraction, sarcomere length in the growth-restricted fetus was smaller. As the sarcomere is critical for cardiac contractility, this adaptation in utero may predispose to future cardiovascular dysfunction [87].

Transgenerational programming of cardiovascular disease

Whilst an adverse early life environment is known to increase susceptibility to non-communicable adulthood disease in the exposed offspring (F1 generation), there is emerging evidence that the risk can be propagated across generations (F2 generations and further) [88]. When the mother presents with an adverse *in utero* environment, it directly affects the F1 generation and its germ cells that will become the F2 generation. Consequently, by definition, transgenerational inheritance should only include offspring from the F3 generation to avoid the confounding effects of the direct exposure to the initial maternal insult. However, as there are fewer studies addressing the F3 generation and beyond, the majority of studies are assessing the multigenerational transmission to the F2 generation [88, 89].

In terms of CVD, there are several studies showing multigenerational transmission of adverse cardiovascular phenotypes following early life exposure to adverse environmental insults including maternal undernutrition, micronutrient deficiency and placental insufficiency. The phenotypes transmitted across generations have included a reduced nephron number, arterial and endothelial dysfunction, and hypertension [90-92]. In a rat model of maternal low protein, the adverse cardiovascular phenotype (elevated blood pressure and reduced nephron number) was observed in both the F1 and F2 generations across both the maternal and paternal lines, but did not transmit to the F3 [91].

Mechanisms underlying the programming of offspring cardiovascular disease

Although the focus of this review is on the long-term impact of nutritional exposures on the cardiovascular health of the offspring, it should be noted that exposure to non-nutritional insults also results in similar phenotypes (Table 1). This implies the possibility of convergent programming pathways (Figure 1). In terms of programming CVD, there are a number of proposed mechanisms such as activation of the RAS, structural changes, oxidative stress and epigenetics.

Renin Angiotensin System – The RAS is a key player in the maintenance of cardiovascular homeostasis and body fluid balance. Dysregulation of this system at both the individual and systemic level has been implicated in the pathogenesis of a variety of conditions. Hypertension is one of the most consistent phenotypes in human and animal models following a variety of early life environmental insults (Table 1). Interestingly, altered expression of both the angiotensin II type 1 (AT_1) and type 2 (AT_2) receptor has been observed in response to maternal undernutrition and hypoxia [30, 33, 93-96]. Moreover, the enzyme renin was reduced in newborn pups from low protein fed dams, and was concomitant with decreased glomerular flow rate, glomerular number and increased blood pressure in adulthood [36]. As nephrogenesis in rodents continues through early postnatal life, insults that occur during this critical period of development are likely to affect organ development, structure and function, thus increasing susceptibility to adulthood disease [97]. Inhibition of the RAS during this critical early postnatal period in pups from healthy dams, reduced glomerular number and flow rate and increased blood pressure in adult life [98]. Suppression of the RAS in newborn offspring is thought to result in impaired kidney development, affecting long-term function and leading to the premature pathogenesis of disease.

In comparison, adult offspring of obese dams have raised blood pressure and an increased renal renin and norepinephrine content. Hypertension in these offspring was abolished through α/β

adrenergic blockade, suggesting hyper-responsiveness of sympathetic tone [83]. Moreover, maternal HFD led to altered renin and Na^+/K^+ ATPase activity in offspring renal tissue [74]. Increased angiotensin converting enzyme in the heart, kidney and lungs was observed in offspring exposed to maternal diabetes [99]. Finally, in addition to both the intra-renal and circulating RAS, maternal HFD has been shown to alter components of the adipocyte RAS which has been associated with offspring hypertension [100].

The importance of the RAS in the programming of hypertension following exposure to a suboptimal early life environment has been further supported by the use of transgenic models and through intervention studies. Programmed increases in adult offspring blood pressure were abolished through the use of the AT_1 receptor antagonist Losartan, whereas treatment with Nifedipine, a calcium channel blocker, had no effect [101]. Further support comes from a transgenic mouse model over-expressing the AT_1 receptor associated protein (ATRAP-Tg), an inhibitor of AT_1 receptor signaling [37]. Although ATRAP-Tg mice had a reduced blood pressure compared to control mice, birth weight was significantly lower in controls compared to the transgenic animals. The interpretation of such data is complicated, as it is unclear whether the effect on birth weight had a direct role [37].

Structural effects on kidney development and nephron endowment – Offspring exposed to maternal undernutrition, diabetes and hypoxia have a reduced kidney nephron number and size in conjunction with a hypertensive phenotype [33, 102, 103]. Whilst, reduced nephron number has been suggested to play a role in the development of hypertension based on Brenner's theory of hyperfiltration [104], it is debated as to whether a reduction in nephron number alone is sufficient to result in pathology. In one study of prenatal protein restriction, adult offspring had a reduced nephron number that was associated with a lower mean arterial pressure [105]. Instead, it is hypothesised that it is the combination of phenotypes in the offspring (such as altered RAS activity, glomerular hypertrophy, sympathetic tone, obesity and a HFD) coupled with a reduction in nephron number that is likely to predispose individuals to hypertension (reviewed in [106, 107]).

Oxidative stress – A situation of oxidative stress occurs as a consequence of excess production of reactive oxygen species (ROS) relative to antioxidant defense capacity. Although ROS are bi-products of physiological respiration, they are responsible for cellular damage and are key players in the pathogenesis of a variety of diseases. Elevated ROS levels in tissues associated with the cardiovascular system have been found in a number of programming animal models, some of which include maternal undernutrition, obesity, hypoxia and treatment with glucocorticoids [81, 108-110].

Intervention studies using antioxidants targeting both the mother and offspring support the mechanistic role of oxidative stress in the programming of CVD. Maternal treatment with vitamin C ameliorated the adverse effects of maternal hypoxia on the cardiovascular health of adult rat offspring [108]. Similarly, treating HFD fed dams with the antioxidant quercetin prevented the development of hypertension, obesity and premature aging in mouse offspring [77]. In a rodent model of postnatal catch-up, treatment of exposed offspring with a mitochondrial antioxidant (Coenzyme Q) prevented premature cardiac aging, coupled with a reduction in oxidative and nitrosative stress [110].

Sympathetic dominance, leptin and insulin signaling – One of the phenotypes consistently associated with the programming of adulthood hypertension in offspring of obese dams is an increased sensitivity and activation of the sympathetic nervous system, coupled with selective leptin hypersensitivity [83]. While these offspring are resistant to the appetite suppressing effects of leptin, they are highly sensitive to its action on the renal sympathetic nerve. A prolonged neonatal leptin surge in early postnatal life has been suggested as a potential mediator of increased cardiac sympathetic activity in rodent offspring of obese dams [83]. Evidence to support this hypothesis comes from an experiment whereby neonatal pups from healthy dams were given exogenous leptin to mimic the prolonged and elevated leptin surge in offspring from obese dams [111]. Accordingly, pups exposed to excess exogenous leptin in early postnatal life developed a cardiovascular phenotype that mirrored offspring of obese dams, with premature onset of hypertension, increased renal norepinephrine, elevated stress response and altered heart rate variability (indicative of increased sympathetic efferent tone) [111]. The causal role for increased sympathetic tone in programming of hypertension in this model was further supported following the normalization of blood pressure after treatment with an adrenoreceptor antagonist. In agreement with these findings, rabbit offspring exposed to maternal HFD developed hypertension that was associated with increased activity of the renal sympathetic nerve [112, 113]. Similarly to the rodent model, these offspring also showed altered responses to leptin, both in terms of appetite and cardiovascular control. The relationship between leptin and increased renal sympathetic nerve activity is complicated by the knowledge that offspring obesity itself has a direct impact on circulating leptin levels. However, there is evidence to support the role of leptin in programming offspring blood pressure prior to the onset of obesity [83, 111]. This highlights that the combined effects of obesity and leptin hypersensitivity may exaggerate the offspring phenotype.

With regards to cardiac tissues, sympathetic dominance has been reported in mouse offspring of obese dams and was explained by an increase in protein expression of the β_1 adrenergic

receptor [80]. In addition to cardiac sympathetic dominance, these offspring developed early cardiac hypertrophy and hyperinsulinemia. As chronic hyperinsulinemia in humans is an important predictor of heart failure and premature mortality [114], increased insulin signaling in cardiac tissue has been suggested as a potential mechanism driving impaired cardiac development and function in offspring exposed to maternal obesity [80]. At 8 weeks of age, despite reduced levels of the cardiac insulin receptor, downstream components of the insulin-signaling pathway were up regulated (p-AKT, p-ERK, p-mTOR, p38MAPK) [81]. Furthermore, in an ovine model of maternal overnutrition, there was dysregulation of insulin signaling components (FOXO3a, mTOR, NFATc3) in fetal cardiac tissue that was coupled with presence of left ventricular wall thickening [71].

Glucocorticoids and programming of CVD – Glucocorticoids play a critical role in tissue maturation, in particular at and around birth. Until late gestation, fetal glucocorticoid exposure is restricted by the activity of placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Maternal treatment with dexamethasone in rats, increased fetal exposure to glucocorticoid due to the inability of 11β-HSD2 to inactivate dexamethasone [115]. Maternal exposure to dexamethasone in rats and sheep, programs an increased blood pressure and cardiac hypertrophy [115, 116]. The importance of the placental enzyme 11β-HSD2 for preventing early exposure of the fetus to glucocorticoids was demonstrated through inhibition of the enzyme using carbenoxolone [117]. Offspring of mothers treated with carbenoxolone during pregnancy had an identical phenotype to those offspring of mothers treated with dexamethasone. Further support for the role of glucocorticoids in programming of CVD, comes from evidence in rats that showed reduced placental 11β-HSD2 enzymatic activity in a model of maternal protein restriction [118]. Notably, the phenotype was reversed by inhibiting glucocorticoid synthesis and recapitulated by the replacement with corticosterone [119].

Epigenetics – Epigenetics is the process by which DNA/chromatin modifications, as well as non-coding RNAs (e.g. microRNA) result in heritable alterations in gene expression, without affecting the DNA sequence. These mechanisms provide phenotypic plasticity, allowing one genotype to present with multiple phenotypes, in response to varying environmental conditions and are therefore of great interest to the DOHaD field [120]. There is evidence to suggest that some epigenetic modifications can be passed to subsequent generations. Consequently, inheritance of such epigenetic marks provides a potential mechanism for the transgenerational inheritance of disease risk.

Changes to maternal diet (such as restriction of folate, B12 and methionine) led to epigenetic modifications in the offspring coupled with an increase in offspring obesity and blood pressure [121].

Evidence from humans provides support that epigenetic modifications are stable long-term. Offspring exposed to the Dutch Hunger Winter in early gestation showed reduced methylation of *IGF2* 60 years after the famine [122]. Using a model of maternal low protein in the rat, hypomethylation of the adrenal AT1b receptor was associated with increased gene expression and offspring hypertension at 4 weeks of age. Maternal glucocorticoid exposure was shown to mediate this effect as both hypomethylation and hypertension in the offspring was abolished following maternal treatment (for the first 14 days of pregnancy) with 11β-hydroxylase inhibitor metyrapone [123]. Hypomethylation of the p53 promoter and reduced DNA cytosine 5 methyltransferase 1 (DNMT1) activity in the rat kidney of growth restricted offspring exposed to uteroplacental insufficiency, was associated with increased p53 expression levels, apoptosis and reduced glomerular number [124]. Human cells from growth-restricted pregnancies showed altered mRNA expression of endothelial nitric oxide synthase (eNOS) and arginase 2. Partial silencing of DNMT1 restored aberrant eNOS expression [125].

In addition to epigenetic modifications that have direct effects on DNA/chromatin, microRNAs have also been implicated in the DOHaD field. MicroRNAs are small (22-25 nucleotides long) non-coding RNA molecules that play a critical role in post-transcriptional regulation of gene expression by suppressing translation or inducing mRNA degradation. Exposure to maternal obesity in nonhuman primates led to the differential expression of microRNAs that were associated with disorders of development and CVD [126].

Future directions

The success of traditional intervention measures for the prevention of CVD has reached a plateau. However, studies into the early origins of CVD highlight that if interventions were focused on both the mother and her offspring in early life, incidence and premature mortality from CVD may be reduced, propagating a reduction in risk that extends to future generations. Studies into such intervention strategies, aimed at the pregnant and nursing mother and her offspring, will provide further clarification on the underlying mechanisms involved in the programming of CVD. In a time when population age is increasing, now more than ever the focus must be on reducing the CVD risk of future generations.

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Disclosures

None

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Table Title

Table 1: Animal models and offspring cardiovascular phenotype

Figure Legend

Figure 1: Exposure to an adverse early life environment programs premature cardiovascular aging and mortality. CHD: Coronary heart disease. IHD: Ischemic heart disease.

Abbreviations

11β-HSD2 - 11β-hydroxysteroid dehydrogenase type 2

AT_1: Angiotensin receptor type 1

AT_2: Angiotensin receptor type 2

ATRAP-Tg: Angiotensin II type 1 receptor-associated protein-transgenic

BMI: Body Mass Index

CVD: Cardiovascular disease

DBP: Diastolic Blood Pressure

DNMT1: DNA cytosine 5 methyltransferase 1

DOHaD: Developmental Origins of Health and Disease

eNOS: Endothelial nitric oxide synthase

HFD: High-fat diet

SBP: Systolic blood pressure

RAS: Renin angiotensin system

ROS: Reactive oxygen species