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The Early Life Origins of Cardiovascular Disease

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Abstract Cardiovascular disease continues to impose a high societal and economic burden. Although it occurs primarily in later life, there is strong evidence that it originates in early life. The nutritional environment that an unborn child is exposed to can heavily influence later disease risk, with nutritional exposures altering organ development and programming metabolic changes that are then maintained during the life course. Epigenetic changes induced by the early life environment are thought to be a key mechanism by which these early life events influence subsequent disease risk. Here, we review the emerging role of epigenetics in the development of cardiovascular disease.

Keywords Cardiovascular disease · Early life origins · Epigenetic changes · Epigenetics

Introduction

Non-communicable diseases (NCDs) such as diabetes, cardiovascular disease, obesity and cancer collectively represent one of the greatest challenges to global health in the twenty-first century [1]. Globally, NCDs kill 38 million people a year, accounting for approximately 8 out of every 10 deaths in the developed world [2]. NCDs are not restricted to industrialized countries; they are also the leading cause of death in both low and middle income countries [3]. Countries undergoing rapid socio-economic improvement are especially vulnerable, as while the burden of infectious diseases decreases with advances in health care provision, the incidence of NCDs has increased rapidly along with the adoption of more sedentary lifestyles and consumption of westernized diets [4, 5]. Together, these factors are predicted to drive a 17 % increase in NCD levels over the next decade [3]. This book chapter will explore the role of the early life environment in the development of cardiovascular disease, and examine the growing evidence that epigenetic changes underlie this link between early life and later CVD disease risk.

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Aetiology of CVD

Cardiovascular disease (CVD) is the single largest cause of death among NCDs, responsible for almost a third of all NCD deaths [2]. CVD encompasses a class of diseases involving both the heart and the wider circulatory system, and includes cardiac hypertrophy, damage to blood vessels, endothelial dysfunction and arterial narrowing that can lead to heart failure, stroke and myocardial infarction. Atherosclerosis and hypertension are considered the two main underlying causes of CVD [6]. There are a number of risk factors associated with CVD including family history and age as well as a number of modifiable risk factors which include obesity, hypertension, high cholesterol concentrations, physical inactivity, diabetes, poor nutrition and smoking [7, 8].

Obesity is the largest modifiable risk factor for CVD [8]. Obesity levels are increasing at a dramatic rate: global obesity levels having doubled since the 1980s, with 55 % of European adults now overweight and 20 % clinically obese [3]. Obesity increases metabolic load due to increased blood volume

serving the greater adipose mass, leading to increased pre-load on the heart, while afterload is increased by arterial stiffness, with obese adults often exhibiting both concentric and eccentric hypertrophy [6, 9]. Obesity is also thought to account for as much as 70 % of essential hypertension [10]. Obesity among women of child-bearing age has also steadily increased over the last 20 years, with some western countries now reporting that two thirds of potential mothers are overweight and a third obese [11, 12]. This is of particular concern as there is mounting evidence that exposure to maternal obesity in utero can increase adult CVD risk. Consistent with the rise in maternal obesity, obesity among children is also increasing globally with some western countries reporting that a third of children are overweight, of whom half are clinically obese [2]. Childhood CVD should be rare, but is increasing along with childhood obesity. Obese children exhibit several physiological signs of cardiovascular dysfunction, independent of obesity related co-morbidities, with altered cardiac structure [13] and increased regional deformation of the left ventricle [14••]. By adolescence, obese children display both diastolic and systolic dysfunction, along with reduced ventricular stain rate [15, 16]. Childhood obesity also promotes endothelial dysfunction leading to atherosclerotic plaque formation, hypertrophy and ultimately, cardiac dysfunction [9, 17].

The Early Life Environment and the Risk of NCDs

Research into CVD and its co-morbidities initially focused on the disease in adulthood, but there is now increasing evidence that CVD may originate in early life [18]. The early life environment has been shown to greatly influence future health, with nutrition during pregnancy and in early post-natal life impacting upon organ development and metabolic regulation, influencing later disease risk [19].

The initial link between adult CVD risk and the early life environment came from a Norwegian study that found an association between CVD in middle age and under nutrition and poverty during childhood and adolescence [20]. Later work in Britain by David Barker and colleagues expanded on these observations by comparing birth measurements with health in middle age. Here, they found a strong correlation between low birth weight (LBW) and coronary heart disease (CHD), as well as diabetes, increased systolic blood pressure and hyperlipidemia [21–24]. Subsequent cohort studies have confirmed these associations, with LBW linked to an increase in CVD risk factors in childhood [25•, 26–28], leading to greater mortality risk from stroke and CHD in adult life [27, 29, 30].

While these epidemiological studies demonstrated the relationship between foetal growth and CVD risk, studies carried out on people whose mothers were exposed to the Dutch Hunger Winter, a famine that occurred in the Netherlands in 1944–1945, revealed the importance of maternal nutrition to the offspring's health in later life. In these studies, individuals born to mothers exposed to famine during the periconceptual period up to the first trimester of pregnancy had an increased risk of CVD and obesity in middle age, whereas individuals that were exposed to famine in the later stages of gestation showed an increased risk of developing insulin resistance and hypertension in adulthood [31, 32]. Such findings also suggest that the timing of the dietary constraint may be important and may determine which organ system is affected.

Postnatal growth trajectory has been linked to CVD risk, with evidence that rapid catch up growth among those born with a low birth weight impacts upon endothelial function and subsequent atherosclerosis [6, 33] leading to hypertension and coronary heart disease in adulthood [26, 34].

A number of studies have also shown a J- or U-shaped relationship between birth weight (BW) and disease risk with babies born at the highest BW also being at increased risk of developing CVD and other NCDs [33, 35–39] (Fig. 1). Maternal obesity and weight gain during pregnancy have also been associated with subsequent obesity [40] and an increase in offspring systolic blood pressure [41]. Further studies have also linked parental BMI and offspring cardiovascular risk factors such as increased diastolic and systolic blood pressure, elevated insulin levels and lowered HDL [8, 42•, 43], and more specifically, shown an association between increased maternal BMI during pregnancy and later death from cardiovascular events [26, 44•]. Maternal obesity has been shown to influence the BMI of the grandchildren [45], implying a transgenerational effect that has far reaching implications for the health of future generations [38]. Maternal obesity may affect the developing foetus through intrauterine interactions and while confounding factors in human studies prevent inferences about the mechanisms of disease, animal models have allowed investigation of the potential mechanisms underlying these associations.

Animal Models of Nutritional Programming

Animal models have sought to replicate findings from human epidemiological studies that show an association between the quality of the early life environment and future disease risk. Models of maternal undernutrition, such as global dietary and protein restrictions, as well as models of maternal overnutrition such as high fat diets and maternal obesity, have resulted in offspring that exhibit persistent metabolic changes often leading to features similar to human cardio-metabolic disease such as obesity, insulin resistance, hypertension and raised serum cholesterol levels in later life [46].

Maternal exposure to a protein-restricted diet alters offspring metabolism, leads to impaired glucose homeostasis [47], increased fat deposition, altered feeding behaviour towards a preference for high-fat foods [48, 49] and vascular

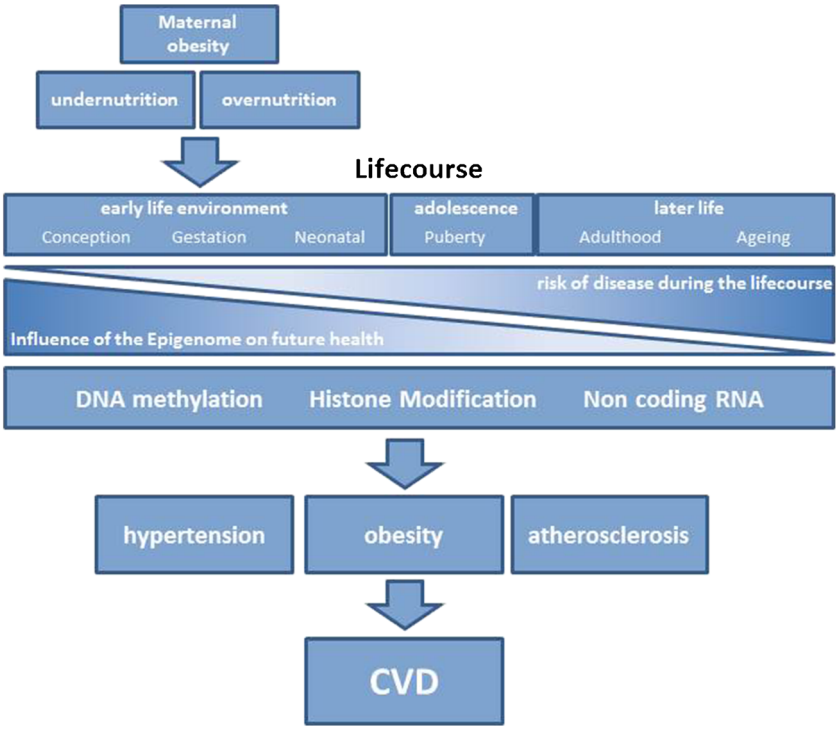

Fig. 1 The association between maternal diet on subsequent offspring CVD risk. Birth weight is often used as a surrogate for an adverse intrauterine environment. Being born either underweight or overweight is associated with an increased CVD risk, effecting cardiovascular health through the development of hypertension and atherosclerosis. There is, however, much evidence that developmental influences can programme increased CVD risk without necessarily affecting birth weight

dysfunction and hypertension [50]. Pre-natal undernutrition, particularly during the late intrauterine period, also results in restricted kidney development that reduces final nephron numbers, which disrupts kidney natriuresis [51–53].

The induction of persistent changes to the metabolism and physiology of the offspring by perturbations in maternal diet is accompanied by changes in the expression of key metabolic regulators [54–56]. For example, maternal protein restriction has been shown to directly impact upon offspring vascular function, promoting hypertension [50, 57] and increasing oxidative stress; the latter is a key inducer of endothelial dysfunction, leading to atherosclerosis and is accompanied by the upregulation of enzymes that produce reactive oxygen species, while at the same time, a decrease in antioxidant activity [58, 59]. Maternal protein restriction has also been shown to alter adrenal gene expression, with offspring exhibiting decreased expression of type II adrenal receptors, reducing the capacity for negative feedback that lowers blood pressure [53, 60, 61], while adrenal type I receptor density was increased, upregulating production of adrenal aldosterone, which raises blood pressure by promoting nephron sodium and water reabsorption [60, 62]. Maternal exposure to global dietary restriction also influences blood pressure by inducing long-term changes in the expression of 11β-hydroxysteroid dehydrogenase type 2 (HSD11β), a key regulator of active glucocorticoid levels that play a central role in regulation of blood pressure [63, 64].

With the increasing prevalence of obesity, particularly among mothers of child-bearing age, several animal models have been used to examine the effects of exposure to a western style maternal diet enriched in fat and sugar or the effects of maternal obesity on the later health of the offspring. Offspring of mice fed an obesogenic diet during pregnancy and lactation developed endothelial dysfunction and hypertension, and also exhibited increased fasting insulin and plasma glucose levels as well as a dysregulation of appetite [65]. Exposure to a maternal high fat diet can also induce structural changes in the foetal heart, with offspring having an accelerated cardiac growth rate leading to impaired baseline cardiac function and cardiac hypertrophy. At a molecular level, maternal obesity triggered re-expression of cardiac foetal genes in the offspring that altered cardiac muscle structure [66•]. Exposure to maternal obesity also alters the regulation of the renin-angiotensin system, which regulates blood pressure and water balance; Guberman and colleagues found that exposure to a maternal high fat diet in a rat model stimulated adipose angiotensin (AGT) production, causing hypertension in the offspring. Additionally, adipose production of AGT stimulated lipogenesis, resulting in increased adiposity that altered adipose tissue angiogenesis and smooth muscle tone, further exacerbating the animals' hypertensive state [67•].

Developmental Plasticity

The influence of the early life environment on later phenotype may in part reflect predictive adaptive responses that allow

organisms to adjust their development in response to environmental cues, to aid fitness or survival [68]. This developmental plasticity allows change and adaption to the environment within a set developmental window, after which changes can persist throughout the life course. Early life adaption could result in later disease, if an organism adapts to one environment but is then exposed to a different environment post birth, creating a mismatch [69]. Mismatches between pre-natal and post-natal environments may be a key factor behind the rapid rise of NCDs in developing countries, as they undergo rapid urbanization and sudden shifts in dietary composition [70–72].

Epigenetics Mechanisms

Genetic differences between individuals cannot explain the inter-individual differences in NCD disease risk [73]. Firstly, the overall proportion of risk variance accounted for by genetic variation accounts for less than 5 % of the observed differences [74•, 75], and secondly, fixed genomic variation cannot explain the observed flexibility of a developing organism to physiologically adapt to the early life environment [19]. Epigenetic mechanisms have the potential to provide both the variability and adaptability required to change the developmental programme in response to environmental cues, and then maintain these changes throughout the life course. Epigenetics is thought to be the key mechanism underpinning the developmental origins of NCDs [73].

'Epigenetic modifications are stably inherited through cell division without alteration of the DNA sequence', and provide a large degree of control over a gene's transcriptional state. The main components of the epigenetic regulatory apparatus, DNA methylation, histone modifications and non-coding RNAs work together to control access to the underlying DNA sequence, determining gene transcription and ultimately defining the role of each cell within the body; DNA methylation at regulatory regions, often upstream of a gene's transcriptional start site, is generally associated with gene repression. The presence of DNA methylation causes recruitment of repressive protein complexes that prevent gene transcription [76]. DNA methylation alters during early development; gametes exhibit high levels of methylation, but shortly after fertilization, global methylation levels decrease, reaching their lowest levels around the time of blastocyst implantation. De novo methylation then occurs within the inner cell mass giving rise to cell lineage-specific methylation patterns that are maintained in differentiated cells [77, 78].

Epigenetics and the Early Life Environment

'There is an increasing body of evidence suggesting that the early life environment can alter the epigenome', and that once these changes have occurred in early life, they are then maintained during the life course. Some of the first clear examples of maternal diet altering DNA methylation in the offspring came from studies of Agouti viable yellow (Avy) mice. Here, 'supplementation of the maternal diet with dietary methyl donors and cofactors (folic acid', vitamin B12, 'choline and betaine) shifted the coat colour of the offspring from yellow (agouti) to brown (pseudo-agouti)' due to increased methylation of the agouti gene [79–82].

Subsequent animal studies have shown that alterations in maternal macronutrient intake can alter the epigenetic regulation of key metabolic genes. For example, a maternal protein-restricted diet-induced altered DNA methylation and expression of genes involved in fat metabolism (PPARα) and stress response (glucocorticoid receptor (GR)) in the liver of both juvenile [55, 56] and adult offspring [54]. Furthermore, these epigenetic changes in PPARα and GR also led to alterations in the activity of their downstream target genes and specific physiological processes.

Altered epigenetic regulation of the renin-angiotensin system, important for kidney natriuresis and a potential cause of hypertension, has been observed in animal models. Maternal protein restriction programmed increased AGTR1 levels in the offspring; this was accompanied by a decrease in DNA methylation at key regulatory sequences within the gene promoter region, suggesting that altered epigenetic regulation was behind the increase in receptor numbers, driving the observed hypertension [60, 83]. In addition to altered receptor expression patterns that favour hypertension, maternal undernourishment also alters the epigenetic regulation of angiotensin converting enzyme (ACE1), the enzyme responsible for converting angiotensin to its active form. Increased levels of ACE1 in mice exposed to maternal protein restriction was accompanied by a reduction in DNA methylation within the gene's promoter and upregulation of miRNAs associated with positive regulation of ACE1 [84].

Over feeding in early life has also been shown to induce hypermethylation of the proopiomelanocortin (POMC) promoter, preventing the upregulation of POMC expression that normally occurs after feeding, promoting satiety. POMC methylation perturbed the normal physiological response to high plasma levels of both leptin and insulin, contributing to the development of obesity in the offspring [85].

Human studies have also found epigenetic changes associated with perturbations in early life nutrition. In studies from the Dutch Hunger Winter, periconceptual famine exposure was associated with altered DNA methylation across the imprint control region of IGF2 in individuals whose mothers had been exposed to famine compared to their non-exposed siblings, while exposure to famine in late gestation showed no altered methylation at the same region [86]. Examination of further genes found the same pattern: periconceptual famine exposure was 'associated with small DNA methylation

changes within multiple loci (including leptin, IL-10, MEG3 and ABCA3)' while a later exposure did not alter DNA methylation [87]. The detection of these epigenetic marks associated with famine exposure in peripheral blood 60 years after famine exposure supports the findings from animal models that early life nutrition can induce epigenetic changes in the offspring that persist long after the nutritional constraint has been removed, and that these epigenetic changes may underlie the long-term changes seen in metabolism and disease risk. Consistent with these findings, Godfrey et al. have shown that the methylation level of a CpG site within the promoter of the RXRA gene in the umbilical cord predicted greater than 25 % of the variation in fat mass in children aged 9 years [88] with replication of the finding in a second group of children aged 6 years. Furthermore, methylation of PGC1A in whole blood of children aged 5–7 years was found to predict adiposity in teenagers [89••]. Such 'findings not only support that hypothesis that developmentally induced epigenetic marks make a significant contribution to later phenotype but also suggest that the detection of epigenetic marks even in peripheral tissue may allow identification of individuals at increased risk of chronic disease in later life before the onset of clinical disease'.

Conclusions

Cardiovascular disease is increasingly viewed as not simply developing in adulthood, but rather as a group of disorders that become apparent in adulthood, but which have their origins in the early life environment [90]. Undernutrition or exposure to an obesogenic environment pre-birth has a great impact upon an individual's future health, with nutritional exposure altering development of the cardiovascular system and kidneys, as well as triggering wide-ranging alterations to gene expression of many critical factors that regulate blood pressure and metabolism. Many of the changes brought about by nutrition in early life are thought to be mediated by epigenetic alterations that regulate how a gene is expressed, with epigenetic changes maintaining this new pattern of expression during an individual's life course, thereby setting them on the path to future disease.

While many factors contribute to an individual's CVD risk, it is the central role of the early life environment and the cyclical nature of disease risk whereby maternal obesity and diet impact upon the health of the next generation that in turn passes on the burden of disease, which must be addressed [5]. Pregnancy and early infancy represents a window of opportunity to promote healthier diets and increased physical activity, with dietary interventions during pregnancy shown to reduce CVD risk associated with undernourishment [7, 19, 91, 92]. Studies on maternal weight loss through bariatric surgery prior to pregnancy have found that transmission of obesity to the next generation can be avoided or reduced [93], suggesting that the transgenerational impact of obesity can be blunted by nutritional intervention. The importance of early life influences on an individual's future cardiovascular wellbeing is central to any health and prevention strategy that seeks to ameliorate the burgeoning rates of cardiovascular-linked mortality, and to tackle what has been described as the most important global health issue of this century [2]. Such preemptive strategies are possible, practical and will provide long-term benefits for public health.

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Compliance with Ethics Guidelines

Conflict of Interest Robert Murray and Karen Lillycrop have no conflicts of interest. Keith Godfrey reports other from Nestle Nutrition Institute, grants from Abbott Nutrition and Nestec, outside the submitted work; In addition, Dr. Godfrey has a patent phenotype prediction pending, a patent predictive use of CpG methylation pending, and a patent maternal nutrition composition pending.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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