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## EARLY INFLUNCES ON CARDIOVASCULAR AND RENAL DEVELOPMENT

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## **ABSTRACT**

The hypothesis that a developmental component plays a role in subsequent disease initially arose from epidemiological studies relating birth size to both risk factors for cardiovascular disease and actual cardiovascular disease prevalence in later life. The findings that small size at birth is associated with an increased risk of cardiovascular disease have led to concerns about the effect size and the causality of the associations. However, recent studies have overcome most methodological flaws and suggested small effect sizes for these associations for the individual, but a potential important effect size on a population level. Various mechanisms underlying these associations have been hypothesized, including fetal undernutrition, genetic susceptibility and postnatal accelerated growth. The specific adverse exposures in fetal and early postnatal life leading to cardiovascular disease in adult life are not yet fully understood. Current studies suggest that both environmental and genetic factors in various periods of life may underlie the complex associations of fetal growth retardation and low birth weight with cardiovascular disease in later life. To estimate the population effect size and to identify the underlying mechanisms, well-designed epidemiological studies are needed. This review is focused on specific adverse fetal exposures, cardiovascular adaptations and perspectives for new studies.

**Key words:** fetal growth – birth weight – cardiovascular disease – fetal origins – epidemiology – follow-up

## INTRODUCTION

Many epidemiological studies from different geographical regions demonstrated consistent association between low birth weight and the risk of cardiovascular disease.<sup>1-3</sup> These associations can not be explained by preterm birth.<sup>4, 5</sup> Also, they seem to be independent of influences in adult life including social class, obesity and smoking habits.<sup>6, 7</sup> The mechanisms underlying these associations are not well known. It has been suggested that developmental adaptations due to suboptimal fetal nutrition permanently program the fetus and lead to an increased risk of coronary heart disease many decades later.<sup>8</sup> It has also been argued that the associations between size at birth and later disease could primarily be the result from common genetic influences. Based on more recent studies, a more general developmental plasticity hypothesis has been proposed.<sup>9</sup> Developmental plasticity is defined as the ability of an organism to develop in various ways, depending on the particular environment or setting.<sup>10</sup> In this process, early environmental influences induces anatomical, physiological and biochemical adaptations in later life. These adaptations may be beneficial for short term survival but could have adverse long term consequences. This latter conceptual basis is extended with the Predictive Adaptive Response (PAR) theory, stating that long-term consequences of these early environmental influences may be especially harmful if the actual postnatal, mature, environment differs from the environment predicted during the plastic, developmental, phase.<sup>11</sup> The greater the degree of mismatch, the greater the disturbance in physiology and the greater the risk of disease.

Studies in humans generally use birth weight as measure of adverse fetal exposure. Birth weight might indeed be an indicator of the quality of the intra-uterine environment.<sup>12</sup> However, the same birth weight might be the result of different growth patterns and exposures in fetal life. Furthermore, a period of compensatory growth will follow after nutritional deficit in utero. The most rapid growth acceleration in low birth weight children occurs in the first

weeks after birth.<sup>13</sup> This accelerated growth rate might also have important consequences later in life.<sup>14</sup> These findings suggest that children with both restricted fetal and infant growth and accelerated childhood weight gain are at particular risk of cardiovascular disease in adult life and its risk factors.<sup>15, 16</sup>

In this paper, we discuss epidemiological studies designed to identify mechanisms underlying the associations of fetal growth retardation and low birth weight with the development of cardiovascular disease in adulthood. We will focus on specific adverse fetal exposures, cardiovascular adaptations and perspectives for new studies.

## SPECIFIC FETAL EXPOSURES

### **Fetal undernutrition**

#### *Maternal anthropometrics, maternal diet and placenta function*

The fetal nutrition supply line includes maternal anthropometrics, diet and placenta function. Maternal anthropometrics during pregnancy are related to their nutritional and health status.<sup>17</sup> <sup>18</sup> Several studies have shown that maternal anthropometric factors such as prepregnancy body mass index and weight gain during pregnancy are associated with fetal growth characteristics and adverse pregnancy outcomes.<sup>19-21</sup> Thus, the maternal nutritional and health status during pregnancy may lead to an adverse fetal environment and might affect fetal growth and development (Table 1).

Studies examining the direct effect of maternal anthropometrics on cardiovascular outcomes in the offspring demonstrated conflicting results (Table 1). Most of these studies were based on retrospective cohorts. We found in a prospective cohort study that maternal weight gain during pregnancy is associated with larger left ventricular mass at the age of 6 months, independent of maternal weight just before pregnancy.<sup>22</sup> Additionally, a recent study showed that greater maternal gestational weight gain is associated with greater offspring body mass index into early adulthood and that this may translate into higher systolic blood pressure in the offspring.<sup>23</sup> Several underlying biological pathways may explain the associations between maternal anthropometrics during pregnancy and vascular development and cardiac growth and development postnatally. One explanation could be that the usual increase in insulin resistance seen in late pregnancy is higher in mothers who show a marked increase in weight during pregnancy, resulting in increased fetal body and cardiac growth.<sup>24, 25</sup> Further studies, in which measures of insulin resistance such as insulin, glucose or HbA1c levels in

pregnancy have been measured, are needed to identify the potential role of insulin resistance for fetal cardiovascular development. The major limitation of weight gain is that the total amount depends on both an increase in fluid and fat mass. Also, it is not clear whether maternal pre-pregnancy weight or weight gain during pregnancy affects cardiovascular development in the offspring.

The fetal nutrition supply line may also be directly affected by dietary intake of the mother during pregnancy. Follow-up of persons who were conceived during the Dutch famine during the second World War demonstrated a doubled risk and an earlier onset of coronary artery disease among subjects who were exposed to famine during fetal life.<sup>16</sup> These results were independent of size at birth and current smoking and social economic status and suggest that severe maternal malnutrition during early gestation contributes to the occurrence of coronary artery disease in the offspring. However, these results could not be replicated in a cohort of adults who were exposed as fetus to severe famine during the siege of Leningrad.<sup>26</sup> The associations of less extreme variations in maternal intake of macronutrients and micronutrients with the development of risk factors for cardiovascular disease in the offspring have also been studied. Prospective cohort studies showed that variation in maternal total protein intake during pregnancy does not program offspring blood pressure already in infancy or in adolescence.<sup>27-29</sup>

Stronger relations have been reported between micronutrients and risk factors for cardiovascular disease in the offspring. Maternal calcium supplementation during pregnancy has been described to be associated with lower systolic blood pressure in the offspring.<sup>30-32</sup> Although, in some follow-up studies the effect disappeared later in childhood and no association were reported in twins.<sup>33,34</sup> Therefore, it is still unclear whether ensuring adequate calcium intake among pregnant women could be a way to prevent hypertension in the next generation. Low folate and high homocystein levels, in combination or independently, have

been shown to be risk factors for endothelial dysfunction and cardiovascular disease.<sup>35, 36</sup> In healthy infants, a relationship between maternal folate levels during pregnancy and vascular endothelial function was demonstrated.<sup>37</sup> More recently developed statistical approaches, such as dietary patterns of maternal nutrition intake during pregnancy, may give more detailed insight into the development of risk factors for cardiovascular disease later in life.

Placental function, including placental weight and haemodynamic function is one of the most important determinants of the fetal supply line. Size of the placenta reflects only an indirect measure of its capacity to transfer nutrients to the fetus, but it is strongly associated with fetal size at birth.<sup>38</sup> A review focused on the associations of placental weight with the risk of cardiovascular disease in the offspring and reported no consistent associations.<sup>39</sup> Preeclampsia is considered as the most extreme form of haemodynamic placental dysfunction. According to recent studies, women with prior preeclamptic pregnancies are at increased risk of cardiovascular disease.<sup>40, 41</sup> Furthermore, preeclampsia has been associated with elevated blood pressure in offspring during childhood and adolescence.<sup>42</sup> Fetal growth restriction due to placental dysfunction or common genetic variants may at least partly explain these associations. A milder form of placental haemodynamic dysfunction is reflected by the resistance in the umbilical artery. An increased umbilical artery resistance is associated with fetal growth restriction and low birth weight.<sup>43</sup>

### *Maternal smoking during pregnancy*

Maternal smoking during pregnancy is strongly associated with fetal growth retardation.<sup>44-46</sup> The effects of smoking on placental vessels could be due to nicotine or hypoxia. This association is partly mediated by restricted blood flow in the vascular beds of the placenta, due to increased resistance of the umbilical-placental circulation.<sup>47, 48</sup> Fetal exposure to maternal smoking might also have adverse and persistent consequences for cardiovascular

growth and development. Recent studies showed associations between intra-uterine exposure to maternal smoking and high blood pressure in childhood and adulthood.<sup>49, 50</sup> However, the association of maternal smoking and offspring blood pressure might be confounded by a comprehensive range of indicators of social economic position. Confounding by social and familial factors is further supported by the similarity of maternal and paternal smoking effects, suggesting that modest differences in childhood blood pressure associated with maternal smoking could be the result of not only biological effects on the intrauterine environment, but also common adverse familial factors.<sup>51</sup> Studies focused on fetal cardiovascular development may unravel these associations. We found in a prospective cohort study that maternal smoking during pregnancy is associated with placental and fetal haemodynamic adaptations indicating increased arterial resistance.<sup>52</sup> These fetal haemodynamic adaptations were subsequently associated with fetal growth retardation and changes in postnatal cardiac structures. Similarly, maternal smoking in pregnancy has also been suggested to be directly associated with changes in fetal cardiac dimensions and volumes.<sup>53, 54</sup>

### **Genetic susceptibility**

The association of fetal growth restriction and low birth weight with the increased risk of cardiovascular disease may also be explained by common genetic variants related to insulin sensitivity or angiogenesis (Table 2).<sup>55</sup> Insulin and insulin-like growth factors are important fetal growth factors.<sup>56</sup> Genetic factors related to insulin or insulin-like growth factors production and sensitivity may lead to both impaired fetal growth and to type 2 diabetes and cardiovascular disease in later life.<sup>55</sup> Previously, Single Nucleotide Polymorphisms (SNPs) in the IGF1 gene and the INS VNTR gene have been suggested to be associated with fetal and postnatal growth. However, these effects seem not to be consistent.<sup>57, 58</sup>

Common polymorphisms of type 2 diabetes gene *PPAR $\gamma$ 2* may also explain previously suggested associations of growth in early life with the risk of cardiovascular disease in later life. Two large birth cohort studies found no association between the *PPAR $\gamma$ 2* polymorphism and birth weight.<sup>59, 60</sup> We recently showed that the *PPAR $\gamma$ 2* Ala12 allele is associated with an increased growth rate in early life. This effect was modified by the duration of breastfeeding.<sup>61</sup> In addition to the *PPAR $\gamma$ 2* polymorphism, other common type 2 diabetes genetic susceptibility variants seem to affect size at birth directly through the fetal genotype. Risk alleles at *CDKAL1* and *HHEX-IDE* were both associated with reduced birth weight. These findings suggest the associations between low birth weight and type 2 diabetes might at least partly explained by common genetic variants.<sup>62</sup> Furthermore, it has been demonstrated that the *PPAR $\gamma$ 2* polymorphism modifies the associations of low birth weight with lipid levels and hypertension.<sup>63, 64</sup>

Glucocorticoids are important regulators of cardiovascular function and metabolism. Studies in rats showed that activity of placental 11 $\beta$ -hydroxysteroid dehydrogenase type 2, which converts physiological glucocorticoids to inactive products, correlates positively with birth weight and negatively with placental weight.<sup>65</sup> In addition, administration of low-dose dexamethasone to pregnant rats not only reduces birth weight but also leads to high blood pressure in young adult offspring.<sup>65</sup> In human studies, it is demonstrated that fetuses with the greatest exposure to maternal glucocorticoids have low birth weight and high placental weight and might be at a higher risk of subsequent hypertension.<sup>66</sup> Increased exposure to cortisol in adults leads to increased risks of cardiovascular disease, type 2 diabetes and obesity.<sup>67, 68</sup> Thus higher exposure to glucocorticoids in fetal and early postnatal life might affect cardiovascular development in fetal life and early childhood. The effects of these hormones, including cortisol, are mediated by glucocorticoid receptors. Glucocorticoid receptor gene (*NR3C1*) SNPs may explain part of the associations between growth characteristics in early life and

disease in adulthood by increasing glucocorticoid sensitivity in the fetus for maternal glucocorticoids. A previous study in adults found an association between the GR-9 $\beta$  polymorphism and an increased risk of cardiovascular disease.<sup>69</sup> We found an association of this GR-9 $\beta$  polymorphism with increased left ventricular mass and systolic blood pressure in children aged two years.<sup>70</sup> No associations were observed between this GR-9 $\beta$  polymorphism and fetal and early postnatal growth.<sup>71</sup> Other recent identified glucocorticoid related polymorphisms, such as the brain-derived neurotrophic factor (BDNF) and the mineral corticoid gene, may affect fetal and postnatal growth by influencing the glucocorticoid metabolism.

Thus far, results of studies focused on the associations of common genetic variants related to both early growth and the risk of cardiovascular disease later in life are inconsistent. Further systematic searches for common genetic variants by means of genome-wide association studies will enable us to obtain a more complete understanding of what genes and polymorphisms are involved in both growth in fetal life and infancy and development of cardiovascular disease in adulthood.

## **CARDIOVASCULAR ADAPTATIONS**

### **Cardiac development**

#### *Stimuli for cardiac development*

It has been demonstrated that fetuses have stiffer fetal ventricles than neonates and the diastolic filling patterns in normally grown fetuses mimic those of the diseased adult heart.<sup>72</sup> Left ventricular elastic compliance increases with gestational age and left ventricular stiffness significantly decreases. In growth restricted fetuses, this process may be affected.<sup>72</sup>

Furthermore, reduced end-diastolic flow velocities in fetal umbilical and maternal uteroplacental arteries have been associated with increased peripheral vascular resistance.<sup>73</sup> This increase in peripheral arterial resistance and subsequently in fetal cardiac afterload may lead to an increase in fetal cardiac performance and to persistent structural left ventricular changes.<sup>74</sup> Decreased fetal growth was also associated with fetal adaptations in cardiac function in the whole range of fetal growth.<sup>75</sup> Furthermore, birth weight and measures of placental vascular resistance and fetal cardiac output were associated with left cardiac structures until the age of two years.<sup>76</sup> This is in line with a previous prospective cohort study in children which demonstrated positive associations of birth weight with total coronary artery diameter, aortic root diameter and left ventricular outflow tract diameter in children aged 9 years.<sup>77</sup> However, inverse associations between birth weight and left ventricular mass in adolescents and adults have been demonstrated.<sup>78, 79</sup> It should be investigated whether these relations persist during later life and are related to the development of cardiovascular disease in adulthood.

#### *Adverse cardiac adaptations*

Studies in children showed that left ventricular mass tracks from childhood to adulthood.<sup>80, 81</sup> This implies that children with smaller left cardiac structures in early postnatal life tend to keep their relatively smaller left cardiac structures in childhood.<sup>76, 80, 81</sup> However, a relatively smaller left ventricle and aortic root may lead to insufficient cardiac functioning for increasing metabolic demands in postnatal life. Subsequently, the heart may respond by growth and adverse remodeling. Since the number of heart cells is established largely in fetal life, adaptation and growth of existing cells may eventually lead to left ventricular dysfunction and hypertrophy. Left ventricular hypertrophy is a strong and independent risk

factor of cardiovascular morbidity and mortality in adulthood.<sup>82, 83</sup> Thus fetal exposures affecting cardiac development may have life long consequences.

## **Renal development**

### *Stimuli for renal development*

Nephrons start to form from day 30 of gestation.<sup>84</sup> Numerous factors, including the renin-angiotensin system (RAS), various growth factors, apoptosis and an adequate supply of nutrients are required for nephrogenesis.<sup>85-87</sup> Nephrogenesis continues until 36 weeks of gestation and the induction of nephron number ceases thereafter.<sup>88, 89</sup> On average  $\pm 750,000$  nephrons per kidney are present, with a wide interindividual range (250,000 – 2,000,000).<sup>90-93</sup>

Animal studies have shown that various determinants of fetal nutrition including low protein intake, relative vitamin A deficiency, reduced placenta perfusion and administration of steroids in late pregnancy cause fetal growth restriction, smaller kidneys and a permanent reduced nephron number.<sup>94-97</sup> Human studies demonstrated that low birth weight infants have lower kidney weight with a reduced number of nephrons.<sup>98, 99</sup> It was also demonstrated that hypertensive subjects have lower nephron numbers.<sup>100</sup> The best surrogate measure for assessing nephron number in epidemiological studies appears to be kidney weight or size measured by ultrasound.<sup>89</sup> A few studies investigated renal length or volume in early life. Being small for gestational age (SGA) is associated with small kidneys at birth and impaired kidney growth in early childhood.<sup>101</sup> Kidney length in preterm SGA infants follows closely the other anthropometric parameters during the first year of life.<sup>102</sup> SGA term infants had shorter kidney length at birth compared to appropriate for gestational age infants, but a similar length from 3<sup>rd</sup> to 24<sup>th</sup> month of life.<sup>103</sup> This may represent either an accelerated renal maturation or early compensatory kidney hypertrophy in the SGA infants. Maternal

anthropometrics, fetal abdominal circumference, fetal blood flow redistribution, and raised placental resistance are associated with both third trimester fetal kidney volume and kidney volume at the age of two years.<sup>104, 105</sup> Since, kidney size tracks from third trimester of pregnancy to early childhood, these adaptations may have persistent consequences.<sup>104</sup>

### *Adverse renal adaptations*

The kidneys respond to this reduced number of nephrons by hyperperfusion and remodelling.<sup>106</sup> According to the hyperfiltration theory, this will lead to more sodium reabsorption, increased systolic blood pressure and albuminuria.<sup>107</sup> This process may be in favor of short-term renal function but may eventually lead to glomerular hypertrophy and damage.<sup>106</sup> Finally, this may predispose the individual to renal failure and hypertension. It has been shown that low birth weight is associated with early onset chronic renal failure. In subjects aged less than 50 years, those who weighted less than 2.5 kg at birth had a higher risk for end-stage renal disease than people who weighted 3-3.5 kg at birth.<sup>108</sup> This association was shown in all groups of primary causes of end stage renal failure in adults (hypertension, diabetes and other causes). Studies in younger subjects have focused on urine albumin excretion, a predictor of cardiovascular and renal disease in diabetic and non-diabetic subjects.<sup>109</sup> Low birth weight is associated with microalbuminuria in children and adults independent of blood pressure and measures of insulin resistance.<sup>110, 111</sup> The pathway leading from small kidneys to hypertension may include the renin-angiotensin system, which has been demonstrated to be altered in the early phase of primary hypertension.<sup>112</sup> An increased activity of the renin-angiotensin system could be a compensatory mechanism in a decreased number of nephrons in order to maintain normal renal filtration. It has been demonstrated that renin activity in umbilical cord blood is inversely related with the size of the kidney at birth.<sup>113</sup>

## **Vascular development**

### *Haemodynamic stimuli for fetal vascular development*

Fetal growth retardation leads to a preferential blood flow to the brain and heart, which deprives other organs of adequate oxygen and nutrients supply. This brain-sparing suggests organ specific vasodilatation and vasoconstriction and has been demonstrated in growth restricted fetuses.<sup>114</sup> In addition, we recently demonstrated that decreased fetal growth is associated with adaptive fetal cardiovascular changes.<sup>75</sup> These changes already occurred before the onset of clinically apparent fetal growth restriction. Future studies are needed to identify whether these adaptations in fetal haemodynamics have consequences for the development of cardiovascular disease in later life.

### *Endothelial function*

The endothelium controls vascular tone, coagulation and inflammatory responses.<sup>115</sup> Endothelial dysfunction is an early event of atherosclerosis, preceding structural changes in the vascular wall.<sup>116</sup> Atherosclerosis is thought to begin in childhood and to develop silently before clinical events such as myocardial infarction or stroke occur. Many studies demonstrated atherosclerotic wall thickening in the arteries of children with cardiovascular risk factors using ultrasound imaging.<sup>117</sup> Furthermore, studies have shown that risk factors for cardiovascular disease measured in childhood are track into adulthood.<sup>118, 119</sup> There is limited direct evidence that risk factors measured in childhood are predictive of atherosclerosis in adulthood.<sup>120, 121</sup> Only a few studies examined the associations of fetal and maternal factors during pregnancy and vascular changes in childhood. Low maternal folate levels during pregnancy and low birth weight are demonstrated to be associated with vascular endothelial dysfunction in newborn infants.<sup>37, 122, 123</sup> Further follow up studies are needed.

### *Arterial stiffness*

Flow may determine vascular growth in the fetal cardiovascular system and thereby a reduction in flow may alter later vascular behaviour.<sup>124</sup> One mechanism that could underlie the association of low birth weight with raised blood pressure may be a suboptimal development of the fetal cardiovascular system due to these circulatory changes, thus increasing the stiffness of the vessel wall and comprising the cardiovascular function.<sup>125</sup> Several studies have attempted to test this hypothesis by investigating the relationship between birth weight and indicators of arterial stiffness such as pulse wave velocity and pulse pressure, but with conflicting results.<sup>126-130</sup> Another mechanism could be that these haemodynamic adaptive changes in the fetal circulation, which occur in a critical period of blood vessel development, may influence rates of elastin synthesis.<sup>129</sup> This may result in a reduced compliance of the large arteries, leading to higher pulse and mean blood pressures. Furthermore, the process of aging causes a gradual loss of elastin and replacement by collagen, which amplifies the increase in blood pressure.<sup>130</sup> Persistent alteration in conduit artery function and arterial stiffness may predispose a person to hypertension and cardiovascular disease in adulthood.

## **PERSPECTIVES**

### **Study designs**

The associations of fetal growth retardation and low birth weight with cardiovascular disease are not yet fully understood. Methodological issues, such as the role of potential confounders in the associations and the population effect size, should be further examined. Well-designed epidemiological studies are necessary to overcome current methodological issues. Population-based prospective cohort studies starting in the preconceptional period or in early fetal life, in which the offspring is followed from early fetal life until young adulthood, seem to be the most suitable epidemiological design (Figure 1). This epidemiological design is the best design for assuring quality of the data, taking account for potential confounders and identifying growth patterns at risk. Recently, various population-based prospective cohort studies have been started worldwide.<sup>131-134</sup> However, a limitation of this design is the long period needed for the studied adult disease to develop. The design of a retrospective cohort study may lead to an earlier availability of data according to cardiovascular disease. However, this design will not take account of all potential confounders and will probably not be able to study the effects of fetal or early postnatal influences.

The effects of many adverse fetal exposures due to maternal life style habits can only be studied in observational designs. However, for assessing the effects of nutritional exposures on fetal growth restriction and the risk of cardiovascular disease, randomized controlled trials would be the design of choice. For example the impact of calcium, folate and other micronutrients on offspring birth weight and blood pressure is examined in randomized controlled trials.<sup>30, 135, 136</sup> Randomized controlled trials should be able to overcome current methodological issues and identify mechanisms in the causal pathway that underlie the associations.

## **Detailed exposure studies**

### *Nutrition*

In Western countries, maternal variation in dietary patterns and intake of micronutrients seems more relevant than a restricted total energy and macronutrient intake for having an effect on fetal growth retardation.<sup>137</sup> Future studies should focus on the intake of particular macronutrients and micronutrients, including calcium, folic acid and homocystein, in specific periods of pregnancy. Identifying critical periods in pregnancy will result in detailed dietary advices aimed at these specific time points in pregnancy. Additionally, dietary patterns during the preconception period have been associated with biomarkers concentrations and related to complex diseases, such as cardiovascular disease.<sup>138, 139</sup> Overall dietary patterns may be easier for the public to interpret or translate into diets.

### *Genome-wide association studies*

Common genetic variants may explain the associations between growth in early life and diseases in adulthood. Large scale genome-wide association studies (GWAS) have revealed links between DNA sequence variation and a growing range of diseases and continuous traits, such as cardiovascular disease and type 2 diabetes.<sup>140-142</sup> The effect of these common genetic variants on growth characteristics and growth patterns may already be present in fetal and early postnatal life. Relating these genetic loci to early growth patterns might identify genes related to both fetal growth retardation and cardiovascular disease.

### *Epigenetics*

Epigenetics is understood as the heritable changes in gene expression potential that are not caused by changes in DNA sequence.<sup>143, 144</sup> DNA methylation is one of the best understood epigenetic modification and is a key epigenetic contributor to maintenance of gene silencing. CpG islands are mostly located in the control regions of genes, for example the promoter region of actively transcribed gene, and are generally unmethylated. Methylation of this promoter region leads to decreased binding of transcription factors and thereby to a reduced gene expression.<sup>145</sup> Maternal diet has been shown to dynamically affect DNA methylation status.<sup>146</sup> Methyl-supplemented diets include the methyl donors such as folic acid, vitamin B12, choline, L-methionine and zinc. Studies in sheep showed associations between reductions in the availability of Vitamin B12 and folate during the periconceptual period and alterations in methylation status of CpG islands in the offspring.<sup>147</sup> This may lead to widespread epigenetic modifications to the genome of the offspring. In humans, lower DNA methylation of the *IGF2* gene was reported in adults who have been exposed to the Dutch Famine in the periconceptual period.<sup>148</sup> These results suggest that early-life environmental conditions can cause epigenetic changes that persist throughout life and could lead to the development of risk factors for hypertension and cardiovascular disease in adult offspring. However, future research is needed to better understand the role of epigenetic dysregulation in the associations between adverse fetal nutritional exposures and diseases in adult life.<sup>149</sup> Since the periconceptual period is a crucial period for establishing and maintaining epigenetic marks, cohort studies starting in the preconceptional period would give important knowledge.<sup>150</sup>

### *Paternal influences*

We discussed substantial affects on fetal programming by maternal prenatal behaviors, specifically by maternal smoking, maternal diet and maternal genetic susceptibility. However,

paternal influences, for example paternal genetic susceptibility, could also underlie the pathways of fetal growth retardation and low birth weight to the development of cardiovascular disease in adulthood. Also, comparing maternal and paternal effects provides a method of separating intra-uterine effects from associations related to familial or environmental factors. Similar associations of maternal and paternal exposures with offspring health outcomes suggest that common factors related to the family or environment may drive the associations, rather than intrauterine effects only. Future research is required to compare associations of both maternal and paternal exposures during pregnancy with components of offspring health.

### **Detailed cardiovascular development studies**

To disentangle the mechanisms underlying the associations of fetal growth restriction and low birth weight with the development of cardiovascular disease, future research should focus on early markers of cardiovascular adaptation. Good repeatability and reproducibility of most left cardiac structures in children measured by 2D ultrasound is previously demonstrated in large-scale multicenter studies in young children.<sup>151, 152</sup> However, newer imaging techniques, such as three-dimensional echocardiography and magnetic resonance imaging, can more precisely calculate physiologic variables of interest.<sup>153</sup> In the future, these new imaging techniques offer great opportunities for detailed cardiovascular measurements in epidemiological research. Thereby, subtle developmental cardiovascular changes can be identified already in fetal or early postnatal life. Furthermore, focusing on other biomarkers of cardiac development, including detailed repeated measurements of right cardiac structures, may give newer inside in the pathway leading to the development of cardiovascular disease.

Although there is limited direct evidence that risk factors measured in childhood are predictive of atherosclerosis in adulthood<sup>154, 155</sup>, less is known about the associations of fetal

and maternal factors during pregnancy and vascular changes in childhood. Endothelial function and structural arterial changes, including arterial resistance and arterial stiffness, can be measured noninvasively in early childhood with high resolution ultrasound to measure brachial artery flow-mediated dilatation and carotid artery intima-media thickness, respectively.<sup>156, 157</sup> Furthermore, future studies should focus on additional markers of vascular structures and function, including retinal arteriolar narrowing. This may lead to peripheral vascular resistance and thereby predispose a person to the development of hypertension and cardiovascular disease.<sup>158</sup>

### **Clinical implications and future research**

The associations between low birth weight and cardiovascular disease in later life seem to be one of the most intriguing and controversial epidemiological findings from the last decade and might have clinical and public health implications. However, the effect size of low birth weight on cardiovascular disease and blood pressure in adulthood presented in current studies seems to be small.<sup>1, 159</sup> Furthermore, the specific adverse exposures and underlying mechanisms are not known. Recently, new areas of research in cardiovascular epidemiology have already become prominent. The focus has increasingly been on genes implicated in cardiovascular diseases.<sup>160-164</sup> However, the focus of most of the studies in cardiovascular epidemiology is still on putative risk factors<sup>165-173</sup>, with particular focus on nutrition<sup>174-177</sup>, on socio-economic factors and health inequalities<sup>178-193</sup>, and, more recently, on physical activity<sup>194-197</sup>. In addition, studies focus on methods of cardiovascular studies<sup>198-203</sup> and on frequency measures and trends in risks of cardiovascular morbidity and mortality<sup>204-213</sup>. For further exploring the underlying mechanisms and to assess potentials for clinical implications, research has to move onwards from birth weight association studies to adverse fetal exposures and detailed early cardiovascular development studies. Since plasticity operates across the

entire range of environment and leads to multigenerational cycles of disease, any rational approach to health care should start early in life and take a cross-generational perspective.<sup>214</sup> Data of prospective cohort studies confirm the existence of a window of opportunity for intervention in early childhood.<sup>215, 216</sup> The growing awareness of the importance of the preconceptional period, when nutrition can have long-lasting effects without causing any change in birth weight, underscores the importance of healthy nutrition during the prepregnancy period. Research should also focus on identifying individuals at greater risk of later poor health and develop strategies aimed at these specific individuals.

## **Conclusion**

The associations between low birth weight and cardiovascular disease are present within the normal and physiologic ranges, and suggest that specific exposures in different periods of fetal and early postnatal life have permanent consequences for cardiovascular growth and function. The mechanisms underlying these associations are not known, but may include environmental and genetic determinants. Future studies should be focused on these mechanisms and epigenetic modifications of specific genes related to cardiovascular development. Furthermore, studies should focus on detailed cardiovascular adaptive responses in fetal life and early childhood by use of new imaging and functional techniques. Eventually results from these studies may lead to improved health in childhood and adulthood by promoting a better fetal environment.

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## **DISCLOSURE OF INTERESTS**

Conflict of Interest: none declared.

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## **FIGURE LEGENDS**

**Figure 1.** A developmental origins study model, studying the fetal origins of cardiovascular disease in epidemiological studies

This model presents core associations that have to be studied to unravel the underlying mechanisms of the associations of fetal growth restriction and low birth weight and cardiovascular disease later in life. The upper part shows associations in mother and father, identifying both determinants of fetal and postnatal growth patterns and environmental and genetic mechanisms. The lower part demonstrates associations in the offspring that have to identify growth patterns and developmental changes in fetal and early postnatal life, resulting in an increased risk of cardiovascular disease in adulthood.

RAAS, Renin-angiotensin-aldosterone system

**Table 1.** Maternal anthropometrics and diet in association with cardiovascular disease later in life

<b>Maternal anthropometric characteristic during pregnancy</b>	<b>Cardiovascular outcome</b>
Maternal anthropometric	
Short stature	Increased death rates from coronary heart disease
Low triceps skin fold thickness	Increased blood pressure
High weight gain during pregnancy	Increased left ventricular mass
Maternal diet	
Total energy intake	Increased risk and earlier onset coronary artery disease
Low protein intake	Increased blood pressure
Low calcium intake	Increased blood pressure
Low folate intake	Endothelial dysfunction

**Table 2.** Common genetic variants (*PPAR $\gamma$ 2* and GR gene) studied to explain the associations between low birth weight with type 2 diabetes and cardiovascular disease later in life

First author (year)	Main finding: effect on pre- and postnatal growth	Main finding: effect on risk factors type 2 diabetes	Main finding: effect on risk factors cardiovascular disease
<i>PPAR<math>\gamma</math>2</i> (rs 1801282)			
Masud et al (2003) <sup>217</sup>		Pro12Ala genotype is associated with higher BMI and obesity.	
Bennett et al (2008) <sup>59</sup>		Pro12Ala genotype is not associated with birth weight.	
Pfab et al (2006) <sup>60</sup>	Pro12Ala genotype is not associated with intra-uterine growth, size at birth and insulin resistance.	Pro12Ala genotype is not associated with intra-uterine growth, size at birth and insulin resistance.	
Mook-Kanamori et al (2009) <sup>61</sup>	Ala12 allele is associated with an increased growth rate in early life. This effect may be influenced by the duration of breastfeeding.	Ala12 allele is associated with an increased growth rate in early life. This effect may be influenced by the duration of breastfeeding.	

Eriksson et al (2003) <sup>63</sup>		Ala12 allele and a lower birth weight is associated with risk of increased lipid levels.	Ala12 allele and a lower birth weight is associated with risk of increased lipid levels.
Yliharsila et al (2004) <sup>64</sup>		Pro12Pro genotype modifies the association between low birth weight and hypertension.	Pro12Pro genotype modifies the association between low birth weight and hypertension.
<b>GR gene (NR3C1)</b>			
Van Rossum et al (2002) <sup>218</sup>		ER22/23EK polymorphism is associated with decreased sensitivity to glucocorticoids and low insulin levels.	ER22/23EK polymorphism is associated with decreased sensitivity to glucocorticoids and low cholesterol levels.
Finken et al (2007) <sup>219</sup>	ER22/23EK polymorphism is associated with a protecting effect against postnatal growth failure and insulin resistance after preterm birth.	ER22/23EK polymorphism is associated with a protecting effect against postnatal growth failure and insulin resistance after preterm birth.	

Van Rossum et al

(2003) <sup>220</sup>

G-allele of the Bcl-I polymorphism is associated with increased glucocorticoid sensitivity and lower BMI.

Rosmond et al (2000)

<sup>221</sup>

G-allele of the Bcl-I polymorphism is associated with increased abdominal obesity and higher cortisol levels in GG-carriers compared to CC-carriers.

Bueman et al (1997) <sup>222</sup>

G-allele of the Bcl-I polymorphism is associated with increased abdominal visceral fat in lean GG-carriers, but not in overweight GG-carriers.

Huizenga et al (1998)

<sup>223</sup>

N363S polymorphism is associated with increased glucocorticoid sensitivity, increased insulin response to Dexamethasone and increased BMI.

Watt et al (1992) <sup>224</sup>

Homozygosity for the G-allele of the Bcl-I polymorphism was more frequent in the group with personal and parental hypertension.

Di Blasio et al (2003)

225

Carrying both the N363S and the Bcl-I polymorphism is associated with higher systolic and diastolic blood pressure and serum cholesterol levels.

Rosmond et al (2001)

226

N363S polymorphism is not associated with BMI or sensitivity to glucocorticoids.

Lin et al (2003) <sup>227</sup>

N363S polymorphism is associated with obesity and overweight, but not with type 2 diabetes.

N363S polymorphism is not associated with hypertension.

Rosmond et al (2000)

228

TthIII polymorphism is associated with diurnal cortisol levels, but not with any anthropometric or glucose related phenotype.

Van den Akker (2008)

69

GR-9 $\beta$  polymorphism is associated with an increased risk of cardiovascular disease.

Geelhoed et al (2009) <sup>71</sup>

GR gene polymorphisms are not associated with growth in fetal and early postnatal life, neither to size at birth or catch-up growth until the age of 2 years.

GR gene polymorphisms are not associated with growth in fetal and early postnatal life, neither to size at birth or catch-up growth until the age of 2 years.

Geelhoed et al (2009) <sup>70</sup>

GR-9 $\beta$  polymorphism is associated with increased systolic blood pressure and increased left ventricular mass at the age of 2 years.

**Figure 1**

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