

## The Fetal Origins of Coronary Heart Disease

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### Introduction

Recent research has shown that babies who were small at birth and during infancy will be at increased risk of developing coronary heart disease, stroke, diabetes or hypertension during adult life. That a person's destiny and lifespan may be determined before birth is well known. Genetically determined diseases such as Huntington's chorea illustrate how a long period of normal development and adult life can be prematurely brought to an end by the action of inherited defects. What is new is the realisation that it is not only the presence or absence of genes that controls our destiny but the way in which gene expression may be permanently changed by the nutrient environment in early life.

There are three reasons why this new field of research has developed. First, the current explanation of coronary heart disease, a 'destructive' model in which inappropriate adult lifestyles hasten aging processes, fails to account for either the time trends of the disease, or its geography, or why one person gets the disease and another does not. Second, the search for alternative explanations led to a strong geographical clue that the role of fetal

life in the genesis of coronary heart disease might be much greater than had been thought.<sup>1</sup> Third, animal experiments show that alternations in nutrition in early life may permanently change the growth and form of the body together with a range of its structures and functions.<sup>2</sup>

### Studies in Animals

The substantial body of evidence on the plasticity of the fetus, its ability to adapt to undernutrition, and the permanent effects of these adaptations, derives from animal experiments carried out by Widdowson and others.<sup>2</sup> These studies allow us to predict two things about the human fetus. Firstly, lack of nutrients or oxygen will cause persisting changes, which include altered metabolism, including glucose and lipid metabolism, altered blood pressure and altered 'settings' of hormonal axes, enzymes and cell receptors. Secondly the long term effects of undernutrition depend on the stage at which it occurs. Tissues and systems tend to be vulnerable to programming during phases of rapid cell replication, and different tissues undergo these 'sensitive' phases of development at different times.

### Small Size at Birth and in Infancy

It has been possible to explore the links between growth in utero and later coronary heart disease because a search of the archives in Britain revealed a number of collections of birth records of men and women born 50 years and more ago. The figure shows findings in a group of 8175 men born in the county of Hertfordshire before 1930. Their weight at one year of age strongly predicted their subsequent death rates from coronary heart disease. Death rates fell steeply between those who were small and those who were large at one year. There were similar trends in coronary heart disease with birthweight in men and women. A study in Sheffield showed that the small babies with high coronary death rates were small in relation to the duration of gestation rather than small because they were prematurely born.

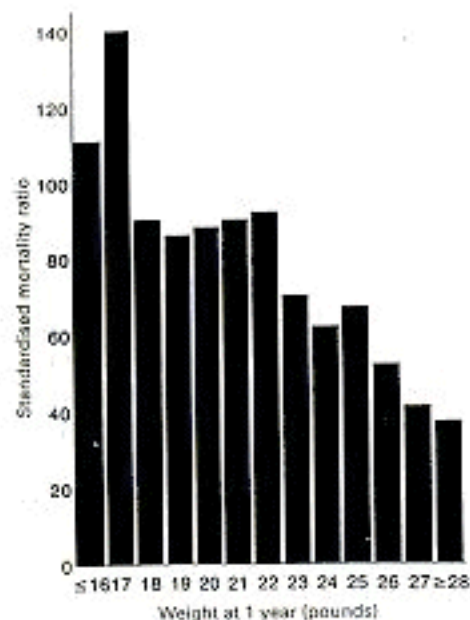


Fig. Standardised mortality ratios for coronary heart disease in 8175 men according to their weight at one year of age

These findings pose the question of what are the processes which link reduced early growth with adult disease. From examining samples of men and women who still live in Hertfordshire, and Sheffield, and in Preston, we now know that babies who were small have, as adults, raised blood pressure, raised serum cholesterol and plasma fibrinogen concentrations and impaired glucose tolerance<sup>4</sup> - the main risk factors for coronary heart disease. Table I shows the mean systolic pressures of men and women aged 64-71 years. Systolic pressure falls progressively between those who were small at birth and those who were large. The relation between birthweight and blood pressure has now been demonstrated in 21 studies of children and adults, and there is a secure base for saying that impaired fetal growth is strongly linked to blood pressure at all ages except during adolescence, when the tracking of blood pressure levels which begins in early childhood is perturbed by the adolescent growth spurt. Differences in blood pressure associated with birthweight are small in childhood but are magnified throughout life. This suggests that there may be amplification as well as initiation processes. We do not know what initiates high blood pressure in intrauterine life, but there are

Table I Mean Systolic Pressure (mmHg) in Men and Women Aged 64-71 years According to Birthweight.

Birthweight pounds (kg)	Men	Women
-5.5 (2.50)	171 (18)	169 (9)
-6.5 (2.95)	168 (53)	165 (33)
-7.5 (3.41)	168 (144)	160 (68)
-8.5 (3.86)	165 (111)	163 (48)
>8.5 (3.86)	163 (92)	155 (26)
Total	166 (418)	161 (184)
Standard deviation	24	26

(Figures in brackets are numbers of subjects)

interesting clues including the work of Edwards and colleagues in Edinburgh which has pointed to the possible role of cortisol.<sup>5</sup>

Table II shows the prevalence of non-insulin dependent diabetes and impaired glucose tolerance according to birthweight in a group of men in Hertfordshire.<sup>6</sup> The prevalence falls sharply between men who were small at birth and men who were large. There are similar findings in women. This association between birthweight and diabetes has been replicated in two other studies in Britain, in two studies in the United States, and one in Sweden.

### Body Proportions at Birth

Studies of men and women who were small at birth have shown that they are resistant to insulin. The occurrence of insulin resistance in adults is characterised in a syndrome, in which diabetes, hypertension and raised plasma triglyceride concentrations coincide in the same patient. Table III shows that, allowing for current body mass, the relative risk of having syndrome X among people who were 6.5 pounds (2.95 kg) or less at birth is around 10 times higher than among people who were more than 9.5 pounds (4.31 kg). This is a large risk. For comparison the risk of coronary heart disease among smokers

compared with nonsmokers is around 2. The insulin resistance syndrome is associated not only with low birthweight but with thinness at birth, as measured by a low ponderal index (birthweight/length<sup>3</sup>). Babies who are thin at birth lack muscle as well as fat and muscle

in adult life is the peripheral site of insulin action. Insulin tolerance tests on men and women aged 50 confirm that those who were thin at birth are less sensitive to insulin.

Raised blood pressure in adult life is associated not only with thinness at birth but also with short body length in relation to head-size. Short babies are thought to have encountered undernutrition in late gestation and to have sustained brain growth at the expense of the trunk, including the abdominal viscera. Table IV shows mean serum cholesterol concentrations in a group of men and women aged 50 according to abdominal circumference at birth. The concentrations of total and LDL cholesterol fall between people who had small and

**Table II** Prevalence of Noninsulin Dependent Diabetes and Impaired Glucose Tolerance in Men Aged 59-70 Years

Birthweight pounds (kg)	Number of men	% with impaired glucose tolerance or diabetes	Odds ratio adjusted for body mass index (95% confidence interval)
5.5 (2.50)	20	40	6.6 (1.5 to 28)
-6.5 (2.95)	47	34	4.8 (1.3 to 17)
-7.5 (3.41)	104	31	4.6 (1.4 to 16)
-8.5 (3.86)	117	22	2.6 (0.8 to 8.9)
-9.5 (4.31)	54	13	1.4 (0.3 to 5.6)
>9.5 (4.31)	28	14	1.0
Total	370	25	

**Table III** Prevalence of Syndrome X (Type 2 Diabetes, Hypertension and Hyperlipidaemia) in Men According to Birthweight

Birthweight pounds (kg)	Total number of men	% with syndrome X	Odds Ratio Adjusted for body mass index (95% confidence interval)
5.5 (2.50)	20	30	18 (2.6 to 118)
-6.5 (2.95)	54	19	8.4 (1.5 to 49)
-7.5 (3.41)	114	17	8.5 (1.5 to 46)
-8.5 (3.86)	123	12	4.9 (0.9 to 27)
-9.5 (4.31)	64	6	2.2 (0.3 to 14)
>9.5 (4.31)	32	6	1.0
Total	407	14	

large abdominal circumferences.<sup>7</sup> Abdominal circumference partly reflects liver size, the liver being disproportionately large in the fetus. An inference from Table IV is that babies who have impaired liver development permanently re-set their cholesterol metabolism. Reduced abdominal circumference at birth is also associated with raised plasma concentrations of fibrinogen, another strong predictor of coronary heart disease. The differences in serum cholesterol and plasma fibrinogen concentrations associated with the range of abdominal circumference at birth are large, equivalent to at least 30 per cent differences in risk of coronary heart disease.

**Table IV** Mean Serum Lipid Concentrations According to Abdominal Circumference at Birth in Men and Women Aged 50-53 Years

Abdominal circumference (inches)	No. of people	Total cholesterol (mmol/l)	Low density lipoprotein cholesterol (mmol/l)
-11.5	53	6.7	4.5
-12.0	43	6.9	4.6
-12.5	31	6.8	4.4
-13.0	45	6.2	4.0
> 13.0	45	6.1	4.0
Total	217	6.5	4.3

**Table V** Effects of Fetal Exposure to Maternal Low Protein Diets on Systolic Blood Pressure in Adult Rats.

Dietary protein percent by weight	No.	Mean (SD) systolic blood pressure 9 weeks after birth (mm Hg)
18	15	137 (4)
12	13	152 (3)
9	13	153 (3)
6	11	159 (4)

## Summary of Programming

This brief review of what is known in animals and man allows a number of conclusions.

1. Restriction of nutrients or oxygen in utero leaves permanent marks on the physiology and structure of the body. As an example Table V shows the blood pressures of the offspring of four groups of pregnant rats given varying amounts of dietary protein. The offspring of rats who had lower protein diets had raised blood pressures nine weeks after birth and this persisted through adult life.
2. Experiments on animals have established that undernutrition at different times in early life has different effects. Undernutrition in early gestation leads to proportionate loss of body size as in the proportionally small newborn human baby. In late gestation undernutrition leads to disproportionate growth, as in the thin or short human baby. Disproportionate growth rather than small size seems to hold a key to the origins of coronary heart disease. Twenty years ago Widdowson showed that undernutrition could effect profound changes in the relative size of the body's organs without any major change in overall body size.<sup>1</sup>
3. The rapidly growing baby is more vulnerable to undernutrition. When rickets was common 70 years ago it was not small babies who got the disease but larger, more rapidly growing ones. Slow growth protects against undernutrition. In some countries such as China, where intra-uterine growth retardation is widespread, coronary heart disease is rare. Growth retardation in China seems to lead to down regulation of growth in early gestation, which could protect the fetus from the

effects of undernutrition later in gestation, and from the development of the disproportion which is associated with coronary heart disease.

Fetal undernutrition, which programmes the body, itself results from inadequate maternal intake of food, or inadequate transport or transfer of nutrients. Studies of the birthweights of families show a strong correlation between the birthweights of people related through their mothers, but not between the birthweight of people related only through their fathers. This and other findings suggest that fetal growth is not predominantly controlled by the fetal genome but by the supply of nutrients and oxygen from the mother.<sup>8</sup> In 1944, for a period of seven months, there was an embargo on food supplies to the population of western Holland. People starved. A generation of babies were conceived or born during famine and we now know something about what happened to them as adults.<sup>9</sup> Girls who were conceived in the famine but born after liberation by the allies, had normal birthweight and grew up to be normal women, but their babies, when they were born, were small. The ability of these women to deliver nutrients to their babies had, it seems, been impaired

by their own fetal experience. This observation illustrates how fetal nutrition depends not only on what the mother eats during pregnancy but on her physiological and metabolic competence, established during her early life, as well as her nutrient stores before pregnancy.

Table VI shows another aspect of the complex links between maternal and fetal nutrition. The mean systolic pressures of a group of men and women are arranged by four groups of birthweight and four groups of placental weight. As expected from previous findings those who were of heavier birthweight had lower blood pressure. But, unexpectedly, at any birthweight men and women who had had larger placentas had higher blood pressure. From studies in animals we know that placental enlargement is an adaptation to lack of nutrients, including oxygen; and in humans three kinds of baby are known to have disproportionately large placentae. They are the offspring of mothers who were anaemic in pregnancy, who exercised during pregnancy or who live at high altitude.<sup>8</sup> The fetus it seems attempts to overcome the deficiency in supply of nutrients or oxygen to it by increasing the area of its attachment to the mother. A high ratio of placental weight to birthweight is

**Table VI** Mean Systolic Blood Pressure (mm Hg) of Men and Women Aged 46 to 54 According to Placental Weight and Birth Weight. Number of Subjects in Parentheses

Birth weight (pounds)	Placental Weight (pounds)				All
	1.0	>1.25	>1.5	>1.5	
<5.5	152(26)	154(13)	153(5)	208(1)	154(45)
5.5-6.5	147(16)	151(54)	150(28)	166(8)	151(106)
6.5-7.5	144(20)	148(77)	145(45)	160(27)	149(169)
>7.5	133(8)	148(27)	147(42)	154(54)	149(129)
All	147(88)	149(171)	147(120)	157(90)	150(449)

linked to cardiovascular disease, impaired glucose tolerance and raised plasma fibrinogen concentrations in later life as well as to hypertension. The placenta seems to play an important role in programming the baby.

### **New Model of Coronary Heart Disease**

A new model for the causation of coronary heart disease is emerging.<sup>8</sup> Under the old model an inappropriate lifestyle, including cigarette smoking and lack of exercise, leads to accelerated destruction of the body in middle and late life, including the more rapid development of atheroma, raised blood pressure, and the development of insulin resistance. Under the new model coronary heart disease results not primarily from external forces but from the body's internal environment, homeostatic settings of enzyme activity, cell receptors, and hormone feed back, which are established in response to undernutrition in utero and lead eventually to premature death.

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