

## 15.4 Ischaemic heart disease

### 15.4.1 Epidemiology

#### 15.4.1.1 Influences acting *in utero* and early childhood

D. J. P. Barker

#### The fetal origins hypothesis

Over the past 10 years epidemiological studies have shown that people who had low birthweight, or who were thin or short at birth, are at increased risk of developing ischaemic heart disease and the related disorders stroke, hypertension, and non-insulin dependent diabetes (NIDDM). Associations between small size at birth and later disease, first recorded in Britain, have now been extensively replicated in studies in Europe and the United States. The associations extend across the whole range of birthweight and depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. They are not the result of confounding variables acting in later life, such as low socio-economic status and smoking.

These observations have given rise to the 'fetal origins hypothesis', which proposes that cardiovascular disease originates through adaptations which are made by a fetus when it is under-nourished. Unlike adaptations made in adult life, those made during early development tend to have permanent effects on the body's structure and function—a phenomenon sometimes referred to as programming.

#### Fetal nutrition

In common with other living creatures, human beings are 'plastic' in their early life, and are shaped by their environment. Although the growth of a fetus is influenced by its genes, studies in humans and animals suggest that it is limited by the environment, in particular by the nutrients and oxygen the fetus receives from the mother. The fetus responds to undernutrition in a number of ways. It can redistribute its cardiac output to protect key organs, the brain in particular; it can alter its metabolism, for example by switching from glucose to amino acid oxidation; and it can change the production of, or tissue sensitivity to, hormones regulating growth, in which insulin has a central role. Slowing of growth is also adaptive because it reduces the requirement for substrate. Experiments show that even minor modifications to the diets of pregnant animals may be followed by life-long changes in the offspring in ways that can be related to human disease, for example raised blood pressure and altered glucose–insulin metabolism.

Birthweight serves as a marker of fetal nutrition and growth, but it is an imperfect one. The fetus can adapt to undernutrition and continue to grow at the same rate, but with permanently altered physiology and metabolism. Furthermore, the same birthweight may be the outcome of many different paths of growth. Where more detailed measurements of body size at birth

are available they can give insights into adaptations that the fetus has made. For example babies that are thin, though within the normal range of birthweight, tend to be insulin resistant as children and adults and are therefore liable to develop NIDDM. It seems that the thin baby responds to under-nutrition through endocrine changes.

#### Ischaemic heart disease

An important clue suggesting that ischaemic heart disease might originate during fetal development came from studies of death rates among babies in Britain during the early 1900s. The usual certified cause of death in newborn babies at that time was low birthweight. Death rates in the new-born differed considerably between one part of the country and another, being highest in some of the northern industrial towns and the poorer rural areas in the north and west. This geographical pattern in death rates was shown to closely resemble today's large variations in death rates from ischaemic heart disease, variations that form one aspect of the continuing inequalities in health in Britain. One possible conclusion suggested by this observation is that low rates of growth before birth are in some way linked to the development of ischaemic heart disease in adult life.

The subsequent studies that confirmed the association between ischaemic heart disease and small size at birth were based on the simple strategy of examining men and women in middle and late life whose body measurements at birth were recorded. In the first study of this kind, 16 000 men and women born in Hertfordshire, United Kingdom, during 1911 to 1930 were traced from birth to the present day. Death rates from ischaemic heart disease fell two-fold between those at the lower and upper ends of the birthweight distribution (Fig. 1). A study in Sheffield, United Kingdom, showed that it was people who were small at birth because they failed to grow, rather than because they were born early, who were at increased risk of the

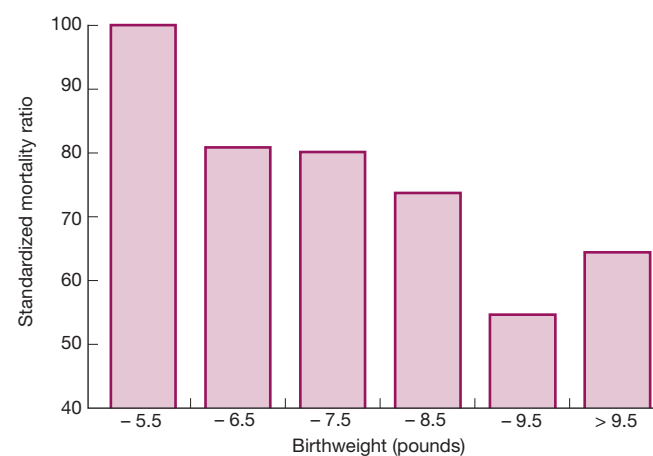


Fig. 1 Death rates from ischaemic heart disease in 15 726 men and women born in Hertfordshire according to their birthweights.

disease. The association between low birthweight and ischaemic heart disease has been confirmed in studies of men in Uppsala (Sweden), Helsinki (Finland), and Caerphilly (Wales), and among women in Helsinki and the United States. Among 80 000 women in the American Nurses Study there was a two-fold fall in the relative risk of non-fatal ischaemic heart disease across the range of birthweight. An association between low birthweight and prevalent ischaemic heart disease has recently been shown in a small study in South India. Among Indian men and women aged 45 years and over the prevalence of the disease fell from 18 per cent in those who weighed 5.5 lb (2.5 kg) at birth to 4 per cent in those who weighed 7 lb (3.2 kg) or more.

Some of these epidemiological studies included birth length, and other measurements of size at birth, in addition to weight. In Sheffield and in India, rates of ischaemic heart disease were higher in men who had short body length at birth. Thinness at birth, as measured by a low ponderal index (birthweight/length<sup>3</sup>), has also been found to be associated with ischaemic heart disease. Among men born in Helsinki, Finland, while low birthweight was associated with raised death rates for ischaemic heart disease, there was a stronger association with thinness at birth, especially in men born at term (Fig. 2). Among women in the same cohort, those who developed ischaemic heart disease also had low birthweight but were short at birth rather than thin. Since the men and women were born to the same group of mothers this difference may reflect intrinsic differences between the sexes in their paths of fetal growth. In the whole cohort, body proportions at birth differed in the sexes: the girls tended to be short while the boys tended to be thin. This may reflect differences in rates of fetal growth at similar levels of maternal nutrition. Female fetuses grow more slowly from an early stage of gestation and are therefore less vulnerable to under-nutrition. The lower rates of ischaemic heart disease among women could be related to their slower rates of growth *in utero*.

## Stroke

The pattern of body proportions at birth which predicts stroke is different to that which predicts ischaemic heart disease. Whereas stroke is similarly associated with low birthweight it is not associated with thinness or shortness. Instead, the studies in Sheffield and Helsinki found increased rates among men who had a low ratio of birthweight to head circumference. One interpretation of this is that normal head growth was sustained at the cost of interrupted growth of the body in late gestation. 'Brain-sparing' patterns of growth can result from diversion of cardiac output to the brain at the expense of the abdominal viscera, importantly the liver. Preliminary evidence suggests that this has lasting effects on liver function including altered regulation of low density lipoprotein cholesterol and raised plasma fibrinogen concentrations, a known risk factor for stroke.

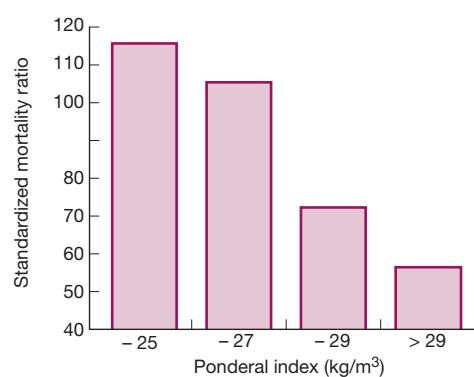


Fig. 2 Death rates from ischaemic heart disease in 3302 Finnish men born at term according to their ponderal indices at birth (birthweight/length<sup>3</sup>).

## Hypertension

Studies of the mechanisms linking low birthweight with ischaemic heart disease have shown that the progressive fall in disease rates across the range of birthweight (Fig. 1) is paralleled by progressive falls in two of its major biological risk factors—hypertension and NIDDM. Associations between low birthweight and raised systolic and diastolic pressure in childhood and adult life have been extensively documented around the world. Averaged across 69 studies, the difference in systolic pressure associated with a 1-kg difference in birthweight is around 3.5 mmHg. In clinical practice this would be small, but it is a large difference between the mean values of populations. Available data suggest that lowering the mean systolic pressure in a population by 10 mmHg would correspond to a 30 per cent reduction in total attributable mortality. Although in these studies alcohol consumption and higher body mass were also associated with raised blood pressure, the associations between birthweight and blood pressure were independent of them. Nevertheless, body mass remains an important influence on blood pressure and, in humans and animals, the highest blood pressures are found in those who were small at birth but become overweight as adults.

Table 1 shows the systolic pressures of a group of 50-year-old men and women who were born at term in Preston, United Kingdom. The subjects are grouped according to their birthweights and placental weights. Consistent with findings in other studies, systolic pressure fell between subjects with low and high birthweight. In addition, however, there was an increase in blood pressure with increasing placental weight. Subjects with a mean systolic pressure of 150 mmHg or more, a level sometimes used to define hypertension in clinical practice, comprised a group who as babies were small in relation to the size of their placentas. A rise in blood pressure with increasing placental weight has also been found in children in Salisbury, United Kingdom, and Adelaide, Australia, but in studies of children and adults the association between placental enlargement and raised blood pressure or ischaemic heart disease has been inconsistent.

As yet, we know little about the mechanisms which underlie the association between low rates of fetal growth and raised blood pressure. One suggestion is that retarded fetal growth leads to a reduced number of nephrons which in turn leads to increased pressure in the glomerular capillaries and the development of glomerular sclerosis. Another hypothesis which is being actively investigated is that fetal undernutrition leads to life-long changes in the fetus' hypothalamic–pituitary–adrenal axis and these in turn reset homeostatic mechanisms controlling blood pressure. Excessive cortisone production, as occurs in Cushing's syndrome, is associated with raised blood pressure and people who were small at birth have elevated plasma cortisol concentrations within the normal range. A third hypothesis derives from the observation that men and women in Sheffield who were small at birth had reduced elasticity in the large arteries of the trunk and legs, and raised blood pressure. The elasticity of larger arteries depends on elastin, which is laid down *in utero* and during infancy and thereafter turns over slowly: its half-life is 40 years. The amount of elastin laid down *in utero* increases with blood flow. 'Brain-sparing' diversion of blood to the brain could therefore lead to permanent loss of elasticity in the large arteries of the trunk.

## Non-insulin dependent diabetes

Both insulin resistance and deficiency in insulin production are thought to be important in the pathogenesis of NIDDM. There is evidence that both may originate during fetal life. Men and women with low birthweight and a low ponderal index have a high prevalence of the 'insulin resistance syndrome', in which impaired glucose tolerance, hypertension, and raised serum triglyceride concentrations occur in the same patient. The patients are insulin resistant and hyperinsulinaemic. A number of studies have shown that people who had low birthweight are already insulin resistant in childhood. A study of men and women who were *in utero* during the war-

**Table 1** Mean systolic blood pressure (mmHg) of men and women aged 50, born after 38 completed weeks of gestation, according to placental weight and birthweight

Birthweight lb (kg)	Placental weight lb (g)				All
	-1.0 (454)	-1.25 (568)	-1.5 (681)	>1.5 (681)	
- 6.5 (2.9)	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)
- 7.5 (3.4)	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)
> 7.5 (3.4)	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)
All	144 (43)	148 (132)	148 (83)	156 (69)	149* (327)

\*s.d. = 20.4

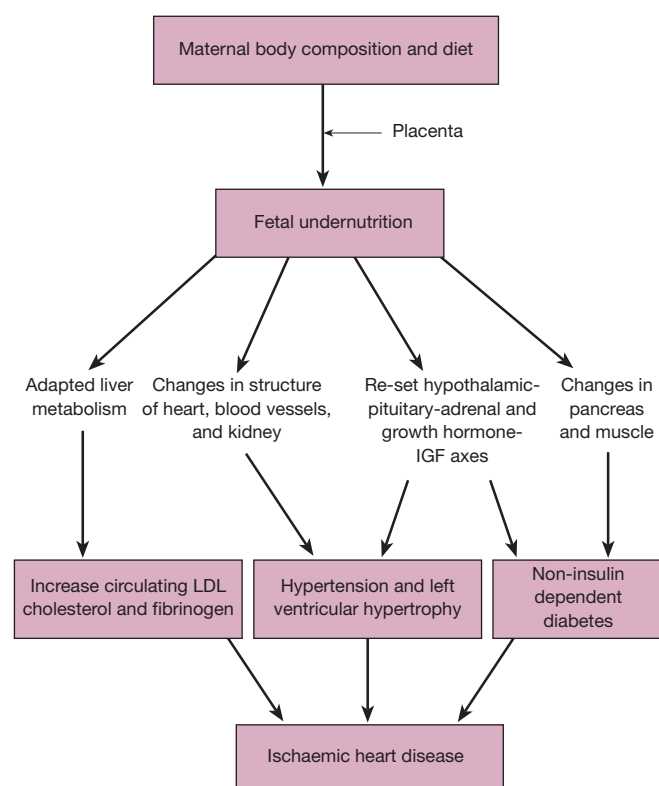
Figures in parentheses are number of subjects.

time famine in Holland provides direct evidence that maternal undernutrition can programme insulin resistance and NIDDM in the offspring. The 'Dutch famine' began abruptly in November 1944 and ended with the liberation of Holland in 1945. The official rations varied between 400 and 800 calories per day. Men and women exposed to the famine *in utero* had higher 2-h plasma glucose concentrations after a standard oral glucose challenge than those born before or conceived after it. They also had higher fasting plasma proinsulin and 2-h plasma insulin concentrations, suggesting insulin resistance.

Figure 3 brings together some of the ideas and findings about the mechanisms through which ischaemic heart disease may be programmed *in utero*. It is a working hypothesis and will need to be re-evaluated as more information becomes available.

### Ischaemic heart disease and childhood growth

As already described, babies that have low birthweight and are thin or short are at increased risk of ischaemic heart disease in adult life. We are begin-

**Fig. 3** Framework of possible mechanisms linking fetal undernutrition and ischaemic heart disease.

ning to learn how childhood growth modifies this risk. In the Helsinki study, ischaemic heart disease was commonest among men who were thin at birth, but who 'caught-up' in weight before the age of 7 years and had above average body mass index thereafter. Among women in the same cohort, those who developed ischaemic heart disease were short at birth but had accelerated growth in height in childhood. Table 2 shows that among men with the lowest ponderal indices at birth, but the highest body mass indices in childhood, the risk of ischaemic heart disease was five times that of men with the highest ponderal indices but lowest body mass indices in childhood. It is not known why accelerated postnatal growth is detrimental. One speculation is based on the observation that restricted fetal growth leads to permanently reduced cell numbers in tissues such as the kidney, in which there is no further cell replication after birth. Accelerated postnatal growth could be deleterious either because overgrowth of a limited cell mass disrupts cell function or because large body size imposes an excessive metabolic demand on a limited cell mass.

Whatever underlies the association between death from ischaemic heart disease and accelerated growth in height and weight in early childhood, imbalances between prenatal and postnatal growth seem to be important in the genesis of adult disease. The effects of adult obesity are a further illustration of this. The highest prevalence of NIDDM is found in people who had low birthweight but become obese as adults. The Dutch famine had its greatest effect on the glucose tolerance of men and women who were overweight as adults.

### Maternal nutrition

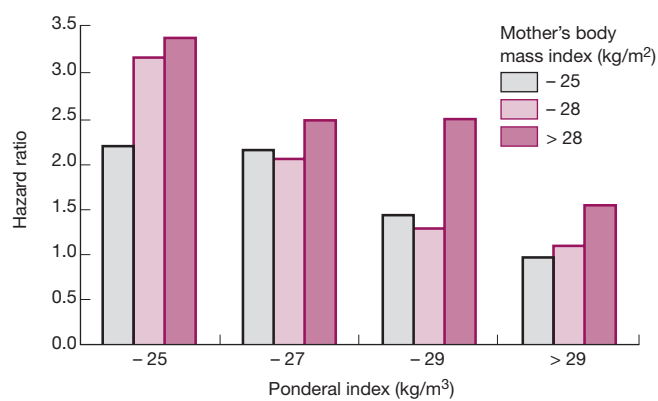
The nutrition of the fetus depends on the nutrition of the mother. In recent years 'maternal nutrition' has been equated with the diets of pregnant women. This is too limited a definition. Mellanby wrote in 1933 that 'it is certain that the significance of correct nutrition in child-bearing does not begin in pregnancy itself or even in the adult female before pregnancy. It looms large as soon as a female child is born and indeed in its intrauterine life'. Maternal nutrition defined in this way encompasses the nutritional experience of the mother from her own conception, through fetal life, childhood, and into adolescence and adult life. The Helsinki study shows that the mother's body composition before and during pregnancy is an important influence in programming the fetus. Figure 4 shows mortality

**Table 2** Hazard ratios for death from ischaemic heart disease according to ponderal index at birth and body mass index at age 11 years, adjusted for length of gestation

Ponderal index (kg/m <sup>3</sup> ) at birth	Body mass index (kg/m <sup>2</sup> ) at age 11 years			
	- 15.5	- 16.5	- 17.5	> 17.5
≤ 25	2.7 (21)	3.3 (26)	3.7 (19)	5.3 (14)
- 27	1.5 (14)	3.2 (40)	4.0 (35)	2.7 (14)
- 29	2.2 (17)	1.6 (18)	1.8 (19)	3.2 (21)
> 29	1.0 (4)	1.7 (11)	1.5 (12)	1.9 (12)

Figures in parentheses are number of deaths.

BMI cutpoints are approximately quartiles.



**Fig. 4** Hazard ratios for ischaemic heart disease in Finnish men according to their ponderal indices at birth (birthweight/length<sup>3</sup>) and their mother's body mass indices (weight/height<sup>2</sup>).

from ischaemic heart disease according to the men's ponderal indices and their mothers' body mass indices (weight/height<sup>2</sup>) in late pregnancy. At any ponderal index, death rates were higher in men whose mothers had a high body mass, so that the highest rates were in men who were thin at birth but whose mothers had a high body mass. The effect of body mass was confined, however, to the offspring of mothers of below average stature (below 1.58 m). The processes by which high body mass in short mothers compounds the increased risk of ischaemic heart disease that is associated with thinness at birth are currently under investigation. The findings already described suggest that raised plasma glucose concentrations in overweight women, which necessarily lead to higher glucose intakes by the fetus, may be one influence.

There is now a body of evidence suggesting that mothers who are thin also afford an unfavourable environment to their fetuses, leading to insulin resistance and raised blood pressure in the offspring. In the Dutch famine, for example, it was people born to mothers with the lowest weights in pregnancy who had the highest 2-h plasma glucose concentrations. Maternal thinness may have different consequences for the fetus depending on whether it is reflected in a low body mass index, low weight gain in pregnancy, or low skinfold thickness. Mothers' diet in pregnancy has been directly related to cardiovascular risk factors in the offspring during adult life in studies in Aberdeen, Scotland. The blood pressures of men and women were related to the balance of animal protein and carbohydrate in their mothers' diets in late pregnancy, while high intakes of fat and protein were associated with insulin deficiency. The findings of this small study are currently being examined in a larger study in Scotland.

## Conclusion

Studies of programming in fetal life and infancy are now established in the agenda for medical research. They have refocused attention on maternal nutrition and fetal growth. The search for the environmental causes of ischaemic heart disease has hitherto been guided by a 'destructive' model. The causes to be identified act in adult life and accelerate destruction processes: the formation of atheroma, rise in blood pressure, and loss of glucose tolerance. There is now a 'developmental' model for the disease. The causes to be identified act on the baby. In responding to them the baby ensures its continued survival and growth at the expense of premature death from ischaemic heart disease.

## Further reading

Barker DJP (1998). *Mothers, babies and health in later life*, 2nd edn. Churchill Livingstone, Edinburgh.

Bateson P and Martin P (1999). *Design for a life*. Jonathan Cape, London.

O'Brien PMS, Wheeler T, Barker DJP (1999). *Fetal programming: influence on development and disease in later life*. RCOG Press, London.

## 15.4.1.2 The epidemiology of ischaemic heart disease

A.R. Ness and G. Davey Smith

### Introduction

Ischaemic heart disease (IHD) is defined by a joint International Society and Federation of Cardiology and World Health Organization task force as 'myocardial impairment due to an imbalance between coronary blood flow and myocardial requirements caused by changes in the coronary circulation.' In this chapter we will focus on the epidemiology of the clinical manifestations of IHD. These include angina pectoris, myocardial infarction, and coronary death.

Atherosclerosis is clearly an important underlying pathological process in IHD. Other non-coronary manifestations of atherosclerotic disease include stroke, peripheral vascular disease, and aortic aneurysm. These different conditions share some epidemiological features but show distinct patterns in other respects. For example there is little correlation between IHD and stroke mortality across countries, and within Britain aortic aneurysm mortality correlates negatively with both stroke and IHD mortality. It therefore makes more sense to consider the epidemiology of these conditions separately rather than together.

The process of atheroma deposition and arterial narrowing in the coronary vasculature cannot be observed directly in life without the use of invasive clinical procedures such as coronary angiography. The thickness of carotid arteries measured ultrasonically is currently under evaluation and may prove to be a useful marker of atheroma. Even so, the study of symptomatic disease rather than the underlying process of atheroma deposition may actually be more appropriate. The clinical disease is, after all, what is experienced and may represent the culmination of a number of pathological processes. Indeed, the fact that changes in atherosclerosis at post mortem over time do not mirror changes in clinical IHD rates suggest that it would be unwise to concentrate on the epidemiology of a single pathological process.

IHD is a—or the—leading cause of death in most developed countries. The rates of such deaths in men and women from the populations participating in the World Health Organization MONICA (monitoring trends and determinants in cardiovascular disease) study, which established arrangements to monitor the mortality and incidence of coronary disease (using comparable coding criteria) over a 10-year period in 37 defined populations (in 21 countries), are shown in Fig. 1. Large differences in disease rates between countries, evidence that risk of disease changes on migration, large differences within countries according to socioeconomic position and area of residence, and relatively rapid changes (both increases and decreases in rates of IHD mortality and incidence over time) suggest that the disease is preventable. In this chapter as we describe the epidemiology of IHD we will attempt to relate these findings to the potential for IHD prevention, considering medical therapy only to the extent that it informs our understanding of disease aetiology and prevention.

### The burden of ischaemic heart disease

Around one-quarter of all deaths amongst men and one-fifth of all deaths of women in Britain are due to IHD. Among women the proportion is relatively stable throughout the adult years, whilst in men it peaks among 55 to 64-year-olds, for whom IHD accounts for a third of all deaths. Around 6 per cent of 55 to 64-year-old men and 3 per cent of 55 to 64-year-old women report experiencing angina; this increases to 13 per cent and 9 per cent respectively for those aged 75 and over. The National Health Service in England deals with around 200 000 inpatient episodes due to