

Fetal undernutrition and disease in later life

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Recent findings suggest that coronary heart disease and stroke, and the associated conditions, hypertension and non-insulin dependent diabetes, originate through impaired growth and development during fetal life and infancy. These diseases may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life results in long-term changes in physiology or metabolism. Animal studies provide many examples of programming, which occurs because the systems and organs of the body mature during periods of rapid growth in fetal life and infancy. There are critical windows of time during which maturation must be achieved; and failure of maturation is largely irrecoverable.

In fetal life the tissues and organs of the body go through what are called 'critical' periods of development (Widdowson and McCance, 1975). Critical periods may coincide with periods of rapid cell division. The main adaptation of the fetus to lack of nutrients or oxygen is to slow its rate of cell division, especially in those tissues that are undergoing 'critical' periods at the time. Cell division slows either as a direct effect of undernutrition on the cell or through altered concentrations of growth factors or hormones, of which insulin and growth hormone are particularly important. Even brief periods of undernutrition may permanently reduce the numbers of cells in particular organs (McCance and Widdowson, 1974; Widdowson and McCance, 1975). This is one of the mechanisms by which undernutrition may permanently change or 'programme' the body (Lucas, 1991). Other lasting 'memories' of undernutrition include change in the distribution of cell types, hormonal feedback, metabolic activity and organ structure.

The diversity of size and form of babies born after normal pregnancies is remarkable. Studies of the birthweights of relatives (Morton, 1955), together with evidence from animal cross-breeding experiments (Walton and Hammond, 1938), have led to the conclusion that this diversity is essentially determined by the intrauterine environment rather than the fetal genome (Carr-Hill *et al.*, 1987). For example, among half-siblings, related through only one parent, those with the same mother have similar birthweights, the correlation coefficient being 0.58. The birthweights of half-siblings with the same father are, however, dissimilar, the correlation coefficient being only 0.1.

Studies of animals show that the supply of nutrients and oxygen is the aspect of the intrauterine environment that usually limits fetal growth (Ounsted and Ounsted, 1966; Gluckman *et al.*, 1990). In humans, low birthweight, and disproportion in head circumference, length and weight, are markers of lack of nutrients at particular stages of gestation. They reflect adaptations that the fetus made to sustain its development – adaptations that, it seems, may permanently programme the structure and function of the body.

It is unquestionable that the human body can be programmed by undernutrition. Rickets has for a long time served as a demonstration that undernutrition at a critical stage of early life leads to persisting changes in structure. What is new is the realization that some of the body's 'memories' of early undernutrition become translated into pathology and thereby determine disease in later life (Barker, 1995). This is perhaps unsurprising given the numerous animal experiments showing that undernutrition *in utero* leads to persisting changes in blood pressure, cholesterol metabolism, insulin response to glucose, and a range of other metabolic, endocrine and immune functions known to be important in human disease (Lucas, 1991; Barker, 1994).

Size at birth and coronary heart disease

An important clue suggesting that coronary heart disease may originate during fetal development came from studies of death rates among babies in Britain during the early 1900s (Barker and Osmond, 1986). The usual certified cause of death in newborn babies at that time was low birthweight. Death rates in the newborn 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 resemble closely today's large variations in death rates from coronary heart disease, variations that form one aspect of the continuing north-south divide in health in Britain (Barker and Osmond, 1986). One possible conclusion suggested by this observation was that low rates of growth before birth are in some way linked to the development of coronary heart disease in adult life. The suggestion that events in childhood influence the pathogenesis of coronary heart disease was not new. A focus on intrauterine life, however, offered a new point of departure for research.

The early epidemiological studies that pointed to the possible importance of programming in coronary heart disease were based on the simple strategy of examining in middle and late life men and women whose body measurements at

Table 1. Death rates from coronary heart disease among 15 726 men and women according to birthweight

Birthweight pounds (kg)	Standardized mortality ratio	Number of deaths
≤5.5 (2.50)	100	57
- 6.5 (2.95)	81	137
- 7.5 (3.41)	80	298
- 8.5 (3.86)	74	289
- 9.5 (4.31)	55	103
>9.5 (4.31)	65	57
Total	74	941

birth were recorded. The birth records on which these studies were based came to light as a result of the Medical Research Council's systematic search of the archives and records offices of Britain – a search that led to the discovery of three important groups of records in Hertfordshire, Preston and Sheffield. The Hertfordshire records were maintained by health visitors and included measurements of growth in infancy as well as birthweight. In Preston and Sheffield, detailed obstetric records documented body proportions at birth (Barker *et al.*, 1990, 1993a).

Sixteen thousand men and women born in Hertfordshire during 1911–1930 have now been traced from birth to the present day. Death rates from coronary heart disease fell by a factor of two between those at the lower and upper ends of the birthweight distribution (Table 1) (Osmond *et al.*, 1993). A study in Sheffield showed that it is people who were small at birth because they failed to grow, rather than because they were born early, who are at increased risk of the disease (Barker *et al.*, 1993a). The association between low birthweight and coronary heart disease has now been confirmed in the USA. Among 80 000 women in the Nurses Study, there was a similar twofold fall in the relative risk of non-fatal coronary heart disease across the range of birthweight (Rich-Edwards *et al.*, 1995). An association between low birthweight and prevalent coronary heart disease has recently been shown in a study in South India (Stein *et al.*, 1996). Among men and women aged 45 years and over, the prevalences of the disease fell from 15% in those who weighed 5.5 pounds (2.5 kg) at birth to 4% in those who weighed 7 pounds (3.2 kg) or more.

In studies exploring the mechanisms underlying these associations, the trends in coronary heart disease with birthweight were found to be paralleled by similar trends in two of its major risk factors: hypertension and non-insulin dependent diabetes mellitus (Barker *et al.*, 1989; Hales *et al.*, 1991). Table 2 illustrates these trends; the prevalence of non-insulin dependent diabetes mellitus and impaired glucose tolerance fell threefold between men who weighed 5.5 pounds (2.5 kg) at birth and those who weighed 9.5 pounds (4.3 kg) (Hales *et al.*, 1991). This association has been confirmed in men and women in three studies in the UK (Barker, 1995), three in the USA (McCance *et al.*, 1994; Valdez *et al.*, 1994; Curhan *et al.*, 1996), and one in Sweden (Lithell *et al.*, 1996).

Table 2. Prevalence of non-insulin dependent diabetes and impaired glucose tolerance in men aged 59–70 years

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

One response to such findings is to argue that people who were exposed to an adverse environment *in utero* and failed to grow continue to be exposed to an adverse environment in childhood and adult life, and it is this later adverse environment that produces the effects attributed to programming *in utero*. However, there is little evidence to support this argument. Rather, associations between birthweight and later disease are found in each social group, and are independent of influences such as smoking and obesity in adult life (Barker, 1995).

However, adult lifestyle does add to intrauterine effects. The highest prevalences of non-insulin dependent diabetes and impaired glucose tolerance, for example, are seen in people who were small at birth but obese as adults (Hales *et al.*, 1991; Lithell *et al.*, 1996). Around the world the communities with high prevalences of diabetes generally conform to this pattern. They include Ethiopian Jews air-lifted to Israel, or Indian people who migrated to the UK, among whom fetal growth was generally poor but obesity common in adult life (Cohen *et al.*, 1988). We know something of why people who had low growth rates *in utero* cannot withstand the stress of becoming obese as adults. There is some evidence that their poor fetal growth resulted in a reduced number of pancreatic β cells and hence a reduced capacity to make insulin. There is stronger evidence that they became resistant to the effects of insulin (Phillips *et al.*, 1994).

Insulin resistance

The Hertfordshire study showed that low birthweight was associated with the so-called insulin-resistance syndrome (Table 3), a common disorder in adult life in which impaired glucose tolerance, raised blood pressure and disturbed lipoprotein metabolism coincide in the same patient (Barker *et al.*, 1993b). Biochemically, the syndrome is characterized by raised serum insulin concentration and it leads to coronary heart disease. Studies in Preston showed that it is specifically thinness at birth, measured by a low ponderal index (birthweight/length³), that is associated with resistance to insulin and its associated disorders in later life. This observation has recently been confirmed in Sweden (Lithell *et al.*, 1996).

Table 3. Prevalence of the insulin resistance syndrome in men aged 59–70 years according to birthweight

Birthweight pounds (kg)	Number of men	Percentage with insulin resistance syndrome	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	30	18.0 (2.6–118)
– 6.5 (2.95)	54	19	8.4 (1.5–49)
– 7.5 (3.41)	114	17	8.5 (1.5–46)
– 8.5 (3.86)	123	12	4.9 (0.9–27)
– 9.5 (4.31)	64	6	2.2 (0.3–14)
> 9.5 (4.31)	32	6	1.0
Total	407	14	

The thin neonate lacks skeletal muscle, as well as fat, and muscle is the main peripheral site of action of insulin, which has a key role in stimulating cell division in fetal life (Fowden, 1989). It is thought that at some point in mid-to-late gestation the thin neonate becomes undernourished, and that in response its muscles become resistant to insulin. Muscle growth is therefore sacrificed but the brain is spared. Studies of the Preston subjects have shown that there are reduced rates of glycolysis in the muscles of adults who were thin at birth (Taylor *et al.*, 1995). This could indicate persistence of a fetal glucose-sparing adaptation. Whether, or how, it is linked to insulin resistance is unclear.

Serum cholesterol and blood clotting

Studies in Sheffield show that the neonate that has a short body in relation to the size of its head, although within the normal range of birthweight, has persisting disturbances of cholesterol metabolism and blood coagulation (Barker *et al.*, 1995a). Disproportion in body length relative to head size is thought to result from undernutrition in late gestation. The fetus uses an adaptive response present in mammals and diverts oxygenated blood away from the trunk to sustain the brain (Dicke, 1987). This affects the growth of the liver, two functions of which, regulation of cholesterol and of blood clotting, seem to be permanently perturbed (Barker *et al.*, 1992; 1995a). Disturbance of cholesterol metabolism and blood clotting are both important features of coronary heart disease.

The Sheffield records include abdominal circumference at birth, as well as length, and it was specifically reduction in this birth measurement that predicted raised serum low density lipoprotein cholesterol and plasma fibrinogen concentrations in adult life. The differences in concentrations across the range of abdominal circumference (Table 4) were large, statistically equivalent to 30% differences in mortality caused by coronary heart disease. The findings for plasma fibrinogen concentrations, a measure of ability of blood to coagulate, were of similar size (Barker *et al.*, 1992).

Since both cholesterol and fibrinogen metabolism are regulated by the liver, one interpretation of these findings is that reduced abdominal circumference at birth reflects

Table 4. Mean serum cholesterol concentrations according to abdominal circumference at birth in men and women aged 50–53 years

Abdominal circumference inches (cm)	Number of people	Total cholesterol (mmol l ⁻¹)	Low density lipoprotein cholesterol (mmol l ⁻¹)
≤ 11.5 (29.2)	53	6.7	4.5
– 12.0 (30.5)	43	6.9	4.6
– 12.5 (31.8)	31	6.8	4.4
– 13.0 (33.0)	45	6.2	4.0
> 13.0 (33.0)	45	6.1	4.0
Total	217	6.5	4.3

impaired liver growth and consequent re-programming of liver metabolism. Further understanding of liver programming may come more rapidly from animal than from human studies. The guinea-pig seems to provide a good animal model of the Sheffield data. Undernutrition of the pregnant animal leads to reduced linear growth in the fetus, which at birth has a normal head but a small abdominal circumference. Liver size is reduced and plasma cholesterol concentrations are increased throughout life (J. Owens, unpublished).

Experiments on rats have shown that undernutrition *in utero* can permanently alter the balance of two liver enzymes, phosphoenol-pyruvate carboxykinase and glucokinase, which are involved, respectively, in the synthesis and breakdown of glucose (Desai *et al.*, 1995). A low protein diet during gestation permanently changes the balance of enzyme activity in the offspring in favour of synthesis. It is thought that this reflects enhancement of cell replication in the area around the portal vein, which carries blood from the gut to the liver, at the expense of the cells around the hepatic vein. These experiments are of particular interest because they show that undernutrition after birth has no effect, and because the two enzymes are not normally synthesized until after birth, which suggests that their production can be regulated before the genes encoding them are transcribed (Desai *et al.*, 1995).

Blood pressure

Associations between low birthweight and raised blood pressure in childhood and adult life have been demonstrated around the world (Law and Shiell, 1996) (Table 5). The relationship is less consistent in adolescence, presumably because the tracking of blood pressure is perturbed by the adolescent growth spurt. Persistent high blood pressure seems to be associated with interference with growth at any stage of gestation, since it is found in people who were thin or short babies, or proportionately small (Law *et al.*, 1993).

Possible mechanisms linking reduced fetal growth and raised blood pressure are persisting changes in vascular structure, including loss of elasticity in vessel walls, and the effects of glucocorticoid hormones (Edwards *et al.*, 1993; Martyn *et al.*, 1995). In animals, modest glucocorticoid excess retards intrauterine growth and programmes raised

Table 5. Mean systolic pressure in men and women aged 60–71 years according to birthweight

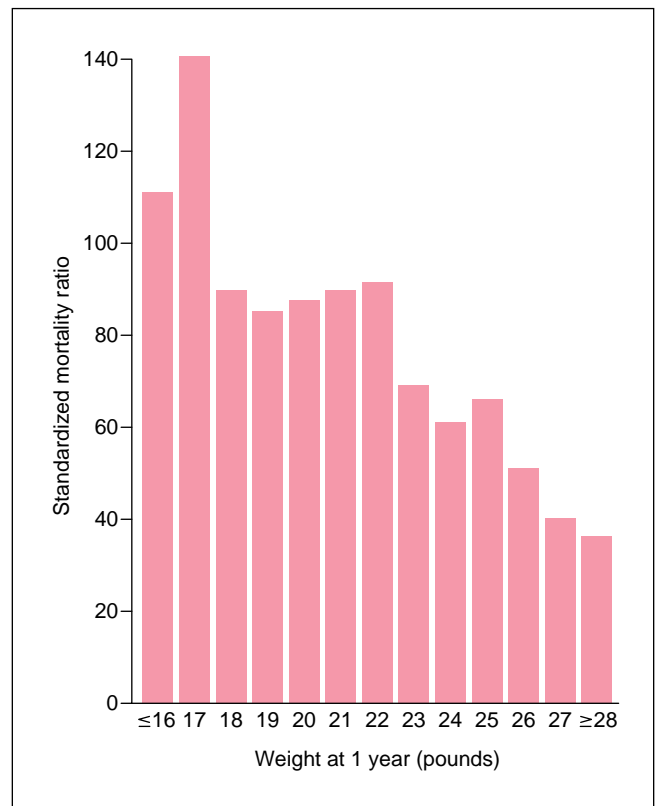
Birthweight pounds (kg)	Systolic blood pressure mm Hg, adjusted for sex (<i>n</i>)
– 5.5 (2.50)	168 (54)
– 6.5 (2.95)	165 (174)
– 7.5 (3.41)	165 (403)
– 8.5 (3.86)	164 (342)
– 9.5 (4.31)	160 (183)
> 9.5 (4.31)	163 (72)
Total	164 (1228)
SD	25

blood pressure. An excess may occur either from fetoplacental stress or from deficiency in the normal placental enzyme barrier that protects the fetus from its mother's glucocorticoids. Such a deficiency can be produced experimentally in rats by undernutrition. Fetal undernutrition during discrete periods of gestation (Langley-Evans *et al.*, 1996) or throughout pregnancy (Langley and Jackson, 1994) also causes persistent high blood pressure in rats, which must encourage the view that fetal undernutrition is causally linked to hypertension in humans and opens up ways in which the underlying mechanisms can be explored.

Growth in infancy

In late gestation, rates of cell division fall and growth slows. After birth, growth mainly consists of the development and enlargement of existing cells rather than the addition of new cells (McCance and Widdowson, 1974; Widdowson and McCance, 1975). Babies who are short at birth, with reduced abdominal circumferences, tend to grow slowly after birth (Villar *et al.*, 1984). Low rates of infant weight gain are highly predictive of coronary heart disease among men (Osmond *et al.*, 1993). In Hertfordshire, men who were small at one year were three times more likely to develop or die from coronary heart disease than those who were large, an association that did not depend on the way in which the infants were fed (Fig. 1).

Low weight gain during infancy is also followed by hypertrophy of the left ventricle in childhood and adult life, which predicts coronary heart disease independently of blood pressure (Vijayakumar *et al.*, 1995; Zureik *et al.*, 1996). One possible explanation of this is that, in short babies, the structure of the heart is permanently changed by the adaptive responses that occurred before birth. Redistribution of blood flow in favour of the brain increases left ventricular blood flow and peripheral resistance, and may therefore lead to muscular hypertrophy. Another possible explanation, for which there is only limited evidence, is that short babies are resistant to growth hormone, which takes over control of growth from insulin in late fetal life, although its predominant effect is on postnatal growth (Barker *et al.*, 1993c). Resistance to growth hormone is associated with high

**Fig. 1.** Mortality from coronary heart disease in 8175 men born during 1911–1930 according to weight at one year.

circulating concentrations of the hormone. Observations on patients with pituitary tumours producing growth hormone have shown that high concentrations cause cardiac enlargement, atheroma in the vessels and death from coronary heart disease. Long-term consequences of programmed patterns of hormone release, altered tissue sensitivity to hormones, or altered exposure to hormones in utero could be important mechanisms underlying other diseases, in particular hormone-related cancers (Ekbom *et al.*, 1992, 1996; Barker *et al.*, 1993c, 1995b, 1996).

The placenta

At an early stage of development an embryo comprises two groups of cells, the inner and outer cell masses. The outer cell mass develops into the placenta, and the inner cell mass becomes the fetus. Experiments in animals suggest that the distribution of cells between the two masses is influenced by nutrition and hormones (Robinson *et al.*, 1994). In sheep, undernutrition in early pregnancy leads to placental enlargement, thought to be an adaptation to extract more nutrients (McCraab *et al.*, 1992). There is evidence that placental enlargement may also be an adaptive response in humans. Ultrasound studies in humans show that at about 18 weeks of gestation, fetuses of a given size already have a range of placental volumes (Wheeler *et al.*, 1994).

Recent observations suggest that expansion of the placenta is another fetal adaptation that exacts a long-term

Table 6. Mean systolic blood pressure (mm Hg) of men and women aged 46–54 years, born after 38 completed weeks of gestation, according to placental weight and birthweight

Birthweight pounds (kg)	Placental weight pounds (kg)					All
	≤1.0 (0.45)	– 1.25 (0.57)	– 1.5 (0.68)	> 1.5 (0.68)		
– 6.5 (2.95)	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)	
– 7.5 (3.41)	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)	
> 7.5 (3.41)	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)	
Total	144 (43)	148 (132)	148 (83)	156 (69)	149 (327)	

Numbers of subjects are shown in brackets.

price. The blood pressures of a group of men and women in Preston were measured and are shown (Table 6) according to their birthweights and placental weight (Barker *et al.*, 1990). As expected, blood pressures fell with increasing birthweight. At any given birthweight, however, pressures rose as placental weight increased, so that the highest pressures were in people who, in fetal life, allocated a greater proportion of their resources to placental development rather than to their own growth. Other studies have shown that placental enlargement is followed in adult life not only by increased blood pressure, but also by impaired glucose tolerance, disordered blood coagulation and death from coronary heart disease (Barker, 1995). Placental enlargement seems therefore to be a general marker of altered fetal development and its consequences, rather than a specific marker of later hypertension.

Fetal undernutrition

As stated already, the weight of evidence from animal cross-breeding experiments and from studies of the birthweights of relatives suggests that, although the growth of a fetus is influenced by its genes, it is usually limited by the nutrient and oxygen supply it receives. In addition, active constraint of fetal growth by the mother has been shown in embryo transfer and crossbreeding experiments; a fetus transferred to a larger uterus will achieve a larger birth size (Snow, 1989). The normal maternal constraint of fetal growth is reflected in the strong association between birthweight and the height and pelvic dimensions of the mother. A baby's birth measurements, however, predict adult disease independently of the mother's pelvic size (Fig. 2). Our studies have focused, therefore, on the influences that determine fetal nutrition rather than on the physiological constraint of fetal growth by the mother (Barker *et al.*, 1993c). This focus on the nutrient and oxygen supply to the fetus is supported by numerous animal experiments showing that poor nutrition may both impair growth during critical periods of fetal life and permanently affect the structure and physiology of a range of organs and tissues, including the endocrine pancreas, liver, and blood vessels (Swenne *et al.*, 1987; Snoeck *et al.*, 1990; Lucas, 1991; Barker, 1994; Langley and Jackson, 1994; Desai *et al.*, 1995).

Fetal nutrition is determined by the combination of the mother's dietary intakes and nutrient stores, together with nutrient delivery to the placenta and the transfer capabilities of the placenta (Owens *et al.*, 1989). Metabolic adaptations to undernutrition are linked to changes in the concentrations of fetal and placental hormones that influence fetal growth. Insulin and the insulin-like growth factors (IGFs), hormones thought to have a central role in the regulation of fetal growth, respond rapidly to changes in fetal nutrition. For example, maternal starvation lowers both fetal nutrient and IGF-I concentrations: infusion of glucose, but not amino acids, restores the IGF-I concentration (Oliver *et al.*, 1993). IGF-I is a direct mitogen for pancreatic β cells and the impaired β -cell development seen in intrauterine growth retardation (Van Assche *et al.*, 1977) may reflect lower IGF-I concentrations in association with hypoglycaemia.

Human studies of maternal nutrition in relation to fetal growth have focused predominantly on either maternal dietary intakes or nutrient stores in isolation. However, experimental studies in sheep in Adelaide, Australia have shown that a period of maternal undernutrition in mid-pregnancy has profoundly different effects on fetal and placental growth, according to whether the mother entered pregnancy with high or low nutritional stores (Robinson *et al.*, 1994). In these studies, the offspring of mothers entering pregnancy with low stores suffered marked impairment of fetal and placental growth if exposed to a further period of undernutrition. In contrast, those whose mothers were well nourished around conception and then had a period of dietary restriction experienced placental hypertrophy. This may be a sensitive early adaptation to sustain nutrient supply from the mother.

Such differing effects of pregnancy undernutrition according to the nutritional state of the mother around the time of conception may, in part, reflect differences in the growth trajectory of the fetus. This is set in the earliest stages of pregnancy and may reflect the particular sensitivity of early embryo growth to the concentrations of nutrients (Leese, 1990). Undernutrition in ewes in the last trimester has a greater adverse effect on the development of fetuses that are growing more rapidly (Harding *et al.*, 1992). In such fetuses, on a fast growth trajectory, maternal undernutrition may result in fetal wasting and consumption of fetal amino acids by the placenta so that it can maintain lactate output to the fetus (Owens *et al.*, 1989). Downward resetting of the growth trajectory may be an important fetal adaptation in early gestation because it reduces the subsequent demand for nutrients in late gestation.

One of the few influences known to be associated with large placental weight in humans is severe maternal anaemia (Beischer *et al.*, 1970). A recent study of 8684 women who delivered in Oxford found that placental weight rose progressively by 18.0 g for each 1 g dl⁻¹ fall in maternal minimum haemoglobin during the pregnancy, and by 13.6 g for each 1 fl fall in maternal mean red cell volume, the latter being an indicator of low iron stores (Godfrey *et al.*, 1991). Much disagreement surrounds the relative contributions of haemodilution and of iron deficiency towards falls in haemoglobin during pregnancy. Bone marrow studies have, however, shown that a pregnancy haemoglobin of less than

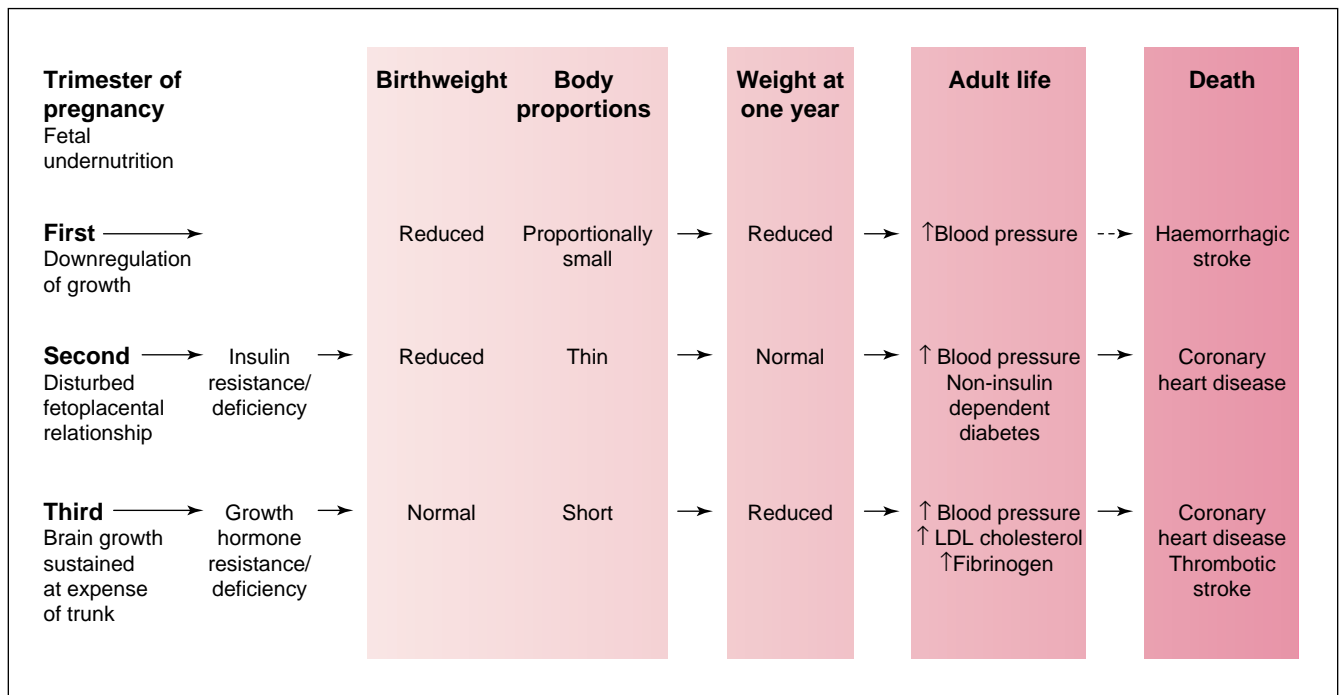


Fig. 2. The effects of fetal undernutrition at different stages in pregnancy. LDL: low density lipoprotein.

11.0 g dl⁻¹ is associated consistently with absent iron stores (de Leeuw *et al.*, 1966) and World Health Organization committees have concluded that pregnancy haemoglobin values below 11.0 g dl⁻¹ should be considered nutritional in origin and not physiological. The relationship between a high placental ratio and both low haemoglobin and a fall in mean cell volume suggests that their findings reflect low maternal iron stores rather than haemodilution.

A number of specific lines of evidence in addition to general considerations on the control of fetal growth now support the general thesis that, in humans, the association between small size or altered body proportions at birth and later cardiovascular disease is a consequence of fetal undernutrition. Maternal age and cigarette smoking, which influence fetal growth, have not been found to be related to cardiovascular disease in the offspring (Law *et al.*, 1991; Whincup *et al.*, 1992). A study in Aberdeen, however, has shown that the blood pressures of middle-aged men and women are related to their mothers' intakes of carbohydrate and protein, which were recorded during the pregnancy (Campbell *et al.*, 1996). At either extreme of the balance of animal protein/carbohydrate intakes, the offspring had raised blood pressure; they also had reduced placental weight at birth – an observation replicated recently in a study of 538 term deliveries in Southampton, UK (Godfrey *et al.*, 1996). Further evidence for the role of nutrition in programming is that alterations in the ratio of placental weight to birthweight, which are known to be associated with maternal anaemia during pregnancy, are also associated with the development of coronary heart disease and hypertension in later life (Barker *et al.*, 1990; Martyn *et al.*, 1996). In addition, a study in Jamaica found that children of mothers

who were thin in early pregnancy, having low skinfold thicknesses, had raised blood pressure at 10 years of age (Godfrey *et al.*, 1994). In South India the prevalence of coronary heart disease was highest in men and women whose mothers had low weight in pregnancy (Stein *et al.*, 1996). Finally, the occurrence of stroke is associated with a pattern of retarded fetal growth that is found in mothers with a 'flat' bony pelvis – a deformity caused by poor nutrition in childhood (Martyn *et al.*, 1996).

The future

If we are to be able to use the information outlined here to prevent disease we need to progress beyond epidemiological associations to greater understanding of the cellular and molecular processes that underlie them. We need to know what factors limit the delivery of nutrients and oxygen to the human fetus; how the fetus adapts to a limited supply; how these adaptations programme the structure and physiology of the body; and by what molecular mechanisms nutrients and hormones alter gene expression. Further research requires a strategy of interdependent clinical, animal and epidemiological studies.

As yet, we do not know the true impact of maternal nutrition on fetal development. The relatively disappointing effects of human interventional studies of maternal nutrition during pregnancy have led to the view that fetal development is little affected by changes in maternal nutrition, except in circumstances of famine. It is, however, clear that birthweight alone is an inadequate summary measure of fetal growth, and that a more sophisticated view of optimal fetal development is necessary, which takes account of the

long-term sequelae of fetal adaptations to undernutrition. Experimental studies in animals indicate the dangers of an overly simplistic view of maternal nutrition in relation to fetal development.

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