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Fetal programming and adult health

Keith M Godfrey* and David JP Barker
MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, UK

Abstract

Low birthweight is now known to be associated with increased rates of coronary heart disease and the related disorders stroke, hypertension and non-insulin dependent diabetes. These associations have been extensively replicated in studies in different countries and are not the result of confounding variables. They extend across the normal range of birthweight and depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. The associations are thought to be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life has permanent effects on structure, physiology and metabolism. Programming of the fetus may result from adaptations invoked when the materno-placental nutrient supply fails to match the fetal nutrient demand. Although the influences that impair fetal development and programme adult cardiovascular disease remain to be defined, there are strong pointers to the importance of maternal body composition and dietary balance during pregnancy.

Keywords
Maternal nutrition
Fetal growth retardation
Coronary heart disease
Hypertension
Non-insulin-dependent diabetes
Maternal body composition

Programming and the 'fetal origins' hypothesis

The 'fetal origins' hypothesis proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing to cardiovascular, metabolic and endocrine disease in adult life[1]. For example, it is thought that coronary heart disease may be a consequence of fetal adaptations to undernutrition that are beneficial for short-term survival, even though they are detrimental to health in post-reproductive life[1].

In fetal life the tissues and organs of the body go through what are called 'critical' periods of development. These may coincide with periods of rapid cell division. In common with other living creatures, human beings are 'plastic' in their early life, and are moulded by the environment. Although the growth of a fetus is influenced by its genes, studies in humans and animals suggest that it is usually limited by the environment, in particular the nutrients and oxygen received from the mother[2]. There are many possible evolutionary advantages in the body remaining plastic during development, rather than having its development driven only by genetic instructions acquired at conception.

'Programming' describes the process whereby a stimulus or insult during a critical period of development has lasting or lifelong effects[3]. Experimental studies in animals have documented many examples of fetal programming, with recent studies showing that alterations in maternal nutrition can have long-term effects on the offspring that are of relevance to human cardiovascular disease. For example, feeding pregnant rats a low protein diet results in life-long elevation of blood pressure in the offspring[4]. Rats whose mothers had been fed a diet with a low ratio of protein to energy during pregnancy exhibited a permanently altered balance between hepatic glucose production and utilization; control rats fed the same diet during post-natal life had no alterations in hepatic glucose metabolism[5]. Other notable long-term effects of alterations in maternal nutrition include changes in cholesterol metabolism, insulin secretion and renal development[1].

Though some effects of nutrition may be direct consequences of alterations in substrate availability, a number are thought to be mediated by hormonal effects[1]. These may alter the development of specific fetal tissues during critical periods, or lead to long-lasting changes in hormone secretion or tissue hormone sensitivity. Experimental studies have implicated the fetal hypothalamus as a key site that can be programmed by transient changes in prenatal endocrine status[1].

Fetal growth and coronary heart disease

At the start of this century the incidence of coronary heart disease rose steeply in Western countries to become the most common cause of death. In many of these countries the steep rise has been followed by a fall over recent decades that cannot be accounted for by changes in adult lifestyle. The incidence of coronary heart disease is now

*Corresponding author: Email kmg@mrc.soton.ac.uk

rising in other parts of the world to which western influences are extending, including China, India and Eastern Europe.

An important clue suggesting that coronary heart disease might originate during fetal development came from studies of death rates among babies in Britain during the early 1900's[1]. 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 closely resemble today's large variations in death rates from coronary heart disease[1], variations that form one aspect of the continuing north–south divide in health in Britain. 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. Although it had been suggested that events in childhood influence the pathogenesis of coronary heart disease, a focus on intrauterine life offered a new point of departure for research.

More direct evidence that an adverse intra-uterine environment might have long-term consequences came from follow-up studies of men and women in middle and late life whose body measurements at birth had been recorded. A study of people born in Hertfordshire, UK, showed for the first time that those who had had low birthweights had increased death rates from coronary heart disease in adult life[1,6]. Thus, among 15 726 people born during 1911 to 1930, death rates from coronary heart disease fell progressively with increasing birthweight in both men and women (Fig. 1)[1,6]. A small rise at the highest birthweights in men could relate to the macrosomic infants of women with gestational diabetes. Another study, of 1,586 men born in Sheffield during 1907 to 1925, showed that it was particularly people who were small at birth as a result of growth retardation, rather than those born prematurely, who were at increased risk of the disease[7].

Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with coronary heart disease in later life. For example, confirmation of a link between low birthweight and adult coronary heart disease has come from studies of 1,200 men in Caerphilly, South Wales[8] and of 70 297 nurses in the United States[9]. The latter study found a two-fold fall in the relative risk of non-fatal coronary heart disease across the range of birthweight[9]. Similarly, among 517 men and women in Mysore, South India the prevalence of coronary heart disease in men and women aged 45 years or older fell from 15% in those who weighed 2.5 kg or less at birth, to 4% in those who weighed 3.2 kg or more[10].

Body proportions at birth and cardiovascular disease

The Hertfordshire records and the Nurses and Caerphilly studies did not include measurements of body size at birth other than weight. The weight of a newborn baby without a measure of its length is a crude summary of its physique. The addition of birth length allows derivation of ponderal index (birthweight/length^3) as a measure of thinness, but cannot adequately distinguish variations in fat and lean mass. With the addition of head circumference the baby whose body and trunk is small in relation to its head, as a result of 'brain-sparing', can also be distinguished. Thinness, shortness and a small trunk are thought to reflect differing fetal adaptations to undernutrition, hypoxia and other influences and they have different long-term consequences.

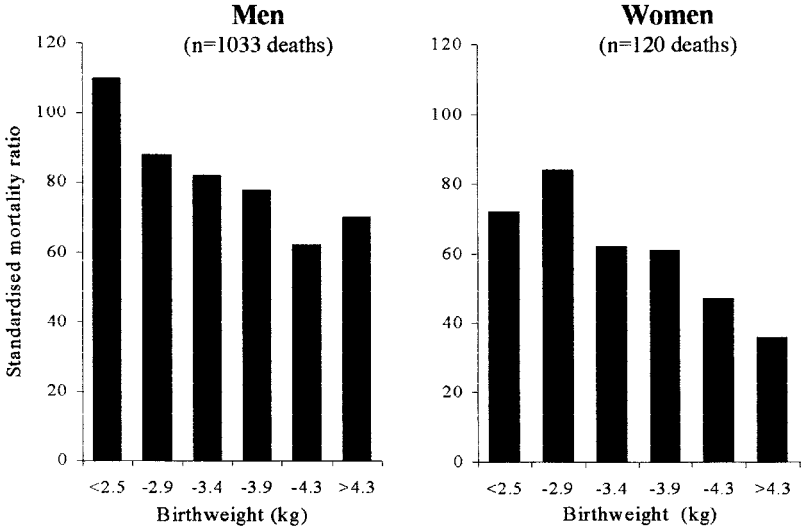

Fig. 1 Coronary heart disease death rates, expressed as standardized mortality ratios, in 10141 men and 5585 women born in Hertfordshire, UK according to birthweight[6]

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Table 1 Standardised mortality ratios for coronary heart disease in 3,302 Finnish men during 1924–33

Birthweight kg [lb]	SMR (No. of deaths)
≤2.5 [5.5]	84 (11)
−3.0 [6.6]	83 (44)
−3.5 [7.7]	99 (124)
−4.0 [8.8]	76 (80)
>4.0 [8.8]	66 (27)
All	85 (286)
P value for trend	0.09
Term babies only Ponderal index at birth (kg/m^3)	SMR (No. of deaths)
≤25.0	116 (59)
−27.0	105 (88)
−29.0	72 (64)
>29.0	56 (33)
All	86 (244)
P value for trend	<0.0001

In Sheffield death rates from coronary heart disease were higher in men who had had a short crown-heel length at birth[11]. The mortality ratio for coronary heart disease in men who were 18.5 inches [47 cm] or less in length was 138 compared with 98 in the remainder[11]. A low ponderal index and thinness at birth were also associated with coronary heart disease[11]. Table 1 shows data for a group of men born in Helsinki, Finland. While low birthweight was associated with raised death rates from coronary heart disease, there was a stronger association with thinness at birth, especially in men born at term[12]. Men who were thin at birth, measured by a low ponderal index, had death rates that were twice those of men who had a high ponderal index.

In Finland raised death rates from coronary heart disease were associated with low placental weight. In Sheffield, however, coronary heart disease showed a U-shaped relation with the ratio of placental weight to birthweight, the highest mortality ratios being at either end of the distribution. The pattern of body proportions at birth which predicts death from coronary heart disease may be therefore summarised as a small head circumference, shortness or thinness, which reflect retarded fetal growth, and either low placental weight or an altered ratio of placental weight to birthweight. The pattern for stroke, which has only been reported in Sheffield, is different. Whereas stroke was similarly associated with low birthweight it was not associated with thinness or shortness. Instead there were increased rates among men who had a low ratio of birthweight to head circumference, or a low ratio of placental weight to head circumference[11]. One interpretation of these associations is that normal head growth has been sustained at the cost of interrupted growth of the body in late gestation, in association with inadequate growth of the placenta.

Confounding variables

These findings suggest that influences linked to fetal and placental growth have an important effect on the risk of coronary heart disease and stroke. It has been argued, however, that people whose growth was impaired *in utero* may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to programming. There is strong evidence that this argument cannot be sustained. In three of the studies which have replicated the association between birthweight and coronary heart disease data on adult lifestyle factors including smoking, employment, diet, alcohol consumption and exercise, were collected[8,9,13]. Allowance for them had little effect on the association between birthweight and coronary heart disease.

In studies exploring the mechanisms underlying these associations, the trends in coronary heart disease with birthweight are paralleled by similar trends in two of its major risk factors – hypertension and non-insulin dependent diabetes mellitus[14,15]. Table 2 illustrates the size of these trends, the prevalence of non-insulin dependent diabetes mellitus and impaired glucose tolerance falling threefold between men who weighed 5.5 pounds at birth and those who weighed 9.5 pounds[14]. These associations with small size at birth were again independent of social class, cigarette smoking, and alcohol consumption. Influences in adult life, however, add to the effects of the intrauterine environment. For example, the prevalence of impaired glucose tolerance is

Table 2 Prevalence of non-insulin dependent diabetes (NIDDM, 2-hour glucose ≥11.1 mmol/L) and impaired glucose tolerance (2-hour glucose 7.8–11.0 mmol/L) in 370 men aged 59–70 years[14]

Birthweight in pounds (kg)	Number of men	% with 2-hour plasma glucose ≥11.1 mmol/L	% with 2-hour plasma glucose ≥7.8 mmol/L	Odds ratio (95% CI)* of NIDDM or impaired glucose tolerance
<5.5 (2.54)	20	10	40	6.6 (1.5–28)
−6.5 (2.95)	47	13	34	4.8 (1.3–17)
−7.5 (3.41)	104	6	31	4.6 (1.4–16)
−8.5 (3.86)	117	7	22	2.6 (0.8–8.9)
−9.5 (4.31)	54	9	13	1.4 (0.3–5.6)
>9.5 (4.31)	28	0	14	1.0
All	370	7	25	

*Adjusted for current body mass index

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highest in people who had low birthweight but became obese as adults.

Hypertension

Associations between low birthweight and raised blood pressure in childhood and adult life have been extensively demonstrated around the world. Figure 2 shows the results of a systematic review of published papers describing the association between birthweight and blood pressure[15] – a review based on 34 studies of more than 66 000 people of all ages in many countries. Each point on the figure with its confidence interval represents a study population and the populations are ordered by their ages. The horizontal position of each population describes the change in blood pressure that was associated with a one kilogram [2.2 pound] increase in birthweight. In almost all the studies an increase in birthweight was associated with a fall in blood pressure; and there was no exception to this in the studies of adults which now total nearly 8,000 men and women. The associations are less consistent in adolescence, presumably because the tracking of blood pressure from childhood through adult life is perturbed by the adolescent growth spurt. These associations were not confounded by socioeconomic conditions at the time of birth or in adult life.

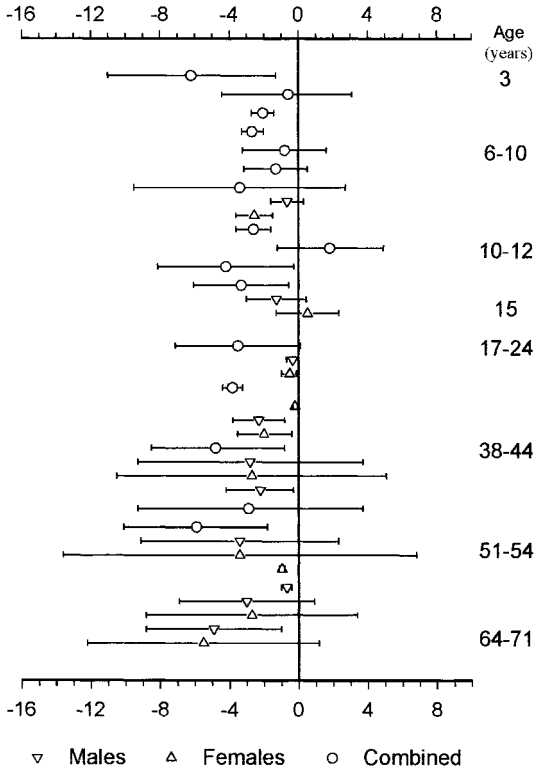

Fig. 2 Difference in systolic pressure (mmHg), with confidence intervals, per kg increase in birthweight (adjusted for weight in children and body mass index in adults) in published studies of people of different ages[15]

The difference in systolic pressure associated with a one kilogram difference in birthweight was around 3.5 mm Hg. In clinical practice this would be a small difference but these are large differences between the mean values of populations and may correspond to a substantial proportion of total attributable mortality.

The association between low birthweight and raised blood pressure depends on babies who were born small for dates, after reduced fetal growth, rather than on babies born pre-term[1]. 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 pressures are found in those who were small at birth but become overweight as adults.

As already discussed, birthweight is a crude measure of fetal growth that does not distinguish thinness or short length, differences in head size, or variations in the balance of fetal and placental size. Analyses of babies born in Preston, UK, defined two groups who developed raised adult blood pressures[16]. The first group had below average placental weight and were thin with a low ponderal index and a below average head circumference. The second had above average placental weight and a short crown-heel length in relation to their head circumference; such short babies tend to be fat and may have above average birthweight. In contrast to the associations between birth size and coronary heart disease those between birthweight and blood pressure are generally as strong as those between thinness, shortness and blood pressure. Associations between blood pressure and thinness and shortness have been found in some studies but not in others[1]. In a longitudinal study of young people in Adelaide associations between blood pressure and thinness and shortness were not apparent at age 8 years but emerged at age 20[17].

Placental size and blood pressure

Table 3 shows the systolic pressure of a group of men and women who were born at term in Preston 50 years ago[16]. Subjects are grouped according to their birthweights and placental weights. As in other studies, systolic pressure falls between subjects with low and high birthweight. In addition, however, there is an increase in blood pressure with increasing placental weight. Subjects with a mean systolic pressure of 150 mm Hg or more, a level sometimes used to define hypertension in clinical practice, comprise a group who as babies were relatively small in relation to the size of their placentas. There are similar trends with diastolic pressure. A rise in blood pressure with increasing placental weight and a higher ratio of placental weight to birthweight was also found in four year old children in Salisbury, UK, and among young adults in Adelaide, Australia[17,18]. In studies of children

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Table 3 Mean systolic blood pressure (mm Hg) of men and women aged 50, born after 38 completed weeks of gestation, according to placental weight and birthweight

	Placental weight lb [g]				
Birthweight lb [kg]	≤1.0 [454]	−1.25 [568]	−1.5 [681]	>1.5 [681]	All
≤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 numbers of subjects.

and adults the association between placental enlargement and raised blood pressure has, however, been inconsistent. For example, in a study of men and women born in Aberdeen, Scotland, after the Second World War, at a time when food was still rationed, raised blood pressure was associated with small placental size[19]. As referred to later, animal studies offer a possible explanation of this inconsistency. In sheep the placenta enlarges in response to moderate undernutrition in mid pregnancy[20]. This effect, thought to be an adaptive response to extract more nutrients from the mother, is however only seen in ewes that were well nourished before pregnancy.

Mother's blood pressure

In some studies the blood pressures of the mothers during and after pregnancy have been recorded. They correlate with the offspring's blood pressure. However, the associations between body size and proportions at birth and later blood pressure are independent of the mothers' blood pressures[1,18,21].

Childhood growth

There are a number of possible mechanisms by which restricted intrauterine growth could either initiate raised blood pressure or lead to accentuated amplification of blood pressure in later life. Studies in the USA, the UK and Holland have shown that blood pressure in childhood predicts the likelihood of developing hypertension in adult life. These predictions are strongest after adolescence. In children the rise of blood pressure with age is closely related to growth and is accelerated by the adolescent growth spurt. These observations have led Lever and Harrap to propose that essential hypertension is a disorder of growth[22]. The hypothesis that hypertension is a disorder of accelerated childhood growth can be reconciled with the association with low birthweight by postulating that postnatal catch-up growth plays an important role in amplifying changes established *in utero*.

Renin-angiotensin system

If the materno-placental supply of nutrients does not match fetal requirements in the last trimester of pregnancy the fetus diverts blood and nutrients to maintain brain metabolism at the expense of the trunk and limbs. This adaptation reduces blood flow to the fetal kidneys and may underlie activation of the fetal renin-angiotensin system in intrauterine growth retardation. This raises the possibility that changes in the system may underlie the programming of hypertension. A follow-up study of men and women born in Sheffield found, however, that those who had been small at birth had *lower* plasma concentrations of inactive and active renin[23]. Causes of raised blood pressure that are not mediated by increased renin release tend to result in low concentrations of renin; these findings therefore suggest that the association between impaired fetal growth and raised blood pressure involves mechanisms other than the renin-angiotensin system. Low concentrations of renin in adult life do not, however, exclude the possibility of an earlier but lasting influence of the renin-angiotensin system.

Renal structure

An alternative explanation for the low plasma renin concentrations of people who were small at birth is that they reflect a relative deficit of nephrons. Brenner suggested that retarded fetal growth leads to reduced numbers of nephrons, increasing pressure in the glomerular capillaries and leading to glomerular sclerosis[24]. This sclerosis results in further loss of nephrons and a self-perpetuating cycle of hypertension and progressive glomerular injury. The numbers of nephrons in the normal population varies widely, from 300 000 to 1 100 000 or more[24]. Studies using fetal ultrasound have shown that babies that are small for gestational age have reduced renal growth during a critical period between 26 and 34 weeks of gestation. This reduces the antero-posterior size of the kidney but does not diminish kidney length[25].

Endocrine

Animal studies have led to the hypothesis that impaired fetal growth alters the fetus' hypothalamic-pituitary-adrenal axis which in turn re-sets homeostatic mechanisms controlling blood pressure[26]. A recent study of 65-year old men in Hertfordshire showed that those who had been small at birth had increased fasting plasma cortisol concentrations[27], preliminary evidence that the hypothalamic-pituitary-adrenal axis can be programmed in humans.

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Vascular structure

The content and arrangement of elastin in the aorta and large conduit arteries plays an important part in minimising the rise of blood pressure in systole and maintaining blood pressure in diastole. Elastin is only synthesised in early life and the gradual loss or fracture of elastin fibres is thought to contribute to the rise in systolic and pulse pressure with ageing. These considerations have led to the hypothesis that impaired fetal development may be associated with a relative deficiency in elastin synthesis, resulting in stiffer arteries and raised blood pressure in postnatal life[28]. This hypothesis is supported by a study of 50 year old men and women showing that those who had a small abdominal circumference at birth tended to have a higher pulse wave velocity and decreased arterial elasticity in adult life[21].

In the growth retarded fetus there are changes in blood flow in several vascular beds, including the descending aorta and cerebral vasculature[29]. If sustained they may lead to reduced growth of the abdominal viscera and shortness at birth. Elastin deposition in fetal blood vessels is related to blood flow and 'brain-sparing' reflexes that reduce flow in the large arteries of the trunk and legs may diminish elastin deposition, leading to less compliant arteries and consequent hypertension.

Recent studies suggest that, in addition to its associations with compliance, low birthweight is also associated with persisting alterations in vascular structure and function. Hertfordshire men who had had low birthweight had narrow bifurcation angles in their retinal blood vessels[1]. People with hypertension have similar changes in retinal vascular geometry. In a study of children, those of low birthweight had reduced flow-mediated dilatation in the brachial artery after the artery had been occluded and released. Flow mediated dilatation depends on the endothelium. These findings suggest, therefore, a link between low birthweight and endothelial dysfunction[30].

Nervous system

People with high blood pressure tend to have a high resting pulse rate. This is associated with high cardiac output, a hyperdynamic circulation and features of increased sympathetic nervous system activity. Among men and women in Preston, those who had low birthweight had a higher resting pulse rate[31]. This is consistent with the hypothesis that retarded growth *in utero* establishes increased sympathetic nervous activity and leads to raised blood pressure in later life.

Non-insulin dependent diabetes

Insulin has a central role in fetal growth, and disorders of glucose and insulin metabolism are therefore an obvious possible link between early growth and cardiovascular disease. Although obesity and a sedentary lifestyle are known to be important in the development of non-insulin dependent diabetes, they seem to lead to the disease only in predisposed individuals. Family and twin studies have suggested that the predisposition is familial, but the nature of this predisposition is unknown. The disease tends to be transmitted through the maternal rather than paternal side of the family.

Size at birth and non-insulin dependent diabetes

A number of studies have confirmed the association between birthweight and impaired glucose tolerance and non-insulin dependent diabetes first reported in Hertfordshire (Table 2)[1,14,32–35]. In the Health Professionals Study, USA, the odds ratio for diabetes, after adjusting for current body mass, was 1.9 among men whose birthweights were less than 5.5 pounds [2.5 kg] compared with those who weighed 7.0 to 8.5 pounds [3.2–3.9 kg][33]. Among the Pima Indians, USA, the odds ratio for diabetes was 3.8 in men and women who weighed less than 5.5 pounds[34]. In Preston it was the thin babies who developed impaired glucose tolerance and diabetes[35]. Lithell and colleagues confirmed the association with thinness in Uppsala, Sweden (Table 4); the prevalence of diabetes was three times higher among men in the lowest fifth of ponderal index at birth[32]. Among the Pima Indians diabetes in pregnancy is unusually common and the association between birthweight and non-insulin dependent diabetes is U-shaped, with an increased prevalence in young people with birthweights over 9.9 pounds [>4.5 kg][34]. The increased risk of diabetes among those of high birthweight was associated with maternal diabetes in pregnancy.

Insulin resistance

Both deficiency in insulin production and insulin resistance are thought to be important in the pathogenesis of non-insulin dependent diabetes. There is evidence that both may be determined in fetal life. Men and women with low birthweight have a high prevalence of the 'insulin resistance syndrome'[35], in which impaired glucose tolerance, hypertension and raised serum triglyceride concentrations occur in the same patient; Table 5 shows results for a sample of 407 men in Hertfordshire. Phillips *et al.*[36] carried out insulin tolerance tests on 103

Table 4 Prevalence of non-insulin dependent diabetes by ponderal index at birth among 60 year old men in Uppsala, Sweden

Ponderal index at birth (kg/m^3)	Number of men	Prevalence (%) of diabetes
<24.2	193	11.9
−<25.9	193	5.2
−<27.4	196	3.6
−<29.4	188	4.3
≥29.4	201	3.5
All	971	5.7
P value for trend		0.001

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Table 5 Prevalence of the insulin resistance syndrome in men aged 59 to 70 years according to birthweight

Birthweight pounds (kg)	Number of men	% with insulin resistance syndrome	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
All	407	14	

men and women in Preston. At each body mass, insulin resistance was greater in people who had a low ponderal index at birth. Conversely, at each ponderal index, resistance was greater in those with high body mass. The greatest insulin resistance was therefore in those with low ponderal index at birth but high current body mass.

A study in San Antonio, Texas, confirmed the association between low birthweight and the insulin resistance syndrome in 30 year old Mexican-Americans and non-Hispanic white people[37]. Among men and women in the lowest third of the birthweight distribution and the highest third of current body mass 25% had the syndrome. By contrast none of those in the highest third of birthweight and lowest third of current body mass had it. A study of young adults in France showed that those who had had intrauterine growth retardation had raised plasma insulin concentrations when fasting and after a glucose challenge[38]. They did not show any of the other abnormalities that occur in the insulin resistance syndrome. This suggests that insulin resistance may be a primary abnormality to which other changes are secondary. A recent study of men and women who were *in utero* during the Dutch famine provides direct evidence that maternal undernutrition can programme insulin resistance and non-insulin dependent diabetes[39]. Those exposed to famine *in utero* had higher two hour plasma glucose and insulin concentrations than those born before or conceived after the famine.

Law reported associations between thinness at birth and raised 30 minute plasma glucose concentrations in seven year old children in Salisbury, UK[40]. In a group of older children, Whincup found that those who had lower birthweight had raised plasma insulin concentrations, both fasting and after oral glucose, suggesting insulin resistance[41]. Among these children, however, those who had low birthweight had normal plasma glucose concentrations, which implies that despite being insulin resistant they were currently able to maintain glucose homeostasis. These findings in children support an intrauterine origin for non-insulin dependent diabetes and suggest that the seeds of diabetes in the next generation have already been sown and are apparent in today's children.

Mechanisms

The processes that link thinness at birth with insulin resistance in adult life are not known. Babies born at term with a low ponderal index have a reduced mid-arm circumference and low muscle bulk. It is possible that thinness at birth is associated with abnormalities in muscle structure and function which originate in mid-gestation and have long term consequences that interfere

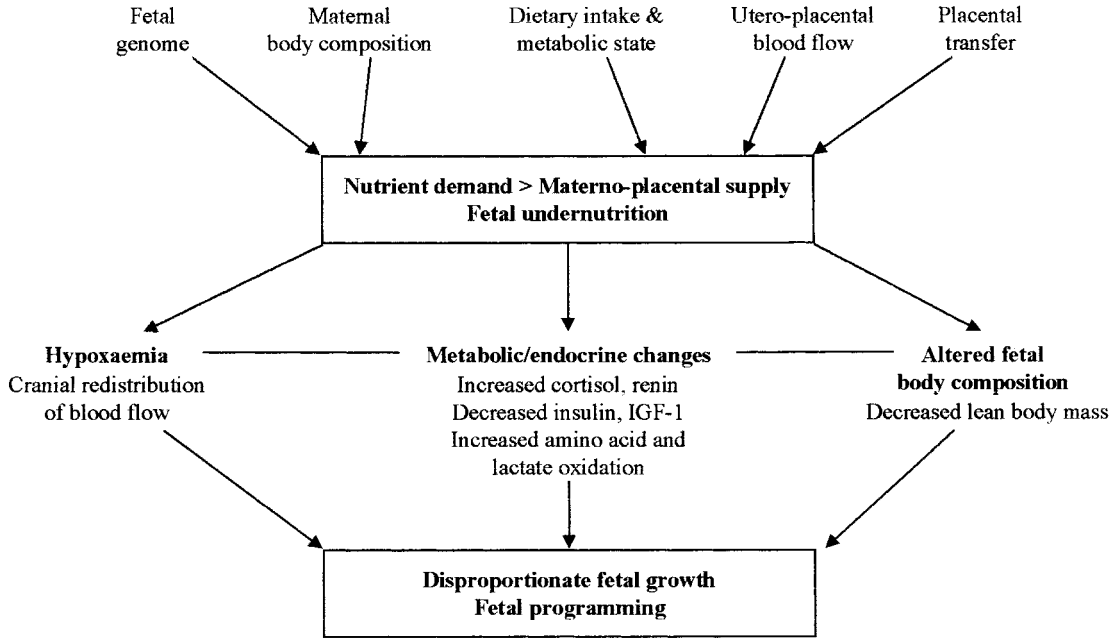

Fig. 3 Framework for understanding the maternal regulation of fetal development and programming

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with insulin's ability to promote glucose uptake in skeletal muscle. Magnetic resonance spectroscopy studies show that people who were thin at birth have lower rates of glycolysis and glycolytic ATP production during exercise[42]. In response to undernutrition a fetus may reduce its metabolic dependence on glucose and increase oxidation of other substrates, including amino acids and lactate (Fig. 3). This has led to the hypothesis that a glucose-sparing metabolism persists into adult life, and that insulin resistance arises as a consequence of similar processes, possibly because of reduced rates of glucose oxidation in insulin-sensitive peripheral tissues.

When the availability of nutrients to the fetus is restricted concentrations of anabolic hormones, including insulin and insulin-like growth factor I fall, while catabolic hormones, including glucocorticoids rise (Fig. 3). Persisting hormonal changes could underlie the development of insulin resistance. Bjorntorp has postulated that glucocorticoids, growth hormone and sex steroids may play major roles in the evolution of the metabolic syndrome[43].

Insulin deficiency

Infants who are small for dates have fewer pancreatic β cells and there is evidence that nutritional and other factors determining fetal and infant growth influence the size and function of the adult β cell complement[44]. Whether and when non-insulin dependent diabetes supervenes will be determined by the rate of attrition of β cells with ageing, and by the development of insulin resistance, of which obesity is an important determinant.

While studies of adults in Preston[45] and Stockholm[46] have found no association between birthweight and insulin responses to infused glucose, it is possible that insulin resistance in adult life changes insulin secretion and obscures associations with fetal growth. Studies of younger people may resolve this. A study of men aged 21 years showed that those with lower birthweight had reduced plasma insulin concentrations 30 minutes after a glucose challenge[47]. Another study of men of similar age showed that a low insulin response to glucose was associated with high placental weight and a high ratio of placental weight to birthweight[48]. In contrast a study of young Pima Indians showed that those with low birthweight had evidence of insulin resistance but no defect in insulin secretion[49].

In Mysore, South India, men and women with non-insulin dependent diabetes showed signs of both insulin resistance and deficiency[50]. As in people from South India living in Britain, there was a high prevalence of insulin resistance and central adiposity in this population. Those in Mysore who had non-insulin dependent diabetes, however, also had a low insulin increment after a glucose challenge, indicating insulin deficiency as well as resistance. Whereas, however, insulin resistance was associated with low birthweight, non-insulin dependent diabetes was associated with shortness at birth in relation to birthweight, that is a high ponderal index, and with maternal adiposity[50].

These findings led to a novel hypothesis to account for the epidemic of non-insulin dependent diabetes in urban and migrant Indian populations[50] (Fig. 4). Widespread fetal undernutrition predisposes the Indian population to insulin resistance. On moving to cities, people's levels of physical activity diminish. Young women, no longer required to do agricultural work or walk long distances to fetch water and firewood, become fatter and therefore more insulin resistant. They are therefore unable to maintain glucose homeostasis during pregnancy, even at relatively low levels of adiposity, and become hyperglycaemic, though not necessarily diabetic. It is known that high plasma glucose concentrations within the normal range influence fetal growth and lead to macrosomia[51].

Serum cholesterol and blood clotting

Studies in Sheffield, UK show that the neonate that has a short body and low birthweight in relation to the size of its head has persisting disturbances of cholesterol metabolism and blood coagulation[1]. Disproportion in body length relative to head size is thought to result from cranial redistribution of blood flow associated with hypoxaemia and undernutrition in late gestation. The fetus diverts oxygenated blood away from the trunk to sustain the brain. This affects the growth of the liver, two

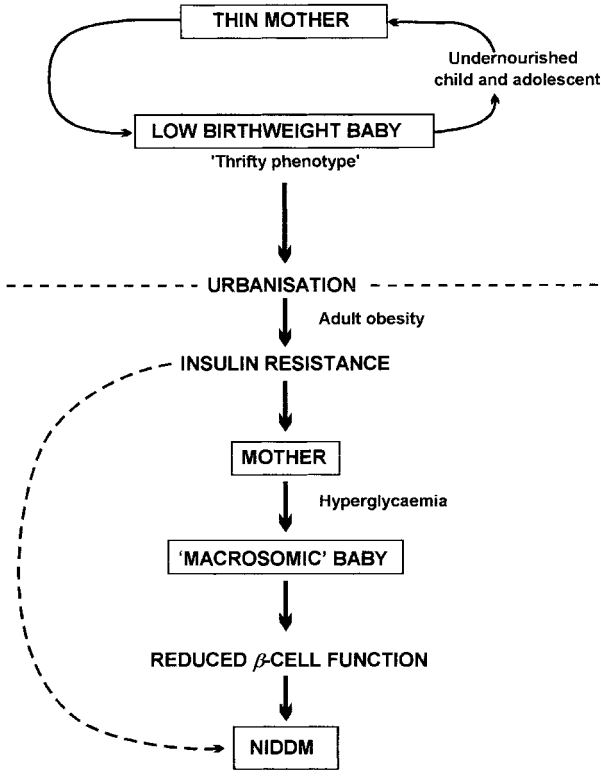

Fig. 4 A model to explain the epidemic of non-insulin dependent diabetes in urban India

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of whose functions, regulation of cholesterol and of blood clotting, seem to be permanently perturbed. Disturbance of cholesterol metabolism and blood clotting are both important features of coronary heart disease.

The Sheffield records included 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[1]. The differences in cholesterol concentrations across the range of abdominal circumference were large, statistically equivalent to 30 per cent differences in mortality from coronary heart disease. Findings for plasma fibrinogen concentrations, a measure of blood coagulability, were of similar size. One interpretation is that reduced abdominal circumference at birth reflects impaired liver growth and consequent re-programming of liver metabolism. Further understanding of liver programming has come from experiments on rats showing that undernutrition *in utero* can permanently alter the balance of two liver enzymes, phosphoenolpyruvate carboxykinase and glucokinase, involved respectively in the synthesis and breakdown of glucose[5]. A low protein diet during gestation permanently changes the balance of enzyme activity in the offspring in favour of synthesis. This is thought to reflect enhanced cell replication in the area around the portal vein, carrying blood from the gut to the liver, at the expense of the cells around the hepatic vein. These experiments are of particular interest because undernutrition after birth had no effect, and because the two enzymes are not normally synthesised until after birth, suggesting that their production can be regulated before the genes encoding them are transcribed.

Fetal nutrition

The demonstration that normal variations in fetal size and proportions at birth have implications for health throughout life has prompted a re-evaluation of the regulation of fetal growth and development. Though the fetal genome determines *growth potential* in utero, the weight of evidence suggests that it plays a subordinate role in determining the growth that is actually achieved[52]. Rather, it seems that the dominant determinant of fetal growth is the nutritional and hormonal milieu in which the fetus develops, and in particular the nutrient and oxygen supply.

Support for the importance of the intra-uterine environment comes from animal cross breeding experiments and from studies of half-siblings related either through the mother or the father[53]. For example, among half-siblings, related through only one parent, those with the same mother have similar birthweights (correlation coefficient 0.58); birthweights of half-siblings with the same father are dissimilar (correlation coefficient 0.1)[53]. A study of babies born after ovum donation illustrates how birth size is essentially controlled by the mother's body and the nutritional environment it affords[54]. The birthweights of the babies were unrelated to the weights of the women who donated the eggs but strongly related to the weight of the recipient mother, heavier mothers having larger babies. While maternal cigarette smoking is known to also restrict fetal growth, follow-up studies have shown that it is not related to levels of cardiovascular risk factors in the offspring[18].

Animal experiments suggest that fetal undernutrition in early gestation produces small but normally proportioned offspring, whereas undernutrition in late gestation may alter body proportions but have less effect on birthweight[1]. The varying critical periods during which organs and systems mature indicate that an adverse intra-uterine environment at different developmental stages is likely to have differing short and long-term effects. For example, there is a critical period for gonadal development early in gestation, as compared with one for renal development later in gestation between 26 and 34 weeks of pregnancy. The observation that babies that were symmetrically small, short, or thin at birth are predisposed to different disorders in adult life[1] may in part reflect an adverse intra-uterine environment at different developmental stages.

With respect to timing, effects manifest late in pregnancy may commonly originate much earlier in gestation. For example, studies of the Dutch famine of 1944–45 led to the dogma that thinness at birth results from exposures in the last trimester of pregnancy[55]. Outside the setting of famine, animal and human studies indicate that fetal undernutrition in late pregnancy is, however, generally a consequence of an inadequate materno-placental supply capacity set up earlier in gestation[20,56]. Thus, while the short and long-term effects of an acute severe famine are of great scientific importance, we must be aware that they could result in erroneous conclusions about timing in the non-famine situation.

Maternal influences on fetal nutrition

Size at birth reflects the product of the fetus's trajectory of growth, set at an early stage in development, and the materno-placental capacity to supply sufficient nutrients to maintain that trajectory. Failure of the materno-placental supply line to satisfy fetal nutrient requirements results in a range of fetal adaptations and developmental changes (Fig. 3). It is thought that these may lead to permanent alterations in the body's structure and metabolism, and thereby to cardiovascular and metabolic disease in adult life. In Western communities, randomised controlled trials of maternal macronutrient supplementation have had relatively small effects on birthweight[57]. These have led to the view that regulatory mechanisms in the maternal and placental systems act to ensure that human fetal growth and development is little influenced

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by normal variations in maternal nutrient intake, and that there is a simple relationship between a woman's body composition and the growth of her fetus. Recent experimental studies in animals and observational data in humans challenge these concepts[1]. These suggest that a mother's own fetal growth and her dietary intakes and body composition can exert major effects on the balance between the fetal demand for nutrients and the materno-placental capacity to meet that demand.

Quite apart from any long-term effects on health in adult life, specific issues that have not been adequately addressed in previous studies of maternal nutrition include; (1) effects on the trajectory of fetal growth, (2) intergenerational effects, (3) paradoxical effects on placental growth, (4) effects on fetal proportions and specific tissues, and (5) the importance of the balance of macronutrients in the mother's diet and of her body composition.

The fetal growth trajectory

A rapid trajectory of growth increases the fetus's demand for nutrients. This reflects effects on both maintenance requirements, greater in fetuses that have achieved a larger size as a result of a faster growth trajectory, and on requirements for future growth. Though the fetal demand for nutrients is greatest late in pregnancy, the magnitude of this demand is thought to be primarily determined by genetic and environmental effects on the trajectory of fetal growth set at an early stage in development. Experimental studies of pregnant ewes have shown that, although a fast growth trajectory is generally associated with larger fetal size and improved neonatal survival, it does render the fetus more vulnerable to a reduced materno-placental supply of nutrients in late gestation. Thus, maternal undernutrition during the last trimester adversely affected the development of rapidly growing fetuses with high requirements, while having little effect on those growing more slowly[58]. Rapidly growing fetuses were found to make a series of adaptations in order to survive, including fetal wasting and placental oxidation of fetal amino acids to maintain lactate output to the fetus[58].

Although the identity of the major genes determining growth potential and the fetal growth trajectory is unknown, animal studies indicate that insulin-like growth factors and their receptors may be important. Experiments in animals have shown that periconceptional alterations in maternal diet and plasma progesterone concentrations can alter gene expression in the pre-implantation embryo to change the fetal growth trajectory[59]. Environmental effects have been demonstrated on both embryonic growth rates and on cell allocation in the pre-implantation embryo. Maternal progesterone treatment can, for example, permanently alter the trajectory of fetal growth by changing the allocation of cells between the inner cell mass that develops into the fetus and the outer trophectoderm that becomes the placenta[59]. The trajectory of fetal growth is thought to increase with improvements in periconceptional nutrition, and is faster in male fetuses. The greater vulnerability of such fetuses on a fast growth trajectory may contribute to the rise in coronary heart disease with Westernization and the higher death rates in men.

Intergenerational effects

Experimental studies in animals have shown that undernutrition over many generations can have cumulative effects on reproductive performance over several generations. Thus, feeding rats a protein deficient diet over twelve generations resulted in progressively greater fetal growth retardation over the generations; following refeeding with a normal diet it then took three generations to normalize growth and development[60].

Strong evidence for major intergenerational effects in humans has come from studies showing that a woman's

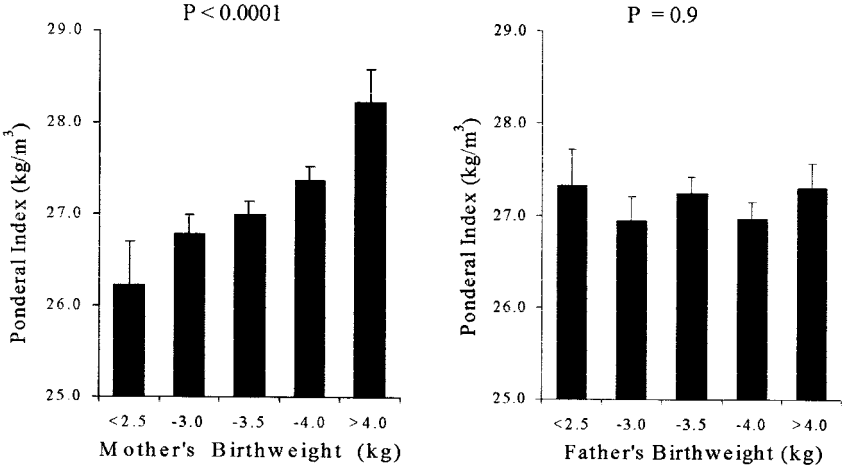

Fig. 5 Ponderal index at birth in 492 term Southampton pregnancies according to the mother's and father's birthweights[56] (Values are means (±SE) adjusted for sex and gestation)

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birthweight influences the birthweight of her offspring[61]. We have, moreover, found that whereas low birthweight mothers tend to have thin infants with a low ponderal index, the father's birthweight is unrelated to ponderal index at birth (Fig. 5); crown-heel length at birth is, however, more strongly related to the father's birthweight than to the mother's[56]. The effect of *maternal* birthweight on thinness at birth is consistent with the hypothesis that the materno-placental supply line may be unable to satisfy fetal nutrient demand in low birthweight mothers. Potential mechanisms underlying this effect include alterations in the uterine or systemic vasculature, programmed changes in maternal metabolic status, and impaired placentation. The strong effect of *paternal* birthweight on crown-heel length may reflect paternal imprinting of genes important for skeletal growth, such as those regulating the concentrations of insulin-like growth factors.

Placental size and transfer capabilities

Though the size of the placenta gives only an indirect measure of its capacity to transfer nutrients to the fetus, it is nonetheless strongly associated with fetal size at birth. Experiments in sheep have shown that maternal nutrition in early pregnancy can exert major effects on the growth of the placenta, and thereby alter fetal development[20]. As previously referred to, the effects produced depended on the nutritional status of the ewe in the periconceptional period. In ewes poorly nourished around the time of conception, high nutrient intakes in early pregnancy increased the size of the placenta. Conversely, in ewes well nourished around conception, high intakes in early pregnancy resulted in smaller placental size[20]. Although this suppression appears paradoxical, in sheep farming it is common practice for ewes to be put on rich pasture prior to mating and then on poor pasture for a period in early pregnancy.

As part of a study designed to evaluate whether the normal variations in maternal diet found in Western communities could influence fetal growth and development, we have found evidence of a similar suppressive effect of high dietary intakes in early pregnancy on placental growth[62]. Thus, among 538 women who delivered at term, those with high dietary intakes in early pregnancy, especially of carbohydrate, had smaller placentas, particularly if combined with low intakes of dairy protein in late pregnancy (Table 6)[62]. These effects were independent of the mother's body size, social class and smoking, and resulted in alterations in the ratio of placental weight to birthweight (placental ratio). Confirmation that maternal diet can alter placental growth has come from analyses of the Dutch famine, where famine exposure in early pregnancy increased placental weight[63].

The U-shaped relation between the placental ratio and later coronary heart disease found in men born earlier this century in Sheffield[11] suggests that effects on placental growth could be of long-term importance. Babies with a disproportionately small placenta may suffer as a consequence of an impaired placental supply capacity; those with a disproportionately large placenta may experience fetal catabolism and wasting to supply amino acids for placental consumption[64]. Consequent fetal adaptations may underlie the increased adult coronary heart death rates in those with both low and high placental ratios.

Table 6 Mean placental weight in 538 women delivered at term in Southampton, UK[62]

		Carbohydrate intake in early pregnancy (g/day)			
		≤265	−340	>340	All
Dairy protein intake in late pregnancy (g/day)	≤18.5	539	507	494	516
	−26.5	556	546	509	540
	>26.5	582	533	536	544
	All	554	531	517	534*

* Overall standard deviation = 121 g.
Values are adjusted for sex and the duration of gestation at delivery. *P* values for associations with placental weight: carbohydrate $P = 0.002$, dairy protein $P = 0.005$.

Effects on specific fetal tissues

Experimental studies in animals have shown that dietary manipulations during early development can have tissue-specific effects, leading to alterations in body proportions. For example, in pigs fed differing diets in the first year of life those fed a protein deficient diet had a disproportionately large head, ears and genitalia compared with those fed an energy deficient diet[2]. Experiments in guinea pigs have shown that maternal undernutrition in pregnancy can result in offspring that have altered body proportions at birth and that exhibit profound elevation of serum cholesterol concentrations when fed a high cholesterol diet in the post-weaning period[65].

In humans, few studies have examined the possibility of maternal nutrition during pregnancy having tissue-specific effects on the fetus, leading to greater alterations in neonatal proportions than in birthweight. We have found that women with low dairy protein intakes in late pregnancy tended to have babies that were thinner at birth[56]; maternal dairy protein intakes were not however related to birthweight[62]. Furthermore, a recent follow-up study of children whose mothers took part in a randomized controlled trial of calcium supplementation in pregnancy found that while maternal supplementation was associated with lowering of the offspring's blood pressure in childhood, this effect was not associated with any change in birthweight[66].

Maternal dietary balance and body composition

Indications that the *balance* of macronutrients in the mother's diet can have important short and long-term effects on the offspring has come from experimental studies in pregnant rats. These have found that maternal

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diets with a low ratio of protein to carbohydrate and fat alter fetal and placental growth, and result in lifelong elevation of blood pressure in the offspring[4]. A follow-up study of 40 year old men and women in Aberdeen, UK suggested that alterations in the maternal macronutrient balance during pregnancy could have similar adverse effects on the offspring[19]; the relations with maternal diet were, however, complex and studies to replicate them are in progress. Among women with low intakes of animal protein, a higher carbohydrate intake was associated with a higher adult blood pressure in the offspring; among those with high animal protein intakes, a lower carbohydrate intake was associated with higher blood pressure. These increases in blood pressure were associated with decreased placental size[19].

Support for the thesis that alterations in fetal and placental development may result from a *low* ratio of animal protein to carbohydrate comes from observational studies of maternal nutrition in pregnancy[62]. Support for adverse effects of a *high* ratio of animal protein to carbohydrate comes from a review of 16 trials of protein supplementation showing that supplements with a high protein density were consistently associated with lower birthweight[67].

Evidence that maternal body composition has important effects on the offspring has come from studies showing that extremes of body composition in pregnancy are associated with adverse long-term outcomes in the offspring. Follow-up of a group of Jamaican children showed that those whose mothers had thin skinfold thicknesses and a low weight gain in pregnancy had higher blood pressure at the age of 11 years[68]. A subsequent study of 11-year-old children in Birmingham, UK found similar associations[69]. Studies in India have found that a low maternal weight in pregnancy is associated with an increased risk of coronary heart disease in the offspring in adult life[10].

At the other extreme of maternal body fatness, evidence for long-term effects of maternal *obesity* has come from follow-up of men in Finland born earlier this century[12]. Markedly raised coronary heart disease death rates were found in men whose mothers had a high body mass index in pregnancy. This effect was independent of an association between thinness at birth and increased rates of adult coronary heart disease. Modeling the data to derive contour lines of similar coronary heart disease death rates indicated that increasing maternal body mass index had little effect on the offspring's death rates in tall women, but strong effects in short women[1,12]. One interpretation of these findings is that greater maternal body fatness may increase fetal growth and hence the fetal demand for nutrients; short women may not be able to meet this increased demand as a result of a constrained nutrient supply capacity determined during their own intra-uterine development[12].

Implications and future work

The demonstration that normal variations in fetal size and thinness at birth have implications for health throughout life has prompted a re-evaluation of the regulation of fetal development. Impetus has been added to this re-evaluation by recent findings showing that a woman's diet and body composition in pregnancy are related to levels of cardiovascular risk factors and the prevalence of coronary heart disease in her offspring in adult life. These observations challenge the view that the fetus is little affected by changes in maternal nutrition, except in circumstances of famine.

The long time-scale over which the effects of an adverse intra-uterine environment act dictate that we now need to progress beyond epidemiological associations to greater understanding of the cellular and molecular processes that underlie them. Szent-Gyorgi wrote that, 'for every complex problem, there is a simple, easy to understand, incorrect answer'; for fetal growth and development the complexities are such that currently available data form only a limited basis for changing dietary recommendations to pregnant women. Future work will need to identify the factors that set the trajectory of fetal growth, and the influences that limit the materno-placental delivery of nutrients and oxygen to the fetus. We also need to define how the fetus adapts to a limited nutrient supply, how these adaptations programme the structure and physiology of the body, and by what molecular mechanisms nutrients and hormones alter gene expression.

If, as we believe, a woman's own fetal growth, and her diet and body composition before and during pregnancy play a major role in programming the future health of her children, mothers will want to know what they can do to optimize the intra-uterine environment they provide for their babies. A recent technical consultation organised by the United States Department of Agriculture, the World Bank and UNICEF concluded that a key area of focus to reduce the burden of low birthweight and its associated morbidities is to improve the nutritional status of adolescent girls and of pregnant women. Similarly, one of the two main recommendations of the recent Acheson Report on Inequalities in Health in the United Kingdom was that 'a high priority is given to policies aimed at improving health and reducing inequalities in women of childbearing age, expectant mothers and young children'[70]. A strategy of interdependent clinical, animal and epidemiological research is required to identify specific recommendations for both whole populations and for vulnerable groups such as teenage pregnancies and single parents. Research is also required to identify the barriers to healthy eating among young women, whose diets are important both for their own health and the health of the next generation. Such an approach may allow us to

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reduce the prevalence of major chronic diseases and diminish social inequalities in health.

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