Fetal, Infant, and Childhood Growth Are Predictors of Coronary Heart Disease, Diabetes, and Hypertension in Adult Men and Women

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Many human fetuses have to adapt to a limited supply of nutrients. In doing so they permanently change their structure and metabolism. These programmed changes may be the origins of a number of diseases in later life, including coronary heart disease, hypertension and noninsulin-dependent diabetes. We review epidemiologic studies in which the incidence of these diseases has been related to the recorded, early growth of individuals, while considering factors in the adult lifestyle, such as obesity and socioeconomic status. We discuss possible mechanisms. For hypertension these mechanisms include placentation, maternal blood pressure, fetal undernutrition; childhood growth, activation of the renin–angiotensin system, renal structure, programming of the hypothalamic–pituitary–adrenal axis, vascular structure, and sympathetic nervous activity. For noninsulin-dependent diabetes we discuss mechanisms concerning both insulin resistance and insulin deficiency. We include a review of evidence for the programming of serum cholesterol and clotting factor concentrations. We address the timing of critical windows for coronary heart disease, reviewing studies that allow assessment of the relative importance of fetal, infant, and childhood growth. We argue for a research strategy that combines clinical, animal, and epidemiological studies. *Key words*: birth weight, childhood growth, coronary heart disease, diabetes, epidemiology, hypertension, infant growth, intrauterine growth, maternal nutrition, programming hypothesis. — *Environ Health Perspect* 108(suppl 3):545–553 (2000).
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Introduction to Programming

In fetal life the tissues and organs of the body go through what are called critical periods of development (*1*). These critical periods may coincide with periods of rapid cell division. Programming describes the process whereby a stimulus or insult at a critical period of development has lasting or lifelong effects (*2,3*). The development of the sweat glands is an interesting example of this process (*4*). In Japan in the early years of this century, military expansion took Japanese soldiers and settlers into unfamiliar climates. There were wide differences in people's abilities to adapt to hot climates. Physiological studies showed this was related to the number of functioning sweat glands. People with more functioning sweat glands cooled down faster. Rather than attributing the differences in sweat gland numbers to genetic effects, Japanese physiologists explored the early development of the glands. They found that at birth all humans have similar numbers of sweat glands, but none of them function. In the first 3 years after birth, a proportion of the glands become functional, depending on the temperature to which the child is exposed. The hotter the conditions the greater the number of sweat glands that are programmed to function. After 3 years the programming is complete and the number of sweat glands is fixed. The development of sweat glands encapsulates the essence of programming—a critical period when the system is plastic and sensitive to the environment, followed by loss of plasticity and a fixed functional capacity.

Programming of an Undernourished Fetus

Undernutrition is one of the influences that program the human body and has lifelong consequences. Rickets demonstrates that undernutrition at a critical stage of early life leads to persisting changes in structure. What is new is the recent realization that some of the body's memories of early undernutrition become translated into pathology and thereby determine disease in later life (*5*). However, this is unsurprising given animal experiments that show 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 (*2,6*).

The human fetus adapts to undernutrition by metabolic changes, redistribution of blood flow, and changes in the production of fetal and placental hormones that control growth (*7*).

Metabolic changes. The immediate metabolic response of the fetus to undernutrition is catabolism: it consumes its own substrates to provide energy (*8*). More prolonged undernutrition leads to a slowing in growth. This enhances the ability of the fetus to survive by reducing the use of substrates and lowering the metabolic rate. Slowing of growth in late gestation leads to disproportion in organ size, since organs and tissues growing rapidly at the time are affected the most. Undernutrition in late gestation may, for example, lead to reduced growth of the kidney, which is developing rapidly at that time. Reduced replication of kidney cells may permanently reduce cell numbers, because after birth there seems to be no capacity for renal cell division to catch-up (*9,10*).

Redistribution of blood flow. While slowing its rate of growth, the fetus may protect tissues that are important for immediate survival, especially the brain. One way in which the brain can be protected is by redistribution of blood flow to favor it (*11,12*). This adaptation occurs in many mammals. In humans it has exaggerated costs for tissues other than the brain, notably the liver and other abdominal viscera, because of the large size of the human brain.

Endocrine changes. Nutrition has profound effects on fetal hormones and on the hormonal and metabolic interactions between the fetus, placenta, and mother on whose coordination fetal growth depends (*8*). Fetal insulin and the insulin-like growth factors (IGF) are thought to have a central role in the regulation of growth and respond rapidly to changes in fetal nutrition (*13*). If a mother decreases her food intake, fetal insulin, IGF, and glucose concentrations fall, possibly through the effect of decreased maternal IGF. This leads to reduction in transfer of amino acids and glucose from mother to fetus and ultimately to lower fetal growth rates (*14*). In late gestation and after birth, the growth hormone and IGF axis of the fetus take over a central role from insulin in driving linear growth. Whereas undernutrition leads to a fall in the concentrations of hormones that control fetal growth, it leads to a rise in cortisol, whose main effects are on cell differentiation (*7*).

Programming of Coronary Heart Disease

The suggestion that coronary heart disease might originate during fetal development came from showing the similarity of the geographic pattern of death rates among babies

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in Britain during the early 1900s (*15*) and the pattern of today's death rates from coronary heart disease. The usual certified cause of death in newborn babies at that time was low birth weight. 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 opportunity for research.

Early epidemiological studies that pointed to the possible importance of programming in coronary heart disease were based on the examination of men and women in middle and late life whose body measurements at birth were recorded. Surviving records were found in Hertfordshire, Preston, and Sheffield in the United Kingdom. The Hertfordshire records were maintained by health visitors and include measurements of growth in infancy as well as birth weight. In Preston and Sheffield, detailed obstetric records documented body proportions at birth (*16,17*).

Sixteen thousand men and women born in Hertfordshire from 1911 to 1930 have now been traced from birth to the present day. Death rates from coronary heart disease fell between those at the lower and upper ends of the birth weight distribution (Table 1) (*18*). A study in Sheffield 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 coronary heart disease (*17*). The association between low birth weight and coronary heart disease has been confirmed in studies of men in Uppsala, Sweden (*19*), and Caerphilly, Wales (*20*), and among women in the United States. Among 80,000 women in the American Nurses Study there was a fall in the relative risk of nonfatal coronary heart disease across the range of birth weights (*21*). An association between low birth weight and prevalent coronary heart disease was also shown in a study in South India (*22*). Among Indian men and women 45 years of age and older the prevalence of the disease fell from 18% in those who weighed 5.5 lb at birth to 4% in those who weighed 7 lb or more.

Table 1. Death rates from coronary heart disease among 15,726 British men and women according to birth weight.

Birth weight, lb (kg)	Standardized mortality ratio	No. 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
All	74	941

Table 2. Standardized mortality ratios for coronary heart disease in 3,302 Finnish men from 1924 to 1933.

Birth weight, kg (lb)	Standardized mortality ratio (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)	Standardized mortality ratio (No. of deaths)
≤ 25	116 (59)
27	105 (88)
29	72 (64)
> 29	56 (33)
All	86 (244)
p value for trend	< 0.0001

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 as crude a summary of its physique, as is the weight of a child or adult without a measure of height. The addition of birth length allows a long, thin baby to be distinguished from a short, fat baby. With the addition of head circumference, the baby whose body is small in relation to its head as a result of brain-sparing may also be distinguished. These phenotypes reflect differing fetal adaptations to undernutrition, hypoxia, and other influences and they have different long-term consequences.

In Sheffield, death rates for coronary heart disease were higher in men who were short at birth (*23*). The mortality ratio for coronary heart disease in men who were 18.5 in. or less in length was 138 compared with 98 in the remainder. Thinness at birth, as measured by a low ponderal index (birth weight/length^3), was also associated with coronary heart disease. Table 2 shows that although among men born in Helsinki, Finland, low birth weight was associated with raised death rates for coronary heart disease, there was a stronger association with thinness at birth, especially in men born at term (*24*). Men who were thin at birth, as measured by a low ponderal index, had death rates that were twice those of men who had a high ponderal index.

In Finland, increased death rates from coronary heart disease were associated with low placental weight. In Sheffield, however, coronary heart disease did not vary with placental weight but showed a U-shaped relation with the ratio of placental weight to birth weight, with the highest mortality ratios at either end of the distribution. The pattern of body proportions at birth that predicts death from coronary heart disease therefore may be summarized 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 birth weight.

These findings suggest that influences linked to early 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* and during infancy 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 (*25–28*). However, in three of the studies that have replicated the association between birth weight and coronary heart disease, data on lifestyle factors including smoking, employment, alcohol consumption, and exercise were collected (*19–21*). Allowance for them had little effect on the association between birth weight and coronary heart disease.

In studies exploring the mechanisms underlying these associations, the trends in coronary heart disease with birth weight were found to parallel similar trends in two of its major risk factors—hypertension and noninsulin-dependent diabetes mellitus (*29,30*). Table 3 illustrates the size of these trends, with the prevalence of noninsulin-dependent diabetes mellitus and impaired glucose tolerance falling 3-fold between men who weighed up to 5.5 lb at birth and those who weighed over 9.5 lb (*29*). These associations with small size at birth are 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

Table 3. Prevalence of noninsulin-dependent diabetes and impaired glucose tolerance in men 59–70 years of age.

Birth weight, lb (kg)	No. of men	% with impaired glucose tolerance or diabetes	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	40	6.6 (1.5–28)
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
All	370	25	

impaired glucose tolerance is highest in people who had low birth weight but become obese as adults.

Programming of Hypertension

Associations between low birth weight and raised blood pressure in childhood and adult life have been extensively demonstrated around the world. Law and Shiell published a systematic review of studies describing the association between birth weight and blood pressure (*31*)—a review based on 34 studies of more than 66,000 people of all ages in many countries. In almost all the studies an increase in birth weight 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, perhaps 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 (*32*). The difference in systolic pressure associated with a kilogram difference in birth weight was around 3.5 mmHg. In clinical practice this would be a small difference, but there are large differences 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% reduction in attributable mortality (*33*).

The association between low birth weight and raised blood pressure depends on babies who were small for dates, after reduced fetal growth, rather than on babies who were born preterm (*16,34*). Although in these studies alcohol consumption and higher body mass index were also associated with raised blood pressure, the associations between birth weight and blood pressure were independent of them. Nevertheless, body mass index remains an important influence on blood pressure and, in humans and animals, the highest pressures are found in people who were small at birth but become overweight as adults.

As has already been discussed, birth weight is a crude measure of fetal growth that does not distinguish shortness and thinness, differences in head size, or variations in the balance of fetal and placental size. In contrast to the associations between birth size and coronary heart disease, those between birth weight and blood pressure are generally as strong as those between thinness or shortness and blood pressure (*35–38*).

Possible Mechanisms

Placentation. Men and women who were born in Sharoe Green Hospital in Preston 50 years ago had systolic blood pressures that fell between subjects with low and high birth weight (*16,35*), as in other studies. In addition, however, their blood pressures increased 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. A rise in blood pressure with increasing placental weight was also found in 4-year-old children in Salisbury, UK, and among 8-year-old children in Adelaide, Australia (*37,39*). However, in studies of children and adults the association between placental enlargement and raised blood pressure has been inconsistent (*40*). For example, in a study of men and women born in Aberdeen, Scotland, after World War II, at a time when food was still rationed, raised blood pressure was associated with small placental size (*41*). Animal studies offer a possible explanation for this inconsistency. In sheep the placenta enlarges in response to moderate undernutrition in mid-pregnancy (*42,43*). This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent response and occurs only in ewes that were well nourished before pregnancy.

Maternal blood pressure. In some studies the blood pressures of the mothers during and after pregnancy have been recorded (*37,44,45*). They correlate with the offsprings' blood pressure. However, the associations between body size at birth and later blood pressure are independent of the mothers' blood pressures. Recent observations show that if the mother's blood pressure is measured throughout a 24-hr period rather than by isolated readings at antenatal clinics, there is a continuous inverse association between birth weight and maternal blood pressure (*46*). It could be argued, therefore, that the association between low birth weight and raised blood pressure reflects an association, possibly genetic, between a mother's ambulatory blood pressure and the blood pressure of her offspring. However, the demonstration that experimental undernutrition during gestation programs blood pressure in animals (*47*) argues against this interpretation. An alternative explanation is that raised blood pressure during pregnancy reflects failure of maternal cardiovascular adaptations to pregnancy, which include peripheral vasodilation, with consequent fetal undernutrition, low birth weight, and raised blood pressure in the offspring.

Fetal undernutrition. Several lines of evidence support the thesis that it is poor delivery of nutrients that programs raised blood pressure in humans. Maternal height, parity, and cigarette smoking, which influence fetal growth, have not been found to be related to the offsprings' blood pressure other than in small preterm babies (*37,48*). In Jamaica children whose mothers had thin triceps skinfolds in early pregnancy and low weight gain during pregnancy (*49*) had raised blood pressure. There were similar findings in a group of children in Birmingham, UK (*50*). In The Gambia, low pregnancy weight gain was associated with higher blood pressure in childhood (*51*). In Aberdeen, Scotland, the blood pressures of middle-age men and women were related to their mothers' intakes of carbohydrate and protein during pregnancy (*41*).

Childhood growth. Studies in the United States, the United Kingdom, 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 (*52*). The hypothesis that hypertension is a disorder of accelerated childhood growth can be reconciled with the association with low birth weight by postulating that postnatal catch-up growth plays an important role in amplifying changes established *in utero.*

Renin–angiotensin system. There is evidence that the fetal renin–angiotensin system is activated during intrauterine growth retardation (*53*). However, in a follow-up study of men and women born in Sheffield, those who had been small at birth had lower plasma concentrations of inactive and active renin (*54*). Causes of raised blood pressure that are not mediated by increased rates of renin release tend to result in low concentrations of renin, and therefore, at first sight, these findings suggest that the association between impaired fetal growth and raised blood pressure must involve mechanisms other than the renin–angiotensin system. However, low concentrations of renin in adult life do not exclude the possibility that the renin–angiotensin system has exerted an earlier but lasting influence.

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 et al. has suggested that retarded fetal growth leads to reduced numbers of nephrons which in turn leads to increased pressure in the glomerular capillaries and the development of glomerular sclerosis (*55,56*). This sclerosis leads to 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 (*55*). Animal and human studies have shown that low rates of intrauterine growth are associated with reduced numbers of nephrons

(*57*). Studies using fetal ultrasound have shown that babies who are small for gestational age have reduced renal growth during the critical period at 26–34 weeks of gestation. This reduces the anteroposterior size of the kidney but does not diminish kidney length (*58*). It has been suggested that during normal childhood development, kidney growth lags behind the increases in body weight, and blood pressure rises to maintain renal homeostasis (*59*).

Endocrine. Animal studies have led to the hypothesis that fetal undernutrition leads to life-long changes in the hypothalamic–pituitary–adrenal axis of the fetus, which in turn resets homeostatic mechanisms controlling blood pressure (*60,61*). A recent study of 9-year-old children in Salisbury, UK, showed that those who had been small at birth had increased urinary adrenal androgen and glucocorticoid metabolite excretion (*62*), preliminary evidence that the hypothalamic–pituitary–adrenal axis is programmed in humans. The growth hormone insulin-like growth factor 1 (IGF-1) axis may also be programmed *in utero*. Children of low birth weight have raised plasma IGF-1 concentrations (*48,63*). The highest concentrations are in children who had the lowest birth weights but attain the largest body size in childhood. Raised IGF-1 concentrations may therefore be linked to catch-up growth. IGF-1 is known to be important for the growth of blood vessels (*64*), and raised concentrations could be one of the processes underlying the suggested association between catch-up growth and raised blood pressure in later life.

Vascular structure. The elastic recoil of the aorta is important in maintaining blood flow in the peripheral circulation and in the coronary arteries during diastole. Reduced elasticity (compliance) in the aorta is a marker of cardiovascular disease (*65*). It is associated with hypertension, and also with left ventricular hypertrophy because the work of the left ventricle is increased (*66,67*). Men and women 50 years of age in Sheffield who were small at birth had reduced compliance in the large arteries of the trunk and legs (44). Martyn and Greenwald have proposed that impaired synthesis of the scleroprotein elastin is one of the mechanisms underlying the association between low birth weight and raised blood pressure (*68*). The elasticity of larger arteries largely depends on elastin (*69*), which is laid down *in utero* and during infancy and thereafter turns over slowly (*69*). Its half-life in humans is approximately 40 years (*70*). Reduced elastin deposition leads to less compliant, stiffer arteries, which will lead to raised blood pressure. The loss of elastin with aging will amplify the increase in blood pressure.

In the growth-retarded fetus there are changes in blood flow in several vascular beds, including the descending aorta and cerebral vasculature (*71*). These are brain-sparing adaptations that lead to preferential perfusion of the brain at the expense of the trunk (*11,12,72*). If sustained they may lead to reduced growth of the abdominal viscera and stunting at birth. Because elastin deposition in a blood vessel *in utero* is related to the flow of blood, reduced flow in the large arteries of the trunk and legs as a consequence of brain-sparing may be associated with reduced elastin deposition, less compliant arteries, and consequent hypertension. Diversion of oxygenated blood away from the trunk to sustain the growth of the brain increases peripheral resistance (*71,73*), and echocardiography has shown that growth-retarded fetuses have hypertrophy of both ventricles (*74,75*). Cardiac myocytes become terminally differentiated before birth and the load on the heart influences their rate of maturation. Early pressure loading leads to fewer but larger myocytes. Left ventricular enlargement is known to be a strong predictor of morbidity and death from coronary heart disease independent of its association with raised systolic blood pressure and increased body mass (*76*). Among 67-year-old men in Hertfordshire those who had had low weight at 1 year of age had concentric enlargement of the left ventricle (*77*). This may reflect the long-term effects of prenatal blood diversion to the brain in a baby who is stunted at birth and whose growth does not catch up in infancy. An association between low weight around the age of 1 year and later concentric left ventricular hypertrophy has also been found in a sample of children and adults in Lorraine, France (*78*).

Recent studies suggest that low birth weight is associated with persisting alterations in vascular structure and function in addition to its associations with compliance. Among men in Hertfordshire, those who had had low birth weight had narrow bifurcation angles in their retinal blood vessels (*79*). People with hypertension have similar changes in retinal vascular geometry. In a study of children in the United Kingdom, those who had low birth weight 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 birth weight and endothelial dysfunction (*80*).

Nervous system. People with high blood pressure tend to have a high resting pulse rate (*81*). This is associated with high cardiac output, hyperdynamic circulation, and features of increased sympathetic nervous system activity (*82*). Among men and women in Preston, those who had low birth weight had a higher resting pulse rate (*83*). This is consistent with the hypothesis that increased sympathetic nervous activity is established through retarded growth *in utero* and leads to raised blood pressure in later life.

Programming of Noninsulin-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 (*13*). Although obesity and a sedentary lifestyle are important in the development of noninsulin-dependent diabetes, they seem to lead to the disease only in predisposed individuals. Family and twin studies have suggested familial predisposition, but the nature of this predisposition is unknown. The disease tends to be transmitted through the maternal rather than paternal side of the family (*84*).

Size at Birth and Noninsulin-Dependent Diabetes

A number of other studies have confirmed the association between birth weight, impaired glucose tolerance, and noninsulin-dependent diabetes that was first reported in Hertfordshire (*18,29,85–88*) (Table 3). In the Health Professionals Study in the United States, the odds ratio for diabetes, after adjusting for current body mass, was 1.9 among men whose birth weights were less than 5.5 lb compared with those who weighed 7–8.5 lb (*89*). Among the Pima Indians in the United States, the odds ratio for diabetes was 3.8 in men and women who weighed less than 5.5 lb (*90*). In Preston it was the thin babies who developed impaired glucose tolerance and diabetes. Lithell and colleagues confirmed the association with thinness in Uppsala, Sweden (*87*) (Table 4). The prevalence of diabetes was 3 times higher among men in the lowest fifth of ponderal index at birth. This was a stronger association than that with birth weight, with the prevalence of diabetes only twice as high among men in the lowest fifth of birth weight. Among the Pima Indians, in whom diabetes in pregnancy is unusually common, young men and women with birth weights over 9.9 lb had an increased prevalence of noninsulin-dependent diabetes (*90*). The association

Table 4. Prevalence of noninsulin-dependent diabetes by ponderal index at birth among men 60 years of age in Uppsala, Sweden.

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

between birth weight and noninsulin-dependent diabetes was therefore U-shaped. The increased risk of diabetes among babies with high birth weights 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 noninsulin-dependent diabetes (*91*). There is evidence that both may be determined in fetal life. Men and women with low birth weight have a high prevalence of the insulin resistance syndrome (*92*) in which impaired glucose tolerance, hypertension, and raised serum triglyceride concentrations occur in the same patient. The patients are insulin resistant and have hyperinsulinaemia. Table 5 shows results for a sample of the men in Hertfordshire. Phillips et al. (*93*) carried out insulin tolerance tests on 103 men and women in Preston. At any value of adult body mass index, insulin resistance was greater in people who had a low ponderal index at birth. In addition, at each ponderal index, resistance was greater in those with high body mass index. The greatest mean resistance was therefore in those with low ponderal index at birth but high body mass index as adults.

A recent study in San Antonio, Texas, confirmed the association between low birth weight and insulin resistance in a different ethnic group. In 30-year-old Mexican Americans and non-Hispanic white people, those with lower birth weight had a higher prevalence of the insulin resistance syndrome (*94*). Among men and women in the lowest third of the birth weight distribution and the highest third of current body mass index, 25% had the syndrome. In contrast, none of the people in the highest third of birth weight and lowest third of current body mass index had the syndrome. In a study of young adults in the city of Haguenau, France, those who had had intrauterine growth retardation had raised plasma insulin concentrations when fasting and after a standard glucose challenge (*95*). They did not show any of the other abnormalities that occur in the insulin resistance syndrome. An interpretation of this is that insulin resistance is 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 fetal undernutrition can program insulin resistance and noninsulin-dependent diabetes (*96*). Men and women exposed to famine *in utero* had higher 2-hr plasma glucose concentrations than those born before or those conceived after the famine. They also had higher fasting proinsulin and 2-hr plasma insulin concentrations, suggesting insulin resistance.

Law et al. reported associations between thinness at birth and raised 30-minute plasma glucose concentrations in 7-year old children in Salisbury, UK (*97*). Whincup et al. studied British children 10–11 years of age and found that those who had lower birth weight had raised plasma insulin concentrations both fasting and after oral glucose (*98*). This is consistent with the association between low birth weight and insulin resistance. Among these children, however, the plasma glucose concentrations of those who had low birth weight were unaltered, which implies that despite being insulin resistant they were able to maintain glucose homeostasis. In contrast Yajnik and colleagues found that Indian children 4 years of age who had low birth weights had raised plasma glucose and insulin concentrations, suggesting that at the levels of poor fetal growth and insulin resistance that prevail in India, even young children are unable to maintain glucose homeostasis (*99*). Forrester and colleagues found an association between shortness at birth and reduced glucose tolerance among children in Jamaica, in whom the serum glycated hemoglobin levels rose progressively between those who were 52 cm or more in length at birth and those who were 46 cm or less (*100*). These findings in children provide further support for the hypothesis that noninsulin-dependent diabetes originates from impaired development *in utero* and 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, which implies that they have a low muscle bulk as well as less subcutaneous fat (*101*). It is therefore possible that thinness at birth is associated with abnormalities in the structure and function of muscle that develop in midgestation and persist into adult life, interfering with insulin's ability to promote glucose uptake. Magnetic resonance spectroscopy studies show that people who were thin at birth have lower rates of glycolysis and glycolytic adenosine triphosphate production during exercise (*102*). In response to undernutrition a fetus may reduce its metabolic dependence on glucose and increase oxidation of other substrates, including amino acids and lactate. 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 IGF-I fall, while catabolic hormones, including glucocorticoids rise. Persisting hormonal changes could underlie the development of insulin resistance. Bjorntorp has postulated that glucocorticoids, growth hormone, and sex steroids may play a major role in the evolution of the metabolic syndrome (*103*).

Recent advances in assay methodology make it possible to specifically measure plasma concentrations of the precursor of insulin, 32-33-split proinsulin (*104,105*). Higher concentrations are found in people who had low birth weight and low weight at 1 year (*29*). The significance of raised plasma split proinsulin concentrations remains unclear, but they are thought to indicate both insulin resistance and pancreatic β-cell dysfunction.

Insulin Deficiency

Infants who are small for dates have fewer β cells (*106*). There are conflicting reports on whether the β-cell mass is reduced in subjects with noninsulin-dependent diabetes (*107*). As a working hypothesis it seems reasonable to propose that nutritional and other factors determining fetal and infant growth influence the size and function of the adult pancreatic β-cell complement. Whether and when noninsulin dependent diabetes supervenes will be determined by the rate of attrition of β cells with aging, and by the development of insulin resistance, of which obesity is an important determinant (*108*).

In a sample of 103 of the men and women who participated in the Preston study, Phillips and colleagues (*109*) measured insulin secretion following intravenous infusion of glucose. The insulin response was not related to birth weight or other

Table 5. Prevalence of the insulin resistance syndrome in men 59–70 years of age according to birth weight.

Birth weight, lb (kg)	No. of men	% with insulin resistance syndrome	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	30	18 (2.6–118)
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
All	407	14	

measurements at birth. This argues against a link between reduced fetal growth and insulin deficiency in adult life. Similarly, a study of men in Stockholm found no association between birth weight and insulin responses to infused glucose (*110*). Birth length and other measures of birth size were not available in that study. There was, however, an association between short stature and a low insulin response. 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 by Robinson and colleagues (*111*) of men 21 years of age showed that those with lower birth weight had reduced plasma insulin concentrations at 30 min. Another study of men of similar age showed that a low insulin response to glucose was associated with a high placental weight and a high ratio of placental weight to birth weight. This study also confirmed the association between low insulin secretion and short stature (*112*). In contrast a study of young Pima Indians showed that those with low birth weight had evidence of insulin resistance but no defect in insulin secretion (*113*).

In Mysore, South India, men and women with noninsulin-dependent diabetes showed signs of both insulin resistance and insulin deficiency (*114*). A high prevalence of insulin resistance, central obesity, and noninsulin-dependent diabetes in people from South India living in Britain has been observed (*115,116*). The study of men and women in Mysore again showed this. Those who had noninsulin-dependent diabetes also had a low insulin increment after a standard challenge, indicating that they were insulin deficient as well as resistant. However, whereas insulin resistance was associated with low birth weight, noninsulin-dependent diabetes was associated with shortness at birth in relation to birth weight (i.e., a high ponderal index) and with maternal adiposity.

These findings led to a novel explanation for the epidemic of noninsulin-dependent diabetes in urban and migrant Indian populations (*114*). Widespread fetal undernutrition predisposes the Indian population to insulin resistance. When these people move to cities, their 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 more insulin resistant. They are therefore unable to maintain glucose homeostasis during pregnancy, even at relatively low levels of obesity, and become hyperglycemic, though not necessarily diabetic. It is known that high plasma glucose concentrations within the normal range influence fetal growth and lead to macrosomia (*117*).

Programming of Serum Cholesterol and Clotting Factor Concentrations

Studies in Sheffield, UK, show that the neonate who has a short body and low birth weight in relation to the size of its head, although within the normal range of birth weight, has persisting disturbances of cholesterol metabolism and blood coagulation (*118–120*). Disproportion in body length relative to head size is thought to result from undernutrition in late gestation. The fetus diverts oxygenated blood away from the trunk to sustain the brain. This affects the growth of the liver, of which two 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 reduction specifically in this birth measurement that predicted raised serum low-density lipoprotein cholesterol and plasma fibrinogen concentrations in adult life (*118,119*). The differences in concentrations across the range of abdominal circumference (Table 6) were large, statistically equivalent to 30% differences in mortality caused by coronary heart disease. The findings for plasma fibrinogen concentrations, a measure of blood coagulability, were of similar size.

Because both cholesterol and fibrinogen metabolism are regulated by the liver, one interpretation of these findings is that reduced abdominal circumference at birth reflects impaired liver growth and consequent reprogramming of liver metabolism. Further understanding of liver programming may come more rapidly from animal studies than from human studies. Experiments with rats have shown that undernutrition *in utero* can permanently alter the balance of two liver enzymes, phosphoenol–pyruvate carboxykinase and glucokinase, that are involved in the synthesis and breakdown of glucose, respectively (*121*). A low-protein diet during gestation permanently changes the balance of enzyme activity in the offspring in favor 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.

Infant and Childhood Growth

Two studies of coronary heart disease and its risk factors in adult life contain data on both birth measurements and postnatal growth. These are the studies in Hertfordshire, UK, and Helsinki, Finland.

In Hertfordshire, health visitors recorded the weight of infants when they reached 1 year of age. In men there have been 853 deaths from coronary heart disease (*18*). Risk was more strongly associated with weight at 1 year of age ($x^2_1 = 27.5$, $p < 0.0001$) than with birth weight ($x^2_1 = 8.5$, $p < 0.005$). Standardized mortality ratios fell progressively from 105 for those who weighed up to 18 lb down to 42 for those who weighed 27 lb or more, a relative risk of 2.5. However, in women, among whom there were only 88 deaths, the closer association was with birth weight ($x^2_1 = 4.3$, $p = 0.04$). Weight at 1 year of age is more weakly associated with systolic blood pressure than is birth weight (*122*), equally as associated with glucose tolerance (*29*) and serum cholesterol concentrations (*118*), and more strongly associated with plasma clotting factor concentrations (*119*).

In Helsinki the maternity hospital records have been linked to school records, which include measurements of height and weight every 6 months between 6 and 16 years of age (*123*). Death from coronary heart disease was associated with low birth weight and more strongly with a low ponderal index at birth (Table 2). Men who died from coronary heart disease had an above-average body mass index at all ages from 6 to 16 years. In a simultaneous regression the hazard ratio for death from the disease increased by 14% (95% confidence interval 8–19%; $p < 0.0001$) for each unit (kg/m^3) decrease in ponderal index at birth and by 22% (10–36%, $p = 0.0001$) for each unit (kg/m^2)

Table 6. Mean serum cholesterol concentrations according to abdominal circumference at birth in men and women 50–53 years of age.

Abdominal circumference, inches (cm)	No. of people	Total cholesterol (mmol/L)	Low-density lipoprotein cholesterol (mmol/L)
≤ 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
All	217	6.5	4.3

increase in body mass index at 11 years of age. Thus, the highest death rates from coronary heart disease occurred in boys who were thin at birth but whose weight caught up so that they had an average or above-average body mass index from 6 years of age. However, there was also some evidence of an interaction. Figure 1 shows contours of hazard ratio for death from coronary heart disease. Those with a high ponderal index at birth cross few contour lines by developing a high body mass index in childhood. In contrast those with a low ponderal index at birth increase their risk more dramatically by developing a high body mass index. Conversely, it is insufficient to know only the body mass index of an 11-year-old boy. His future risk of death from coronary heart disease depends on his intrauterine growth. To predict the future, we need to know both the present and the past.

Catch-up growth could be associated with adverse outcomes through altered body composition in later life. Babies who are thin at birth lack muscle. It is possible that if they develop a high body mass index in childhood, they have a disproportionately high fat mass.

Summary

Associations between low birth weight and coronary heart disease, raised blood pressure, and noninsulin-dependent diabetes have been repeatedly demonstrated. Relatively few studies have had access to measurements of birth size other than weight. This is a major limitation because birth weight is a crude summary index of growth, and because blood pressure and glucose/insulin metabolism can be programmed by nutritional influences that do not alter birth weight. Studies that include birth length suggest that thinness at birth is associated with the development of insulin resistance. Other associations, for example, those with blood pressure, are less consistent. One interpretation of this is that blood pressure can be programmed at various stages of gestation, whereas insulin resistance is programmed in late gestation, when disproportionate fetal growth is manifest. This is, however, an uncertain inference and is not borne out by the Dutch famine study in which reduced glucose tolerance was associated with exposure to famine at any stage of gestation. Associations between placental size and later disease differ among studies. In animals placental responses to undernutrition depend on the mother's nutritional state before pregnancy, but we have little information about this in humans. However, placental growth and function do seem to be influences that program the fetus, even when the placenta is not clinically abnormal.

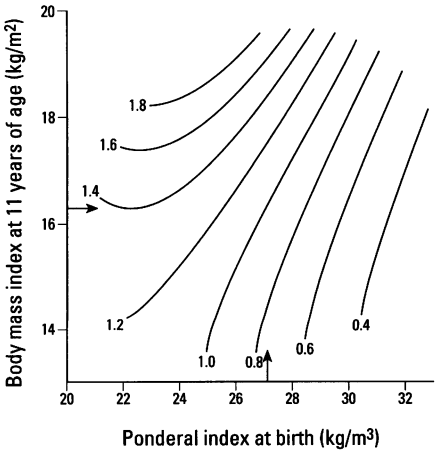

Figure 1. Hazard ratios for death from coronary heart disease according to ponderal index at birth and body mass index at 11 years of age. Arrows indicate average values. Subjects are 3,641 men born at the Helsinki University Central Hospital from 1924 to 1933.

The Future

If we are to use the information outlined here, to prevent disease we need to progress beyond epidemiologic 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 program 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 epidemiologic studies.

As yet, we do not know the true impact of maternal nutrition on fetal development. The relatively disappointing effects of nutritional interventions in pregnancy on fetal growth in humans have led to the view that fetal development is little affected by changes in maternal nutrition except in circumstances of famine. However, it is clear that birth weight alone is an inadequate summary measure of fetal growth; we need a more sophisticated view of optimal fetal development that takes account of the long-term sequelae of fetal adaptations to undernutrition.

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