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Human Growth and Disease in Later Life

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INTRODUCTION

Coronary heart disease and the related disorders, stroke, hypertension, and type 2 diabetes, are more common among people whose birthweights were toward the lower end of the normal range. The associations depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. They are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development. Impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. It seems likely that the placenta plays a central role in programming the baby, but as yet little is known about this. Common chronic diseases arise through a series of interactions between environmental influences and the pathways of growth and development that precede them.

There is now clear evidence that the pace and pathway of early growth is a major risk factor for the development of a group of chronic diseases that includes coronary heart disease (CHD) and type 2 diabetes, a disorder which predisposes to cardiovascular disease. This has led to a new "developmental" model for the disease.[1,2] The model proposes that nutrition during fetal life, infancy, and early childhood changes gene expression and thereby establishes functional capacity, metabolic competence, and responses to the later environment.[2,3]

To explore the developmental origins of chronic disease required studies of a kind that had not hitherto been carried out. It was necessary to identify groups of men and women now in middle or late life whose size at birth had been recorded at the time. Their birthweight could thereby be related to the later occurrence of CHD. In Hertfordshire, UK, from 1911 onwards, when women had their babies they were attended by a midwife, who recorded the birthweight. A health visitor went to the baby's home at intervals throughout infancy, and the weight at 1 year was recorded. Table 1 shows the findings in 10,636 men born between 1911 and 1930.[1,4] Hazard ratios for CHD fell with increasing birthweight. There were stronger trends with weight at 1 year. A subsequent study confirmed a similar trend with birthweight among women but no trend with weight at 1 year.[4] Table 2 shows findings for a sample of men who had glucose tolerance tests.[5]

The percentage with impaired glucose tolerance or type 2 diabetes fell steeply with increasing birthweight. The association between low birthweight and CHD has now been replicated among men and women in Europe, North America, and India.[6–12] Low birthweight has been shown to predict altered glucose tolerance in studies of men and women around the world.[13–17] The associations between low birthweight and later disease depend on slow fetal growth rather than premature birth.

BIOLOGICAL BASIS

Like other living creatures in their early life human beings are "plastic" and able to adapt to their environment. The development of the sweat glands provides a simple example of this. All humans have similar numbers of sweat glands at birth 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 process is complete and the number of sweat glands is fixed. Thereafter, the child who has experienced hot conditions will be better equipped to adapt to similar conditions in later life, because people with more functioning sweat glands cool down faster.

Table 1 Hazard Ratios (95% Confidence Intervals) for Death from Coronary Heart Disease According to Weight at Birth and at Age 1 Year in 10,636 Men in Hertfordshire

	Death from CHD	
Weight (lb)	Before 65 yr	All Ages
At birth		
≤5.5	1.50 (0.98-2.31)	1.37 (1.00–1.86)
−6.5	1.27 (0.89 to 1.83)	1.29 (1.01 to 1.66)
−7.5	1.17 (0.84 to 1.63)	1.14 (0.91 to 1.44)
−8.5	1.07 (0.77 to 1.49)	1.12 (0.89 to 1.40)
−9.5	0.96 (0.66 to 1.39)	0.97 (0.75 to 1.25)
>9.5	1.00	1.00
p for trend	.001	.005
Age 1 yr		
≤18	2.22 (1.33 to 3.73)	1.89 (1.34 to 2.66)
−20	1.80 (1.11 to 2.93)	1.58 (1.15 to 2.16)
−22	1.96 (1.23 to 3.12)	1.66 (1.23 to 2.25)
−24	1.52 (0.95 to 2.45)	1.36 (1.00 to 1.85)
−26	1.36 (0.82 to 2.26)	1.29 (0.93 to 1.78)
≥27	1.00	1.00
p for trend	<0.001	<0.001

Table 2 Percentage of Men Aged 64 Years with Impaired Glucose Tolerance or Diabetes according to Weight at Birth in 370 Men in Hertfordshire

Weight (lb)	% of Men with 2 h Glucose of ≥7.8 mmol/L	Odds Ratio (95% CI)*
≤5.5	40	6.6 (1.5 to 28)
−6.5	34	4.8 (1.3 to 17)
−7.5	31	4.6 (1.4 to 16)
−8.5	22	2.6 (0.8 to 8.9)
−9.5	13	1.4 (0.3 to 5.6)
>9.5	14	1.0
p for trend	<0.001	

*Adjusted for current body mass index.

This brief description encapsulates the essence of developmental plasticity: a critical period when a system is plastic and sensitive to the environment, followed by loss of plasticity and a fixed functional capacity. For most organs and systems the critical period occurs in utero. There are good reasons it may be advantageous in evolutionary terms for the body to remain plastic during development. It enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype was produced in all environments. Developmental plasticity is defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development.[18] Plasticity during intrauterine life enables animals and humans to receive a "weather forecast" from their mothers that prepares them for the type of world in which they will have to live.[19] If the mother is poorly nourished, she signals to her unborn baby that the environment it is about to enter is likely to be harsh. The baby responds to these signals by adaptations, such as reduced body size and altered metabolism, which help it to survive a shortage of food after birth. In this way plasticity gives a species the ability to make short-term adaptations, within one generation, in addition to

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the long-term genetic adaptations that come from natural selection. Because, as Mellanby noted long ago, the ability of a human mother to nourish her baby is partly determined when she herself is in utero, and by her childhood growth, the human fetus is receiving a weather forecast based not only on conditions at the time of the pregnancy but on conditions a number of decades before.[3,20] This may be advantageous in populations that experience periodic food shortages.

Until recently we have overlooked a growing body of evidence that systems of the body that are closely related to adult disease, such as the regulation of blood pressure, are also plastic during early development. In animals it is surprisingly easy to produce lifelong changes in the blood pressure and metabolism of a fetus by minor modifications to the diet of the mother before and during pregnancy.[21,22.]

The different size of newborn human babies exemplifies plasticity. The growth of babies has to be constrained by the size of the mother, otherwise normal birth could not occur. Small women have small babies: in pregnancies after ovum donation they have small babies even if the woman donating the egg is large.[23] Babies may be small because their growth is constrained in this way or because they lack the nutrients for growth. As McCance wrote, “The size attained *in utero* depends on the services which the mother is able to supply. These are mainly food and accommodation.[24]” Research into the developmental origins of disease has focussed on the nutrient supply to the baby, while recognizing that other influences, such as hypoxia, stress, and maternal size also influence fetal growth. This focus on fetal nutrition was endorsed in a recent review.[25] The availability of nutrients to the fetus is influenced by the mother’s nutrient stores and metabolism, as well as by her diet during pregnancy. In developing countries many babies are undernourished because their mothers are chronically malnourished. Despite current levels of nutrition in Western countries, the nutrition of many fetuses and infants remains suboptimal because the nutrients available are unbalanced or because their delivery is constrained by maternal metabolism. Globally, size at birth in relation to gestational age is a marker of fetal nutrition.[25]

A striking feature of the associations between birthweight and later disease is that they are graded, extending across the entire range of birthweights. This implies that what were regarded as normal variations in the delivery of nutrients to the human fetus have profound long-term effects on the health of the next generation.[3]

DEVELOPMENTAL ORIGINS HYPOTHESIS

The developmental origins hypothesis proposes that CHD, stroke, hypertension, and type 2 diabetes originate in developmental plasticity, in response to undernutrition during fetal life and infancy.[2,26] Why should fetal responses to undernutrition lead to disease in later life? The general answer is clear: “life history theory,” which embraces all living things, states that during development increased allocation of energy to one trait, such as brain growth, necessarily reduces allocation to one or more other traits, such as tissue repair processes. Smaller babies, who have had a lesser allocation of energy, must incur higher costs and these, it seems, include disease in later life. A more specific answer to the question is that people who were small at birth are vulnerable to later disease through three kinds of process. First, they have less functional capacity in key organs, such as the kidney: one theory holds that hypertension is initiated by the reduced number of glomeruli found in people who were small at birth.[27] A second process is the setting of hormones and metabolism. An undernourished baby may establish a “thrifty” way of handling food. Insulin resistance, which is associated with low birthweight, may be viewed as persistence of a fetal response by which blood glucose concentrations were maintained for the benefit of the brain but at the expense of glucose transport into the muscles and muscle growth.[28]

A third link between low birthweight and later disease is that people who were small at birth are more vulnerable to adverse environmental influences in later life. Observations on animals show that the environment during development permanently changes not only the body’s structure and function but also its responses to environmental influences encountered in later life.[19] Table 3 shows the effect of low income in adult life on CHD among men in Helsinki.[29] As expected, men who had a low taxable income had higher rates of the disease There is no agreed explanation for this but the association between poverty and CHD is a major component of the social inequalities in health in many western countries. Among the men in Helsinki the association was confined to men who had slow fetal growth and were thin at birth, defined by a ponderal index (birthweight/length^3) of less than 26 kg/m^3 (Table 3). Men who were not thin at birth showed no association of CHD with income, which implies that they were resilient to the effects of low income.

One explanation for these findings emphasizes the psychosocial consequences of a low position in the social hierarchy, as indicated by low income and social class, and suggests that perceptions of low social status and lack of success lead to changes in neuroendocrine pathways and hence to disease.[30] The findings in Helsinki seem consistent with this. People who were small at birth are known to have persisting alterations in responses to stress, including raised serum cortisol concentrations.[31] It is suggested that persisting small elevations of cortisol concentrations for many years may have effects similar to those seen when tumors lead to more sudden, large increases in glucocorticoid concentrations. People with Cushing’s syndrome, the result of overactivity of the adrenal cortex, are insulin-resistant and have raised blood pressure, both of which predispose to CHD.

INFANT AND CHILDHOOD GROWTH AND CORONARY HEART DISEASE

Figure 1 shows the growth of 357 men who were either admitted to hospital with CHD or died from it.[32] They belong to a cohort of 4,630 men who were born in Helsinki. Their mean height, weight, and body mass index (BMI, weight/height^2) at each month from birth to 2 years of age, and at each year from 2 to 11 years of age, are expressed as standard deviations (z scores). The mean z score for the cohort is set at zero and a boy maintaining a steady position as tall or short, or fat or thin, in relation to other boys would follow a horizontal path in Figure 1. The mean body size of the boys who later had CHD was approximately 0.2 standard deviations below the average and they were thin. Between birth and 2 years of age, mean z scores for each measurement fell, so that at 2 years the boys were thin and short. After 2 years of age their z scores for BMI began to increase and continued to do so. In a simultaneous regression, both low BMI at 2 years of age and high BMI at 11 years of age were associated with later coronary events ($p < .001$ and $p = .05$ respectively). When BMI at birth was added to the model, the measurements of body size at each of the three ages were associated with later coronary events ($p = .04$ for low BMI at birth, $p = .001$ for low BMI at 2 years of age, and $p = .03$ for high BMI at 11 years of age).

As with the boys, the mean body size of the 87 girls who later had coronary events was below the average (Figure 1). They tended to be short at birth rather than thin, but their mean z scores for BMI fell progressively after birth so that, like the boys, they were thin at 2 years of age. After 4 years of age the z scores began to increase and continued to do so, reaching the average at

Table 3 Hazard Ratios (95% CI) for Coronary Heart Disease in 3,629 Men in Helsinki According to Ponderal Index at Birth (Birthweight/Length^3) and Household Income in Adult Life

Household Income in £/Yr	Ponderal Index ≤ 26.0 kg/m^3 (n = 1,475)	Ponderal Index > 26.0 kg/m^3 (n = 2,154)
>15,700	1.00	1.19 (0.65 to 2.19)
15,700	1.54 (0.83 to 2.87)	1.42 (0.78 to 2.57)
12,400	1.07 (0.51 to 2.22)	1.66 (0.90 to 3.07)
10,700	2.07 (1.13 to 3.79)	1.44 (0.79 to 2.62)
≤8,400	2.58 (1.45 to 4.60)	1.37 (0.75 to 2.51)
p for trend	<.001	.75

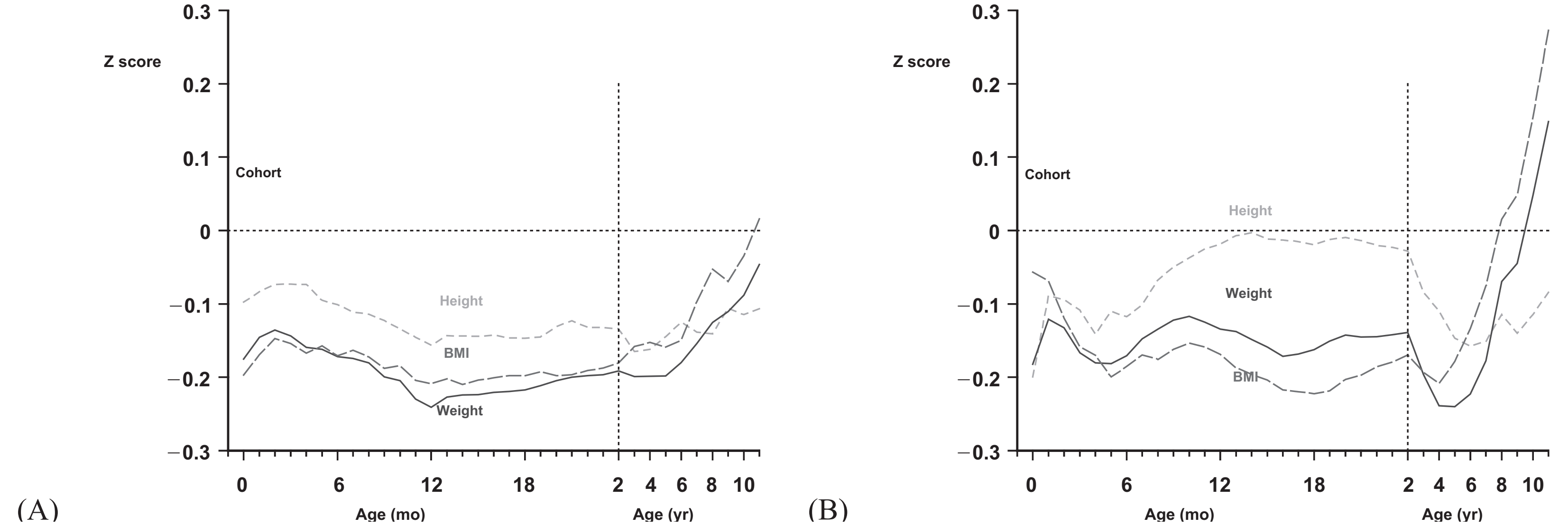

Figure 1 Mean *z* scores for height, weight, and body mass index in the first 11 years after birth among **(A)** boys and **(B)** girls who had coronary heart disease as adults. The mean values for all boys and all girls are set at zero, with deviations from the mean expressed as standard deviations (*z* scores).

approximately 8 years of age. Similarly to the boys, in a simultaneous regression body size at each of the three ages was associated with later coronary events ($p = .02$ for short length at birth, $p = .002$ for low BMI at 2 years of age, and $p = .02$ for high BMI at 11 years of age).

In Table 4 findings for boys and girls have been combined to show the simultaneous effect of birth weight and BMI at 2 years of age, divided into three, on hazard ratios for coronary events. The highest hazard ratios were among subjects with birthweights below 3.0 kg and BMIs at 2 years of age of 17 kg/m^2 or less. Table 5 shows the simultaneous effects of BMI at 2 and 11 years of age. The highest hazard ratios were among people with BMIs below 16 kg/m^2 at 2 years of age and above 17.5 kg/m^2 at 11 years of age. The hazard ratios in Tables 4 and 5 were a little changed if they were adjusted for socioeconomic status or income in adult life.

These observations demonstrate that CHD is independently associated with both prenatal and postnatal growth.[33] One explanation of the associations with small body size at birth and thinness at 2 years of age is that babies who are thin or short at birth and during infancy lack muscle, a deficiency that will persist into childhood as there is little cell replication in muscle after around 1 year of age.[34] Rapid weight gain in childhood may lead to a disproportionately high fat mass in relation to muscle mass. This could underlie the strong associations between low birthweight, low BMI at 2, and high BMI at 11 and later insulin resistance, which was found when 2,003 subjects in the Helsinki cohort were examined at the age of 62 years.[32]

The Helsinki study gives no support to the recent hypothesis that promoting early growth with high intake of nutrients in the first few months after birth will adversely affect cardiovascular health.[35] This hypothesis arose from studies of intermediary markers among young people born prematurely. In the Helsinki cohort at any birthweight and at any period up to 2 years of age, greater weight gain was associated with a lower incidence of CHD in later life.

Table 4 Hazard Ratios (95% Confidence Intervals) for Coronary Heart Disease According to Birthweight and Body Mass Index (BMI) at 2 Years of Age for Boys and Girls Combined

	BMI at Age 2 (kg/m^2)		
Birthweight (kg)	<16	16 to 17	>17
<3.0	1.9 (1.3 to 2.8)	1.9 (1.2 to 3.0)	1.3 (0.7 to 2.2)
3.0 to 3.5	1.5 (1.0 to 2.1)	1.6 (1.1 to 2.2)	1.2 (0.8 to 1.8)
>3.5	1.7 (1.2 to 2.5)	1.5 (1.1 to 2.2)	1.0

Table 5 Hazard Ratios (95% Confidence Intervals) for Coronary Heart Disease According to Body Mass Index (BMI) at 2 and 11 Years of Age for Boys and Girls Combined

	BMI at Age 11 (kg/m^2)		
BMI at Age 2 (kg/m^2)	<16	16 to 17.5	>17.5
<16	1.6 (0.8 to 3.3)	2.4 (1.2 to 4.9)	3.0 (1.4 to 6.3)
16 to 17	1.4 (0.7 to 3.1)	1.6 (0.8 to 3.3)	1.9 (0.9 to 3.9)
>17	1.0	1.3 (0.6 to 2.7)	1.1 (0.5 to 2.3)

TYPE 2 DIABETES AND HYPERTENSION

People who were small at birth remain biologically different to people who were larger, and these differences include an increased susceptibility to type 2 diabetes and hypertension. Table 6 shows odds ratios for these two disorders according to birthweight and fourths of BMI at age 11 years. The two disorders are associated with the same general pattern of growth as CHD.[26] Risk of disease falls with increasing birthweight and rises with increasing BMI.

Associations between low birthweight and type 2 diabetes shown in Table 2 have been found in other studies.[5,13–17] The association with hypertension has also been found elsewhere.[36] There is a substantial body of literature showing that birthweight is associated with differences in insulin sensitivity and blood pressure within the normal range.[5,13,17,37] These differences are found in children and adults but they tend to be small. A 1 kg difference in birthweight is associated with around 3 mm Hg difference in systolic pressure. The contrast between this small effect and the large effect on hypertension (see Table 6) suggests that lesions that accompany poor fetal growth and that tend to elevate blood pressure, and which may include a reduced number of glomeruli, have a small influence on blood pressure within the normal range because counterregulatory mechanisms maintain normal blood pressure levels. As the lesions progress, however, possibly through hyperfiltration of the reduced number of glomeruli and consequent glomerulosclerosis, these mechanisms are no longer able to maintain homeostasis. This may initiate a cycle of rise in blood pressure resulting in further progression of the lesions and further rise in blood pressure.[27,38] Rapid increase in body size after birth may exacerbate glomerular injury because

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Table 6 Odds Ratios (95% Confidence Intervals) for Type 2 Diabetes and Hypertension According to Birthweight and BMI at Age 11 Years Among 13,517 Men and Women in Helsinki

	BMI at Age 11 (kg/m^2)			
Birthweight (kg)	<15.7	−16.6	−17.6	>17.6
Type 2 diabetes (698 cases)				
<3.0	1.3 (0.6 to 2.8)	1.3 (0.6 to 2.8)	1.5 (0.7 to 3.4)	2.5 (1.2 to 5.5)
−3.5	1.0 (0.5 to 2.1)	1.0 (0.5 to 2.1)	1.5 (0.7 to 3.2)	1.7 (0.8 to 3.5)
−4.0	1.0 (0.5 to 2.2)	0.9 (0.4 to 1.9)	0.9 (0.4 to 2.0)	1.7 (0.8 to 3.6)
>4.0	1.0	1.1 (0.4 to 2.7)	0.7 (0.3 to 1.7)	1.2 (0.5 to 2.7)
Hypertension (2,997 cases)				
<3.0	2.0 (1.3 to 3.2)	1.9 (1.2 to 3.1)	1.9 (1.2 to 3.0)	2.3 (1.5 to 3.8)
−3.5	1.7 (1.1 to 2.6)	1.9 (1.2 to 2.9)	1.9 (1.2 to 3.0)	2.2 (1.4 to 3.4)
−4.0	1.7 (1.0 to 2.6)	1.7 (1.1 to 2.6)	1.5 (1.0 to 2.4)	1.9 (1.2 to 2.9)
>4.0	1.0	1.9 (1.1 to 3.1)	1.0 (0.6 to 1.7)	1.7 (1.1 to 2.8)

greater body size leads to increased excretory loads and glomerular hyperfiltration.[39] Direct evidence in support of this has come from a study of the kidneys of people killed in road accidents. Those being treated for hypertension had fewer, but larger, glomeruli.[40]

THE ROLE OF THE PLACENTA

Table 7 shows the systolic pressures of a group of men and women who were born at term.[41] They are grouped according to their birthweight and placental weight. As expected systolic pressures fall between those with low birthweight and high birthweight. In addition the pressures increase with increasing placental weight. People with a mean systolic pressure of 150 mm Hg or more, a level used to define hypertension, comprise a group who as babies were relatively small in relation to the size of their placentas. In Table 7 the fall in pressures of 10 mm Hg across the range of birthweight is statistically opposed by the rise of 12 mm Hg associated with increasing placental weight. These large trends are concealed when all pressures at a given birthweight are combined as in the right-hand column.

In studies of children and adults the association between placental enlargement and raised blood pressure has been inconsistent.[42] Animal studies offer a possible explanation of this. In sheep the placenta enlarges in response to moderate undernutrition in mid-pregnancy.[43] This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent response but occurs only in ewes that were well nourished when they conceived. In the Helsinki birth cohort people who had both hypertension and type 2 diabetes had slow placental weight at birth, whereas those with hypertension alone had large placental weight in relation to birthweight.[44] These statistically opposing trends may also explain why some studies have failed to find associations between placental weight and later blood pressure.

Animal studies show that the placenta is highly responsive to hypoxia and maternal undernutrition. The inconsistency of the epidemiological findings has led some researchers to discount its role in programming. This seems premature as placental biology suggests that it will play a central role, though one about which remarkably little is known.

PATHWAYS TO DISEASE

New studies, especially the Helsinki studies with their detailed information on child growth and socioeconomic circumstances, increasingly suggest that the pathogenesis of CHD and the disorders related to it depend on a series of interactions occurring at different stages of development. To begin with, the effects of the genes acquired at conception may be conditioned by the early environment. Table 8 is based on a study of 476 elderly people in Helsinki.[45] It shows mean fasting plasma insulin concentrations according to which of two polymorphisms of the peroxisome proliferators-activated receptor (PPAR)-γ gene was present. The Pro12Pro polymorphism is known to be associated with insulin resistance, indicated by elevated fasting plasma insulin concentrations. Table 8 shows, however, that this effect occurs only among men and women who had low birthweight. Conversely, low birthweight has been consistently linked to later insulin resistance,[28] but Table 8 shows that this effect occurs only among people with the Pro12Pro polymorphism. As birthweight serves as a marker of fetal nutrition,[25] this gene birthweight interaction may reflect a gene–nutrient interaction during development.

The effects of the intrauterine environment on later disease are conditioned not only by events at conception but also by events after birth. Table 6 shows how the effects are conditioned by childhood BMI. Table 3 shows that the effects of low ponderal index at birth are conditioned by living conditions in adult life. Table 9 shows how the

Table 7 Mean Systolic Blood Pressure (mmHg) of Men and Women Aged 50, Born after 38 Weeks 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	152	151	167	152
−7.5 (3.4)	139	148	146	159	148
>7.5 (3.4)	131	143	148	153	149
All	144	148	148	156	149

Table 8 Mean Fasting Insulin Concentrations (pmol/L) in Elderly People in Helsinki According to Peroxisome Proliferators-Activated Receptor (PPAR)-γ Gene Polymorphism and Birthweight

	Birthweight (kg)			
	<3.0	3.0 to 3.5	>3.5	*p* for trend
Pro12Pro	84 (56)*	71 (161)	65 (107)	.003
Pro12Ala/Ala12Ala	60 (37)	60 (67)	65 (48)	.31
p for difference	.008	.02	.99	

*Figures in parentheses are numbers of subjects.

Table 9 Cumulative Incidence (%) of Hypertension According to Birthweight and Father's Social Class in 8,760 Men and Women in Helsinki

	Father's Social Class			
Birthweight (g)	Laborer	Lower Middle Class	Upper Middle Class	*p* for Trend
<3,000	22.2	20.2	10.5	.002
−3,500	18.8	15.2	10.6	<.001
−4,000	14.5	12.5	10.3	.04
>4,000	11.1	15.6	15.7	.11
p for trend	<.001	.05	.79	

effects of low birthweight on later hypertension are conditioned by living conditions in childhood, indicated by the occupational status of the father.[46] Among all the men and women, low birthweight was associated with an increased incidence of hypertension, as has been shown before.[36] This association, however, was present only among those who were born into families where the father was a laborer or of lower middle class.

It seems that the pathogenesis of cardiovascular disease and type 2 diabetes cannot be understood within a model in which risks associated with adverse influences at different stages of life add to each other. Rather, disease is the product of branching paths of development. The environment triggers the branchings. The pathways determine the vulnerability of each individual to what lies ahead.[39,47]

A clinical study of 2003 people within the Helsinki birth cohort showed that two different paths of fetal, infant, and childhood growth preceded the development of hypertension in adult life (unpublished). In one, which was associated with more severe hypertension in people who tended to be overweight, small body size at birth, and during infancy were followed by rapid weight gain, so that at age 11 years the children's body size was around the average. This is the same path of growth that led to insulin resistance and CHD (Figure 1) in the other path of growth, which was associated with less severe hypertension, slow linear growth in utero, and during infancy were followed by persisting small body size so that at age 11 years the children were short and thin. A similar path of growth leads to stroke.[48] One possible process underlying this is that slow growth is associated with impaired development of the cerebral vasculature during a period of rapid brain growth, and also with altered lever metabolism and the development of an atherogenic liver profile. The two different paths of growth may lead to hypertension through different biological mechanisms and may produce two groups of patients who respond differently to medication.

We are beginning to understand the processes through which different paths of development initiate hypertension.[39] The changes occur at different levels and include allocation of stem cells and alteration of gene expression in the embryo, changes in renal growth, and alteration in haemostatic set-points that control blood pressure. These changes can make the affected systems more vulnerable to disruptive influences in postnatal life, which include rapid weight gain, oxidative stress, environmental stress, and a high salt intake.

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