Human Growth and Cardiovascular Disease

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Abstract

Low birthweight is now known to be associated with increased rates of coronary heart disease (CHD) and the related disorders, stroke, hypertension and type 2 diabetes. Associations between low birthweight and later disease have been extensively replicated in studies in different countries. 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 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. Recent observations have shown that impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. CHD and the disorders related to it 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 [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

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**Table 1.** Hazard ratios (95% confidence intervals) for death from coronary heart disease (CHD) according to weight at birth and at age 1 year in 10,636 men in Hertfordshire

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>Death from CHD before 65 years</th>
<th>Death from CHD all ages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5</td>
<td>1.50 (0.98–2.31)</td>
<td>1.37 (1.00–1.86)</td>
</tr>
<tr>
<td>3.0</td>
<td>1.27 (0.89–1.83)</td>
<td>1.29 (1.01–1.66)</td>
</tr>
<tr>
<td>3.5</td>
<td>1.17 (0.84–1.63)</td>
<td>1.14 (0.91–1.44)</td>
</tr>
<tr>
<td>4.0</td>
<td>1.07 (0.77–1.49)</td>
<td>1.12 (0.89–1.40)</td>
</tr>
<tr>
<td>4.5</td>
<td>0.96 (0.66–1.39)</td>
<td>0.97 (0.75–1.25)</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>At age 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.0</td>
<td>2.22 (1.33–3.73)</td>
<td>1.89 (1.34–2.66)</td>
</tr>
<tr>
<td>9.0</td>
<td>1.80 (1.11–2.93)</td>
<td>1.58 (1.15–2.16)</td>
</tr>
<tr>
<td>10.0</td>
<td>1.96 (1.23–3.12)</td>
<td>1.66 (1.23–2.25)</td>
</tr>
<tr>
<td>11.0</td>
<td>1.52 (0.95–2.45)</td>
<td>1.36 (1.00–1.85)</td>
</tr>
<tr>
<td>12.0</td>
<td>1.36 (0.82–2.26)</td>
<td>1.29 (0.93–1.78)</td>
</tr>
<tr>
<td>≥12.5</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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.

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 why 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 the long-term genetic adaptations that come from natural selection. Because, as Mellanby [20] 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]. 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 [24] wrote, ‘The size attained in utero depends on the services which the mother is able to supply. These are mainly food and accommodation.’ Research into the developmental origins of disease has focused 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: the ‘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 $\leq 26$ kg/m$^3$ (table 3). Among men who were not thin at birth CHD was not associated 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

### Table 3. Hazard ratios (95% CI) for coronary heart disease in 3,629 men in Helsinki according to the ponderal index at birth (birthweight/length$^3$) and household income in adult life

<table>
<thead>
<tr>
<th>Household income in GBP/year</th>
<th>Ponderal index $\leq 26.0$ kg/m$^3$ (n = 1,475)</th>
<th>Ponderal index $&gt;26.0$ kg/m$^3$ (n = 2,154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;15,700$</td>
<td>1.00 (0.65–2.19)</td>
<td>1.42 (0.78–2.57)</td>
</tr>
<tr>
<td>15,700</td>
<td>1.54 (0.83–2.87)</td>
<td>1.66 (0.90–3.07)</td>
</tr>
<tr>
<td>12,400</td>
<td>1.07 (0.51–2.22)</td>
<td>1.44 (0.79–2.62)</td>
</tr>
<tr>
<td>10,700</td>
<td>2.07 (1.13–3.79)</td>
<td>1.37 (0.75–2.51)</td>
</tr>
<tr>
<td>$\leq 8,400$</td>
<td>2.58 (1.45–4.60)</td>
<td>1.42 (0.78–2.57)</td>
</tr>
<tr>
<td>p for trend</td>
<td>$&lt;0.001$</td>
<td>0.75</td>
</tr>
</tbody>
</table>
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/height²) 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 on figure 1. At birth 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, the 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 < 0.001 and p = 0.05, 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 = 0.04 for low BMI at birth, p = 0.001 for low BMI at 2 years of age, and p = 0.03 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 average at birth (fig. 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 approximately 8 years of age. Similar to the boys, in a simultaneous regression, body size at each of the three ages was associated with later coronary events (p = 0.02 for short length at birth, p = 0.002 for low BMI at 2 years of age, and p = 0.02 for high BMI at 11 years of age).

In table 4 the findings for boys and girls have been combined to show the simultaneous effect of birthweight and BMI at 2 years of age, divided into thirds, 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 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 at 2 years of age and above 17.5 at 11 years of age. The hazard ratios in tables 4 and 5 were little changed if they were adjusted for socioeconomic status or income in adult life.

Fig. 1. Mean z scores for height, weight and body mass index (BMI) in the first 11 years after birth among boys and 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).
These observations demonstrate that CHD is independently associated with both prenatal and postnatal growth [33]. One explanation for 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 one 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.

### 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 among 13,517 men and women in Helsinki.

<table>
<thead>
<tr>
<th>Birthweight, kg</th>
<th>BMI at age 11</th>
<th>Type 2 diabetes (n = 698)</th>
<th>Hypertension (n = 2,997)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;15.7</td>
<td>16.6</td>
<td>17.6</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>1.3 (0.6–2.8)</td>
<td>1.3 (0.6–2.8)</td>
<td>1.5 (0.7–3.4)</td>
</tr>
<tr>
<td>3.5</td>
<td>1.0 (0.5–2.1)</td>
<td>1.0 (0.5–2.1)</td>
<td>1.5 (0.7–3.2)</td>
</tr>
<tr>
<td>4.0</td>
<td>1.0 (0.5–2.2)</td>
<td>0.9 (0.4–1.9)</td>
<td>0.9 (0.4–2.0)</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>1.0</td>
<td>1.1 (0.4–2.7)</td>
<td>0.7 (0.3–1.7)</td>
</tr>
</tbody>
</table>

The 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 substantial 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 an around 3-mm Hg difference in systolic pressure. The contrast between this small effect and the large effect on hypertension (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 counter-regulatory 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]. A rapid increase in body size after birth may exacerbate glomerular injury because 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].
Table 7. Mean fasting insulin concentrations (pmol/l) in elderly people in Helsinki according to PPAR-γ gene polymorphism and birthweight

<table>
<thead>
<tr>
<th>Birthweight, kg</th>
<th>&lt;3.0 (n = 56)</th>
<th>3.0–3.5 (n = 161)</th>
<th>&gt;3.5 (n = 107)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro12Pro</td>
<td>84</td>
<td>71</td>
<td>65</td>
<td>0.003</td>
</tr>
<tr>
<td>Pro12Ala/Ala12Ala</td>
<td>60 (n = 37)</td>
<td>60 (n = 67)</td>
<td>65 (n = 48)</td>
<td>0.31</td>
</tr>
<tr>
<td>p for difference</td>
<td>0.008</td>
<td>0.02</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

The number of subjects is given in parentheses.

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 7 is based on a study of 476 elderly people in Helsinki [41]. It shows mean fasting plasma insulin concentrations according to which of two polymorphisms of the peroxisome proliferator-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 7 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 7 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 a low ponderal index at birth are conditioned by living conditions in adult life. Table 8 shows how the effects of low birthweight on later hypertension are conditioned by living conditions in childhood, indicated by the occupational status of the father [42]. 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, 43].

A clinical study of 2,003 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 [44]. In one, which was associated with more severe hypertension in people who tended to be overweight, small body size at birth and during infancy was 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 (fig. 1). In the other path of growth, which was associated with less severe hypertension, slow linear growth in utero and during infancy was 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 [45]. 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 liver 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 alterations in hemostatic 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.

### Table 8. Cumulative incidence (%) of hypertension according to birthweight and father’s social class in 8,760 men and women in Helsinki

<table>
<thead>
<tr>
<th>Birthweight, g</th>
<th>Father’s social class</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>manual worker</td>
<td>lower middle class</td>
</tr>
<tr>
<td>&lt;3,000</td>
<td>22.2</td>
<td>20.2</td>
</tr>
<tr>
<td>3,500</td>
<td>18.8</td>
<td>15.2</td>
</tr>
<tr>
<td>4,000</td>
<td>14.5</td>
<td>12.5</td>
</tr>
<tr>
<td>&gt;4,000</td>
<td>11.1</td>
<td>15.6</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
</tbody>
</table>
References


Discussion

Dr. Haschke: One of your slides indicates that low BMI at 1 and 2 years of age is a predictor of poor outcome. If we look at the BMI of breastfed and formula-fed infants we know exactly that breastfed infants grow faster during the first 3 months of life and then they fall back. They clearly have a lower BMI at 1 and 2 years of age than formula-fed infants; the difference being up to 0.3 z scores. The industry is now trying to develop formulas to mimic the growth of the breastfed infants, but is this really the right thing to do to move to a lower BMI with regard to the nutritional factors that influence growth? What is your opinion?

Dr. Barker: Firstly, almost all the children in the Helsinki birth cohort were breastfed because they were born in the 1930s and 1940s, and so the Helsinki data don't permit us to answer your question. But isn't that the kind of thing that the industry should be funding? It would not be difficult to study the age of adiposity rebound of breastfed and formula-fed babies. There is a lot of heterogeneity in the body composition of infants, and paths of growth will be optimal or not according to baby's initial body composition, and no doubt other factors as well.

Dr. Giovannini: To what extent would the quality of a child's physical activity change or reverse an unfavorable programming condition? Is physical activity always beneficial to those born growth-restricted?

Dr. Barker: I can't answer that question. Dr. Prentice is more likely to be able to answer than anybody in the room.
Dr. Prentice: Thank you Dr. Barker, but I don’t think I can either. Intuitively, one would say that physical activity is almost always a good thing. One thing we know about physical activity in very young children is that it is driven more internally than externally.

Dr. Barker: We have a colleague in Oregon who studies obesity in monkeys. She measures physical activity using an accelerometer. The monkeys are given a surfeit of food, and obesity is unrelated to the diet they eat. It is all about patterns of activity and there is a wide variation in the amount of activity among different individual monkeys, and individual patterns of activity are stable over time. Some monkeys are very active and others are very inactive.

Dr. Walker: You mentioned and very elegantly described the impact of low birthweight and rapid weight gain on long-term disease. What about the flip side of that, because a major problem in developing countries and in developed countries is the obese woman who becomes pregnant, who then produces a child who is excessively overweight, who then continues to be overweight, and develops the same adult diseases as your prototype.

Dr. Barker: Thank you for pointing that out. It is of course true that women who are overweight may have macrosomic babies who are poor at making insulin and at risk of developing obesity and type 2 diabetes. We are not seeing that this is a path of growth that leads to coronary heart disease or stroke, but it certainly leads to diabetes. A conclusion from that is that there is more than one path of growth leading to a particular disease. In fact there are three known paths of growth leading to diabetes. One begins with small size at birth; the second begins with normal size at birth but slow infant growth; and the third is the one that you have alluded to.

Dr. Cameron: I just wanted to make a comment on the physical activity question earlier. It is always said in research on human growth that a certain minima of physical activity is necessary for normal growth but nobody knows what that certain minima actually is. It appears from research in adults that it is not necessarily the activity one undertakes but how fit one is as a result of that activity that is the risk factor for coronary heart disease and so on. Perhaps that is also true for children; it may not be the activity they do but how their body responds to the activity in terms of fitness.

Dr. Eriksson: I also would like to come back briefly to the question regarding physical activity. The truth is that we don’t know how active these children were when they were young, but we know how active they were in adult age. We have one study in which it was shown that those people with the lowest birthweight if they were more active in later life were completely protected against the negative influences of low birthweight, but type 2 diabetes was the outcome [1].

Dr. Vaidya: Dr. Barker’s hypothesis worries me for two reasons. The first is that I myself had a low birthweight, I grew a little faster, and my blood pressure is slightly increased. But my main worry is that, in my country where there are so many low birthweight babies, the entire focus of the government, the Indian Academy, pediatricians, mothers and parents is to achieve good growth. There are so many nutritional interventions going on in my country; mothers want their children to grow, pediatricians want the children to grow, and people start to use growth hormone to make IUGR infants grow. Unless this entire process of growth promotion is in some way curtailed, I am very seriously worried about the implications, especially in a country which has such a large low birthweight population.

Dr. Barker: It is well known in India that people become insulin-resistant at levels of fat accumulation which are low by Western standards and it is partly about the tendency of Indian people to accumulate fat centrally. In order to improve the development of babies you have to focus on improving the nutrition of young girl children.
because much of a mother's metabolic competence is set in her early life. I entirely agree that governments need to be aware that investments need to be made against longer term outcomes.

Dr. Ogra: That was a very elegant outline of your hypothesis, Dr. Barker. For the past 20 years, more or less, we have been talking about the effects of environmental influences on growth. Have you or anyone else come up with any basic biological markers which can be used more consistently to determine or to predict who may be really at high risk of stroke or heart disease as a function of the nutritional alterations in the fetal or perinatal period, or later in life?

Dr. Barker: That is a central question because that is clearly where we need to go, to develop biological markers of vulnerability which can be measured in children so that individuals can be protected.

Dr. Ogra: We all recognize that every society or country has priorities for its economic resources. In some places priorities with regard to fetal and infant nutrition may not be as high as providing jobs or investing in vaccinations for infections. Therefore, identifying more basic markers and mechanisms of such vulnerability will be very helpful in establishing a high priority for such nutritional approaches.

Dr. Barker: I agree with you and I'd like to add one further point. A group of people who are extremely supportive of this are the economists because early development affects cognitive function and it clearly affects the ability to be a productive part of a work force. Politicians may not care about health but they do care about economics and productivity. So economists are very entranced with ideas about how if money is put into early development it could improve economic productivity, and there is direct evidence of that. In the Helsinki Birth Cohort men who were short at birth earn less, and in a democracy like Finland what you earn is a demonstration of your physiological capacity, of your cognitive capacity.

Dr. K. Bergmann: Looking at statistics on causes of death, one thing that impresses me quite a bit is that the average age at death from cardiovascular diseases is much higher than life expectancy. So dying from cardiovascular diseases may be a sign of being protected from dying from something occurring a lot earlier. Another point is we think that perhaps half or two thirds of all causes of death are from cardiovascular diseases. It is a death of the old people. It may not be necessary to prevent cardiovascular diseases, it may only be necessary to prevent early death from cardiovascular diseases, which also occurs. What does this look like in your studies? Do people die early from cardiovascular disease or do more people die from cardiovascular disease, which makes a big difference?

Dr. Barker: There are a number of points there. Firstly it is a blessing really that what promotes good growth and cognitive development in children also diminishes cardiovascular disease in later life. So there isn't a situation as far as we know that you have to make a decision: are you going to be smart and die young or are you going to be stupid and have a long life, it doesn't work like that. It's a characteristic of places where coronary heart disease is epidemic, and India is an excellent example, that people get it at extraordinarily young ages by Western standards. The same for stroke; there are people in China who have strokes at the age of 25. It's the same with renal failure; In South Carolina in the USA there are large numbers of people on dialysis for chronic renal failure at the age of 25. So the short answer to your question is that poor development is linked to early death; it is also linked to life expectancy in a rather complicated way. Birthweight is a poor predictor of longevity, the biology of that is more complicated but we are starting to make progress with it.

Dr. Wilson: I am going to ask a question from a point of ignorance. I wonder if you could tell me, on a population basis what is the fraction of risk attributable to these
birth and early growth differences for the diseases you have been discussing? How does the attributable risk vary from one population to another?

**Dr. Barker:** A recent policy document of the National Institute of Child Health states that antenatal nutrition is more important than adult behavior in determining coronary heart disease. Attempts to prevent heart disease by modifying adult lifestyle have been fantastically disappointing. I can’t answer your question because the figures are not there. If you review everything that is known, as the UN committee did, you come to the conclusion that the point of action is conception to 24 months, but that doesn’t mean that adult lifestyle doesn’t play a part. It may be important for vulnerable people and may be unimportant for nonvulnerable people. In the Helsinki study the men with low incomes have more heart disease which is a general phenomenon across all Western societies. When you break it down that relationship is confined to one quarter of men defined by being thin at birth having a low ponderal index (birthweight/length^2). If they have a ponderal index of ≤26, their income is linked to heart disease, strongly; lower income, more heart disease. For the three quarters of men who are not thin at birth it makes absolutely no difference, it’s completely unrelated. We know something about the biology of this. Current ideas focus on the psychosocial stress of having a lower place in a hierarchy, however defined, and there is direct evidence for that. People who are small at birth have enhanced stress responses. Before birth cortisol plays a dominant role in the maturation of tissues and after birth the settings of the HPA axis are retained and become part of the stress responses.

**Dr. Mantaring:** You showed us a slide with the z scores for length, weight and BMI in the first 10 years after birth of boys who developed coronary heart disease. I am interested in the comparison group. How different are they from the z scores of those who did not develop coronary heart disease?

**Dr. Barker:** I am sorry, I didn’t explain that slide clearly. There were 4,000 boys. The zero point was set from the whole cohort and the standard deviations were calculated from this. The body size of boys who went on to develop coronary heart disease was calculated as standard deviations in relation to the mean of the entire cohort. The boys who went on to get coronary heart disease were small up to the age of 2 in relation to all other boys, and then they had rapid weight gain after 2 in relation to all the other boys.

**Dr. Björkstén:** You mentioned two of the major causes of death: coronary heart disease and stroke. Is there anything known regarding very early infant nutrition in relation to either disease or particular forms of cancer?

**Dr. Barker:** There is a limited literature on hormonally related cancers, people who develop breast cancer tend to have slightly higher birthweight as a group. What that means, we don’t know. There is a theory that exposure to maternal estrogens in some way leads to breast cancer in later life. This is a field that is just starting to wake up because the data are available. The model of cancer says that there is some stressor in adult life which only triggers it in a certain group of vulnerable people. The vulnerability may not be genetic for breast cancer; it may be an acquired vulnerability in early life. I think that over the next 3 years there will be a lot advances made.

**Dr. Al Ghamdi:** Those babies born with a low birthweight who remain with a low bodyweight for the rest of their lives, are they at the same risk of having diabetes and hypertension?

**Dr. Barker:** A component of increased risk for coronary heart disease is rapid weight gain after the age of 2. If that does not happen, as a group the children will be at lower risk. Coronary heart disease is a disease of affluence, it increases as countries become more affluent but it settles in the poorer people. We have always been looking
for two things in the causation of coronary heart disease: one is an affluence factor and one is a poverty factor. The poverty factor may be events before 2 years, and the affluence factor may be abundance and rapid weight gain after 2 years.

_Dr. Al Ghamdi_: What can we do for those children who had a low birthweight and increased their bodyweight after the age of 2 years? When we see them at 10 years, is there anything we can do to decrease those risk factors?

_Dr. Barker_: The long-term solution is to invest in better nutrition for young girls and adolescent girls. In the short-term the protection of infant growth, not necessarily the promotion of infant growth, but the protection of it from obviously adverse influences, like recurrent minor infections and poor weaning practices, is the quickest fix. At present we are bit stuck on preventing rapid weight gain in childhood: childhood obesity is rising and we do not understand why.

_Dr. Malka_: Low birthweight is associated with hypertension. You say that birth weight is not the major determinant for childhood blood pressure, but that the current weight is more important. Systolic blood pressure has been measured in adolescents and compared to their birthweight, and no significant relation was found.

_Dr. Barker_: There are studies of children which have shown that the relationship with birthweight is small and as you say the relationship with current weight is dominant. When you come to adults with actual hypertensive disease, which is the real issue, the birthweight relationships are very strong. It seems that if you acquire a lesion antenatally, say fewer nephrons, you are still able to maintain homeostasis through childhood into adult life. The differences associated with birthweight in 18-year-olds are only 3 mm Hg of systolic pressure; they are small. It is not logical, however, to say that birthweight doesn’t matter, because birth weight matters a lot for the ultimate need to take drugs to lower your blood pressure when you are 50.

_Dr. R. Bergmann_: In your low birthweight high risk group, did you control for cigarette smoking? We know that social status and smoking prevalence are inversely related.

_Dr. Barker_: It’s interesting, a lot of studies have addressed that question because cigarette smoking in the mother does slow fetal growth, and while smoking has a short-term effect it does not have long-term effects. The evidence is that, surprisingly perhaps, smoking which presumably acts through hypoxia, does not have the kind of long-term effects that we are seeing in association with differences in the mother’s body composition and dietary intake.

_Dr. R. Bergmann_: I am interested in the adult smoker, the person of low social status, the poor worker, who is smoking and therefore more at risk of coronary disease and stroke.

_Dr. Barker_: But clearly it is possible to take these into account. Where they have been taken into account, in the American Nurses study, for example, they simply do not contribute to the relationship between low birthweight and later stroke. During the past 15 years this question must have been examined by just about anybody who had a set of data, and that is how it works out. It’s convenient to blame the poor for their own ill health, it’s what politicians like to do. But it doesn’t work, the poor get sick because they are vulnerable not because they are mischievous.

_Dr. Walker_: Given the importance that you put on antenatal development, antenatal growth, should we be routinely following babies in utero from a grid looking at their growth so we know what we can anticipate? Given the fact that chronic disease takes a long time to develop, should we be looking at biomarkers of these diseases so we can get on top of it in a preventive way?

_Dr. Barker_: I think everyone would agree with both those thoughts. What is an optimal dynamic of postnatal growth must presumably be linked to something more subtle than the body size at birth because the same body size at birth can be acquired by growing fast early and slow later or slow early and fast later. In India the path of
growth seems to be characterized by rapid early growth which cannot be sustained in late gestation, and the results of that would be different from what is the Chinese path of growth, which is slow growth sustained from the beginning to end of gestation. The long term consequences might be different although it may lead to the same birthweight.

References