

Review

The Developmental Origins of Adult Disease

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Low birthweight is now known to be associated with increased rates of coronary heart disease and the related disorders stroke, hypertension and non-insulin dependent diabetes. These associations have been extensively replicated in studies in different countries and are not the result of confounding variables. They extend across the normal range of birthweight and depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. The associations are thought to be consequences of 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. A new vision of optimal early human development is emerging which takes account of both short and long-term outcomes.

Key teaching points:

- Studies have shown an association between low birthweight and risk for cardiovascular diseases and other chronic conditions later in life.
- Developmental plasticity describes the fetuses ability to respond to their mother's diet in utero.
- Low birthweight and inadequate nutrition early in life may lead to lifelong alterations in the body's setting of metabolism and hormones as well as the number of cells in key organs.
- Low birthweight followed by rapid weight gain during infancy has been shown to further increase risk for disease.

Developmental Origins

The recent discovery that people who develop coronary heart disease grew differently to other people during fetal life and childhood has led to a new 'developmental' model for the disease [1]. 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—late life, whose size at birth had been recorded at the time. Their birthweight could thereby be related to the later occurrence of coronary heart disease. 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 one year was recorded. Table 1 shows the findings in 10,636 men born during 1911–

1930. Standardized mortality ratios for coronary heart disease fell with increasing birthweight. There were stronger trends with weight at one year. A subsequent study confirmed a similar trend with birthweight among women, but no trend with weight at one year [2]. Table 2 shows findings for the first sample of men to have glucose tolerance tests [3]. The percentage with impaired glucose tolerance or type 2 diabetes fell steeply with increasing birthweight, and with weight at one year. There were similar trends with birthweight among women.

The association between low birthweight and coronary heart disease has now been replicated among men and women in Europe, the USA and India [4–9]. The association between low weight gain in infancy and coronary heart disease in men has been confirmed in Helsinki, Finland [10]. Low birthweight has been shown to predict altered glucose tolerance in studies around the world [11–15].

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Table 1. Hazard Ratios (95% CI) for Death from Coronary Heart Disease according to Birthweight and Weight at One Year in 10,636 Men in Hertfordshire

Weight (pounds)	Death from Coronary Heart Disease	
	Before 65 Years	All Ages
Birthweight:		
≤5.5 (n = 486)	1.50 (0.98 to 2.31)	1.37 (1.00 to 1.86)
–6.5 (n = 1385)	1.27 (0.89 to 1.83)	1.29 (1.01 to 1.66)
–7.5 (n = 3162)	1.17 (0.84 to 1.63)	1.14 (0.91 to 1.44)
–8.5 (n = 3308)	1.07 (0.77 to 1.49)	1.12 (0.89 to 1.40)
–9.5 (n = 1564)	0.96 (0.66 to 1.39)	0.97 (0.75 to 1.25)
≥10 (n = 731)	1.00	1.00
<i>p</i> for trend	0.001	0.005
One year old:		
≤18 (n = 715)	2.22 (1.33 to 3.73)	1.89 (1.34 to 2.66)
–20 (n = 1806)	1.80 (1.11 to 2.93)	1.58 (1.15 to 2.16)
–22 (n = 3404)	1.96 (1.23 to 3.12)	1.66 (1.23 to 2.25)
–24 (n = 2824)	1.52 (0.95 to 2.45)	1.36 (1.00 to 1.85)
–26 (n = 1391)	1.36 (0.82 to 2.26)	1.29 (0.93 to 1.78)
≥27 (n = 496)	1.00	1.00
<i>p</i> for trend	<0.001	<0.001

Confounding Variables

These findings suggest that influences linked to early growth have an important effect on the risk of coronary heart disease and type 2 diabetes. 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 intrauterine influences. There is now strong evidence that this argument cannot be sustained.

In a number of studies data on lifestyle, including smoking habits, employment, alcohol consumption and exercise were collected. In the Nurses' Health Study in the USA allowance for these influences had little effect on the association between birthweight and coronary heart disease [5]. Similar results came from Sweden and the UK [3,4]. In studies of type 2 diabetes and blood pressure the associations with size at birth are again independent of social class, cigarette smoking and alcohol consumption. Adult lifestyle, however, adds to the effects of early life: for example, the prevalence of impaired glucose tolerance is highest in people who had low birthweight but became obese as adults [3,11–15]. As described later in this paper, slow fetal growth may also alter the body's response to socio-economic influences in later life. Associations between low birthweight and altered glucose tolerance and raised blood pressure have been found in numerous studies of children which is a further argument against these associations being the product of confounding variables in adult life.

Biological Basis

Like other living creatures in their early life, human beings are 'plastic' and able to adapt to their environment. During development the organs and systems of the body go through

'critical' periods when they are plastic and sensitive to the environment. 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 [16]. Plasticity during intra-uterine 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 [17]. 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. Since, as Melanby 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 [18]. This may be advantageous in places which experience periodic food shortages.

Until recently we have overlooked a growing body of evidence that systems of the body which are closely related to adult disease, such as the regulation of blood pressure, are also plastic during early development. In animals it is surprisingly

Table 2. Percentage of Men Aged 64 with Impaired Glucose Tolerance or Diabetes according to Birthweight and Weight at Age One Year in 370 Men

	% (no.) of Men with 2-hour Glucose (mmol/L) of ≥ 7.8	Odds Ratio (95% Confidence Interval)*
Birthweight (pounds)		
≤ 5.5 (n = 20)	40	6.6 (1.5 to 28)
-6.5 (n = 47)	34	4.8 (1.3 to 17)
-7.5 (n = 104)	31	4.6 (1.4 to 16)
-8.5 (n = 117)	22	2.6 (0.8 to 8.9)
-9.5 (n = 54)	13	1.4 (0.3 to 5.6)
> 9.5 (n = 28)	14	1.0
p for trend	< 0.001	
Weight at age one year (pounds)		
≤ 18 (n = 23)	43	8.2 (1.8 to 38)
-20 (n = 63)	32	4.8 (1.2 to 19)
-22 (n = 107)	30	4.2 (1.1 to 16)
-24 (n = 105)	18	2.1 (0.5 to 7.9)
-26 (n = 48)	19	2.1 (0.5 to 9.0)
≥ 27 (n = 24)	13	1.0
p for trend	< 0.001	

* Adjusted for body mass index.

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 [19,20].

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 [21]. Babies may be small because their growth is constrained in this way or because they lack the nutrients for growth. As McCance wrote long ago, "The size attained in utero depends on the services which the mother is able to supply. These are mainly food and accommodation" [22]. Since mother's height or pelvic dimensions are generally not found to be important predictors of the baby's long-term health, research into the developmental origins of disease has focused on the nutrient supply to the baby, while recognizing that other influences such as hypoxia and stress also influence fetal growth. This focus on fetal nutrition was endorsed in a recent review [23]. 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 sub-optimal, because the nutrients available are unbalanced or because their delivery is constrained by the long and vulnerable fetal supply line. Around the world size at birth in relation to gestational age is a marker of fetal nutrition [23].

Fetal Origins Hypothesis

The fetal origins hypothesis proposes that coronary heart disease, type 2 diabetes, stroke and hypertension originate in developmental plasticity, in response to undernutrition during fetal life and infancy [24,25]. 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 fewer cells 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 [26]. A reduced number necessarily leads to increased blood flow through each glomerulus. Over time this hyperfiltration is thought to lead to the development of glomerulo-sclerosis which, combined with the loss of glomeruli that accompanies normal ageing, leads to accelerated age-related loss of glomeruli, and a self-perpetuating cycle of rising blood pressure and glomerular loss. Direct evidence in support of this hypothesis has come from a study of the kidneys of people killed in road accidents. Those being treated for hypertension had fewer but larger glomeruli [27].

Another process by which slow fetal growth may be linked to later disease is in 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

Table 3. Hazard Ratios (95% CI) for Coronary Heart Disease in 3,676 Men according to Ponderal Index at Birth (Birthweight/Length³) and Taxable Income in Adult Life

Household Income in Pounds Sterling per Year	Ponderal Index	
	≤26.0 kg/m ³ (n = 1475)	>26.0 kg/m ³ (n = 2154)
>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)
<i>p</i> for trend	<0.001	0.75

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 [17]. Table 3 shows the effect of low income in adult life on coronary heart disease 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 coronary heart disease 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/length³) of less than 26 kg/m³ (Table 3). Men who were not thin at birth were resilient to the effects of low income on coronary heart disease.

One explanation of 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 are 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 over 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 are insulin resistant and have raised blood pressure, both of which predispose to coronary heart disease.

Childhood Growth and Coronary Heart Disease

Fig. 1 shows the growth of 357 men who were either admitted to hospital with coronary heart disease or died from it [10]. They belong to a cohort of 4630 men who were born in Helsinki, and their growth is expressed as Z-scores. The Z-score for the cohort is set at zero, and a boy maintaining a steady position as large or small in relation to other boys would follow a horizontal path on the figure. Boys who later developed coronary heart disease, however, were small at birth, remained small in infancy but had accelerated gain in weight

and body mass index thereafter. In contrast, their heights remained below average. As in Hertfordshire, the hazard ratios for coronary heart disease fell with increasing weight at one year, and also with increasing length and, more strongly, with body mass index. Small size at this age predicted coronary heart disease independently of size at birth. There therefore appear to be at least two pathways of development that lead to coronary heart disease among men in this cohort. One begins with slow growth in utero, and low birthweight and thinness at birth, thought to be a consequence of fetal undernutrition. The other begins with poor weight gain during infancy. The effect of rapid weight gain after infancy, shown in Fig. 1, is confined to men on the first pathway. Rapid weight gain has no effect on the risk of disease among men following the second pathway [10].

Among the 4130 girls in the same birth cohort, the 87 who later developed coronary heart disease showed a broadly similar pattern of growth to the boys [32]. They were, however, short at birth rather than thin. They had rapid height growth in infancy, but became thin. This persisted up to the age of 4 years, after which they gained weight rapidly. In both sexes disease risk was related to the tempo of weight gain rather than to body size at any particular age.

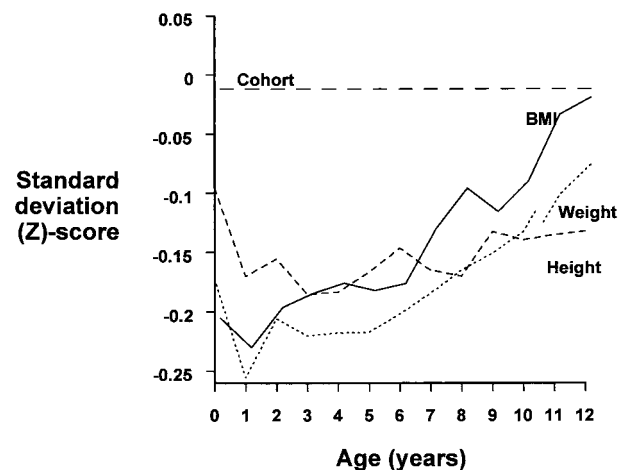


Fig. 1. Mean Z-scores for height, weight and body mass index during childhood in 357 boys who later developed coronary heart disease within a cohort of 4630 boys. At any age, the mean Z-score for the cohort is set at 0, while the standard deviation is set at 1.

Type 2 Diabetes and Hypertension

People who were small at birth remain biologically different from people who were larger, and these differences include an increased susceptibility to hypertension and type 2 diabetes. These two disorders are associated with the same general pattern of growth as coronary heart disease. In both sexes risk of disease falls with increasing birthweight and rises with rapid weight gain in early childhood [3,11–15,33]. Table 4 shows hazard ratios according to birthweight and fourths of body mass index at age 11 years among 13,517 men and women born in Helsinki during 1924–44.

There is a substantial literature showing that birthweight is associated with differences in blood pressure and insulin sensitivity within the normal range [3,11–15,34]. These differences are found in children and adults but they tend to be small. A one-kilogram 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 (Table 4) suggests that lesions that accompany poor fetal growth and tend to elevate blood pressure, 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, these mechanisms are no longer able to maintain homeostasis and blood pressure rises. There may be a cycle of rise in blood pressure resulting in further progression of the lesions and further rise in blood pressure [35]. Evidence to support the development of self-perpetuating cycles comes from a study of elderly people in Helsinki among whom the effect of birthweight on blood pressure was confined to those being treated for hypertension [36]. Despite their treatment the blood pressures of those who had low birthweight were markedly higher, whereas among the normotensive subjects birthweight was unrelated to blood pressure. Whether measured in the clinic or by ambulatory methods, there was a more than 20 mmHg difference in systolic pressure between those who weighed 2500 g (5.5 pounds) or less at birth and those who

weighed 4000 g (8.8 pounds) or more. An inference is that by the time they reached old age most of the people with lesions acquired in utero had developed clinical hypertension. Studies in South Carolina bear on this issue. They showed that among 3236 hypertensive patients the blood pressures of those with low birthweight tended to be more difficult to control [37].

Table 5 shows the relation between age at 'adiposity rebound' and later type 2 diabetes [38]. After the age of 2 years the degree of obesity of young children, as measured by body mass index, decreases to a minimum around 6 years of age before increasing again—the so-called adiposity rebound. The age at adiposity rebound ranges from around 3 years to 8 years or more. Table 5 shows that early adiposity rebound is strongly related to a high body mass index in later childhood, as has previously been shown [39]. It also predicts an increased incidence of type 2 diabetes in later life. This new observation has now been replicated in a longitudinal study in Delhi, India [40]. In both studies an early adiposity rebound was found to be associated with thinness at birth and at one year. It is not therefore the young child who is overweight who is at greatest risk of type 2 diabetes but the one who is thin but subsequently gains weight rapidly.

Compensatory Growth

When undernutrition during early development is followed by improved nutrition many animals and plants stage accelerated or 'compensatory' growth [25]. Compensatory growth has costs, however, which in animals include reduced life-span [41]. There are a number of processes by which, in humans, undernutrition and small size at birth followed by rapid childhood growth could lead to cardiovascular disease and type 2 diabetes in later life [10,13]. Rapid growth may be associated with persisting hormonal and metabolic changes. Larger body size may increase the functional demand on functional capacity that has been reduced by slow early growth—fewer glomeruli for example. Rapid weight gain may lead to an unfavorable body composition. Babies that are small and thin at birth lack

Table 4. Odds Ratios (95% Confidence Intervals) for Type 2 Diabetes and Hypertension according to Birthweight and Body Mass Index at 11 Years among 13,517 Men and Women

Birthweight (kg)	Body Mass Index at 11 Years (kg/m ²)			
	–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 (2997 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)

Odds ratios adjusted for sex and year of birth.

Table 5. Body Mass Index at 11 Years of Age and Cumulative Incidence of Type 2 Diabetes according to Age at Adiposity Rebound in 8760 Men and Women

Age at Adiposity Rebound (Years)	Mean Body Mass Index (kg/m ²) at Age 11	Cumulative Incidence of Diabetes % (n)		
		Men	Women	All
≤4	19.7	8.1 (86)	8.9 (112)	8.6 (198)
5	17.6	6.2 (904)	2.5 (864)	4.4 (1768)
6	17.0	3.7 (1861)	2.5 (1456)	3.2 (3317)
7	16.8	2.4 (249)	2.1 (243)	2.2 (492)
≥8	16.7	3.0 (135)	0.7 (150)	1.8 (285)
<i>p</i> for trend	<0.001	<0.001	0.002	<0.001

Figures in parentheses are numbers of subjects.

muscle, a deficiency which will persist as the critical period for muscle growth occurs in utero and there is little cell replication after birth [42]. If they develop a high body mass during later childhood they may have a disproportionately high fat mass in relation to lean body mass, which will lead to insulin resistance [43].

Pathways to Disease

New studies, especially the Helsinki studies with their detailed information on child growth and socio-economic circumstances, increasingly suggest that the pathogenesis of coronary heart disease 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 [44]. For example, the Pro12Pro polymorphism of the PPAR- γ gene is known to be associated with insulin resistance, indicated by elevated fasting plasma insulin concentrations. A study of 476 elderly people in Helsinki suggests that this effect occurs only among men and women who had low birthweight.

The effects of the intrauterine environment on later disease are conditioned not only by events at conception, but by events after birth. Table 4 showed how the effects are conditioned by childhood weight gain. Table 3 showed that the effects of low ponderal index at birth are conditioned by living conditions in adult life. Table 6 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 [45]. Among all the men and women low birthweight was associated

with an increased incidence of hypertension, as has been shown before [33]. 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 branchings are triggered by the environment. The pathways determine vulnerability of each individual to what lies ahead. The pathway to coronary heart disease can originate either in slow fetal growth as a consequence of undernutrition, or in poor infant growth as a consequence of poor living conditions.

The effects of slow fetal growth and low birthweight, and the effects of post-natal development, depend on environmental influences and paths of development that precede and follow them. Low birthweight, or any other single influence, does not have 'an' effect that is best estimated by a pooled estimate from all published studies. As René Dubos wrote "the effects of the physical and social environments cannot be understood without knowledge of individual history" (*Mirage of Health*, 1987). Unravelling disease causation, and hence the way to prevent it, will therefore require an understanding of heterogeneity.

Strength of Effects

Low birthweight, though a convenient marker in epidemiological studies, is an inadequate description of the phenotypic characteristics of a baby that determine its long-term health.

Table 6. Cumulative Incidence (%) of Hypertension According to Birthweight and Father's Social Class in 8,760 Men and Women

Birthweight (g)	Father's Social Class			<i>p</i> for trend
	Laborer	Lower Middle Class	Upper Middle Class	
–3000	22.2	20.2	10.5	0.002
–3500	18.8	15.2	10.6	<0.001
–4000	14.5	12.5	10.3	0.04
>4000	11.1	15.6	15.7	0.11
<i>p</i> for trend	<0.001	0.05	0.79	

The wartime famine in Holland produced lifelong insulin resistance in babies who were in utero at the time, with little alteration in birthweight [46]. In babies, as in children, slowing of growth is a response to a poor environment, especially undernutrition, but body size at birth does not adequately describe the long-term morphological and physiological consequences of undernutrition. The same birthweight can be attained by many different paths of fetal growth and each is likely to be accompanied by different gene-environment interactions [23]. Nevertheless birthweight provides a basis for estimating the magnitude of the effects of the fetal phase of development on later disease, though it is likely to underestimate them.

Because the risk of cardiovascular disease is influenced both by small body size at birth and during infancy and by rapid weight gain in childhood, estimation of the risk of disease attributable to early development requires data on fetal, infant and childhood growth. Currently the Helsinki studies are the main source of information [25]. If each man in the cohort had been in the highest third of ponderal index at birth, and each woman in the highest third of birth length, and if each man or woman had lowered their body mass index between age 3 and 11 years, the incidence of coronary heart disease would have been reduced by 25% in men and 63% in women [25].

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