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Coronary heart disease: a disorder of growth

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The search for the causes of CHD has been guided by a 'destructive' model, which proposes that influences acting in adult life, such as smoking, obesity or high saturated fat intakes, lead to an acceleration of age-related destructive processes, including a rise in blood pressure and the formation of atheroma. One explanation for the failure of the model to account for, or indeed to prevent rising epidemics of CHD, is that individuals are heterogeneous in their responses to such influences. This heterogeneity in response is linked to different paths of early growth. The recent discovery that individuals who develop CHD grew differently from other individuals during fetal life and in childhood has led to a new 'developmental' model for the disease. Reduced fetal growth followed by poor growth in infancy leads to an increased risk of development of CHD, and its associated conditions, stroke, hypertension and impaired glucose tolerance. These effects are compounded by accelerated weight gain, which may represent 'compensatory growth' in childhood.

CHD: Fetal programming: Fetal growth: Childhood growth

The search for the causes of CHD, and the way to prevent it, has been guided by a 'destructive' model. The principal causes to be identified are thought to act in adult life and to accelerate destructive processes, e.g. the formation of atheroma, rise in blood pressure and loss of glucose tolerance, which accompany ageing. This model, however, has had limited success. Obesity, diets high in saturated fat, cigarette smoking and psycho-social stress have all been implicated. The effects of modifying adult lifestyle, when formally tested in randomised trials have, however, been disappointingly small (Ebrahim & Davey Smith, 1997; Hooper *et al*. 2001). The model has proved incapable of answering important questions. For example, in Western countries the steep increase in the disease has been associated with rising prosperity, so why do the poorest individuals in the poorest places have the highest rates (Acheson, 1998)?

One explanation for our failure to understand and to prevent rising epidemics of CHD is that individuals are heterogeneous in their responses to environmental influences. Smoking, for example, is harmful to some individuals but less harmful to others. Some statisticians argue that we therefore need much larger studies to overcome this, while geneticists argue that the heterogeneity results from genes as yet unknown. There is, however, another way forward, which is to examine the biological basis of the differences between individuals. The recent discovery that individuals who develop CHD grew differently from other individuals during fetal life and childhood encourages this view (Eriksson *et al*. 2001), and has led to a new 'developmental' model for the disease (Barker, 1995, 1998).

Growth and CHD

Fig. 1 shows the growth of 357 men who were either admitted to hospital with CHD or who died from it (Eriksson *et al*. 2001), from a cohort of 4630 men who were born in and who grew up in Helsinki, Finland. 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 CHD were small at birth. They remained small in infancy, but had accelerated gain in weight and BMI thereafter. In contrast, their heights remained below average. Table 1 shows the hazard ratios for CHD according to size at birth. The hazard ratios fall with increasing birth weight and, more strongly, with increasing ponderal index (birth weight/length^3), a measure of thinness at birth. These trends were found in babies born at term and in those born prematurely, and

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Fig. 1. Growth of 357 men who later developed CHD in a cohort of 4630 men born in Helsinki, Finland. (—), BMI; (– –), height; (----), weight; (·····), SD (Z)-score for the cohort is set at zero. (From Eriksson *et al.* 2001.)

Table 1. Hazard ratios for CHD according to body size at birth for men born in Helsinki, Finland (from Eriksson *et al.* 2001) (Values are hazard ratios and 95% CI)

	Hazard ratios	95 % CI	No. of cases	No. of men
Birth weight (g):				
≤2500	3·63	2·02, 6·51	24	160
2501–3000	1·83	1·09, 3·07	45	599
3001–3500	1·99	1·26, 3·15	144	1775
3501–4000	2·08	1·31, 3·31	123	1558
>4000	1·00		21	538
For trend: *P*	0·006			
Ponderal index (kg/m^3):				
≤ 25	1·66	1·11, 2·48	104	1093
25–27	1·44	0·97, 2·13	135	1643
27–29	1·18	0·78, 1·78	84	1260
> 29	1·00		31	578
For trend: *P*	0·0006			

Table 2. Hazard ratios for CHD according to body size at 1 year for men born and in Helsinki, Finland (From Eriksson *et al.* 2001) (Values are hazard ratios and 95 % CI)

	Hazard ratios	95 % CI	No. of cases	No. of men
Weight (kg): ≤ 9	1·82	1·25, 2·64	96	781
9–10	1·17	0·80, 1·71	85	1126
10–11	1·12	0·77, 1·64	89	1243
11–12	0·94	0·62, 1·44	49	852
>12	1·00		38	619
For trend: *P*	< 0·0001			
Height (m): ≤0·73	1·55	1·11, 2·18	79	636
0·73–0·75	0·90	0·63, 1·27	68	962
0·75–0·77	0·94	0·68, 1·31	87	1210
0·77–0·79	0·83	0·58, 1·18	64	1011
> 0·79	1·00		59	802
For trend: *P*	0·007			
BMI (kg/m^2): <16	1·83	1·28, 2·60	72	654
16–17	1·61	1·15, 2·25	89	936
17–18	1·29	0·91, 1·81	83	1136
18–19	1·12	0·77, 1·62	59	941
> 19	1·00		54	954
For trend: *P*	< 0·0004			

therefore reflect slow intra-uterine growth. Table 2 shows that the hazard ratios also fall with increasing weight, height and BMI at age 1 year. Small size at this age predicts CHD independently of size at birth (Eriksson *et al.* 2001). In a simultaneous analysis with birth weight the hazard ratio associated with each unit decrease in Z-score for weight between birth and 1 year is 1·21 (1·08, 1·36 95 % CI, P=0·001).

The association between CHD and small size at birth has been shown in studies in Europe (Barker *et al.* 1989; Frankel *et al.* 1996; Leon *et al.* 1998), North America (Rich-Edwards *et al.* 1997) and India (Stein *et al.* 1996). The association with poor weight gain in infancy was first shown in Hertfordshire (Barker *et al.* 1989), and confirmed in Helsinki (Eriksson *et al.* 2001); the strength of the association being similar in the two studies. The association between CHD and rapid childhood weight gain was first shown in a study of an older cohort of men born in Helsinki (Eriksson *et al.* 1999), while the association with low rates of height growth is consistent with the known association between the disease and short adult stature in men (Marmot *et al.* 1984).

Fig. 2, based on the same data as that used in Fig. 1 shows the combined effects of ponderal index at birth and BMI in childhood on hazard ratios for CHD in the Helsinki cohort (Eriksson *et al.* 2001). The lines shown in Fig. 2 join points with the same hazard ratios. For example, the line for the highest ratio, 1·75, is associated with low ponderal index at birth but above average BMI in childhood. Boys who had a low ponderal index at birth increased their risk of CHD if they attained even average BMI in childhood. In contrast, among boys with a high ponderal index at birth, no increased risk was associated with a high childhood BMI. The interaction between ponderal index at birth and BMI in childhood is strongly statistically significant (P<0·001). Findings among girls are similar (Forsen *et al.* 1999), and again the risk of CHD is determined more by the tempo of weight gain in childhood than the body size attained.

Growth and hypertension and type 2 diabetes

There is now a substantial body of evidence showing that individuals who were small at birth remain biologically different from individuals who were larger. The differences include an increased susceptibility to hypertension and type 2 diabetes in adult life, two disorders closely linked to CHD (Hales *et al.* 1991; Curhan *et al.* 1996; Eriksson *et al.* 2000; Forsen *et al.* 2000). Table 3 shows the odds ratios for

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hypertension and type 2 diabetes among 13 517 men and women from two Helsinki cohorts combined (Eriksson *et al*. 2000; Forsen *et al*. 2000; Barker *et al*. 2002) according to weight at birth and BMI at age 11 years. These two disorders are associated with the same general pattern of growth as CHD. The highest risk for each disease occurs among men and women who had low birth weight but who were in the highest BMI group at 11 years. Similarly to CHD, the risk of disease is not determined only by the absolute value of BMI in childhood, but by the combination of body size at birth and during childhood (Eriksson *et al*. 2000; Forsen *et al*. 2000). It is the tempo of growth as well as the attained body size that determine risk.

The associations between slow fetal and infant growth and later CHD are strong and graded. In the Helsinki cohort boys who at birth had a ponderal index >26 kg/m^3 and who at 1 year of age were above the cohort average for BMI (17·7 kg/m^2) and height (0·762 m) were at half the risk of developing CHD before the age of 65 years (Eriksson *et al*. 2001). This finding, together with the data on hypertension and type 2 diabetes (Table 3) confirms the strong effects of early growth on disease.

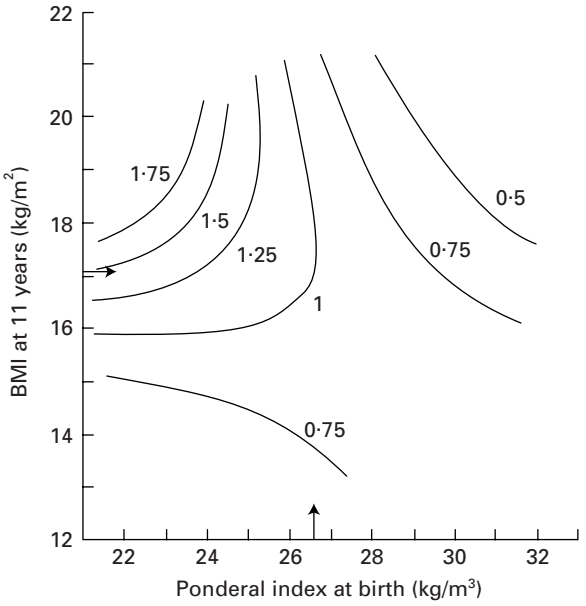

Fig. 2. Hazard ratios for CHD according to ponderal index (weight/length^3) at birth and BMI (kg/m^2) at 11 years for men born in Helsinki, Finland. (→), Average values; (—), joins points with the same hazard ratios. (From Eriksson *et al*. 2001.)

Biological mechanisms

The associations between altered growth and CHD suggest that the disease may originate in two phenomena associated with development, 'phenotypic plasticity' and 'compensatory growth'. Phenotypic plasticity is the phenomenon whereby one genotype gives rise to a range of different physiological or morphological states in response to different environmental conditions during development (West-Eberhard, 1989; Bateson & Martin, 1999). Such gene–environment interactions are ubiquitous in development. Their existence is demonstrated by the numerous experiments showing that minor alterations to the diets of pregnant animals, which may not even change body size at birth, can produce lasting changes in the offspring's physiology and metabolism, including altered blood pressure and glucose–insulin and lipid metabolism (Desai & Hales, 1997; Kwong *et al*. 2000). The evolutionary benefit of phenotypic plasticity is that, in a changing environment, it enables the production of phenotypes that are better matched to their environment than would be possible if one genotype produced the same phenotype in all environments (West-Eberhard, 1989). When undernutrition during devel-

Table 3. Odds ratios (OR)* for type 2 diabetes and hypertension according to birth weight and BMI at 11 years for 13 517 men and women from two Helsinki, Finland cohorts born 1924–44 (from Barker *et al*. 2002)
(Values are OR and 95 % CI)

		BMI at 11 years (kg/m^2)							
		≤15·7		15·7–16·6		16·7–17·6		>17·6	
	Birth weight (kg)	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
No. of men and women	≤3·0	991		719		581		560	
	3·0–3·5	1394		1422		1264		1246	
	3·5–4·0	827		984		1122		1110	
	>4·0	167		254		413		463	
Type 2 diabetes (698 cases)	≤3·0	1·3	0·6, 2·8	1·3	0·6, 2·8	1·5	0·7, 3·4	2·5	1·2, 5·5
	3·0–3·5	1·0	0·5, 2·1	1·0	0·5, 2·1	1·5	0·7, 3·2	1·7	0·8, 3·5
	3·5–4·0	1·0	0·5, 2·2	0·9	0·4, 1·9	0·9	0·4, 2·0	1·7	0·8, 3·6
	>4·0	1·0		1·1	0·4, 2·7	0·7	0·3, 1·7	1·2	0·5, 2·7
Hypertension (2997 cases)	≤3·0	2·0	1·3, 3·2	1·9	1·2, 3·1	1·9	1·2, 3·0	2·3	1·5, 3·8
	3·0–3·5	1·7	1·1, 2·6	1·9	1·2, 2·9	1·9	1·2, 3·0	2·2	1·4, 3·4
	3·5–4·0	1·7	1·0, 2·6	1·7	1·1, 2·6	1·5	1·0, 2·4	1·9	1·2, 2·9
	>4·0	1·0		1·9	1·1, 3·1	1·0	0·6, 1·7	1·7	1·1, 2·8

*Adjusted for gender and year of birth.

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opment is followed by improved nutrition, many animals stage accelerated or 'compensatory' growth in weight or length. This growth restores the animal's body size but may have long-term costs, which include a reduced lifespan (Metcalfe & Monaghan, 2001).

There are several possible mechanisms by which reduced fetal and infant growth followed by accelerated weight gain in childhood may lead to CHD. Babies who are thin at birth lack muscle, a deficiency that will persist as the critical period for muscle growth is around 30 weeks *in utero*, and there is little cell replication after birth (Widdowson *et al*. 1972). If they develop a high BMI in childhood they may have a disproportionately high fat mass. This situation may be associated with the development of insulin resistance, since children and adults who had low birth weight but are currently heavy are insulin resistant (Barker *et al*. 1993; Lithell *et al*. 1996; Bavdekar *et al*. 1999).

Small babies have reduced numbers of nephrons (Merlet-Benichou *et al*. 1993; Brenner & Chertow, 1994). It has been suggested that this leads to hyperperfusion of each nephron and resulting glomerular sclerosis, further nephron death and a cycle of increasing blood pressure and nephron death. This process may be exacerbated if accelerated growth increases the degree of hyperperfusion. This framework fits with the hypothesis that essential hypertension is a disorder of growth involving two separate mechanisms, a growth-promoting process in childhood and a self-perpetuating mechanism in adult life (Lever & Harrap, 1992). The existence of such self-perpetuating cycles, initiated *in utero*, but triggered by ageing or other influences in later life, would explain the small effects of birth size on blood pressure levels in the normal population (Huxley *et al*. 2000), but its large effects on the risk of hypertension.

Responses to adult living standards

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 (Bateson & Martin, 1999). Men who had low birth weight are more vulnerable to developing CHD and type 2 diabetes if they become overweight (Frankel *et al*. 1996; Lithell *et al*. 1996). Table 4 shows the effect of low income in adult life on CHD among men in Helsinki (Barker *et al*. 2001). As expected, men who had a low taxable income had higher rates of the disease (Marmot & McDowell, 1986; Acheson, 1998; Macintyre *et al*. 2001). There is no known explanation for this relationship, and it is a major component of the social inequalities in health in Western countries. The effect of low income, however, is confined to men who had slow fetal growth and who were thin at birth, defined by a ponderal index $< 26\,kg/m^3$. Men who were not thin at birth were resilient to the effects of low income on CHD, so that there was a statistically significant interaction between the effects of fetal growth and adult income (P=0·005).

One explanation of these findings emphasises the psycho-social 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 (Marmot & Wilkinson, 2001). The findings from Helsinki (Barker *et al*. 2001) seem consistent with this explanation. Individuals who are small at birth are known to have persisting alterations in responses to stress, including raised serum cortisol concentrations (Phillips *et al*. 2000). Rapid childhood weight gain could exacerbate these effects.

Mothers and babies today

The principal determinant of growth rates in early life is the availability of nutrition. As yet we do not know the impact of maternal nutrition on fetal development (Godfrey & Barker, 2001). The relatively disappointing effects of dietary interventions in pregnancy on birth weight in human subjects have led to the view that fetal nutrition is little affected by maternal nutrition (Harding, 2001). It is becoming clear, however, that the concept of maternal nutrition must be extended beyond the mother's diet in pregnancy to include her body composition and metabolism both during pregnancy and at the time of conception (Jackson & Robinson, 2001). Moreover, birth weight is an inadequate description of those phenotypic characteristics of a baby that determine its long-term health (Barker, 1998; Ravelli *et al*. 1998). As birth weight and ponderal index are crude measures of how fetal nutrition has affected body composition, the true size of the effect of fetal growth on later disease is hard to measure (Robinson, 2001), and we therefore need a more sophisticated view of optimal fetal development that takes account of the long-term sequelae of fetal responses to undernutrition. If we are to protect babies, we must also protect girls in childhood and adolescence. Body composition is established by childhood growth and obesity, and eating habits that are entrained during childhood and adolescence (Dietz, 1996). Given the body of evidence showing that CHD, and the related disorders stroke, hypertension and type 2 diabetes, originate through undernutrition and other adverse influences *in utero*, followed by accelerated weight gain thereafter, protecting the nutrition and health of young women and their babies must be part of any effective strategy for preventing these diseases.

As Westernisation improves the nutrition of undernourished populations, fetal nutrition improves more slowly than nutrition during childhood or adult life, because the fetus is linked to its mother by a long and precarious supply line that is partly established during the mother's fetal life. It may require more than one generation of improved nutrition before fetal growth responds, whereas child growth responds in one generation. During this phase of development children who were small at birth undergo accelerated, compensatory growth. This is the path of growth that leads to CHD and, it seems, may generate the epidemics of the disease (Fig. 1). Through phenotypic plasticity and the costs of compensatory growth, individuals who follow this path are permanently biologically different and at increased risk of CHD. They are also more vulnerable to the effects of poor living standards (Table 4), obesity and other adverse influences in adult life.

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Table 4. Hazard ratios for CHD according to ponderal index at birth (kg/m^3) and taxable income in adult life for men born and in Helsinki, Finland (from Barker *et al*. 2001)
(Values are hazard ratios and 95% CI)

Household income		Ponderal index ≤26·0 (*n* 1475)		Ponderal index >26·0 (*n* 2154)	
10^3 mark/year	£/year	Hazard ratio	95 % CI	Hazard ratio	95 % CI
>140	15 700	1·00		1·19	0·65, 2·19
111–140	15 700	1·54	0·83, 2·87	1·42	0·78, 2·57
96–110	12 400	1·07	0·51, 2·22	1·66	0·90, 3·07
76–95	10 700	2·07	1·13, 3·79	1·44	0·79, 2·62
≤75	8400	2·58	1·45, 4·60	1·37	0·75, 2·51
For trend: *P*		<0·0001		0·75	

Conclusion

The effect of a high body mass in childhood on risk of CHD, and related disorders, is conditioned by size at birth (Fig. 2). The effect of poor living standards in adult life is also conditioned by size at birth (Table 4). The effects of any single influence therefore depend on the path of development that preceded it, and the pathogenesis of CHD or 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 (Kuh & Ben-Shlomo, 1997). Rather, the consequences of adverse influences depend on events at earlier critical stages of development (Eriksson *et al*. 2001). This embodies the concept of developmental 'switches' triggered by the environment (Bateson & Martin, 1999). The effects of any particular birth weight on disease will not only depend on the subsequent path of development, but also on the path of growth that led to that birth weight. The same weight can be attained by many different paths of fetal growth, and each path is likely to be accompanied by different gene-environment interactions, although this remains to be demonstrated (Harding, 2001).

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