Fetal programming of coronary heart disease

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People who develop coronary heart disease grow differently from other people both *in utero* and during childhood. Slow growth during fetal life and infancy is followed by accelerated weight gain in childhood. Two disorders that predispose to coronary heart disease, type 2 diabetes and hypertension, are preceded by similar paths of growth. Mechanisms underlying this are thought to include the development of insulin resistance *in utero*, reduced numbers of nephrons associated with small body size at birth and altered programming of the micro-architecture and function of the liver. Slow fetal growth might also heighten the body's stress responses and increase vulnerability to poor living conditions in later life. Coronary heart disease

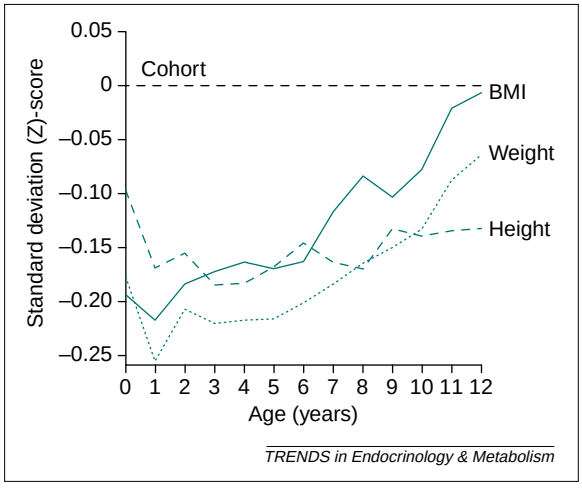

Fig. 1. Growth of 357 boys who later developed coronary heart disease in a cohort of 4630 boys born in Helsinki. Abbreviation: BMI, body mass index.

The search for the causes of coronary heart disease has hitherto been guided by a 'destructive' model. The causes to be identified were thought to act in adult life and to accelerate destructive processes, such as the formation of atheroma, rise in blood pressure and loss of glucose tolerance. However, it has recently been shown that the growth of people who develop coronary heart disease differs from that of other people during fetal life, infancy and childhood. This has led to a new 'developmental' model for the disease [1–3]. Figure 1 shows the growth of 357 boys who in later life were either admitted to hospital with coronary heart disease or died from it [1]. They belong to a cohort of 4630 men who were born in Helsinki during 1934–1944, and their growth is expressed as standard deviation or 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. However, boys who later developed coronary heart disease were small at birth, remained small in infancy, but had accelerated gain in weight and body mass index (BMI) thereafter. By contrast, their heights remained below average, which is consistent with the known association between coronary heart disease and short adult stature [4]. Findings in girls are similar but among those who later developed coronary heart disease accelerated weight gain began around the age of four years.

Table 1 shows hazard ratios for coronary heart disease according to size at birth [1]. The hazard ratios fall with increasing birthweight and, more strongly, with increasing ponderal index (birthweight/length^3), a measure of thinness at birth. These trends were found in babies born at term or prematurely and therefore reflect slow intrauterine growth. Table 2 shows that the hazard ratios also fell with increasing weight, height and BMI at age one year. Low weight gain during infancy predicts coronary heart disease independently of size at birth. In a simultaneous analysis with birthweight the hazard ratio associated with each unit decrease in Z-score for weight between birth and one year was 1.21 (95% CI, 1.08–1.36, $P = 0.001$). The association between coronary heart disease and small size at birth has been shown in studies in Europe, North America and India [5–9]. The association with poor weight gain in infancy was first shown in a study of 5654 men born in Hertfordshire during 1911–1930 [5], and confirmed in Helsinki [1], the strength of the association being similar in the two studies.

Table 3, based on the same data used in Fig. 1, shows the combined effects of ponderal index at birth and change in BMI between one and 11 years of age [1]. The table uses BMI at age 11 years, but the BMI at ages around this gives similar results. Boys who had a low ponderal index at birth increased their risk of coronary heart disease if their body mass rose in childhood. The interaction between ponderal index at birth and BMI in childhood is highly statistically significant. Findings among girls are similar. In both sexes the risk of coronary heart disease is determined more by the tempo of weight gain than the body size attained [10].

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 1043-2760/02/$ – see front matter PII: S1043-2760(02)00689-6

Table 1. Hazard ratios for coronary heart disease according to body size at birth[a]

	Hazard ratio (95% CI)	No. of cases/ No. of men
Birthweight (g)		
<2500	3.63 (2.02–6.51)	24/160
–3000	1.83 (1.09–3.07)	45/599
–3500	1.99 (1.26–3.15)	144/1775
–4000	2.08 (1.31–3.31)	123/1558
>4000	1.00	21/538
P for trend	0.006	
Ponderal index (kg m^{-3})		
<25	1.66 (1.11–2.48)	104/1093
–27	1.44 (0.97–2.13)	135/1643
–29	1.18 (0.78–1.78)	84/1260
>29	1.00	31/578
P for trend	0.0006	

[a]Data taken from Ref. [1].

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Growth and hypertension and type 2 diabetes

There is now a substantial body of evidence showing that people who were small at birth remain biologically different to people who were larger. The differences include an increased susceptibility to hypertension and type 2 diabetes mellitus (T2DM), two disorders that are closely linked to coronary heart disease [11–15] and which are associated with the same general pattern of growth as coronary heart disease. The risks for each disease fall with increasing birthweight and rise with increasing childhood BMI. Similar to coronary heart disease, risk is not determined only by the absolute value of BMI in childhood but by the combination of body size at birth and during childhood [11,13]. It is the tempo of growth in addition to the attained body size that determines risk. There is also a substantial literature showing that birthweight is associated with differences in blood pressure and insulin secretion within the normal range [14,15]. These differences are found in children and adults but they tend to be small. For example, a 1-kg difference in birthweight is associated with ~1–2 mm Hg difference in systolic pressure [15]. This contrasts with the large effects of birthweight on hypertension. In the Helsinki cohort born 1934–1944, the cumulative incidence of hypertension requiring medication fell from 20.2% in men and women weighing <3000 g at birth to 12.3% in those weighing >4000 g [16].

Table 2. Hazard ratios for coronary heart disease according to body size at one year of age[a]

	Hazard ratio (95% CI)	No. of cases/ No. of men
Weight (kg)		
–9	1.82 (1.25–2.64)	96/781
–10	1.17 (0.80–1.71)	85/1126
–11	1.12 (0.77–1.64)	89/1243
–12	0.94 (0.62–1.44)	49/852
>12	1.00	38/619
P for trend	<0.0001	
Height (cm)		
–73	1.55 (1.11–2.18)	79/636
–75	0.90 (0.63–1.27)	68/962
–77	0.94 (0.68–1.31)	87/1210
–79	0.83 (0.58–1.18)	64/1011
>79	1.00	59/802
P for trend	0.007	
Body mass index (kg m^{-2})		
≤16	1.83 (1.28–2.60)	72/654
–17	1.61 (1.15–2.25)	89/936
–18	1.29 (0.91–1.81)	83/1136
–19	1.12 (0.77–1.62)	59/941
>19	1.00	54/954
P for trend	0.0004	

[a]Data taken from Ref. [1].

Table 3. Hazard ratios (95% CI) for coronary heart disease according to ponderal index at birth and change in body mass index between one and 11 years of age

Ponderal index (kg m^{-2})	Change in body mass index (kg m^{-2})	
	Fall	Rise
–25	1.3 (0.7–2.3)	2.5 (1.4–4.4)
–27	1.3 (0.8–2.3)	2.2 (1.3–4.0)
–29	1.3 (0.7–2.2)	1.3 (0.7–2.6)
>29	1.0	1.1 (0.4–2.9)

Biological mechanisms

The association between altered growth and coronary heart disease has led to the suggestion that the disease might originate in two phenomena associated with development – 'developmental, or 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 [17]. 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 their offspring's body size at birth, can produce lasting changes in their physiology and metabolism – including altered blood pressure and glucose/insulin and lipid metabolism [18,19]. Evidence of gene–nutrient interactions in the genesis of type 2 diabetes is beginning to appear [20]. The effects of a polymorphism of the gene encoding peroxisome proliferator-activated receptor γ2 (*PPARG2*) depends on birthweight, which serves as a marker for intrauterine nutrition. It has been suggested that the Pro12Ala polymorphism of the gene increases tissue sensitivity to insulin and

Table 4. Mean fasting insulin concentration and HOMA-IR index according to PPAR-γ gene polymorphism and birthweight[a,b]

	Birthweight (g)			
	–3000	–3500	>3500	P^b
Fasting insulin (pmol l^{-1})				
Pro12Pro (n)	84 (56)	71 (161)	65 (107)	0.003
Pro12Ala/Ala12Ala (n)	60 (37)	60 (67)	65 (48)	0.31
P^c	0.008	0.02	0.99	

[a]Abbreviations: HOMA-IR, homeostasis model assessment-insulin resistance; PPAR-γ, peroxisome proliferator-activated protein-γ. [b]Numbers of subjects in each cell are shown within parentheses. [b]For the difference among birthweight groups. [c]For the difference between the Pro12Pro and Pro12Ala/Ala12Ala genotypes.

thereby protects against T2DM. Table 4 is based on a study of 476 elderly people in Helsinki. The Pro12Ala polymorphism only influenced fasting plasma insulin concentrations in men and women who had low birthweight. As has been shown many times, low birthweight was associated with raised plasma insulin concentrations, indicating insulin resistance. This, however, was confined to people with the Pro12Pro polymorphism: the Pro 12Ala polymorphism protected against the effect. The interaction between the effects of the gene and of birthweight was statistically significant ($P = 0.03$).

When undernutrition during development is followed by improved nutrition, many animals stage accelerated or 'compensatory' growth in weight or length. This restores the animal's body size but might have long-term costs, which include reduced lifespan [21]. There are several possible mechanisms by which reduced fetal and infant growth followed by accelerated weight gain in childhood might lead to coronary heart disease. Babies who are thin at birth lack muscle, a deficiency that will persist because the crucial period for muscle growth is ~30 weeks *in utero*, and there is little cell replication after birth [22]. If they gain weight rapidly in childhood, they are liable to put on fat rather than muscle, leading to a disproportionately high fat mass in later life. This might be associated with the development of insulin resistance because children and adults who had low birthweight but are currently heavy are insulin resistant [14,23,24].

Another mechanism linking retarded early growth followed by compensatory growth with later disease is through the effect of growth on the kidney. Small babies have reduced numbers of nephrons [25,26]. It has been suggested that this leads to hyperperfusion of each nephron and consequent glomerular sclerosis. Rapid childhood growth is thought to increase the hyperperfusion. Aging brings nephron loss, nephron death and a cycle of increasing blood pressure, glomerular sclerosis and nephron death is initiated, leading to the development of hypertension. This framework fits with the hypothesis that essential hypertension is a disorder of growth with two separate mechanisms, a growth-promoting process in childhood and a self-perpetuating mechanism, which might be initiated early but acts in adult life [27]. The existence of such self-perpetuating cycles, initiated *in utero*, but triggered by aging or other influences in later life, would explain the small effects of birth size on blood pressure levels in the normal population, but its large effects on the risk of hypertension [16].

Findings in Hertfordshire suggest that one of the mechanisms linking poor weight gain in infancy with coronary heart disease is altered liver function, reflected in raised serum concentrations of total and low density lipoprotein cholesterol, and raised plasma fibrinogen concentrations [28,29]. Unlike organs such as the kidney, the liver remains 'plastic' during its development until the age of around five years. Its function might be permanently changed by influences that affect its early growth [30–32]. Support for an important role for liver development in the early pathogenesis of coronary heart disease comes from findings in Sheffield [33]. Among men and women reduced abdominal circumference at birth, a measure that reflects reduced liver size, gave stronger predictions of later serum cholesterol and plasma fibrinogen than any other measure of body size at birth.

Table 5. Hazard ratios (95% CI) for coronary heart disease according to ponderal index at birth and taxable income in adult life

Household income 1000 marks (pounds sterling) per year	Ponderal index (kg m^{-3})	
	<26.0 (n = 1475)	>26.0 (n = 2154)
>140 (15 700)	1.00	1.19 (0.65 to 2.19)
111–140 (15 700)	1.54 (0.83 to 2.87)	1.42 (0.78 to 2.57)
96–110 (12 400)	1.07 (0.51 to 2.22)	1.66 (0.90 to 3.07)
76–95 (10 700)	2.07 (1.13 to 3.79)	1.44 (0.79 to 2.62)
≤75 (8 400)	2.58 (1.45 to 4.60)	1.37 (0.75 to 2.51)
P for trend	<0.001	0.75

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 [34]. Table 5 shows the effect of low income in adult life on coronary heart disease among men in Helsinki [35]. As expected, men who had a low taxable income had higher rates of the disease [36,37]. There is no agreed explanation for this and it is a major component of the social inequalities in health in Western countries. However, the effect of low income is confined to men who had slow fetal growth and 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 coronary heart disease, 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 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 [38]. 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 [39]. It is suggested that persisting small elevations of cortisol concentrations over many years might have effects similar to those seen when tumours lead to more sudden, large increases in glucocorticoid concentrations. People with Cushing's syndrome are insulin resistant and have raised blood pressure.

Interactions

New studies, especially those of the two exceptionally well-documented cohorts in Helsinki, increasingly suggest that coronary heart disease and the disorders related to it develop through a series of interactions. The effects of genes are conditioned by fetal growth [20]: the effects of small body size at birth are conditioned by growth during childhood [1], and by living conditions in childhood [16] and adult life [35]. Any one influence, such as low income, does not have a single quantifiable risk associated with it. Its risk to an individual is conditioned by events at earlier crucial stages of development. This embodies the concept of development 'switches' triggered by the environment.

Statements such as 'low birthweight explains only a small proportion of diabetes' [40] are incorrect. The results in Tables 1–5 show that the large effects [41] of small body size at birth extend across the range of birthweight and are not confined to those conventionally described as having low birthweight, <2.5 kg (5.5 lb). The effects of birthweight cannot be quantified as 'small proportion' or 'large proportion'. Fetal life is an important phase in a branching path of development. The branchings are triggered by the environment and determine the vulnerability of each individual to what lies ahead. Birthweight, although a convenient marker in epidemiological studies, is an inadequate description of the phenotypic characteristics of a baby that determine its long-term health. The wartime famine in Holland produced lifelong insulin resistance in babies who were *in utero* at the time, with little alteration in birthweight [42]. In babies, as in children, slowing of growth is a response to a poor environment, but it does not describe the morphological and physiological consequences [43]. The same birthweight can be attained by many different paths of fetal growth and each is probably accompanied by different gene–environment interactions.

Conclusion

The associations between slow fetal, infant and childhood growth and later coronary heart disease are strong and graded. Boys who at birth had a ponderal index above 26 kg m^{-3} and who at one year of age were above the cohort average for BMI (17.7 kg m^{-3}) and height (76.2 cm) were at half the risk of developing coronary heart disease before the age of 65 years [1]. Such findings confirm the strong effects of early growth on later disease [41].

The principal determinant of growth rates in early life is the availability of nutrition [43]. As yet, we do not know the impact of maternal nutrition on fetal nutrition. However, it is becoming clear 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 [44]. Moreover, birthweight is an inadequate summary measure of fetal experience, and we need a more sophisticated view of optimal fetal development, which takes account of the long-term sequelae of fetal responses to undernutrition.

References

1 Eriksson, J.G. *et al.* (2001) Early growth and coronary heart disease in later life: longitudinal study. *Br. Med. J.* 322, 949–953
2 Barker, D.J.P. (1995) Fetal origins of coronary heart disease. *Br. Med. J.* 311, 171–174
3 Barker, D.J.P. (1998) *Mothers, Babies and Health in Later Life* (2nd edn), Churchill Livingstone
4 Marmot, M.G. *et al.* (1984) Inequalities in death – specific explanations of a general pattern? *Lancet* 1, 1003–1006
5 Barker, D.J.P. *et al.* (1989) Weight in infancy and death from ischaemic heart disease. *Lancet* 2, 577–580
6 Leon, D. *et al.* (1998) Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *Br. Med. J.* 317, 241–245
7 Frankel, S. *et al.* (1996) Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet* 348, 1478–1480
8 Rich-Edwards, J.W. *et al.* (1997) Birthweight and risk of cardiovascular disease in a cohort of women followed up since 1976. *Br. Med. J.* 315, 396–400
9 Stein, C.E. *et al.* (1996) Fetal growth and coronary heart disease in South India. *Lancet* 348, 1269–1273
10 Forsen, T. *et al.* (1999) Growth *in utero* and during childhood among women who develop coronary heart disease: longitudinal study. *Br. Med. J.* 319, 1403–1407
11 Eriksson, J.G. *et al.* (2000) Fetal and childhood growth and hypertension in adult life. *Hypertension* 36, 790–794
12 Curhan, G.C. *et al.* (1996) Birthweight and adult hypertension and obesity in women. *Circulation* 94, 1310–1315
13 Forsen, T. *et al.* (2000) The fetal and childhood growth of persons who develop type 2 diabetes. *Ann. Intern. Med.* 133, 176–182
14 Lithell, H.O. *et al.* (1996) Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *Br. Med. J.* 312, 406–410
15 Huxley, R.R. *et al.* (2000) The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J. Hypertens.* 18, 815–831
16 Barker, D.J.P. *et al.* Growth and living conditions in childhood and hypertension in adult life: longitudinal study. *J. Hypertens.* (in press)
17 West-Eberhard, M.J. (1989) Phenotypic plasticity and the origins of diversity. *Annu. Rev. Ecol. Syst.* 20, 249–278
18 Kwong, W.Y. *et al.* (2000) Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. *Development* 127, 4195–4202
19 Desai, M. and Hales, C.N. (1997) Role of fetal and infant growth in programming metabolism in later life. *Biol. Rev. Camb. Philos. Soc.* 72, 329–348
20 Eriksson, J.G. *et al.* (2002) The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 51, 2321–2324
21 Metcalfe, N.B. and Monaghan, P. (2001) Compensation for a bad start: grow now, pay later? *Trends. Ecol. Evol.* 16, 254–260

22 Widdowson, E.M. *et al.* (1972) Cellular development of some human organs before birth. *Arch. Dis. Child.* 47, 652–655
23 Barker, D.J.P. *et al.* (1993) Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 36, 62–67
24 Bavdekar, A. *et al.* (1999) Insulin resistance syndrome in 8-year-old Indian children. Small at birth, big at 8 years, or both? *Diabetes* 48, 2422–2429
25 Brenner, B.M. and Chertow, G.M. (1994) Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am. J. Kidney Dis.* 23, 171–175
26 Merlet-Bénichou, C. *et al.* (1993) Retard de croissance intra-utérin et déficit en néphrons. (Intrauterine growth retardation and inborn nephron deficit). *Médecine/Sciences* 9, 777–780
27 Lever, A.F. and Harrap, S.B. (1992) Essential hypertension: a disorder of growth with origins in childhood? *J. Hypertens.* 10, 101–120
28 Fall, C.H.D. *et al.* (1992) Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *Br. Med. J.* 304, 801–805
29 Barker, D.J.P. *et al.* (1992) Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *Br. Med. J.* 304, 148–152
30 Gebhardt, R. (1992) Metabolic zonation of the liver: regulation and implications for liver function. *Pharmacol. Ther.* 53, 275–354
31 Desai, M. *et al.* (1995) Adult glucose and lipid metabolism may be programmed during fetal life. *Biochem. Soc. Trans.* 23, 331–335
32 Kind, K.L. *et al.* (1999) Restricted fetal growth and the response to dietary cholesterol in the guinea pig. *Am. J. Physiol.* 277, R1675–R1682
33 Barker, D.J.P. *et al.* (1993) Growth *in utero* and serum cholesterol concentrations in adult life. *Br. Med. J.* 307, 1524–1527
34 Bateson, P. and Martin, P. (1999) *Design for a Life: How Behaviour Develops*, Jonathan Cape
35 Barker, D.J.P. *et al.* (2001) Size at birth and resilience to the effects of poor living conditions in adult life: longitudinal study. *Br. Med. J.* 323, 1273–1276
36 Marmot, M. and McDowell, M.E. (1986) Mortality decline and widening social inequalities. *Lancet* 2, 274–276
37 Macintyre, K. *et al.* (2001) Relation between socio-economic deprivation and death from a first myocardial infarction in Scotland: population based analysis. *Br. Med. J.* 322, 1152–1153
38 Marmot, M. and Wilkinson, R.G. (2001) Psychosocial and material pathways in the relation between income and health: a response to Lynch *et al. Br. Med. J.* 322, 1233–1236
39 Phillips, D.I.W. *et al.* (2000) Low birthweight predicts elevated plasma cortisol concentrations in adults from three populations. *Hypertension* 35, 1301–1306
40 Zimmet, P. *et al.* (2001) Global and societal implications of the diabetes epidemic. *Nature* 414, 782–787
41 Barker D.J.P. *et al.* (2002) Fetal origins of adult

Early programming of glucose–insulin metabolism

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Epidemiological studies have revealed strong inverse relationships between birthweight and the risk of developing type 2 diabetes mellitus (T2DM) and the metabolic syndrome. The mechanistic basis of these relationships remains the subject of research and debate. Evidence for the importance of the fetal environment has been obtained from both human and rodent studies. Studies of monozygotic twins have shown that genetic effects cannot explain these relationships entirely, if at all. Fetal and early postnatal growth restriction produced by feeding a reduced protein diet to rat dams leads to T2DM in old male offspring and, if combined with an obesity-inducing diet after weaning, to all the features of the metabolic syndrome.

Published online: 12 September 2002

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As many as 70 years ago, it was recognized that the early environment in which a child grows could have long-term effects on its health [1]. This was based on observations in the UK and Sweden that death rates in specific age groups depended more upon the date of birth of individuals than upon the year under consideration [1]. Further evidence for the importance of the early environment came from a study by Forsdahl *et al.* [2], who looked at geographical variations in current death rates from arteriosclerotic heart disease in Norway. This showed that there was a significant positive correlation between these current death rates and geographical variation in past infant mortality rates. No such relationship was observed with current infant mortality rates [2]. Similarly, it was subsequently shown that the geographical pattern of mortality from cardiovascular disease (CVD) in England and Wales was related to maternal and neonatal mortality earlier in the century [3]. The hypothesis that this pattern could be explained by a relationship between poor nutrition in fetal and early life and CVD was supported by a study of men in England for whom birthweight records were available: men of low birthweight and low weight at one year of age experienced increased death rates from ischaemic heart disease later in life [4]. An inverse relationship has also been observed between birthweight and systolic blood pressure [5].

Fetal and neonatal life are known to be crucial periods for pancreatic β-cell development, because by one year of age, around half of the adult β mass is already present [6]. In light of this information and the findings of epidemiological studies, a relationship between early growth and the subsequent development of glucose intolerance and type 2 diabetes mellitus (T2DM) was sought, initially in a group of men in Hertfordshire, UK. Glucose tolerance tests were performed on these 64-year old men for whom birthweight records were available [7]. The proportion of men with impaired glucose tolerance

  PII: 10.1016/S1043-2760(02)00666-5