CONGENITAL HEART DISEASE

Fetal and infant markers of adult heart diseases

Marjo-Riitta Järvelin
Department of Public Health Science and General Practice, University of Oulu, Finland and Department of Epidemiology and Public Health, Imperial College School of Medicine, London, UK

There is growing evidence of an increasingly complex and multifactorial aetiology of heart diseases.[1 w1] It seems likely that the large geographic variations in cardiovascular disease (CVD) morbidity and mortality,[w2] even though at least partly genetic in origin, are influenced by factors acting prenatally and in early life, or by a combination of factors present throughout the life course. Changes in fetal growth pattern have been related to adult disease risk,[1] and there are many theories about the underlying mechanisms affecting cell division during critical periods of tissue development. The critical periods vary according to the tissue in question, and that is why there have been attempts to explore the timing of exposure in order to predict more specifically the adult disease risk.

This article examines: firstly the historical evolution of theories on childhood factors which have an influence in adulthood; secondly what is known today about the effect of early life factors on heart disease risk; and thirdly the specific problems in longitudinal studies which explore these factors and adult disease risk.

Dawn of the "hypothesis of the 20th century"

Biological programming: a new theoretical model about the aetiology of heart disease

The dawn of modern epidemiology came after the second world war, first with ecological studies comparing CVD incidence and mortality, and subsequently multicentre cross sectional and follow up studies on CVD.[w3] The studies showed that populations with high CVD mortality have high cholesterol and high blood pressure, and that smoking and obesity are common among these populations.[w4] This led to the *lifestyle model* in understanding the aetiology of chronic diseases, where the key issues are health behaviour and the interaction between genes and an adverse environment in adult life. This was consequently followed by intervention programmes, which have significantly improved heart disease risk status in many countries.[w3] However, lifestyle factors only explain part of the heart disease risk, which is why other reasons have been sought. For example, in the mid 1980s Rose pointed out that the well established risk factors for coronary heart disease (CHD)—cigarette smoking, high serum cholesterol, and high blood pressure—have a limited ability to predict disease risk in adults.[w5] In the large international MONICA (monitoring trends and determinants in cardiovascular disease) project,[w2 w4] only 25% of the variance in CHD mortality was explained by conventional risk factors. Could childhood influences explain this gap in our understanding of the aetiology of CVD?

In Norway in the 1970s, Forsdahl[2] put forward the hypothesis that the geographical differences in CVD mortality might not be related to the contemporary circumstances, but to poverty or deprivation in early life (table 1). However, the importance of fetal and early life circumstances for adult health had been suggested almost a century earlier by the chief medical officer to the Board of Education in Britain, who wrote: "recent progress has shown that the health of the adult is dependent upon the health of the child and that the health of the child is dependent upon the health of the infant and its mother".[w6]

A new hypothesis developed following observations in the 1980s by Barker and colleagues, in accordance with Forsdahl, based upon positive relations between the areas with the highest CVD and infant mortality rates,[3] and lower birth weight and increased risk of CVD mortality[4] (table 1). These historical cohort studies[3–5 w7 w8] and evidence from animal experiments[1 w9] suggest that chronic diseases are biologically "programmed" in utero or in early infancy. Programming is the process where a stimulus or insult (for example, undernutrition, hormones, antigens, drugs or sensory stimuli) at a critical period of development induces long lasting changes in cells which in turn changes the structure or function of organs, tissues or body systems.[w7 w10] In the case of heart disease, it is hypothesised that fetal undernutrition during middle gestation in particular raises the risk of later disease by the programming of blood pressure, cholesterol metabolism, blood coagulation, and hormonal settings.[5] Consequently, it was suggested that the lifestyle model in the evolution of adult degenerative diseases needs to be replaced by a new model, the central feature of which is the concept *of biological programming in fetal and infant life*. This revolutionary model of the 20th century has received both an enthusiastic and sceptical response. Critical testing of this model is warranted owing to inevitable biases related to historical studies.

Social programming and adult diseases

During the past 10 years sociomedical research has pointed out the importance of social differences between countries and populations in explaining differences in health. This ideology has created *a social programming model* in parallel to the biological programming model.[6] Social programming means that the effect of the early social environment on health is mediated by the social environment and school achievement during growth, and by employment opportunities, living conditions, and lifestyle factors. The social programming model is supported by various studies showing an inde-

Correspondence to: Professor Marjo-Riitta Järvelin, Department of Epidemiology and Public Health, Imperial College School of Medicine, Norfolk Place, London W2 1PG, UK
email: m.jarvelin@ic.ac.uk

pendent effect of childhood social circumstances on adult health.[7 w11]

Evidence for an association between childhood factors and heart disease risk

Heart disease morbidity and mortality

The first studies reporting an association between birth weight and CHD came from Hertfordshire and Sheffield study populations.[4 8] Both in men and women—even though the relation was weaker in women[9]—CHD mortality decreased progressively with increasing birth weight. Since then there have been several, mainly retrospective cohort studies which have replicated these observations and also demonstrated the association between size at birth and non-fatal CHD.[w12 w13] To date, there have been over 400 papers published during the past 15 years dealing with prenatal and early life factors related to CVD mortality and disease risk.

The association between birth weight and disease outcomes is, with few exceptions,[10] consistent with data based upon the older generations born in the early 1920s or 1930s from

Table 1 Early fetal origin hypotheses developing studies

Author and title of study	*Year of publication*	*Study population*	*Main observations and interpretations*
Forsdahl. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? [2]	1977	20 northern counties in Norway; men and women aged 40–69 who lived their infancy, childhood and youth in 1896 to 1925.	In the counties where infant mortality (INFmo) was high, the same generation had both a high total mortality and ischaemic heart disease (IHD) mortality in middle age. Variations in IHD mortality rate between counties is linked to variations in poverty in childhood and adolescence because INFmo is a reliable index of standard of living. Forsdahl suggested that poverty followed by prosperity is a risk factor for IHD.
Barker *et al*. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales.[3]	1986	England and Wales; county boroughs (CBs, larger towns), London boroughs (LBs), urban areas (metropolitan boroughs and urban districts), rural areas within counties. IHD rates in 1968-78 (35–74 years); INFmo in 1921-25.	On division of the country into 212 local authority areas a strong geographical relation was found between IHD mortality rates at ages 35–74 years and INFmo in 1921-25. IHD mortality rates are highest in the least affluent areas. It was suggested that poor nutrition in early life increases susceptibility to the effects of an affluent diet in later life, and that predisposition to IHD is related to nutrition during prenatal period and early childhood.
Barker *et al*. Weight in infancy and death from ischaemic heart disease.[4]	1989	Six districts of Hertfordshire, England; 5654 men born in 1911-30.	One of the first articles about hypothesis of an effect of early life factors on IHD. Men with the lowest weights at birth and at 1 year had the highest death rates from IHD. The standardised mortality ratio (SMR) fell from 104 in men whose birth weight was 2.5 kg or less to 62 in those who weighed between 4.0–4.3 kg, but rose slightly in the highest birth weight category. The paper showed the relation for the first time. Though inaccuracies, eg, in birth weight measurements, exist this gives evidence of the importance of fetal life on subsequent diseases. The interpretation was that greater early growth will reduce deaths from IHD. Later in 1990s it was shown that those who where thin at birth but caught up during infancy were particularly prone to IHD risk.
Barker *et al*. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease.[13]	1989	England, Wales, and Scotland. (1) In 1970 one week sample, n=9921 in the analyses. (2) In 1946 one week stratified sample (MRC national survey), n=3259.	In children at 10 years and adults at 36 years systolic blood pressure was inversely related to birth weight (independent of gestational age). Within England and Wales 10 year olds living in areas with high cardiovascular disease (CVD) mortality were shorter and had higher resting pulse rates than those living in other areas. Their mothers were also shorter with higher diastolic blood pressure. This suggested there are persisting geographical differences in the childhood environment that predispose to differences in CVD mortality.
Barker *et al*. Fetal and placental size and risk of hypertension in adult life.[12]	1990	Preston, Lancashire, UK n(men and women)=449	In both sexes systolic and diastolic blood pressure were strongly related to placental weight and birth weight. The highest blood pressures occurred in the people who had been small babies with large placentas. Discordance between placental and fetal size may lead to circulatory adaptation in the fetus, altered arterial structure in the child, and hypertension in the adult. It was discussed that women's nutrition in childhood may be linked to blood pressure in the next generation.
Hales *et al*. Fetal and infant growth and impaired glucose tolerance at age 64.[14]	1991	468 men born in 1920-30, (in Hertfordshire, England) aged 64 had a standard 75 g oral glucose tolerance test.	Men who were found to have impaired glucose tolerance or diabetes had had a lower mean birth weight and a lower weight at 1 year. Reduced early growth was also related to a raised plasma concentration of 32-33 split proinsulin. These trends were independent of current body mass. The results may be a consequence of fetal undernutrition and programming of the endocrine pancreas. The researchers favoured environmental explanation for their findings instead of genetic determination, on the one hand because disturbance of insulin production was manifested by growth failure in early life long before the onset of adult glucose intolerance, and on the other hand because maternal nutrition was thought to have a strong influence on fetal and infant growth.
Barker *et al*. The relation of small head circumference and thinness at birth to death for cardiovascular disease in adult life.[8]	1993	Sheffield, England n(men)= 1586	SMR for cardiovascular disease fell from 119 in men who weighed 5.5 pounds (2495 g) or less at birth to 74 in men who weighed more than 8.5 pounds (3856 g). The fall was significant for premature cardiovascular deaths up to 65 years of age. SMR also fell with increasing head circumference and increasing ponderal index. They were not related to the duration of gestation. The findings showed that reduced fetal growth is followed by increased mortality from CVD. Based on this further evidence for the first time it was proposed that CVD originates through programming of the body's structure by the environment during fetal life.

Theoretical models on the evolution of chronic disease

- Lifestyle model in the 1960s-70s
- Biological programming in fetal and infant life model in 1980s-90s
- Social programming model in the 1990s
- Life course model in 2000, incorporating both biological and social environments, and their interactions

different countries. However, it is not known how these observations apply to younger generations assuming that younger generations must have had better nutritional status in early life. The historical cohorts on which these observations are mainly based are liable to bias owing to selective survival and availability of data records.

Early life factors and intermediate heart disease risk factors/conditions

The associations between markers of fetal growth and intermediate risk factors are less consistent than evidence for morbidity and mortality. These include birth measures in relation to plasma concentrations of cholesterol, apolipoprotein B,[w14] and fibrinogen,[11] blood pressure,[12 13] and liability to impaired glucose tolerance and diabetes.[14–16]

Blood pressure has been suggested as one link between the intrauterine environment and the risk of CVD. Baker and colleagues studied the correlation between birth weight and subsequent blood pressure in three adult populations in Hertfordshire, Preston, and Sheffield in the UK[w15] as well as in children of different ages.[4 17 w16] Other studies replicating Barker's have been made on various child populations.[18 19 w17–19] The key findings include an inverse independent relation between birth weight and subsequent systolic blood pressure, amplified by age,[12 18 19 w17–19] and an association of lower birth weight and thinness at birth with an increased risk of insulin resistance,[16 w20 w21] which is an important risk factor for heart diseases. Observations are not consistent; weak, non-linear or insignificant correlations between birth weight and blood pressure have been reported,[20 w22] particularly among younger populations.

A correlation between possible undernutrition and serum cholesterol has been noted in men and women in some studies,[w14 w21] but there are also studies which show no relation.[w23] The association between body length at birth and cholesterol might reflect abnormal intrauterine growth, in which retarded trunk and visceral growth is associated with alterations in lipid metabolism. Abdominal circumference at birth, which reflects visceral growth, has been related to serum cholesterol concentration in adults.[5]

Lower birth weight and weight at 1 year of age have been associated with subsequent development of type 2 diabetes mellitus in adult life. In the Hertfordshire study, the men with impaired glucose tolerance and diabetes had lower weight gain prenatally and during infancy than men without.[14] The plasma 32-33 split proinsulin concentration fell with increasing weight at 1 year. All the findings were independent of current body mass index (BMI).[14] In the Preston study, impaired glucose tolerance was also related to lower birth weight and smaller head circumference.[21] Gestational age had no influence on the results. A follow up study of 297 women aged 60–71 years suggests, in accordance with previous studies, that those who had lower birth weight had higher plasma concentrations of glucose and insulin.[w21] Obesity in adult life adds to the disadvantage of low birth weight; the women who were light at birth but are currently obese have the least favourable risk factor profile.[w21] A longitudinal study of diabetes and its complications conducted among the American Indian population in Arizona, however, showed the prevalence of non-insulin dependent diabetes mellitus to be greatest not only in those with the lowest birth weights, but also in those with the highest birth weights.[22] This study is supported by a study on Mexican American families.[23]

Patients with type 2 diabetes and hypertension often have other abnormalities, such as high plasma insulin concentrations, high serum triglyceride concentrations, low serum HDL (high density lipoprotein) concentrations, and high body mass indices and waist-to-hip ratios. This combination of abnormalities has been called syndrome X or "small baby syndrome",[w24] but may be better known as insulin

Table 2 Summary of the main associations between birth weight and other growth measures and heart disease

Exposure	*Type of association*	*Outcome*
• Birth weight	Inverse linear; in some studies inverse J shaped	CHD mortality and morbidity; in particular among men, weaker in women
	Inverse (linear), J shaped or U shaped	Fasting glucose, insulin, insulin resistance, impaired glucose tolerance, type 2 diabetes, metabolic syndrome
	Inverse linear, but not consistently	Blood pressure
• Birth length	Inverse	CHD particularly in women, LDL cholesterol
	Positive or negative (placental weight acts as effect modifier), effect marginal	Blood pressure
• Head circumference	Inverse	CVD mortality in men, impaired glucose tolerance
• Ponderal index	Inverse, inverse U shaped	CHD (CVD) mortality, impaired glucose tolerance, insulin resistance, type 2 diabetes
• Abdominal circumference	U shaped Inverse	CHD morbidity LDL cholesterol, plasma fibrinogen
• Catch up growth in particular if thin at birth	Positive	CHD mortality, blood pressure
• Weight at 1 year	Inverse	CHD mortality among men; type 2 diabetes mellitus, plasma fibrinogen, factor VII

CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low density lipoprotein.

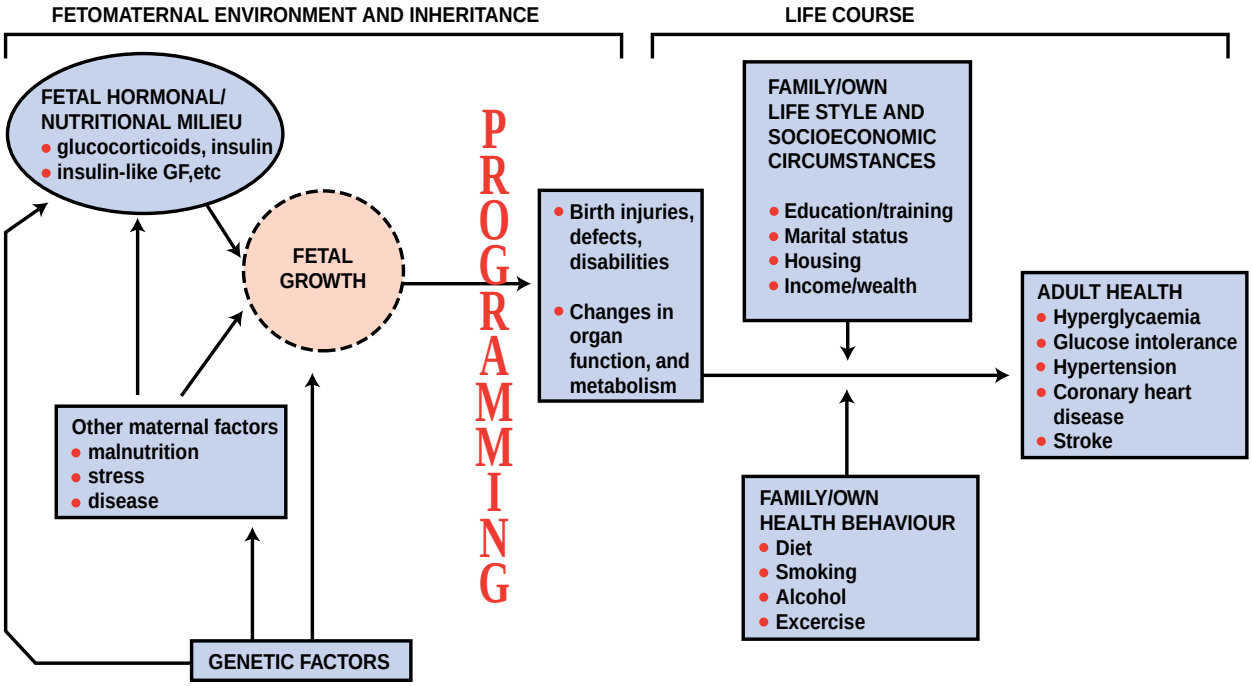

Figure 1. Intrauterine programming by prenatal determinants and life course factors in heart diseases (GF, growth factor).

resistance or metabolic syndrome. Metabolic syndrome is characterised by compensatory hyperinsulinaemia[w24] and is associated with increased mortality from CHD.[w25] The association of both type 2 diabetes and hypertension with reduced fetal growth has raised the possibility that these and other components of the syndrome may have a common origin in suboptimal development at a particular stage of intrauterine life.[14 21] In the Preston study,[21] the prevalence of metabolic syndrome in both men and women decreased progressively as their birth weights increased. The association between metabolic syndrome and low birth weight was independent of gestational age and possible confounding variables, including cigarette smoking, alcohol consumption, and social class currently or at birth.

Several reports, however, have been more equivocal about the relation of birth related factors to CVD and its risks, particularly studies in adolescents and young adults, and the authors have questioned the basis and rationale for these associations and the underlying mechanisms.[24 25 w22 w23 w26–30]

The main associations between birth weight and other growth measures and heart disease are summarised in table 2.

Suggested biological/environmental mechanisms underlying the evolution of heart disease risk

Nutritional factors during pregnancy

There are numerous factors and mechanisms which affect both fetal growth,[w31–33] and adult CVD outcomes,[w4 w34] which makes the analyses of the associations and their interpretation extremely complex (fig 1). Among them, in the light of early programming, are: (1) restricted maternal nutrition itself; and (2) maternal or pregnancy induced physiological, metabolic or hormone related conditions which may impair fetal nutrition or otherwise affect growth.

A primary fetal origin hypothesis from the early 1990s stated that adult disease such as CVD is programmed by poor maternal nutrition during pregnancy, leading to fetal growth retardation and a permanent effect on the body's structure, physiology, and metabolism.[5 w8] Based on rodent experiments and human studies it nowadays also covers other mechanisms.

Maternal nutrition

In rodents, dietary changes during gestation induce not only growth retardation but also permanent changes in metabolism[w35] which can be transmitted through several generations.[w36] Though well supported by animal studies,[26] the evidence for similar processes in humans is patchy and complex.[w23 w37] Among indicators of *maternal nutrition* in humans, low prepregnancy weight, height, and BMI are associated with lower birth weight.[w31 w38] which in itself is associated with heart disease risk.[w30] However, in men born in the 1920s and '30s, high maternal BMI together with low ponderal index was associated with their offspring's highest standardised mortality ratio for CHD. One explanation for this contradictory finding may be that, as suggested by animal studies,[w39] the mothers themselves may have been smaller at birth and, as a result, accumulated more fat. Maternal height, reflecting long term nutrition, may be an even better indicator of disturbed long term nutrition than weight in relatively well nourished populations. For example, Forsen and colleagues reported that offspring of short, heavy mothers have higher rates of CHD than those of taller women.[27] Small studies in humans, directly examining nutritional

intake, suggested that women who have a high intake of carbohydrates in early pregnancy and a low intake of dairy protein in late pregnancy tend to have infants who are thin at birth.[w40 w41]

Fetal nutrition

Other indicators of possible disturbed fetal nutrition not directly related to maternal nutrition (for example, pregnancy induced hypertension, pre-eclampsia)[w33 w42] have rarely been studied in relation to adult disease risk in humans. Evidence that hypertension during pregnancy in humans affects adult CVD risk is inconsistent,[w43–47] although animal data are supportive.[26] One difficulty, to date, has been separating pregnancy induced hypertension from essential hypertension because few studies record blood pressure measurements during pregnancy, at least not during early pregnancy, or present data on pre-pregnancy hypertension. High maternal blood pressure has, however, been associated with low birth weight of offspring,[w31 w42] which in itself is associated with high blood pressure in adult life, but it is unclear to what extent this reflects maternofetal undernutrition during pregnancy or genetic factors.

Growth patterns

The growth of the fetus is a complex process which is still insufficiently understood. A key concept in the "fetal origin hypothesis" is fetal undernutrition, and its relation with adult diseases. The human evidence, as described above, is based on studies where birth measures have been related to different adult heart disease outcomes in different populations. This is strongly supported by the animal experiments, and stresses the importance of the fetomaternal environment. Barker[5] has differentiated undernutrition during pregnancy by trimesters, and he suggests that the down regulation of growth during the first trimester leads to a proportionately small child who has increased risk of raised blood pressure and may possibly die of haemorrhagic stroke. Undernutrition during the second trimester leads to a disturbed fetoplacental relation, and insulin resistance or deficiency; consequently birth weight is reduced and the baby is thin, and has an increased risk of raised blood pressure, non-insulin dependent diabetes, and death from CHD. Undernourished babies during the last trimester in turn may have growth hormone resistance or deficiency, and consequently they are short but birth weight is within the normal range. These adults may have raised blood pressure, raised LDL (low density lipoprotein) cholesterol concentration, and increased risk of CHD and thrombotic stroke.

Later growth patterns, particularly catch-up growth,[w48] have been reported to relate to heart disease risk. For example, children who are thin at birth but become obese in later life or have high catch-up growth in infancy[w48] appear to be at higher risk. However, it is not known why catch-up growth is detrimental, but one possibility is that fetal growth restriction leads to reduced cell numbers, and subsequent catch-up growth is achieved by overgrowth of a limited cell mass.

Hormonal evidence related to fetal growth and later heart disease risk

Fetal growth is also affected by several hormones, growth factors, and genetic factors (fig 1). A recently proposed underlying mechanism, based mainly on animal studies, suggests that increased blood pressure in adult life is caused by increased exposure to corticosteroids during fetal life. This might result from reduced placental 11β-hydroxysteroid dehydrogenase (11β-OHSD) activity or increased corticosteroid release secondary to disturbed nutrition.[w9 w49–51] Increased exposure in turn may lead to permanent tissue damage, and programming of adult disease.[1 w52] There are data supporting similar mechanisms in humans—for example, studies have found that birth weight is correlated with placental 11 β-OHSD activity,[w50] and cortisol concentrations in adult life correlate with birth weight[w53] and adult blood pressure. [w54]

Insulin and insulin-like growth factors are likely to have a substantial influence on fetal growth. Insulin stimulates growth through several mechanisms: by increasing uptake and utilisation of nutrients; by direct mitogenic actions; and by increasing the release of other hormones and growth factors.[w55] However, the final role of these factors in the evolution of adult disease risk is largely unknown, although it can be speculated that via the effects on fetal growth the disturbances in the regulation of these factors lead to increased risk of adult chronic diseases.

Genetic evidence

The role of genetic factors is poorly understood even though a familial aggregation of CHD and hypertension is clear. A complementary explanation for the observed associations between fetal growth and adult phenotypes could be provided by genomic variation which alters the function and/or regulation of genes influencing both phenotypes. Recently the first small genetic studies have been published which stress the importance of possible gene–environmental interaction.[w56 w57] Disturbances or variations in genes which regulate either insulin or glucocorticoid action or metabolism may reduce birth weight[w58] and thus possibly increase the risk of insulin resistance in adulthood. In Mexican American families, Stern and colleagues[23] dissected the relation between birth weight and adult insulin resistance into two components: (1) a sporadic, environmental association between *low* birth weight and adult insulin resistance; and (2) a genetic association between *high* birth weight and adult insulin resistance. This is in agreement with the studies suggesting non-linear association between birth weight and impaired glucose tolerance.[22] There is a debate over whether these effects/associations are truly genetic or whether they are caused by the environment—that is, phenotypic. A future challenge is to determine the relative contributions of genes *and* environmental factors to the fetal and adult phenotypes.

Other possible models in the evolution of heart diseases and limitations of the studies

In Europe there are more than 20 large longitudinal studies in which the main focus has been or is to study prenatal or early life factors in relation to adult disease risk. Many of them are historical cohort studies, or data collection has started after birth retrospectively at various points of life. The most important historical cohort studies, from the point of view of the fetal origin hypothesis, are the Hertfordshire,[4 14] Preston,[12 21] and Sheffield[8] studies, as well as the Helsinki[27] and Uppsala[28] cohort studies.

The studies to date have had a number of important limitations that complicate interpretation. They have not been able to address the complexities of interactions between environmental and genetic factors in explaining the associations between maternal, fetal, and later life factors in the evolution of adult CVD risk. This is because they have been variously too small; retrospective and therefore subject to survival and selection biases; or prospective, but in children and adolescence and therefore have not been able to examine adult phenotypes. It has also been questioned whether a study with a completely different *a priori* hypothesis should be used at all for other purposes. However, the use of old data for studying early life factors is justified considering the latency between early exposure and adult outcomes. For example, Barker's studies based on early last century cohorts have been extremely valuable hypotheses developing studies, which should now be replicated in younger cohorts reaching adult age.

An important consideration and future challenge to explore from the point of view of the biological programming model is the extent to which associations between the fetal environment and adult health may be confounded by or interact with measures taken later in life.[20 w1 w29] For example, adult weight and height have been reported to be stronger predictors of blood pressure than birth measures,[w47] but observations from different studies are inconsistent. A further question concerns the relative influence of childhood and adult measures of socioeconomic status, and health behaviour. Several studies report a powerful association between markers of social status or wealth in childhood or adulthood, and the risk of adult chronic diseases and mortality.[18 w59] The risk of premature death from CVD appears to be particularly sensitive to socioeconomic influences acting in early life,[w60] but the results from different studies vary.[18 28 w61–63] A recent review of the influence of early-life socioeconomic environment on the risk of adult disease concluded that both early-life and later circumstances are important.[7]

Figure 1 shows a simplified framework for the different associations between the various factors in the prenatal period and their effect on adult health. It is evident that no single model is able to explain heart disease risk. This is mainly because there is a vast amount of evidence that: (1) socioeconomic and living circumstances have an independent effect on adult health; (2) health behaviour affects disease risk[w3]; (3) genetic factors may have an important role in the programming process and possible gene–environment influences; and (4) the impact of chain effects and clustering of disadvantageous factors on disease risk. The clustering effect differs from programming in that it does not expect necessarily to take into account any critical period. It has been questioned if "critical periods" should be taken into account not only during fetal life but later over the life course.

It is reasonable to assume that early programming is a result of an interaction between fetomaternal environment and individual genotype. The "inborn" predisposition to later disease is in turn modified by factors along the life course. The variate of social and biological programming, the multidisciplinary *life course model* provides an alternative way of exploring the association between early life environment, both social and biological, and adult disease risk. This approach points out that there is a clear need to establish studies by assembling cohorts where measures of pre- and postnatal determinants have been previously recorded in different populations living under different conditions in order to explore pathways and mechanisms in the evolution of heart diseases.

Early life factors and adult heart disease risk: summary

- A number of factors throughout the life course affect adult disease risk, starting in utero
- A number of studies show that fetal growth is related to adult heart disease mortality, morbidity, and risk factors
- Several factors affect fetal growth and subsequently may contribute to adult disease risk
- There are only a few studies in humans with extensive life course data to explore the association between prenatal and infancy exposures and adult disease or risk outcomes
- We do not know the mechanisms by which the observed associations are evoked or mediated in humans, or whether the same relations apply to older and younger cohorts

Conclusions

Inconsistencies between and within studies exist, and relations of varying degrees of strength have been described. With the available evidence of the relation between early life factors, intermediate CVD risk factors, disease

incidence, and mortality, it remains unclear whether the associations are primarily a manifestation of intrauterine programming of CVD risk due to poor maternal nutrition itself or other influences in utero unrelated to maternal undernutrition, such as defective placentation, and hypertension or other aspects of the genetic, metabolic or circulatory milieu. Studies need to address the extent to which fetal environment and early life experiences act on adult health through independent or intermediary mechanisms, and the extent to which the associations between birth variables and disease risk are independent of later social environment and living habits.

1. Nyirenda M, Seckl JR. Intrauterine events and the programming of adulthood disease: the role of fetal glucocorticoid exposure [review]. *Int J Molecular Med* 1998;**2**:607–14.
- *A review of the role of fetal glucocorticoid exposure in the programming of adulthood disease. During fetal development glucocorticoids are involved in control of growth and maturation of fetal organs in preparation for extrauterine life. The experiments have shown that fetal exposure to exogenous glucocorticoids reduces birth weight and causes permanent hyperglycaemia and hypertension in the adult rat offspring. This may provide a new insight into the pathophysiology and control of cardiovascular and metabolic diseases.*

2. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Social Med* 1977;**31**:91–5.

3. Barker DJP, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;i:1077–81.

4. Barker DJP, Winter PD, Osmond C, *et al.* Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;ii:577–80.

5. Barker DJP. Fetal origins of coronary heart disease. *BMJ* 1995:**311**:171–4.
- *This review article, based on the main hypotheses developing papers, provides a framework of ideas of possible pathways and mechanisms leading from fetal undernutrition to later abnormalities. The consequences of fetal undernutrition are presented separately depending on the trimester of pregnancy.*

6. Vågerö D, Illsley R. Explaining health inequalities: beyond Black and Barker. *European Sociology Review* 1995:**11**:1–23.

7. Davey Smith G. Socioeconomic differentials. In: Kuh D, Ben-Shlomo Y, eds. *A life course approach to chronic disease epidemiology.* Oxford: Oxford University Press, 1997:242–73.
- *Social class at different stages of life is associated with morbidity and mortality risk in adulthood to a variable degree, depending upon the outcome of interest. For CVD mortality, poor early life social conditions appear to make an important contribution to disease risk in adulthood. An index of life course social position, which combines data regarding social position from different stages of life, is more strongly related to CVD mortality than is any indicator relating to just one point in time. This is an excellent overview and secondary data source analysis of the influence of social position on morbidity and mortality.*

8. Barker DJP, Osmond C, Simmonds SJ, *et al.* The relation of small head circumference and thiness at birth to death from cardiovascular disease. *BMJ* 1993;**306**:422–6.

9. Osmond C, Barker DJP, Winter PD. Early growth and death from cardiovascular disease in women. *BMJ* 1993;**307**:1519–24.
- *This study showed that death rates from CVD among women fell progressively between the low and high birth weight groups women (n = 5585, born in 1923–30); earlier the association had been obvious only among men. The results suggested that the association between CVD and birth weight is similar in both sexes. However, in many studies the associations among women are weak or non-significant.*

10. Vågerö D, Leon D. Ischemic heart disease and low birth weight: a test of the fetal origins hypothesis from the Swedish Twin Registry. *Lancet* 1994;**343**:260–263.
- *This study tested the fetal origins hypothesis, examining ischaemic heart disease (IHD) mortality among Swedish twins (8174 female and 6612 male twins, born between 1886 and 1925). IHD was not found to be any higher among twins compared to the general population. However, the shorter twin in a twin pair was more likely to die of heart disease than the taller. The study suggested that postnatal influences may well be as important as prenatal influences in producing any effect on IHD mortality, and that the type of growth retardation in utero experienced by twins may not constitute a risk for IHD in adulthood. The missing association may also be caused by the fact that in this design socioeconomic confounding is well controlled for, or by the fact that growth retardation experienced by twins is different from that experienced by low birth weight singletons.*

11. Barker DJP, Meade TW, Fall CHD, *et al.* Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *BMJ* 1992;**304**:148–52.
- *This study involved 591 men, born in 1920–30, aged around 64 years, and 148 men born in 1935–43, aged around 50 years. Plasma fibrinogen and factor VII concentrations were inversely related to weight at 1 year and fibrinogen concentration fell progressively as the ratio of placental weight to birth weight decreased, but not for both study populations. Neither plasma fibrinogen nor factor VII concentration was related to birth weight. The results are thought to be caused by impaired liver development during a critical early period, but further studies are needed.*

12. Barker DJP, Bull AR, Osmond C, *et al.* Fetal and placental size and risk of hypertension in adult life. *BMJ* 1990; **301**:259–62.

13. Barker DJP, Osmond C, Golding J, *et al.* Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;**298**:564–7.

14. Hales CN, Barker DJP, Clark PMS, *et al.* Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;**303**:1019–22.

15. Phipps K, Barker DJP, Hales CN, *et al.* Fetal growth and impaired glucose tolerance in men and women. *Diabetologia* 1993; **36**:225–8.
- *Standard oral glucose tolerance tests were carried out on 140 men and 126 women born in 1935–43, aged 50. Subjects with impaired glucose tolerance or non-insulin dependent diabetes mellitus had lower birth weight (independent of gestational age), a smaller head circumference, and were thinner at birth (adjusted for body mass index). They also had a higher ratio of placental weight to birth weight. The results may be caused by reduced growth of the endocrine pancreas, which in turn may be a consequence of maternal undernutrition during pregnancy or other failure, such as placental defect, in fetal nutrition.*

16. Lithell HO, McKeigue PM, Berglund L, *et al.* Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 1996;**312**:406–10.
- *This study involved 1333 men born in 1920–24 and resident in Uppsala, Sweden, in 1970. There was a weak inverse correlation between ponderal index at birth and 60 minute insulin concentrations in the intravenous glucose tolerance test at age 50 years. This association was stronger in the highest third of the distribution of body mass index than in the other two thirds. Prevalence of diabetes at age 60 years was higher (8%) in men whose birth weight was < 3250 g compared with men with birth weight 3250 g or more (5%). There was a stronger association between diabetes and ponderal index. Correlations were adjusted for body mass index. These results gave fairly strong support to the fetal origin hypothesis.*

17. Law CM, de Swiet M, Osmond C, *et al.* Initiation of hypertension in utero and its amplification throughout life. *BMJ* 1993;**306**:24–7.
- *A study on four different populations aged 0–10 years, 36 years, 46–54 years, and 59–71 years. In all four populations the inverse relation between birth weight and systolic blood pressure was apparent and the relation became larger with increasing age. According to this, the results from older generations would be applicable to younger generations, but this needs replication.*

18. Whincup PH, Cook DG, Papacosta O. Do maternal and intrauterine factors influence blood pressure in childhood? *Arch Dis Child* 1992;**67**:1423–9.

19. Williams S, George I, Silva P. Intrauterine growth retardation and blood pressure at age seven and eighteen. *J Clin Epidemiol* 1992;**45**:1257–63.
- *This study involved children aged 7 and 18 years, born in 1972–73. At age 7, after adjusting for sex and weight, the differences between normal and intrauterine growth retarded (IUGR) children were 0.9 mm Hg (95% CI –0.1 to 2.2) for systolic and 0 mm Hg (95% CI –1.7 to 2.0) for diastolic blood pressure, respectively. At age 18 the differences were less pronounced. These results give only weak support to the hypothesis of evolution of hypertension already in utero, alhough the number of IUGR children was comparatively low (at age 7, 70 and at age 18, 68).*

20. Seidman DS, Laor A, Gale R, *et al.* Birth weight, current body weight, and blood pressure in late adolescence. *BMJ* 1991;**302**:1235–7.
- *This study involved 32,580 17 year old subjects (19,734 men and 12,846 women) born in Jerusalem during 1964–71. Diastolic and systolic blood pressures were associated with birth weight, but the correlation coefficients were low. Body mass index was significantly linked with high systolic blood pressure in both men and women. The results can be interpreted that a high body weight rather*

than a low birth weight was linked with higher systolic and diastolic pressure in both men and women, which stresses the importance of life course in the evolution of disease risk.

21. Barker DJP, Hales CN, Fall CHD, *et al.* Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;**36**:62–7.

22. McCance DR, Pettitt D, Hanson RL, *et al.* Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *BMJ* 1994;**308**:942–5.
- *This study involved 1179 American Indians born in 1940–72 whose glucose tolerance was evaluated at ages 20–39 years. The prevalence of non-insulin dependent diabetes mellitus was greatest in those with the lowest and highest birth weights (a U shaped relation). When age, sex, body mass index, maternal diabetes during pregnancy, and birth year were controlled for, subjects with birth weight < 2500 g had a higher rate than those with weights of 2500–4499 g. The U shaped relation was seen primarily in subjects with a parental history of diabetes. A genetic background seems to have a clear effect on non-insulin dependent diabetes mellitus, but it does not seem to explain the U shaped relation.*

23. Stern MP, Bartley M, Duggirala R, *et al.* Birth weight and the metabolic syndrome: thrifty phenotype or thrifty genotype. *Diabetes/Metabolism Research and Reviews* 2000;**16**:88–93.

24. Whincup PH, Cook DG, Adshead F, *et al.* Childhood size is more strongly related than size at birth to glucose and insulin levels in 10–11-year-old children. *Diabetologia* 1997;**40**:319–26.
- *This study involved 10–11 year old children. One group (n = 591) was studied fasting, the other (n = 547) was studied 30 minutes after a standard oral glucose load. Neither fasting nor post-load glucose concentrations showed any consistent relation with birth weight or ponderal index at birth. After adjustment for childhood height and ponderal index, both fasting and post-load insulin concentrations fell with increasing birth weight. However, the proportional change in insulin for a 1 SD increase in childhood ponderal index was much greater than that for birth weight. Obesity in children is, evidently, a stronger determinant of insulin concentrations and insulin resistance than size at birth.*

25. Paneth N, Ahmed F, Stein AD. Early nutritional origins of hypertension: a hypothesis still lacking support. *J Hypertens* 1996;**14**(suppl 5):121–9.
- *This review focuses on the hypothesis of reduced birth weight and subsequent elevated blood pressure in light of four causal criteria: specificity, consistency, strength, and biological coherence. Aspects of the methodology used in studies of the hypothesis are also examined. According to this study, the evidence thus far provided does not support the hypothesis. Further studies have provided more evidence, but it is still patchy.*

26. Langley-Evans SC. Hypertension induced by foetal exposure to a maternal low-protein diet, in the rat, is prevented by pharmacological blockage of maternal glucocorticoid synthesis. *J Hypertens* 1997;**15**:537–44.
- *In this experiment involving rats(14 dams, 136 offspring), the dams were fed a low protein or a control diet after conception. All the pups had a standard diet. At the age of 7 weeks the blood pressures of all the offspring were determined. Blood pressures of rats exposed to maternal low protein diets in utero were raised significantly relative to control rats. These results are consistent with Barker's hypothesis on programming.*

27. Forsén T, Eriksson JG, Tuomilehto J, *et al.* Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. *BMJ* 1997;**315**:837–40.

28. Leon DA, Koupilova I, Lithell HO, *et al.* Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* 1996;**312**:401–6.
- *This study involved 1333 men born during 1920–24 and resident in Uppsala, Sweden, in 1970. There was a small decrease in systolic blood pressure as birth weight increased. Much stronger effects were observed among men who were born at term and were in the top third of body mass index at age 50. Men who were light at birth (< 3250 g) but were of above median adult height had particularly high blood pressure. It is suggested that it is a failure to express one's full growth potential in utero, rather than small size at birth per se, that is related to raised adult blood pressure. This is consistent with already known aetiological factors and still supports the fetal origin hypothesis.*

website *extra*

Additional references appear on the Heart website

www.heartjnl.com