Chapter 8: Fetal origins of adult disease

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> *The rewards of good health care in childhood, especially health promotion and preventative interventions, are unique because the benefits may last a lifetime and maybe passed onto future generations.*
> House of Commons Health Select Committee, 1997[1]

Not only do unfavourable conditions during life in the womb and in childhood affect health in childhood, they also predispose to increased risk of disease in adulthood. The research that points to this link began as a means of explaining the geographical inequalities in the rates of CHD in the UK. These differences cannot be explained by known risk factors such as obesity and smoking. In areas where there are high death rates from cardiovascular disease, there were high infant death rates in the past. This suggests that influences that have an adverse effect on infant health have persisting adverse effects in adult life.

8.1 The programming theory of health

Adverse influences during fetal and infant life, importantly malnutrition, change the structures, hormonal and metabolic processes of the body for life. This phenomenon is known as 'programming'.[2] In animals it is surprisingly easy to produce lifelong changes in the physiology and metabolism of the offspring by minor modifications to the diet of the mother before and during pregnancy.[3-5] The steep rise in CHD in the UK during this century has been associated with rising prosperity, but the poorest people in the least affluent places have the highest rates of the disease. These differences in CHD are a major contributor to the socioeconomic inequalities of life expectancy in the UK and are discussed in more detail in **Chapter 3**. The geographical distribution of neonatal mortality (deaths before one month of age) in England and Wales in the early years of the twentieth century closely resembled the distribution of death rates from cardiovascular disease today.[6] At that time, most neonatal deaths were attributed to low birthweight. An interpretation of this geographical association is that harmful influences that act in fetal life, and slow fetal growth, permanently programme the body in ways that predispose to cardiovascular disease in later life.

The large geographical and social class differences in fetal and infant growth which existed in the UK when today's generation of middle-aged and elderly people were

born, were reflected in the wide range of infant mortality. In 1921 to 1925, infant mortality ranged from 44 deaths per 1,000 births in rural west Sussex to 114 per 1,000 births in Burnley.[7] The highest rates were generally in northern counties where large manufacturing towns had grown up around the coal seams, and in impoverished rural areas such as north Wales. They were lowest in counties in the south and east, which have the best agricultural land and are historically the wealthiest. A series of Government inquiries on child and maternal mortality from 1910 onwards, prompted by revelations of the poor physique of military recruits, showed how these differences in infant mortality were related to differences in the nutritional state, physique and health of young women, and in infant feeding practices, housing and overcrowding.[8]

In fetal life, the tissues and organs of the body go through what are called 'critical' periods of development, which may coincide with periods of rapid cell division. 'Programming' describes the process whereby a stimulus or insult at a critical period of development has lasting effects. Rickets has, for a long while, served as a demonstration that malnutrition at a critical stage of early life leads to persisting changes in the body's structure. Only recently have we realised that some of the persisting effects of early undernutrition become translated into pathology, and thereby determine chronic diseases, including cardiovascular disease, type II diabetes, osteoporosis, obesity, asthma and certain forms of cancer in later life.[2,4] That this has gone unremarked for so long is perhaps surprising, given the numerous animal experiments showing that undernutrition in utero leads to persisting changes in blood pressure, cholesterol metabolism, insulin response to glucose, and a range of other metabolic, endocrine and immune functions known to be important in human disease.[3-5]

8.2 The placenta

A baby's birthweight depends not only on the mother's nutrition but also on the placenta's ability to transport nutrients to it from its mother. The placenta seems to act as a nutrient sensor regulating the transfer of nutrients to the fetus according to the mother's ability to deliver them, and the demands of the fetus for them.[9] The weight of the placenta, and the size and shape of its surface, reflect its ability to transfer nutrients. The shape and size of the placental surface at birth has become a new marker for chronic disease in later life.[10] The predictions of later disease depend on combinations of the placenta size and shape of the surface and the mother's body size. Particular combinations have been shown to predict CHD,[11] hypertension,[12] chronic heart failure,[13] and certain forms of cancer.[14] Variations in placental size and shape reflect variations in the normal processes of placental development, including implantation, growth and compensatory expansion.[10] These variations are accompanied by variations in nutrient delivery to the fetus.

8.3 Undernutrition in utero

The human fetus adapts to undernutrition by metabolic changes, redistribution of blood flow and changes in the production of fetal and placental hormones that control growth.[15] Its immediate response to undernutrition is catabolism; it consumes its own substrates to provide energy.[16] More prolonged undernutrition leads to a slowing in growth. This enhances the fetus' ability to survive, by reducing the use of substrates and lowering the metabolic rate. Slowing of growth in late gestation leads to disproportion in organ size, since organs and tissues that are growing rapidly at the time are affected the most. Undernutrition in late gestation may, for example, lead to reduced growth of the kidney, which develops rapidly at that time. Reduced replication of kidney cells in late gestation will permanently reduce cell numbers, because after birth there seems to be no capacity for renal cell division to 'catch-up'.[17]

Maternal nutrition and its long-term effects on health and wellbeing are explored in detail in the 2009 BMA report *Early life Nutrition and lifelong health*.[18]

Animal studies show that a variety of different patterns of fetal growth result in similar birth size. A fetus that grows slowly throughout gestation may have the same size at birth as a fetus whose growth was arrested for a period and then 'caught up'. Different patterns of fetal growth will have different effects on the relative size of different organs at birth, even though overall body size may be the same. Animal studies show that blood pressure and metabolism can be permanently changed by levels of undernutrition that do not influence growth.[5] Preliminary observations point to similar effects in humans. Such findings emphasise the severe limitation of birthweight as a summary of fetal nutritional experience.

While slowing its rate of growth, the fetus may protect tissues that are important for immediate survival, the brain especially. One way in which the brain can be protected is by redistribution of blood flow to favour it.[19] This adaptation is known to occur in many mammals but in humans it has exaggerated costs for tissues other than the brain, notably the liver and other abdominal viscera, because of the large size of the human brain. Metabolic fetal adaptations may result in the baby sacrificing muscle growth and being born thin.[20]

It is becoming increasingly clear that nutrition has profound effects on fetal hormones, and on the hormonal and metabolic interactions between the fetus, placenta and mother on whose coordination fetal growth depends.[16] Fetal insulin and the insulin-like growth factors (IGF) are thought to have a central role in the regulation of growth and to respond rapidly to changes in fetal nutrition. If a mother decreases her food intake, fetal insulin, IGF and glucose concentrations fall, possibly through the effect of decreased maternal IGF. This leads to reduced transfer of amino acids and glucose from mother to fetus, and ultimately to reduced rates of fetal growth.[21] In late gestation and after birth, the

fetus' growth hormone and IGF axis take over from insulin, and play a central role in driving linear growth. Whereas undernutrition leads to a fall in the concentrations of hormones that control fetal growth, it leads to a rise in cortisol, whose main effects are on cell differentiation.[15] One current line of research aims to determine whether the fetus' hormonal adaptations to undernutrition tend, like many other fetal adaptations, to persist after birth and exert lifelong effects on homeostasis and hence on the occurrence of disease. Undernutrition during pregnancy can affect both placental size and body size of the baby at birth, and recent research has shown that both of them can predict health in later life (see also **Chapter 4**).

8.4 Cardiovascular disease

Cardiovascular disease and body size at birth

The early epidemiological studies on the intrauterine origins of CHD and stroke were based on the simple strategy of examining men and women in middle and late life whose body measurements were recorded at birth. The birth records on which these studies were based came to light as a result of a systematic search of the archives and records offices of the UK – a search that led to the discovery of three important groups of records in Hertfordshire, Preston and Sheffield. The Hertfordshire records were maintained by health visitors and include measurements of growth in infancy as well as birthweight. In Preston and Sheffield, detailed obstetric records documented body proportions at birth.

Sixteen thousand men and women born in Hertfordshire during 1911 and 1930 were traced from birth to the present day. Death rates from CHD fall two-fold between those at the lower and upper ends of the birthweight distribution (see **Table 8.1**).

Table 8.1: Death rates from CHD among 15,726 men and women according to birthweight

Birthweight pounds*	Standardised mortality ratio	Number of deaths
≤ 5.5 (2.50)	100	57
- 6.5 (2.95)	81	137
- 7.5 (3.41)	80	298
- 8.5 (3.86)	74	289
- 9.5 (4.31)	55	103
> 9.5 (4.31)	65	57
Total	**74**	**941**

*Figures in parentheses are kilograms.

Source: Osmond C, Barker DJP, Winter PD et al (1993) Early growth and death from cardiovascular disease in women. *British Medical Journal* **307**: 1519-24. Reproduced with the permission of the British Medical Journal.

A study in Sheffield showed that it was people who were small at birth because they failed to grow, rather than because they were born early, who were at increased risk of disease.[22] The association between low birthweight and CHD has been confirmed in studies of men in Uppsala, Sweden,[23] and Caerphilly, Wales,[24] and among 80,000 women in the USA who took part in the American Nurses Study.[25] An association between low birthweight and prevalent CHD has also recently been shown in a study in South India.[26]

Cardiovascular disease and body proportions at birth

The Hertfordshire records, and the American Nurses and Caerphilly studies, did not include measurements of body size at birth other than weight. The weight of a newborn baby without a measure of its length is as crude a summary of its physique as is the weight of a child or adult without a measure of height. The addition of birth length allows a thin baby to be distinguished from a stunted baby with the same birthweight. With the addition of head circumference, the baby whose body is small in relation to its head, which may be a result of 'brain-sparing' redistribution of blood flow, can also be distinguished. Thinness, stunting and a low birthweight in relation to head size are the result of differing fetal responses to undernutrition, and other influences, and they have different consequences, both immediately and in the long term.[22]

In Sheffield, death rates for CHD were higher in men who were stunted at birth.[27] The mortality ratio for CHD in men who were 47cm or less in length was 138 compared with 98 in the remainder.[27] CHD in South India was also associated with stunting.[26] Thinness at birth, as measured by a low ponderal index (birthweight/length^3), is also associated with CHD.[28] **Table 8.2** shows findings among men born in Helsinki, Finland during 1924 and 1933. Death rates for CHD were related to low birthweight.[28] There was, however, a much stronger association with thinness at birth. Men who had a low ponderal index had death rates that were twice those of men who had a high ponderal index (see **Table 8.3**).

Table 8.2: Hazard ratios for CHD in 3641 Finnish men born during 1924-1933

Birthweight kg*	Number of men	Hazard ratios	Number of deaths
≤2.5 (5.5)	145	1.13	11
- 3.0 (6.6)	557	1.23	44
- 3.5 (7.7)	1328	1.46	133
- 4.0 (8.8)	1165	1.11	88
> 4.0 (8.8)	446	1.00	30
p value for trend adjusted for gestation = 0.05			

*Figures in parentheses are pounds.

Source: Forsen T, Eriksson JG, Tuomilehto J et al (1997) Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow-up study. *British Medical Journal* **315**: 837-40. Reproduced with the permission of the British Medical Journal.

Table 8.3: Hazard ratios by thinness at birth (ponderal index) for CHD in 3641 Finnish men born during 1924-1933

Ponderal index at birth (kg/m^3)	Number of men	Hazard ratios	Number of deaths
≤25	724	2.07	82
- 27	1099	1.75	106
- 29	1081	1.33	80
>29	722	1.00	41
p value for trend adjusted for gestation <0.0001			

Source: Forsen T, Eriksson JG, Tuomilehto J et al (1997) Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow-up study. *British Medical Journal* **315**: 837-40. Reproduced with the permission of the British Medical Journal.

Cardiovascular disease and infant growth

Information routinely recorded in Hertfordshire included the infant's weight at the age of one year. In men, failure of weight gain during the first year of life predicted CHD and stroke independently of birthweight.[29] **Table 8.4** shows that among men who weighed 8.0kg or less at one year of age, rates of CHD were twice those among men who weighed 12.2kg or more. The highest rates of the disease among men and women were in those who had both low birthweight and low weight at one year of age.[30]

Confounding effects of childhood circumstances

These findings suggest that influences linked to fetal and infant growth have an important effect on the risk of CHD and stroke. People whose growth was impaired in utero and during infancy are likely to continue to be exposed to an adverse environment in childhood and adult life. Some have argued that it is this later environment that produces the effects attributed to programming.[31] There is strong evidence against this. The associations between birthweight and CHD are little changed by allowing for lifestyle in later life.[25] Paths of fetal growth, however, determine vulnerability to the effects of an adverse lifestyle. Low income, for example, is only related to CHD among men who were thin at birth.[32]

Table 8.4: Death rates from CHD in 10,141 men according to weight at one year

Weight (pounds)	Weight (pounds) Cause of death														
	CHD			All cardiovascular disease			All other causes			Lung cancer			All causes		
	Standardised mortality ratio	95% confidence interval	No. of deaths	Standardised mortality ratio	95% confidence interval	No. of deaths	Standardised mortality ratio	95% confidence interval	No. of deaths	Standardised mortality ratio	95% confidence interval	No. of deaths	Standardised mortality ratio	95% confidence interval	No. of deaths
At birth:															
≤ 5.5 (n = 458)	102	76 to 134	51	96	74 to 122	65	90	70 to 115	67	116	70 to 181	19	93	78 to 110	132
6-6.5 (n = 1317)	83	68 to 99	118	80	68 to 94	155	76	65 to 89	162	64	43 to 92	30	78	70 to 87	317
7-7.5 (n = 2991)	82	72 to 92	266	80	72 to 89	353	79	72 to 88	383	75	59 to 93	80	80	74 to 86	736
8-8.5 (n = 3166)	75	67 to 85	266	79	71 to 87	377	77	68 to 85	401	79	64 to 97	92	78	72 to 83	778
9-9.5 (n = 1505)	56	45 to 68	97	61	51 to 72	144	74	64 to 85	190	57	40 to 81	33	68	61 to 75	334
≥ 10 (n = 704)	66	50 to 86	55	69	54 to 86	78	79	64 to 96	97	94	61 to 138	26	74	63 to 86	175
At 1 year:															
≤ 18 (n = 559)	105	82 to 133	68	101	81 to 124	89	77	61 to 97	74	98	61 to 149	21	89	76 to 103	163
19-20 (n = 1702)	83	71 to 97	158	84	73 to 96	217	92	82 to 104	261	89	67 to 115	56	88	81 to 97	478
21-22 (n = 3288)	85	76 to 95	305	86	78 to 95	420	78	71 to 86	415	73	58 to 90	86	82	77 to 88	835
23-24 (n = 2754)	65	57 to 75	201	66	59 to 75	277	68	60 to 76	309	58	44 to 75	59	67	62 to 73	586
25-26 (n = 1359)	65	53 to 79	98	66	55 to 78	135	79	68 to 92	178	92	68 to 123	46	73	65 to 82	313
≥ 27 (n = 479)	42	26 to 63	23	46	32 to 64	34	77	59 to 99	63	66	34 to 115	12	62	50 to 76	97
Total (n = 10141)	76	71 to 81	853	77	72 to 81	1172	78	74 to 82	1300	75	67 to 85	280	77	74 to 80	2472

Source: Osmond C, Barker DJP, Winter PD et al (1993) Early growth and death from cardiovascular disease in women. *British Medical Journal* **307**: 1519-24. Reproduced with the permission of the British Medical Journal.

Processes linking fetal growth and coronary heart disease

In studies exploring the mechanisms underlying the association between CHD and birthweight, the trends have been found to be parallelled by similar trends in two of the major risk factors – hypertension and non-insulin dependent diabetes mellitus (see **Table 8.5**).[33,34]

Table 8.5: Prevalence of non-insulin dependent diabetes mellitus (NIDDM) and impaired glucose tolerance in men aged 59 to 70 years

Birthweight Pounds*	Number of men	% with impaired glucose tolerance or NIDDM (plasma glucose <7.8 mmol/l)	Odds ratio adjusted for BMI (95% confidence interval)
≤ 5.5 (2.50)	20	40	6.6 (1.5 to 28)
- 6.5 (2.95)	47	34	4.8 (1.3 to 17)
-7.5 (3.41)	104	31	4.6 (1.4 to 16)
- 8.5 (3.86)	117	22	2.6 (0.8 to 8.9)
- 9.5 (4.31)	54	13	1.4 (0.3 to 5.6)
> 9.5 (4.31)	28	14	1.0
Total	**370**	**25**	

*Figures in parentheses are kilograms.

Source: Hales CN, Barker DJP, Clark PMS et al (1991) Fetal and infant growth and impaired glucose tolerance at age 64. *British Medical Journal* **303**: 1019-22. Reproduced with the permission of the British Medical Journal.

The associations between small size at birth and hypertension and NIDDM are again independent of social class, cigarette smoking and alcohol consumption. Influences in adult life, however, add to the effects of the intrauterine environment. The prevalence of impaired glucose tolerance, for example, is highest in people who had low birthweight but became obese as adults.

8.5 Hypertension

Hypertension and body size at birth

Associations between low birthweight and raised blood pressure in childhood and adult life, such as those in a sample of the Hertfordshire cohort shown in **Table 8.6**, have been extensively demonstrated around the world.

Table 8.6: Mean systolic pressure in men and women aged 60 to 71 years according to birthweight

Birthweight pounds*	Systolic blood pressure mm Hg (adjusted for sex)**
- 5.5 (2.50)	168 (54)
- 6.5 (2.95)	165 (174)
- 7.5 (3.41)	165 (403)
- 8.5 (3.86)	164 (342)
- 9.5 (4.31)	160 (183)
>9.5 (4.31)	163 (72)
All	**164 (1228)**
Standard deviation	25

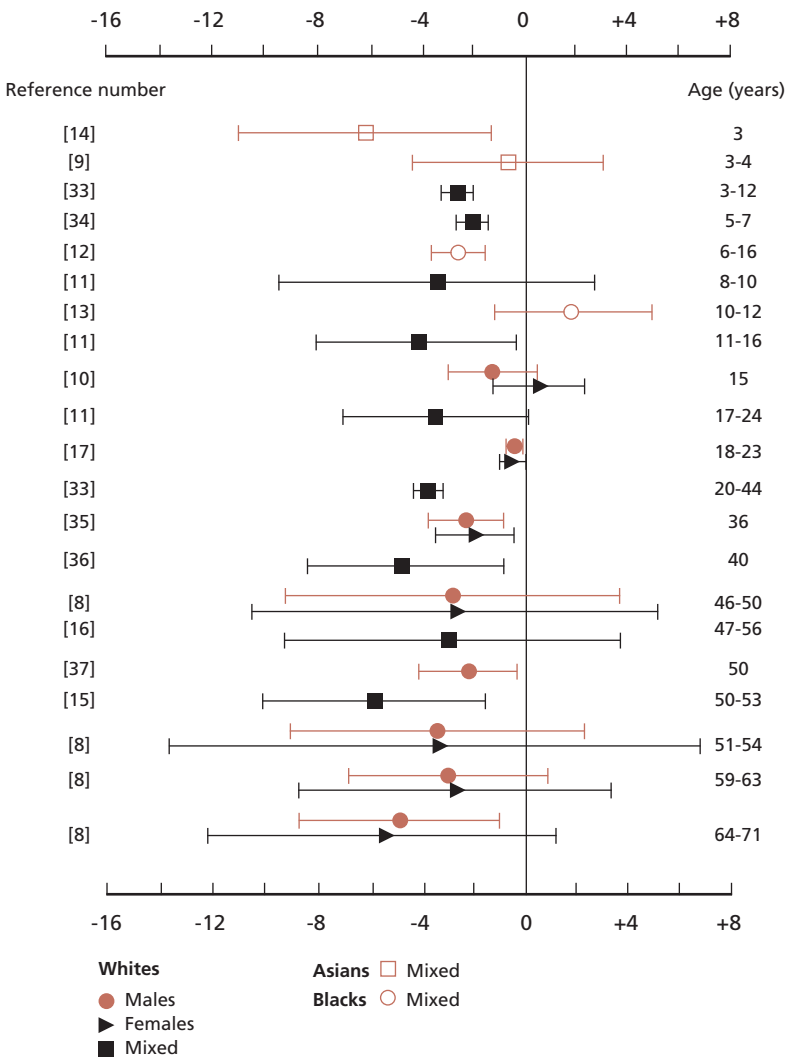
*Figures in parentheses are kilograms.

**Figures in parentheses are numbers of subjects.

Source: Law CM, de Swiet M, Osmond C et al (1993) Initiation of hypertension in utero and its amplification throughout life. *British Medical Journal* **306**: 24-7. Reproduced with the permission of the British Medical Journal.

Figure 8.1 shows the results of a systematic review of published papers describing the association between birthweight and blood pressure. The review was based on 34 studies of more than 66,000 people of all ages in many countries.[33] Each point on the figure, with its confidence interval, represents a study population and the populations are ordered by their ages. The horizontal position of each population describes the change in blood pressure that was associated with a 1kg increase in birthweight. In almost all the studies, an increase in birthweight was associated with a fall in blood pressure. The associations are less consistent in adolescence, presumably because the tracking of blood pressure from childhood through adult life is perturbed by the adolescent growth spurt. The associations between birthweight and blood pressure are not confounded by socioeconomic conditions at the time of birth or in adult life.[35] Although the differences in mean systolic pressure are small by clinical standards, their public health implications are significant. Available data suggest that lowering the mean systolic pressure in a population by 10mmHg would correspond to a 30 per cent reduction in total attributable mortality.[36] Similarly to CHD and stroke, the association between low birthweight and raised blood pressure depends on babies who were small for dates, after reduced fetal growth, rather than on babies who were born pre-term.[23]

Figure 8.1: Difference in systolic pressure (mmHg) per kg increase in birthweight (adjusted for weight in children and BMI in adults)



Source: Law CM & Shield AW (1996) Is blood pressure inversely related to birthweight? The strength of evidence from a systematic review of the literature. *Journal of Hypertension* **14**: 935-41. Reproduced with the permission of the Journal of Hypertension.

Although in the various studies of adults alcohol consumption and higher body mass have also been associated with raised blood pressure, the associations between birthweight and blood pressure were independent of them. Nevertheless, body mass remains an important influence on blood pressure and, in humans and animals, the highest pressures are found in people who were small at birth but become overweight as adults. The BMA's 2007 report on *Fetal alcohol spectrum disorders – a guide for healthcare professionals* also highlighted the adverse effects of prenatal alcohol exposure on the developing fetus and the spectrum of structural anomalies, and behavioural and neurocognitive impairments, that can result.[37]

Hypertension and placental size

Table 8.7 shows the systolic pressure of a group of men and women who were born, at term, in Sharoe Green Hospital in Preston, 50 years ago.

Table 8.7: Mean systolic blood pressure (mmHg) of men and women aged 50, born after 38 completed weeks of gestation, according to placental weight and birthweight

Birthweight pounds*	**Placental weight****				
	≤ 1.0 (454)	**- 1.25 (568)**	**- 1.5 (681)**	**>1.5 (681)**	**All**
- 6.5 (2.9)	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)
- 7.5 (3.4)	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)
> 7.5 (3.4)	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)
Total	**144 (43)**	**148 (132)**	**148 (83)**	**156 (69)**	**149≠ (327)**

*Figures in parentheses are kilograms.

**Figures in parentheses are number of subjects.

≠SD = 20.4 at term

Source: Barker DJP, Bull AR, Osmond C et al (1990) Fetal and placental size and risk of hypertension in adult life. *British Medical Journal* **301**: 259-262. Reproduced with the permission of the British Medical Journal.

The subjects are grouped according to their birthweights and placental weights. Consistent with findings in other studies systolic pressure falls between subjects with low and high birthweight. In addition, however, there is an increase in blood pressure with increasing placental weight. Subjects with a mean systolic pressure of 150mmHg or more, a level sometimes used to define hypertension in clinical practice, comprise a group who, as newborn babies, were relatively small in relation to the size of their placentas.

Hypertension and fetal undernutrition

Several lines of evidence support the thesis that it is poor delivery of nutrients and oxygen that programmes raised blood pressure in humans. First, experimental undernutrition of pregnant animals is known to cause lifelong elevation in the blood pressure of the offspring.[38,39] In humans, a mother's fatness, weight gain in pregnancy, and diet are all related to the offspring's blood pressure, whereas other influences on fetal growth, including maternal height, parity (the number of times the mother has given birth) and cigarette smoking are unrelated to the offspring's blood pressure, other than in small pre-term babies.[40,41] In Jamaica, children whose mothers had thin triceps skinfolds in early pregnancy and low weight gain during pregnancy had raised blood pressure.[40] In the Gambia, low pregnancy weight gain was associated with higher blood pressure in childhood.[42] In Aberdeen, the blood pressures of middle-aged men and women were found to be related to their mother's intakes of carbohydrate and protein during pregnancy.[43] Both low ratios of protein to carbohydrate and high ratios were associated with raised blood pressure. A number of possible mechanisms linking reduced fetal growth and raised blood pressure are currently being investigated.[17,44]

8.6 Non-insulin dependent diabetes mellitus

Insulin has a central role in fetal growth, and disorders of glucose and insulin metabolism are an obvious possible link between early growth and cardiovascular disease. Although obesity and a sedentary lifestyle are known to be important in the development of NIDDM, they seem to lead to the disease only in predisposed individuals.

8.7 Non-insulin dependent diabetes mellitus and body size at birth

A number of studies have confirmed the association between birthweight, impaired glucose tolerance and NIDDM, first reported in Hertfordshire.[45-50] Studies in Preston, UK and Uppsala, Sweden, where detailed birth measurements were available, found that thinness at birth was more strongly related than birthweight to impaired glucose tolerance and NIDDM.[47] **Table 8.8** shows that in Uppsala the prevalence of diabetes was three times higher among men in the lowest fifth of ponderal index at birth.

Table 8.8: Prevalence of non-insulin dependent diabetes by ponderal index at birth among 60 year old men in Uppsala, Sweden

Ponderal index at birth (kg/m³)	Number of men	Prevalence (%) of diabetes
< 24.2	193	11.9
24.2 -	193	5.2
25.9 -	196	3.6
27.4 -	188	4.3
≥29.4	201	3.5
Total	**971**	**5.7**
P value for trend 0.001		

Source: Lithell HO, McKeigue PM, Berglund L et al (1996) Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. *British Medical Journal* **312**: 406-10. Reproduced with the permission of the British Medical Journal.

Among the Pima Indians in the USA, a raised prevalence of NIDDM was associated with both low birthweight and with birthweights over 4.5kg.[50] The increased risk of NIDDM among babies with high birthweights was associated with maternal diabetes in pregnancy, which is unusually common in this community.

The adverse effects of low birthweight and thinness at birth on glucose/insulin metabolism are already evident in childhood. Seven-year-old children in Salisbury who were thin at birth had raised plasma glucose concentrations after an oral load.[51] In a group of older British children, those who had lower birthweight had raised plasma insulin concentrations, both fasting and after oral glucose.[52] This is consistent with the association between low birthweight and insulin resistance. Low birthweight or stunting at birth have been found to be associated with reduced glucose tolerance among children in India and Jamaica. These findings in children provide further support for the hypothesis that NIDDM originates from impaired development in utero and that the seeds of the disease in the next generation have not only been sown but are already apparent in today's children.

Mechanisms

The processes that link thinness at birth with insulin resistance in adult life are not known. Babies born at term with a low ponderal index have a reduced mid-arm circumference, which implies that they have a low muscle bulk as well as less subcutaneous fat. One possibility is that thinness at birth is associated with abnormalities in muscle structure and function which persist into adult life, interfering with insulin's ability to promote glucose uptake.[53] Another possibility is that insulin resistance represents persistence of a glucose-sparing metabolism adopted in fetal life in response to undernutrition. The

undernourished fetus reduces its metabolic dependence on glucose and increases oxidation of other substrates, including amino acids and lactate. A third possibility is that persisting hormonal changes underlie the development of insulin resistance. Glucocorticoids, growth hormone and sex steroids are thought to play a major role in the evolution of the insulin resistance syndrome.[54]

8.8 Serum cholesterol and blood clotting

Studies in Sheffield show that the neonate that has a reduced abdominal circumference at birth, although within the normal range of birthweight, has persisting disturbances of cholesterol metabolism and blood coagulation which predispose to CHD.[55,56] This is thought to reflect impaired growth of the liver, two of whose functions are regulation of cholesterol and blood clotting. The differences in serum total and low density lipoprotein cholesterol concentrations across the range of abdominal circumference are large, statistically equivalent to 30 per cent differences in mortality caused by CHD (**see Table 8.9**).

Table 8.9: Mean serum cholesterol concentrations according to abdominal circumference at birth in men and women aged 50-53 years

Abdominal circumference inches*	Number of people	Total cholesterol (mmol/l)	Low density lipoprotein cholesterol (mmol/l)
≤11.5 (29.2)	53	6.7	4.5
- 12.0 (30.5)	43	6.9	4.6
- 12.5 (31.8)	31	6.8	4.4
- 13.0 (33.0)	45	6.2	4.0
> 13.0 (33.0)	45	6.1	4.0
Total	**217**	**6.5**	**4.3**

*Figures in parentheses are centimetres.

Source: Barker DJP, Martyn CN, Osmond C et al (1993) Growth in utero and serum cholesterol concentrations in adult life. *British Medical Journal* **307**: 1524-7. Reproduced with the permission of the British Medical Journal.

8.9 Chronic bronchitis and fetal growth

Much of the socioeconomic and geographical inequality in death rates in the UK is the result of differences in the occurrence of cardiovascular disease and chronic airflow obstruction. Death rates from 'chronic bronchitis' are highest in the cities and large towns; and people born in cities and large towns in the UK have an increased risk of death from chronic bronchitis irrespective of where they move to in later life, either within or outside the country.[57,58] This suggests that the disease originates in early life.

In Hertfordshire, standardised mortality ratios for chronic bronchitis among men with birthweights of 2.5kg or less were twice those among men with birthweights of more than 4.3kg.[59]

For many years there has been interest in the hypothesis that lower respiratory tract infection during infancy and early childhood predisposes to chronic airflow obstructions in later life.[60-64] The large geographical differences in death rates from chronic bronchitis in England and Wales are closely similar to the differences in infant deaths from respiratory infection earlier in the twentieth century.[65] Follow-up studies of individuals provide direct evidence that respiratory infection in early life has long-term effects. When the national sample of 3,899 British children born in 1946 were studied as young adults, those who had had one or more lower respiratory infections before two years of age had a higher prevalence of chronic cough.[66] A link between lower respiratory tract infection in early childhood and reduced lung function and death from chronic bronchitis in adult life has been shown in follow-up studies in Hertfordshire (see **Table 8.10**) and Derbyshire.[59,67,68]

Table 8.10: Mean forced expiratory volume in one second (FEV1) litres, adjusted for height and age among men aged 59-67 years according to birthweight and the occurrence of bronchitis or pneumonia in infancy

Birthweight pounds*	**Bronchitis or pneumonia in infancy****	
	Absent	**Present**
≤ 5.5 (2.5)	2.39 (22)	1.81 (4)
- 6.5 (2.9)	2.40 (70)	2.23 (10)
- 7.5 (3.4)	2.47 (163)	2.38 (25)
- 8.5 (3.9)	2.53 (179)	2.33 (12)
- 9.5 (4.3)	2.54 (103)	2.36 (5)
> 9.5 (4.3)	2.57 (43)	2.36 (3)
Total	**2.50 (580)**	**2.30 (59)**

*Figures in parentheses are kilograms.

** Figures in parentheses are numbers of men.

Source: Barker DJP, Godfrey KM, Fall C et al (1991) Relation of birthweight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *British Medical Journal* **303**: 671-5. Reproduced with the permission of the British Medical Journal.

This suggests that infancy may be a critical period in which infection may change lung function. Further evidence of the long-term effects of respiratory infection in early life came from a study of 70-year-old men in Derbyshire, England, which also made use of health visitors' records.[68] The FEV1 of men who had had pneumonia before the

age of two years was 0.65 litres less than that of other men, a reduction in FEV1 of approximately twice that associated with lifelong smoking.

The simplest explanation of these observations is that the infection of the lower respiratory tract during infancy has persisting deleterious effects that, when added to the effects of poor airway growth in utero, predispose to the development of chronic bronchitis in later life. Factors implicated in 'programming' of the respiratory system include exposure to viral respiratory infections during infancy.[69]

8.10 Preventing chronic disease in the UK

The findings outlined here suggest that CHD, stroke, NIDDM, hypertension and chronic airflow obstruction originate in utero. Emerging evidence suggests that prenatal development may also contribute to other chronic diseases, including osteoporosis,[70] cancers of the reproductive system,[71,72,73] other cancers[74] and schizophrenia.[75] The emergence of epigenetics is giving insights into the molecular mechanisms that underly this. Protecting the nutrition and health of girls and young women and their babies must be a public health priority. The history of the UK gives an insight into social conditions that have been harmful to mothers and babies in the past. Poverty, inadequate food, poor housing, and overcrowding led to the deaths of many infants, reduced the life expectancy of those who survived, and laid the foundations for today's inequalities in health.[76,77]

The daily exposure to weight-related articles in newspapers, magazines and on television, and the thinness of role models in the fashion industry contributes to feelings of insecurity and self-doubt about acceptable body image and puts pressure on women to become unduly thin.[78,79] The babies of thin women may be at increased risk of CHD, NIDDM and raised blood pressure.[4,26,42,80-82] Encouraged by an obesogenic environment, other young women today are unduly fat. The babies of women who are overweight may also be at increased risk of CHD and NIDDM.[28,83] The effects of a mother's body size are largely independent of its effects on the size of the baby. So too, it seems, are the effects of what she eats in pregnancy. Even famine has unexpectedly small effects on growth but the baby's physiology and metabolism are permanently altered.[84]

The new developmental model for chronic disease

Under the new developmental model for the origins of chronic disease, the causes to be identified are linked to normal variations in the processes of development that lead to variations in the supply of nutrients to the baby.[85] These variations programme the function of a few key systems that are linked to chronic disease, including the immune system, anti-oxidant defences, inflammatory responses, the number and quality of stem cells and the balance of the autonomic system. There is not a separate cause for each different disease. Rather, as cigarette smoking has shown, one cause can have many different disease manifestations. Which chronic disease originates during development

may depend more on timing during development than on qualitative differences in experience.

Exploration of the developmental model will illuminate people's differing responses to the environment through their lives. As René Dubos wrote long ago, 'The effects of the physical and social environments cannot be understood without knowledge of individual history'.[86] The model will also illuminate geographical and secular trends in disease. Because the human body has changed over the past 200 years, different chronic diseases have risen and then fallen, to be replaced by other diseases.[87,88]

Coronary heart disease, NIDDM, breast cancer and other chronic diseases are unnecessary. Their occurrence is not mandated by genes passed down to us through thousands of years of evolution. Chronic diseases are not the inevitable lot of humankind. They are the result of the changing pattern of human development. We could readily prevent them, had we the will to do so. Prevention of chronic disease, and an increase in healthy aging, require improvement in the nutrition of girls and young women. Many babies in the womb in the western world today are receiving unbalanced and inadequate diets. Many babies in the developing world are malnourished because their mothers are chronically malnourished. Protecting the nutrition and health of girls and young women should be the cornerstone of public health. Not only will it prevent chronic disease but it will produce new generations who have better health and wellbeing through their lives.

The Southampton Initiative for Health

The Southampton Initiative for Health may point to a way forward in the UK.[89-91] This is a programme of public health interventions in collaboration with the Sure Start Children's Centres that aims to optimise the nutritional status and health of women of childbearing age and their families. The Southampton Women's Survey has shown that women from disadvantaged backgrounds eat a less varied and balanced diet and are less physically active than women from more advantaged circumstances. Further work with disadvantaged women in Southampton has demonstrated that the barriers to healthy eating are often related to a lack of self-efficacy and a low sense of control. The Southampton Initiative aims to improve the health behaviours of disadvantaged women and their children in Southampton. This is being achieved by training health and social care staff in behaviour change skills that enable them to help women address barriers to behaviour change and set goals for themselves.

8.11 Recommendations

Interventions to improve maternal nutrition

- Young women should receive consistent dietary messages to encourage consumption of fruit and vegetables, starchy foods and oily fish, and to limit consumption of dietary fat, salt and added sugar. This should be accompanied by the message that poor diet

and nutritional status could impact on their ability to meet the nutrient needs of future pregnancies.

- Targeted environmental changes can have an impact and should be tried. Interventions to change aspects of the food environment, so that consumers are encouraged to choose healthier foods, may offer important opportunities to achieve change in eating habits. For example, changing the location of fruit and vegetables in supermarkets may have an effect.
- Work should be undertaken to improve the knowledge base of young women. Interventions that include elements of education or counselling, support and empowerment can improve nutrition knowledge and behaviour among young women.
- A multifaceted approach should be used to improve diet during pregnancy. Interventions that combine food supplementation, nutrition counselling and referral to health and social services, can lead to improvements in maternal diet during pregnancy, increased maternal weight gain and increased breastfeeding rates.
- Cooking and food preparation skills are key to a good diet; help with these should be offered. Practical cooking/food sessions should be delivered by peers, which aim to give low-income families food knowledge and skills to bring about dietary change and improve food practices among recipients.
- The efficacy of health visitors and others at increasing breastfeeding rates should be recognised and resourced. Interventions that educate women about the benefits and practice of breastfeeding are effective at increasing breastfeeding initiation. Appropriate support for breastfeeding mothers can prolong the duration of breastfeeding.