

The intrauterine origins of cardiovascular and obstructive lung disease in adult life

The Marc Daniels Lecture 1990

The aim of this lecture is to present evidence that retardation of growth during critical periods of development in fetal life and infancy is associated with cardiovascular and obstructive lung disease.

Geographical studies

The large geographical differences in death rates from cardiovascular and obstructive lung disease in England and Wales remain unexplained. Variations in adult diet and cigarette smoking do not explain why the highest cardiovascular death rates are in industrial areas in the north and west of the country, and in some of the less affluent rural areas such as North Wales. Rates are low throughout the south and east, including London. It is a paradox that, although the steep increase in ischaemic heart disease during this century has been associated with rising prosperity, the disease is now more common in poorer areas, and in lower-income groups. The highest death rates from obstructive lung disease occur in cities and large towns, and again differences in cigarette smoking may contribute to this distribution but cannot explain it.

One possibility is that these differences in mortality derive not from the current environment but from the environment to which people were exposed during childhood. The existence of detailed records of infant mortality from the beginning of the century allows one to compare current death rates in any area of England and Wales with infant mortality rates 60 or more years ago. This comparison can be made with the country divided into 212 local-authority groupings. The correlations between past infant mortality and current mortality from both cardiovascular and obstructive lung disease are remarkably strong [1,2], the correlation coefficients being 0.73 and 0.82 respectively. Infant mortality is a general indicator of an adverse environment, and the conclusion drawn from these correlations is that poor living conditions in childhood are a risk factor for cardiovascular disease—a conclusion first put forward in 1977 by Forsdahl who found a similar geographical relation between infant and cardiovascular mortality in the counties of Norway [3].

The detailed infant mortality records in England and Wales make it possible to distinguish neonatal mortality (deaths before one month of age) from post-neonatal mortality (deaths from one month to one year). They reveal the new and surprising clue that cardiovascular mortality in adults is closely linked to neonatal mortality [4]. In the past, neonatal mortality was high in places where many babies had a low birth-weight [5]. High neonatal mortality was generally associated with high maternal mortality rates which were found in places where women had poor physique and health [6]. There is, therefore, a geographical association between poor maternal physique and health, poor fetal growth, and high death rates from cardiovascular disease.

In contrast, the geographical distribution of chronic obstructive lung disease closely resembles the pattern of post-neonatal mortality, and in particular infant deaths from bronchitis and pneumonia [2]. High infant death rates from lower respiratory tract infection occurred in places where overcrowding resulted both from a high density of housing and from overcrowding within houses.

The recent fall in stroke mortality in Britain and many other Western countries is consistent with improvement in maternal health during the past century. The fall in mortality from chronic obstructive lung disease is consistent with the reduction in overcrowding, a consequence of the falling birth rate and improvements in housing. To explain the rise in ischaemic heart disease it seems necessary to postulate two groups of causes: one associated with poor living standards and acting in infancy, and the other associated with prosperity and linked, presumably, to the Western diet.

Follow-up studies

Further epidemiological exploration of the relation of early growth and infection to adult disease requires studies of adults in middle and old age for whom records of their early development are available. In Hertfordshire, from 1911 onwards every baby born in the county was weighed at birth, visited periodically by health visitors throughout the first year and weighed again at one year. From 1923 onwards all illnesses in children aged up to five years were recorded. The records for the whole county have been preserved and it is therefore possible to trace men and women born

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around 60 years ago, and to relate their early development to the later occurrence of illness and death and the presence of known risk factors [7].

Obstructive lung disease

In our first study we followed up 6,500 men who were born in eight districts of the county between 1911 and 1930, all of whom were breastfed at birth. Fifty-two had died from obstructive lung disease. In Table 1 death rates are expressed in relation to a national average of 100 allowing for the age distribution of the men. The standardised mortality ratios fell sharply with increasing weight at one year of age.

We also measured the lung function of 775 men who still live in the districts where they were born. The forced expiratory volumes (FEV₁) adjusted for the man's current height are shown in Table 2. They rise progressively with increasing birthweight. It has been argued that such findings only show that an adverse early environment, indicated by lower birthweight, results in lower adult FEV₁ in consequence of the cumulative effects of a variety of influences acting during childhood and adolescence. We reject this. In these men birthweight was not associated with social class, and the same relation between birthweight and FEV₁ was found within each social class. We interpret this relation as evidence of the long-term effects of an adverse environment during a critical period of rapid lung growth *in utero*, an example of so-called 'programming'. The adverse environment retards the weight gain of the fetus and constrains irrecoverably the growth of the airways. This interpretation is consistent with findings in rats in whom a period of malnutrition around the time of birth permanently reduces lung size and DNA content [8].

Another finding which we interpret as an effect of programming is that the mean FEV₁ of 57 men whose records show that they had had an attack of bronchitis or pneumonia during infancy was lower at each birth-

weight (unpublished data). The FEV₁ was not reduced when the attack of bronchitis or pneumonia had occurred between the ages of one and five years. This is consistent with infection causing permanent damage to the airways during infancy but not at older ages when rates of lung growth decline, though lung expansion continues. Evidence of a permanent effect of early infection on adult respiratory function has come from other studies, notably those on the 1946 birth cohort [9].

The reduction in FEV₁ associated with lower birthweight interacts with the effects of smoking, so that the highest FEV₁ (2.79 litres) was in men in the upper third of the birthweight distribution who had never smoked, and the lowest (2.21 litres) was in men in the lower third of the birthweight distribution who were current smokers.

Ischaemic heart disease

Table 3 shows standardised mortality ratios for ischaemic heart disease in the 6,500 men, of whom 469 had died from the disease. The ratios fall steeply with increasing weight at one year, a trend not shown by deaths from non-circulatory causes. Ischaemic heart disease mortality also falls with increasing birthweight,

Table 1. Standardised mortality ratios for obstructive lung disease, according to weight at one year, in 6,500 men born during 1911-30

Weight at one year (lb)	Chronic obstructive lung disease
≤ 18	103 (5)
- 20	98 (14)
- 22	52 (13)
- 24	70 (14)
- 26	48 (5)
≥ 27	26 (1)
All	66 (52)

Numbers of deaths in parentheses
1 lb = 0.45 kg

Table 2. FEV₁ adjusted for height in men aged 64 years

Birthweight (lb)	Number of men	FEV ₁ (litres)
-5.5	30	2.24
-6.5	93	2.37
-7.5	245	2.41
-8.5	230	2.48
-9.5	122	2.50
>9.5	55	2.53
All	775	2.44

Table 3. Standardised mortality ratios for ischaemic heart disease according to weight at one year in 6,500 men born during 1911-30

Weight at one year (lb)	Ischaemic heart disease	All non-circulatory disease
≤ 18	100 (36)	74 (39)
- 20	84 (90)	99 (157)
- 22	92 (180)	74 (215)
- 24	70 (109)	67 (155)
- 26	55 (44)	84 (99)
≥ 27	34 (10)	72 (31)
All	78 (469)	78 (696)

Numbers of deaths in parentheses

Table 4. Mean plasma fibrinogen in men aged 64 years

Weight at one year (lb)	Number of men	Fibrinogen (g/l)
≤18	31	3.29
-20	73	3.16
-22	140	3.16
-24	145	2.99
-26	61	2.91
≥27	25	3.01
<i>All</i>	<i>475</i>	<i>3.08</i>

though the relation is not as strong as with weight at one year. Stroke mortality shows similar trends. An interpretation of this is that programming of cardiovascular disease occurs partly during fetal life and partly in infancy. This interpretation is consistent with the findings on cardiovascular risk factors.

Dr T. W. Meade and his colleagues at Northwick Park have measured the plasma fibrinogen levels in 475 of the men in Hertfordshire. High-plasma fibrinogen is a strong predictor of both ischaemic heart disease and stroke [10,11]. Levels fall with increasing weight at one year (Table 4). They do not, however, fall with birthweight. This contrasts with systolic blood pressure which falls with birthweight (Table 5) but is unrelated to weight at one year. This specificity of the relation of the two risk factors to weight either at birth or at one year is a further argument in favour of long-term effects being determined during critical, often brief periods of early development.

Blood pressure

In Table 6 the men have been divided approximately into thirds according to birthweight and current body-mass index (weight/height²). Systolic pressure falls with increasing birthweight and rises with body-mass index. The highest mean pressures (172mmHg) were in men in the lowest third of birthweight and the highest third of body-mass index; the lowest pressures (156mmHg) were in men in the highest third of birth

Table 5. Mean systolic pressure in men aged 64 years

Birthweight (lb)	Number of men	Systolic pressure (mmHg)
-5.5	31	169
-6.5	95	166
-7.5	251	165
-8.5	233	163
-9.5	125	162
>9.5	56	162
<i>All</i>	<i>791</i>	<i>164</i>

Table 6. Mean systolic pressure (mmHg) in men aged 64 years

Body mass index (kg/m ²)	Birthweight (lb)			Total
	-7.25	-8.25	8.25+	
-25.2	161	159	156	156 (269)
-25.2-27.9	167	168	165	167 (255)
>27.9	172	163	164	167 (261)
<i>Total</i>	<i>167</i> <i>(243)</i>	<i>163</i> <i>(268)</i>	<i>162</i> <i>(274)</i>	<i>164</i> <i>(785)</i>

Numbers of men in parentheses

weight and the lowest third of body-mass index.

Birthweight is a summary measure of fetal growth which includes head size, length, and fatness. We now know that it greatly underestimates the relation between fetal growth and blood pressure. In order to explore the association between measurements at birth and adult blood pressure we examined 449 men and women aged around 50 years who were born in one hospital in Preston [12]. At that hospital, Sharoe Green, unusually detailed observations were made at birth. Table 7 shows the mean systolic pressures according to birthweight and placental weight. There are opposing trends, such that systolic pressure falls by around 10mmHg with increasing birthweight and rises by around 12mmHg with increasing placental weight. Adjustment for gestation did not affect these trends.

An important aspect of the findings is that most people with high systolic pressure were not unusually small at birth. Rather, their birthweights were within the normal range but did not match the weight of the

Table 7. Mean systolic pressures (mmHg) of men and women aged 46 to 54 years according to birthweight and placental weight

Birthweight (lb)	Placental weight (lb)				All
	-1.0	-1.25	-1.5	>1.5	
-5.5	152 (26)	154 (13)	153 (5)	206 (1)	154 (45)
-6.5	147 (16)	151 (54)	150 (28)	166 (8)	151 (106)
-7.5	144 (20)	148 (77)	145 (45)	160 (27)	149 (169)
>7.5	133 (6)	148 (27)	147 (42)	154 (54)	149 (129)
<i>All</i>	<i>147</i> <i>(68)</i>	<i>149</i> <i>(171)</i>	<i>147</i> <i>(120)</i>	<i>157</i> <i>(90)</i>	<i>150</i> <i>(449)</i>

Numbers of people in parentheses

placenta. A feature of babies born with the heaviest placentas, weighing more than 1.5 lb, among whom adult blood pressures were highest, was that they were disproportionate at birth, being relatively short in relation to their head circumference. This suggests that one process linking fetal growth with adult blood pressure may be diversion of fetal cardiac output away from the trunk to favour the brain.

Large placental weight is associated with clinical hypertension in later life as well as higher mean blood pressure. Among the 449 men and women the risk of having treatment for hypertension was 3.7 times greater among those with placentas weighing more than 1.5 lb than among those whose placentas weighed 1.0 lb or less. The causes of large placental size are largely unknown. In Preston, however, only four out of 56 (7%) of babies born at term to mothers in social class 1 and 2 had placentas exceeding 1.5 lb. This compared with 62 out of 254 (24%) for mothers in the lower social classes. We suggest that the influence which links low social class with large placental weight is poor nutrition. A recent study of 8,684 births in Oxford has shown that iron deficiency anaemia is associated with heavier placental weight (unpublished data).

Conclusion

Retarded fetal and infant growth are strongly related to death from obstructive lung disease and cardiovascular disease and to risk factors for these diseases. These long-term associations of retarded growth may reflect restraint of tissue growth by an adverse environment during a critical, sometimes brief, period of fetal or infant development. Which tissues are affected depends on the nature of the adverse influence and its timing. The phenomenon of 'programming' has been demonstrated on a range of structures and functions in experimental animals [13–15]. It probably occurs widely in human development and has an important effect on the development of degenerative disease. Long-term human studies now in progress will extend our knowledge of its occurrence and may give insight into the timing of critical periods.

The relation of early growth with risk factors and disease rates is continuous. FEV₁ rises progressively up to the highest values of birthweight (Table 2) while systolic blood pressure falls (Table 5). It follows, therefore, that while an average birthweight is usual it may not be optimal. If the criterion of successful fetal growth is adult health and longevity, assessment of the newborn must at the least include placental weight and the proportions of the baby.

The effects of programming interact with influences in the adult environment, including cigarette smoking and body weight (Table 6). The existence of programming does not imply that adult influences should be discounted—though in the past we have probably overestimated their importance.

Our findings are open to the interpretation that genetic influences which are immediately manifest as growth failure in early life reveal themselves in adult life through the occurrence of degenerative disease. However, studies of the birthweights of the first-born children of mothers and daughters suggest that genetic factors play only a small part in determining birthweight [16]. Experiments in which newborn mice were randomly assigned to foster mothers show that individual variations in post-weaning growth rates are more related to the nutritional status of the foster mother than to the origins of the offspring [15].

We favour an environmental explanation of our findings and suspect that maternal nutrition is important. Research is needed into the maternal influences which regulate fetal and infant growth. We need to know why the children of women living in rural southern England in the early years of this century have had such low death rates from cardiovascular and obstructive lung disease. We can reasonably suspect that the seeds of ill health in the next century are being sown today wherever girls and mothers have nutritional deficiencies whose nature we do not yet know.

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