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Fetal origins of adult hypertension

Our studies into the relation between fetal and infant life and adult hypertension started because of the limited ability of known risk factors to predict the occurrence of cardiovascular disease in both populations and individuals. Globally cardiovascular disease is associated with affluence, yet in England and Wales death rates from cardiovascular disease are highest in areas of the country which have indicators of low socio-economic status[1]. In individuals, hypertension and high plasma cholesterol concentrations increase an individual's risk of ischaemic heart disease, but for a non-smoking man in the lowest risk groups of cholesterol and blood pressure, the commonest cause of death is still coronary heart disease[2]. One possible explanation is that the causes of cardiovascular disease begin to operate not in adult life, but in fetal life and infancy.

Our first studies were geographical. Records of infant mortality dating from the beginning of the century allowed recent death rates in the 212 local authority areas of England and Wales to be compared with infant mortality rates in the same places 60 or more years ago. The correlation between past infant mortality and recent mortality from cardiovascular disease ($r = 0.73$) was strikingly close[1]. Infant mortality is, of course, no more than a general indicator of early adverse environmental conditions. But such a strong relation is suggestive that some aspect of poor living conditions in early life determines risk of cardiovascular disease. However, maps and area statistics only tell us about places, not people. To test our hypothesis further we needed to study individuals.

From 1911 onwards, every baby born in the county of Hertfordshire (a rural and relatively affluent county just north of London) was weighed at birth, visited periodically by a health visitor during infancy, and weighed again at one year of age. Records of these visits have survived, so that it is possible to trace, through the National Health Service Central Registry, men and women who were born 60 and more years ago, and to relate their weight at birth and one year of age, to the later occurrence of illness and death, and to levels of known risk factors for cardiovascular disease. The first study in Hertfordshire was of death rates from cardiovascular disease in 6500 men, born in the eastern part of the country between 1911–30. Among men who weighed 18 pounds (8.2 kg) or less at one year of age, death rates from ischaemic heart disease were almost three times higher than among those who weighed 27 pounds (12.3 kg) or more (Table 1)[3]. In subsequent studies similar relations were found for women[4], and for men born in a different part of the country[5].

Studies of death rates have limited information on individuals. Could it be, for instance, that the relation between birthweight and death from cardiovascular disease was confounded by adult obesity? To examine these issues further we have undertaken follow up studies of individuals who are still alive. In addition to those in Hertfordshire[6], we have studied people in Preston[7] and Sheffield, cities in the industrial north of England, where detailed maternity records have been preserved.

In all three follow up studies, and in a national cohort study[8], those who weighed less at birth had raised blood pressure as adults. Amongst 59 to 70 year old men in Hertfordshire, for example, systolic blood pressure fell from a mean of 169 mmHg in those who weighed five and a half pounds (2.5 kg) at birth to 162 mmHg in those who weighed 9 and a half pounds (4.3 kg) or more (Table 2). As would be expected, blood pressure was higher in people who were

Weight at one year (pounds)	SMR: Ischaemic heart disease	SMR: 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)
Total	78 (469)	78 (696)

Table 1. *Standardised mortality ratios (SMR) for ischaemic heart disease according to weight at one year in 6500 men born during 1911–30. (Numbers of deaths: Hertfordshire).*

Birthweight (pounds)	Systolic pressure	
–5.5	169	(31)
–6.5	166	(95)
–7.5	165	(251)
–8.5	163	(233)
–9.5	162	(125)
>9.5	162	(56)
Total	164*	(791)

Table 2. *Mean systolic blood pressure (mm Hg) in men aged 59 to 70 years. (Number of people: Hertfordshire), * overall standard deviation 24 mm Hg.*

currently obese (measured by body mass index: weight/height^2), but men who had lower birthweight tended to have higher systolic pressure at any level of current body mass. The relation between birthweight and blood pressure was independent of current alcohol intake and smoking habit and was seen at all levels of social class (a measure of socio-economic status). Furthermore, in Hertfordshire, where weight at one year was also available, higher blood pressure was associated only with lower birthweight, and not with lower weight at one year[9]. This suggests that the critical period for blood pressure development is in fetal life, not infancy.

High blood pressure was not confined to those adults who as babies had had clinically defined intrauterine growth retardation, such as birthweight <2.5 kg: indeed, in the older populations few of these babies would have survived. Rather blood pressure fell progressively across the whole range of birthweights. This was seen in both sexes and for systolic and diastolic pressures, although the differences were stronger for systolic pressure. From the studies in Preston[7] and Sheffield (C. Martyn unpublished), where duration of gestation was also recorded, we know that the inverse relation between birthweight and blood pressure was independent of gestation. Thus it is poor fetal growth, rather than prematurity, which is associated with higher blood pressure in adult life. However, birthweight is a crude measure of fetal growth, including length, head size and fatness. Animal experiments have shown that the timing of adverse events, for instance undernutrition in pregnancy, many influence body proportions at birth[10]. Undernutrition in early gestation tends to produce a small but normally proportioned baby, so called "symmetrically" small. The fetus may also enlarge the placenta as an adaptive mechanism. Undernutrition in late gestation may have profound effects on body proportions, for instance a baby who is thin, with less effect on absolute birthweight or placental weight. Thus the study of body proportions at birth may give further insights into the timing which underlies the relation between birthweight and subsequent blood pressure.

In the Preston maternity records detailed measurements of the baby's size at birth were recorded, along with the placental weight. Men and women with high blood pressure tended to be those who had been thin at birth, with below average weight but above average length[11]. High pressures were also found amongst those who had large placentas at birth, especially if the placenta was large relative to the birthweight (Table 3)[7]. Thus signs of poor fetal growth in both early and late gestation were associated with higher blood pressure in adult life.

Although cardiovascular disease and hypertension are not disorders of childhood, there are important reasons for studying the relation between fetal growth and subsequent blood pressure in children. Firstly, demonstration of an inverse relation between birthweight and subsequent blood pressure in children would show that impaired fetal growth is still associated with later effects. Thus, the studies of adults

Birthweight (pounds)	Placental weight (pounds)				
	–1.0	–1.25	–1.5	>1.5	All
–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)
All	147 (68)	149 (171)	147 (120)	157 (90)	150 * (449)

Table 3. *Mean systolic blood pressure (mmHg) of men and women aged 46 to 54 years according to birthweight and placental weight. (Number of people: Preston), * overall standard deviation men 20 mmHg, women 23 mmHg.*

Ponderal index at birth (kg/m³)	Systolic pressure	
≤23	107	(81)
–25	106	(90)
–27.5	105	(99)
>27.5	103	(89)
Total	105*	(359)

Table 4. *Mean systolic blood pressure (mmHg) of 4 year old children, according to ponderal index at birth. (Number of children: Salisbury), * overall standard deviation 10 mmHg.*

described above would have important implications for current and future public health, rather than simply reflecting an historical phenomenon. If the relations were visible in children then prospective studies, using modern measurements of fetal growth, such as ultrasound scanning, would be feasible. Lastly, if the relation between lower birthweight and higher blood pressure were present in children, this would remove the possibility that the association in adults was due only to confounding factors in adult lifestyle, which were related both to adult hypertension and lower birthweight.

A relation between lower birthweight and higher blood pressure has now been demonstrated in eight studies of children in Britain and elsewhere[9, 12–18]. This relation is independent of the child's current size, which is itself a powerful predictor of childhood blood pressure[19]. In general systolic pressure rises by 1 to 2 mmHg for every kilogram decrease in birthweight. Tracking of blood pressure, (the persistence of rank order of an individual from one time to the next), has been repeatedly observed in studies of children and adults[20]. This suggests that at least some components of both hypertension and the population distribution of blood pressure are established early in life. In one study of children detailed measurements of size at birth were also available[15]. Thinness at birth (measured by ponderal index: weight/height^3) was associated with higher blood pressure at 4 years (Table 4), paralleling the relation seen in adults. However, four studies of teenagers have shown only weak associations between birthweight and blood pressure[18, 21–23]. This is perhaps explained by the fact that tracking is perturbed during the period of rapid growth in adolescence[24].

The changes in mean blood pressure between one group of size at birth and another, all within the normal range of fetal growth, may seem small of those used to dealing with hypertensive patients, or with severely growth retarded babies. However there are two important points to note on the size of the effects which have been described. Firstly, the differences in blood pressure associated with birthweight are large compared with those associated with the adult environment, of which salt has received much attention. A recent cross-cultural study in 52 centres concluded that lowering the daily intake of sodium from 170 mmol to 70 mmol corresponded to a 2 mmHg reduction in systolic pressure[25]. This is a small effect compared to the difference in systolic pressures across the range of birthweights in the Hertfordshire and Preston studies.

Secondly, small potential shifts in the population distribution of blood pressure may have large effects on disease. Prevention of blood pressure related disorders focuses on two strategies. One relies on the treatment of individuals at very high risk i.e. those with hypertension. A considerable fall in blood pressure must be achieved to reduce an individual's risk, and such individuals form only a small proportion of the population. The second strategy reduces the mean blood pressure of the population, thereby decreasing the risk of all individuals by a small amount. Of the two strategies the second has the greater potential to decrease the burden of disease in the whole

population. For instance, it has been calculated that a reduction in the mean population blood pressure of adults in England and Wales of 2 to 3 mmHg would have the same effect on reducing hypertension-associated deaths as all anti-hypertensive treatment currently prescribed[26].

What, then, of the mechanisms which underlie the relations between early growth and adult blood pressure? We have hypothesized that hypertension arises from fetal adaptations to an adverse environment in utero. In adapting to an adverse environment, to suboptimal nutrition in particular, the growth of some fetal organs and tissues, including the liver and pancreas, is constrained while that of others, including the brain, may be spared[10]. Numerous animal experiments have shown that poor nutrition during periods of rapid growth in early life may permanently change the structure and physiology of a range of organs and tissues. This phenomenon is known as programming. For instance, female rats were given diets with differing protein content before and throughout pregnancy[27]. The diets were suboptimal rather than grossly deficient. Normal feeding was restored after birth and the offspring were allowed to develop normally. As would be expected the rats on lower protein diets had lower weight gain during pregnancy. Nine weeks after birth, offspring of all three groups fed on a low protein diet had significantly higher systolic pressure than the offspring of those on a normal 18 per cent protein intake. These differences persisted to 21 weeks, by which time the rats were mature. These observations illustrate how impaired nutrient supply during fetal development may have significant physiological consequences in later life, without major effects on birth size.

Although there is a wealth of evidence in animals that maternal nutrition programmes longterm physiology and metabolism, little is known in humans. However our data do provide some support for the hypothesis of programming of blood pressure in utero. The differences in systolic pressure among children who were of low and high birthweight are seen from the early years of life but are small compared to those seen in adults[9]. During adult life, those differences are increased so that the biggest differences are seen in the oldest subjects. An interpretation of these findings is that blood pressure is initially raised in utero and thereafter a magnifying process may progressively amplify the difference throughout life. The existence of initiating and amplification mechanisms was first proposed by Folkow[28]. It is clear that amplification occurs in secondary hypertension: in patients with phaeochromocytoma, Conn's syndrome or renal artery stenosis, hypertension can persist even after the primary (initiating) cause, the tumour or stenosis is removed[24].

We hypothesize that essential hypertension is programmed in utero, possibly as a consequence of impaired maternal nutrition. This initiation process is followed by an amplification mechanism, with other postnatal influences acting to modify the risk initiated pre-natally. This explanation does not imply that the environment and individual behaviour in adult life are unimportant, although it may limit the potential for therapeutic intervention. If we accept this hypothesis there are major implications for public health. Primary prevention of hypertension may be possible. The gulf between this theoretical possibility and improved health is wide. To bridge that gulf we will need not only a greater understanding of the mechanisms which underly the associations between fetal growth and adult blood pressure, but also a fundamental shift in preventive strategies, from programmes addressing adult lifestyle and screening for treatable hypertension, to the health of mothers and babies.

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