

Hotline Editorial

The fetal origins of coronary heart disease

Studies carried out in Hertfordshire, U.K., showed for the first time that coronary heart disease is associated with low birthweight. From 1911 onwards every baby born in the county was weighed at birth and again at one year. These weights were recorded in ledgers, which have been preserved. 15 726 men and women born during 1911–30 were traced^[1,2]. Death rates from coronary heart disease among them fell progressively between those who weighed less than 5.5 pounds (2.5 kg) at birth and those who weighed 9.5 pounds (4.31 kg). Another study, in Sheffield, showed that it was babies who were small because they failed to grow, rather than small because they were born prematurely, who are at increased risk of coronary heart disease^[3]. The association between low birthweight and coronary heart disease has recently been confirmed in a large cohort of nurses in the U.S.A. among whom there was a two-fold change in the relative risk of non-fatal coronary heart disease across the range of birthweight^[4].

Small size at birth is also associated with several coronary risk factors: high blood pressure, non-insulin dependent diabetes, and high serum cholesterol and plasma fibrinogen concentrations^[5]. These findings have led to the hypothesis that the disease is programmed in utero. The fetal origins hypothesis proposes that adaptations made by the fetus in response to undernutrition led to persisting changes in metabolism and organ structure^[5]. This hypothesis is supported by experimental evidence in which offspring of undernourished pregnant animals show permanent changes including raised blood pressure and abnormal glucose-insulin and lipid metabolism.

A study recently published in the *Lancet* confirms that small size at birth is a risk factor for coronary heart disease in India^[6]. Rates of death from coronary heart disease in India are rising rapidly and it has become the commonest cause of death under 70 years of age^[7]. High rates of coronary heart disease have also been recorded in Indian populations living in the U.K. and are largely unexplained by known coronary risk factors^[8]. The recent study followed-up 517 men and women who were born in a mission hospital in Mysore, South India^[6]. To achieve this required a house-to-house census in a 2 square mile area of a poor, crowded area of the city.

The prevalence of coronary heart disease defined by standard criteria was 10%, which is similar to rates in Europe, and elsewhere in India. Rates in women were similar to those in men, though only one woman in the study smoked. Rates were highest in men of low social class, who were thin.

All the measurements of body size at birth were low by western standards; 29% of the men and women weighing less than 5.5 pounds (2.5 kg) at birth. The prevalence of coronary heart disease fell from 11% in those who weighed 5.5 pounds (2.5 kg) to 3% in those whose birthweights were more than 7 pounds (3.1 kg). High rates of the disease were also found in people whose mothers had a low body weight during pregnancy. The highest prevalence of the disease (20%) was in people who weighed 5.5 pounds (2.5 kg) or less at birth and whose mothers weighed less than 100 pounds (45 kg) in pregnancy. These findings in India need to be confirmed in other studies, and the work in Mysore is currently being extended. This is the first study in which low maternal weight has been linked to coronary heart disease. It provides further evidence that the fetal growth failure which leads to coronary heart disease is a consequence of fetal undernutrition.

Another recent confirmation of the association between birthweight and coronary heart disease comes from the Caerphilly Study, a follow-up study of 2500 men over a period of 15 years^[9]. The men were asked to obtain their birthweights from their mothers or other female relatives and half of them were able to do so. The incidence of coronary heart disease fell with increasing birthweight, but this effect was restricted to men who were overweight as adults. The authors conclude that risk of coronary heart disease is defined by the 'combined effect of early-life and later-life exposures'. The findings in this study do not accord with those in the studies in Hertfordshire and India, where associations between size at birth and during infancy were independent of adult body weight^[6,10]. Furthermore, studies of the associations between birth size and coronary risk factors show that whereas the effects of poor growth in utero on some risk factors, for example impaired glucose tolerance, is greater in obese subjects, the effects on others, for example serum low density lipoprotein

cholesterol concentrations and increased left ventricular thickness are independent of adult weight^[5].

Other forms of cardiovascular disease, in particular stroke, might be expected to show associations with fetal undernutrition. Stroke shares some of the epidemiological features of coronary heart disease, including a similar geographical distribution within the U.K. Some risk factors, including hypertension and raised plasma fibrinogen concentrations are common to both disorders^[11]. There are, however, important differences. The incidence of stroke has been falling in western countries for many years, whereas, until lately, the incidence of coronary heart disease has been rising. Recently reported studies on men in Sheffield and Hertfordshire confirm that death rates from stroke fall with increasing birthweight^[12]. The pattern of restricted fetal growth associated with stroke and coronary heart disease is, however, different. Stroke is associated with low placental weight in relation to head size. This is a pattern of growth found in the offspring of mothers who had flat bony pelvis, a marker of their poor nutrition in childhood. These findings suggest that stroke may originate through poor nutrition in a mother's childhood which deforms the bony pelvis and subsequently impairs her ability to sustain placental growth. Coronary heart disease, on the other hand, is associated with thinness or shortness at birth and an altered ratio of placental weight to birthweight. This suggests that it may originate in adaptations made by the fetus to inadequate delivery of nutrients when it occurs for reasons other than failure of placental growth.

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