Commentary: Developmental origins of raised serum cholesterol

DJP Barker

Human beings are plastic during development, and a single genotype can produce more than one alternative form of structure or physiological state in response to environmental conditions.1 There is now a considerable body of evidence that coronary heart disease (CHD) originates in developmental plasticity.2 That being the case environmental conditions during development should be linked to the major biological risk factors for the disease. In this issue of the International Journal of Epidemiology, Liisa Lauren and colleagues3 review the evidence that low birthweight, a marker of an adverse intrauterine environment, is linked to abnormalities in blood lipid concentrations.

Animal experiments have unequivocally demonstrated that undernutrition during gestation permanently changes lipid metabolism.4 This is associated with alteration in the microstructure of the liver. The literature, as the authors of the review comment, is ‘vast’. They find, however, that the 39 published studies on humans do not strongly support a link between birthweight and blood lipid levels in later life, other than a consistent relationship between small size at birth and elevated serum triglyceride concentrations. The studies include children and adults. Although serum cholesterol concentrations are known to track from early childhood it does not follow that the effects of an adverse prenatal influence would necessarily be apparent in childhood. The effect of low birthweight on childhood blood pressure, for example, is trivial. Presumably for much of life other regulatory mechanisms can compensate for reduced nephron numbers or some other functional limitation acquired before birth. Ultimately, with ageing, homeostasis can no longer be maintained and disease develops.

Notwithstanding this, it is necessary to consider why an effect on lipid metabolism that is so easily demonstrated in laboratory animals cannot be so readily shown in humans. One explanation could be that there are, as yet, insufficient data; but there are other, more interesting possibilities. An obvious one is that effects of birthweight are being obscured by the subsequent effects of infant feeding. There has been considerable speculation that the high cholesterol and saturated fat content of human milk may be important in establishing how the liver synthesizes and excretes cholesterol in later life. The liver is one of the few organs that continues to be plastic after birth, while other organs such as the kidney have completed their critical periods of development. Although the authors write that the evidence is ‘contradictory’, a recent systematic review of 37 studies concluded that breastfeeding is associated with lower serum concentrations of total and low-density lipoprotein (LDL) cholesterol in adult life.5

Another possibility is that birthweight is not the appropriate marker for these aspects of intrauterine conditions, more specifically nutrition, that affect lipid metabolism. People who were conceived during the Dutch famine had a more atherogenic profile than people not exposed to famine in utero.6 They had higher ratios of LDL to high-density lipoprotein (HDL) cholesterol. The effect of famine was independent of size at birth. Among middle-aged men in Beijing elevated total and LDL cholesterol concentrations were not related to low birthweight, but were related to low maternal body mass index in early pregnancy—a finding that accords with that in the Dutch famine.7 Both these observations in humans resonate with those in animals. In rats a brief 4-day period of maternal

---

76 Henry JA, Bolla M, Osmond C, Fall C, Barker DJP, Humphries SE. The effects of genotype and infant weight on adult plasma levels of fibrinogen, factor VII, and LDL cholesterol are additive. J Med Genet 1997;34:553–58.
undernutrition at the time of conception was found to reduce liver size at birth. In a study of middle-aged men and women in Sheffield, cited in the review, neither total nor LDL cholesterol concentrations were related to birthweight, but each was strongly inversely related to abdominal circumference at birth. This measurement reflects liver size as well as abdominal fat, and the association was specific: chest circumference at birth, for example, was not related to serum lipid concentrations. A small abdominal circumference at birth also predicted death from CHD among men. Unfortunately, very few data sets include this birth measurement, and the observation has not been replicated.

Measures of maternal nutrition, or measures related to fetal liver development may therefore be needed to understand the developmental origins of elevated serum cholesterol concentrations. The authors of the review mention another possibility. Interactive effects of a common genetic polymorphism and birthweight on indices of insulin resistance have recently been reported in the Helsinki study. The polymorphism was only associated with insulin resistance in people who had low birthweight: low birthweight was only associated with insulin resistance in people with the polymorphism. There are similar findings for total and LDL cholesterol concentrations (unpublished).

Interactions with the effects of birthweight are not confined to genes. The effects of low birthweight on hypertension depend on living conditions in childhood. The effects of low ponderal index (birthweight/length$^3$) on CHD depend on social class and income in adult life. We are beginning to understand how the same disease can be the result of different pathways of development. There is not ‘an’ effect of low birthweight on a biological risk factor such as raised serum cholesterol—an effect best estimated from all published studies. There are a number of effects, depending on what, in a particular individual, preceded low birthweight and what followed. The systematic review published here gives a helpful overview, but understanding of disease causation will require disentangling heterogeneity. The assumption of homogeneity in a single pooled analysis, as in a recent review of birthweight and blood pressure, will not give useful insights into the developmental origins of adult disease and health.

References