Invited commentary

Fatal flaw in the fetal argument

Over the past 20 years there has been an increasing amount of attention given over to the idea that size at birth may be an important determinant of chronic disease, and in particular of CVD, in later life. Although not an entirely new concept, with variants of the theory having first been propounded back in the early 20th century by Kermack *et al.* (1934) and then later by Forsdahl (1977), its more recent resurgence was in part due to the suggestion that classical risk factors, such as blood pressure, cholesterol and smoking, had limited ability to predict CHD (Godfrey & Barker, 2000).

The fetal origins hypothesis suggests that, as a response to an intra-uterine assault such as inadequate nutrition, the fetus adapts by selectively partitioning the nutrient supplies to organs such as the brain at the expense of visceral organs, including the liver and muscle, a process known as 'brain-sparing' (Barker, 1993). Consequently, depending on the timing of the intra-uterine assault, the infant is either born small-for-gestational-age or born with normal body weight but with a disproportionate body size (e.g. long and thin). Such a response is thought to confer a survival advantage on the undersized baby, but subsequently to render the individual susceptible to the development of chronic disease risk factors, including high blood pressure, insulin resistance and abnormal lipid profiles in adult life (Barker, 1993). Most of the evidence in support of the hypothesis has come from observational epidemiological studies that have related small size at birth to increased risk of disease in later life. Such studies, however, are often beset by a number of methodological problems – chief among which is confounding, and if the study is small, random error (or 'chance') – both of which may generate a spurious association between a risk factor and an outcome (MacMahon & Collins, 2001).

One method by which to overcome the role of chance in generating an association (i.e. reduce random error) is to aggregate all available data in a meta-analysis (Egger & Davey Smith, 1997). We recently published a meta-analysis of seventy-nine studies (with information on more than 70 000 individuals) that reported on the association between birth weight and lipid variables (Huxley *et al.* 2004). It was concluded that size at birth had a negligible impact on total cholesterol levels in adult life and that previous impressions of a robust link may have been reinforced by the large number of reports of associations between birth weight and other components of the lipid profile (Huxley *et al.* 2004). For example, in that review, associations with birth weight were also provided for blood levels of HDL-cholesterol in forty-six of the seventy-nine studies, LDL-cholesterol in thirty-four studies, triacylglycerols in forty-three studies, apo A in thirteen studies, and apo B in fourteen studies. But most of these associations were null, including those for triacylglycerols

(in contrast with a recent review; Lauren *et al.* 2003), and – as was the case for total cholesterol – inverse associations tended to be observed more commonly in smaller studies. In line with these findings, the study by Tuya *et al.* (2006), published in the present issue of *British Journal of Nutrition*, showed no evidence of a relationship between birth size and later lipid levels among twins, whereas in the smaller sample of singletons, weak inverse associations between birth weight and total cholesterol, and with LDL-cholesterol, were reported. Similar to previous twin studies that were unable to demonstrate associations between size at birth and subsequent risk, the authors invoke the '*post hoc*' proposal that twins might experience a special type of growth retardation to explain these differences (Vågerö & Leon, 1994).

An alternative, simpler explanation is that confounding, for example by social class, may have generated the reported inverse associations between birth weight and cholesterol in singletons. Although the authors controlled for the important effects of age, sex and gestational age, they were unable to adjust for social class, an important limitation when considering the impact of socio-economic status on lifestyle factors (such as smoking, physical activity and diet) that are related both to birth weight and, independently, to cardiovascular risk factors (including blood cholesterol; Luepker *et al.* 1993; Bucker & Ragland, 1995). In an earlier review of the association between birth weight and subsequent blood pressure we demonstrated how failing to adjust for important confounders could substantially inflate the reported inverse association between birth weight and subsequent blood pressure (Huxley *et al.* 2002*a*).

An advantage of twin studies is that because twins experience similar environments before birth and in childhood, studies within twin pairs should be less prone to the effects of confounding by other factors than are studies involving singleton births. Moreover, analysis of monozygotic twin pairs alone should avoid any genetic effects on the association between birth weight and blood cholesterol level in later life. Twins also tend to differ more substantially in weight (often by as much as 1 kg) than do singletons, so any associated differences in subsequent risk factor levels should be greater between twins. The lack of any association between birth size and lipids in twins reported by Tuya *et al.* (2006) suggests that confounding, rather than a differential growth process, may be driving the weak inverse associations observed in singletons.

Supporters of the fetal origins hypothesis criticize birth weight as being a crude measure of fetal growth, which it is, and advocate it should be replaced by more accurate indicators of maternal and fetal nutrition. However, evidence from animal and human studies of maternal diet also tends to suggest that maternal undernutrition and lower birth weight are not strongly associated with higher

blood cholesterol levels in offspring. For example, one study found that restricting protein intake by pregnant rats led both to reduced birth weight and to reduced – rather than increased – blood cholesterol levels in the adult offspring (Lucas *et al.* 1996). Similarly, in human populations, the Dutch Famine study found that individuals who were exposed *in utero* to maternal undernutrition during mid or late gestation had lower – not higher – blood cholesterol levels in adult life than did non-exposed controls (Roseboom *et al.* 2000). Nor was any association found between birth weight and subsequent blood total cholesterol in either the Dutch Famine study (Roseboom *et al.* 2000) or the Leningrad Siege study (Stanner *et al.* 1997). In contrast, there is some evidence from a randomized trial of preterm infants that nutrition in early infancy may influence subsequent lipid levels in adolescents (Singhal *et al.* 2004).

Since large babies tend to become large adults, even if there is a causal association between lower birth weight and higher blood cholesterol, this effect might well be outweighed by the lower cholesterol level that is associated with the lower current weight associated with lower birth weight. Moreover, realistic increases in birth weight would be associated with total cholesterol levels only 0.005 mmol/l lower, which might be expected to reduce coronary disease risk by less than 0.025 % (Huxley *et al.* 2002*b*). Hence, from a public health perspective, small changes in birth weight are unlikely to materially influence cardiovascular risk in later life. Moreover, with recent epidemiological studies demonstrating that classical risk factors can explain between 80 and 90 % of the global burden of CVD (Yusuf *et al.* 2004), the suggestion that the early-life environment is an important determinant of subsequent CVD risk remains, at best, controversial.

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