infancy. They found that the effect of birthweight on motor development was not fully mediated by infant growth measures.

Moreover, the impact of fetal and infant exposures may be modified by the childhood environment. For example, Kelly et al.\textsuperscript{13} investigate potential effect modification of the association between birthweight and childhood behaviour by social class. Although their study is inconclusive, this line of investigation should be applied in other studies of birthweight and health. Estimating the presence and extent of modification is important not only to understanding the underlying causal processes but also in designing public health and social policy interventions.

Whereas most of the studies in this issue concern the period after birth, Shaw et al.\textsuperscript{12} and Raum et al.\textsuperscript{13} focused on the period before it. For insight into underlying processes which can illuminate the direction as well as the components of causal relationships, it is vitally important to collect information about the prenatal period.

**Confounding by social class**

Those sceptical of the fetal origins hypothesis can still make a plausible argument that confounding by social environment may explain the observed associations. Social class, for example, is strongly related to birthweight as well as child and adult health. Most of the studies presented in this issue adjust for social class through proxies such as maternal education but none of the measures are entirely satisfactory. Given the strength of social class effects and the more modest associations between birthweight and health, residual confounding due to measurement error is entirely possible. Twin studies might refute this challenge,\textsuperscript{14} but these are few and the results are sometimes inconsistent. Novel study designs may be needed before the controversy can be put to rest. One such approach may be to compare health outcomes in a large number of same sex siblings who are discordant on measures of early experience such as birthweight.

In sum, the collection of studies in this issue are revealing both of how far the field of fetal origin research has come and of how far it still has to go. As we continue to improve the measures of early experience, to formulate better the causal pathways we want to test, and to implement new approaches to control for social class confounding, further advance will undoubtedly result.

**References**

accompanied by an emerging interest in its relevance to a wide range of other outcomes from breast cancer to schizophrenia. Some researchers, particularly in perinatal epidemiology, have embraced the fetal origins hypothesis seeing in it a fresh rationale for their work. This is illustrated by the paper by Raum et al. in this issue of the *International Journal of Epidemiology*. They report that maternal education is inversely associated with impaired fetal growth in East as well as West Germany in the period around the collapse of the Berlin Wall in 1989. This is an important observation in its own right, providing further demonstration of the existence of socio-economic differences in societies organized on a very different basis to those of Western Europe and North America. However, what is striking is that the authors motivate their study (in part) by stating that ‘Poor intrauterine growth … determines human susceptibility to disease … in later life.’ While this appeal to the fetal origins hypothesis is understandable it reflects the view that regardless of cause, all variation in fetal growth or size at birth leads to variation in risk of later disease. However, this is clearly not the case, as has been shown by the observation that twins, despite being lighter at birth than singletons, do not as a group have higher blood pressure or an increased risk of coronary heart disease. Intra-uterine growth is a complex outcome that is influenced by a wide range of factors including fetal genotype, maternal physiology and behaviour as well as the function of that crucial interface—the placenta. Whether the type of intra-uterine growth retardation seen in mothers with low education is associated with an increase in risk of later disease in the offspring is an important but unanswered question.

The role of maternal nutrition in the fetal programming debate is a particularly vexed one. The crucial distinction between fetal and maternal nutrition is one that is spelt out in the incisive contribution by Harding also in this issue of the *IJE*. She identifies some of the key problems that exist in generalizing to humans from the impressive body of work based on animal models that provides unequivocal proof of concept that manipulation of maternal nutrition can programme the physiology of offspring. The human epidemiological evidence, however, is meagre and equivocal. The results of follow-up of people *in utero* during the Dutch Hunger winter, while suggestive, are far from conclusive. Thus Law et al. in their paper in this issue of the *IJE*, are absolutely right in saying that ‘the long-term effects on the offspring of the promotion of nutrition and health of girls and young women deserve further study’. The evidence for such interventions having any substantial effect on size at birth, let alone later blood pressure or risk of cardiovascular disease is minimal. The follow-up of offspring involved in nutritional and other trials to improve pregnancy outcome is a priority for future research.

If fetal, and even maternal nutrition, has a role in programming in humans it may be that it is the balance of particular nutrients or levels of micronutrients that are important rather than the absolute levels of macronutrients. While not usually considered in the fetal origins debate the crucial influence of maternal micronutrient intake in pregnancy on fetal development is exemplified by the increased risk of neural tube defects associated with maternal folate deficiency. It is thus interesting that the paper by Shaw et al. in this issue of the *IJE*, suggests that low maternal weight gain during pregnancy is associated with increased risk of neural tube defects even with adjustment for a host of known risk factors (including folate supplementation). However, their interpretation of this association is suitably cautious, and they suggest that carrying a fetus with a neural tube defect in itself may lead to lower weight gain. This sort of ‘reverse causality’ explanation could be usefully deployed in the main-stream fetal origins debate. Could it be that impaired fetal growth is a consequence of some specific environmentally induced changes in fetal development that are themselves associated with risk of later disease? In this respect, size at birth is simply an epi-phenomenon, with no direct causal role, consistent with some of the animal work that has shown that manipulations in pregnancy can programme later function in the offspring without affecting size at birth.

The current focus on the fetal origins of conditions such as cardiovascular disease, diabetes and cancer overshadows the fact that the oldest and largest literature on ‘early’ and prenatal origins of later disease relates to psychological and mental disorders. Two other papers in this issue of the *IJE* can be seen as a return to these older preoccupations. Cheung et al. relate the development of motor skills in childhood to *in utero* and postnatal growth in Pakistani infants while Nilsson et al. look at whether birth weight is associated with performance in psychological tests used at Swedish military conscription to identify men resistant to stress.

The literature on the early life antecedents of psychological and mental disorders predates the current interest in fetal programming by many years. In the couple of decades following the end of the second world war there was considerable interest in the fetal and obstetric determinants of ‘mental disorders’ and ‘mental retardation’ in particular. Much of this earlier literature was based on a model of injury to the brain either *in utero* or at delivery, rather than with more subtle changes in structure and function thought to be associated with growth impairment that are central to the current models of fetal programming. In a 1953 paper on the association of maternal and fetal factors with ‘mental deficiency’, Pasamanick and Lilienfeld suggested that there ‘is a continuum of reproductive causality, consisting of brain damage incurred during the prenatal and paranatal periods as a result of abnormalities during these periods, leading to a gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, behaviour disorder and mental retardation’. A few years later MacMahon and Sawa in one of several large reviews of this area, talked of the ‘voluminous’ literature on ‘prenatal influences in mental disease’. In the concluding paragraph of their review it is intriguing that they appear to anticipate the more recent interest in the later consequences of fetal growth: ‘The possibility that functional disorders may be related to … birth weight are facts that have a theoretical significance far deeper than that which is immediately apparent.’

In the 1960s researchers in the UK and the US were particularly active in working on the aetiology of ‘menta retardation’. Indeed David Barker himself published work on the fetal and obstetric antecedents of intelligence, funded in part by the America Association for the Aid to the Crippled Child. This organization also funded one of the largest population based surveys of ‘mental retardation’ conducted anywhere. The 1962 Aberdeen Reading Survey administered standard psychometric tests to 14 000 primary school children and linked them to details concerning their births and other earlier childhood
factors. One of the central concerns of this study was to disentangle the effects of fetal and postnatal socio-economic factors. It concluded that the risk of ‘mental retardation’ (excluding children with IQ < 50) was related to ‘an interaction of social-environmental circumstances, familial factors and ill-defined features of reproductive inadequacy’. This in many respects is a ‘life-course’ perspective which acknowledges the complex interplay between biological and social factors played out from conception to adulthood.

The Aberdeen cohort is currently being revived as a platform for investigating fetal and postnatal influences with a primary focus on adult and physician health and disease. In a similar way, the initial interest in the consequences of maternal malnutrition on the intelligence of offspring that drove the early work on the Dutch Hunger winter has now given way to studies that look at the effect of in utero exposure to famine on cardiovascular disease and diabetes. Addressing the current debate about the role of maternal nutrition in the programming of adult disease, it is salutary to recall that the initial research on prenatal exposure to the Dutch famine failed to find any evidence of an effect on mental performance at age 19 years.

Finally, it is worth observing that the current interest in the fetal programming of adult disease shares a key theme with the older tradition: the sensitivity of the developing brain in utero. Whereas the earlier work on mental disorders sought to find evidence of the brain’s vulnerability to in utero insults, one view on the programming of cardiovascular disease is that it is the consequence of fetal adaptations to impaired nutrition that are made in order to protect the developing brain. Efforts to integrate the emerging evidence that fetal growth impairment may affect mental disorders and cognition with the ‘brain-sparing’ explanation for the fetal programming of cardiovascular disease are likely to be highly informative.

References
