

Fetal origins of cardiovascular risk: evidence from studies in children

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Increasing evidence has suggested that events occurring before birth and in infancy may influence the risk of adult cardiovascular disease (Barker, 1994). A remarkable series of historical cohort studies has demonstrated associations between small size at birth and increased prevalence of and mortality from adult cardiovascular disease (Barker *et al.* 1989, 1993*b*; Fall *et al.* 1995). Associations have also been demonstrated between size in early life and adult cardiovascular risk factors. Small size at birth or in infancy has been consistently related to higher levels of adult blood pressure (Barker *et al.* 1989, 1990; Leon *et al.* 1996) glucose intolerance and non-insulin-dependent diabetes mellitus (NIDDM; Hales *et al.* 1991; Barker *et al.* 1993*a*; Phipps *et al.* 1993; Lithell *et al.* 1996). A smaller number of studies have also suggested associations between small size at birth and elevated levels of total and LDL-cholesterol (Barker *et al.* 1993*b*) and plasma fibrinogen (Martyn *et al.* 1995*b*). Although these associations could in theory be confounded, particularly by social and behavioural factors operating later in the life course (Elford *et al.* 1991; Paneth & Susser, 1995), this has not been demonstrated in practice (Barker *et al.* 1990; Hales *et al.* 1991; Fall *et al.* 1995). It has been suggested that maternal undernutrition underlies these relationships between small size at birth and adult cardiovascular risk, and that improvement in maternal nutrition might lead to reduction in adult cardiovascular risk (Barker, 1994). Programming, a process in which stimuli acting at a critical period of development have a long-term influence on biological structure or physiological function (Lucas, 1991), has been implicated as a potential mechanism of these associations.

The 'fetal origins' hypothesis: outstanding questions

Several important issues about the 'fetal origins' hypothesis have still to be clarified. First, most of the original historical cohorts were based on subjects born in the early years of the twentieth century, when environmental circumstances during pregnancy and childbirth (reflected in markedly higher perinatal and infant mortality rates) were different from those prevailing today. However, the public health importance of the 'fetal origins' hypothesis

depends on the influence of fetal factors on the development of cardiovascular risk in contemporary mothers and children. A second important issue is the relative importance of the fetal environment and the environment later in life (including both the childhood and the adult environment). Studies of migration in adults have consistently demonstrated that the adult environment makes an important contribution to the development of adult cardiovascular risk (Elford *et al.* 1989). More recently, several studies examining the relationship between fetal factors and adult cardiovascular risk have suggested that the effects may be concentrated in subjects who have become obese in adult life (Frankel *et al.* 1996; Leon *et al.* 1996; Lithell *et al.* 1996). It is important, therefore, to establish not only whether the associations between fetal factors and later cardiovascular risk become apparent in childhood, but also to examine the interplay of fetal factors and later influences, particularly subsequent obesity. Although it is clearly not possible to examine cardiovascular events as outcomes in this age-group, the associations between size at birth and risk factors, particularly blood pressure, glucose tolerance and insulin (which show the most consistent relations in adulthood), can be examined in childhood.

Size at birth and cardiovascular risk factors in childhood

Birth weight and blood pressure

Consistent inverse relationships have been described between birth weight and blood pressure in several studies in pre-adolescent children aged between 3 and 11 years (Whincup *et al.* 1989, 1992, 1995; Law *et al.* 1991; Hashimoto *et al.* 1996; Moore *et al.* 1996; Taylor *et al.* 1997*a*). The strength of these associations has been reasonably consistent, with an increased systolic pressure of about 2 mmHg/kg reduced birth weight (Law & Shiell, 1996). While in early childhood the effects appear to be similar in both sexes, at the end of the first decade the effect appears to be concentrated in girls (Whincup *et al.* 1995; Taylor *et al.* 1997), for reasons which are not apparent. However, in virtually all studies, the presence of the inverse

relationship between birth weight and blood pressure in childhood has been dependent on previous adjustment for current body size, usually adjusted in the form of weight (Law & Shiell, 1996).

Size at birth, glucose tolerance and insulin resistance

The limited data on associations between birth weight, glucose tolerance and insulin resistance in earlier studies in children have been inconsistent. Yajnik *et al.* (1995) studied two groups of Indian children, one with a history of normal birth, the second a group of predominantly low-birth-weight infants looked after in a special care baby unit. The first (normal birth) study suggested that low birth weight was related to raised post-load glucose concentration. However, this finding was not supported by the second study, nor by two studies of older British children (Law *et al.* 1995; Whincup *et al.* 1997) and a study of Jamaican children (Forester *et al.* 1996). Neither of the studies by Yajnik *et al.* (1995) and Law *et al.* (1995) showed any relationship between birth weight and fasting insulin, although in the Yajnik *et al.* (1995) study of normal births, birth weight showed an inverse association with post-load insulin. The larger studies of Whincup *et al.* (1997), however, showed consistent inverse relationships between birth weight and both fasting and post-load insulin after adjustment for current body size. The suggestion that low birth weight was related to insulin resistance in these subjects was supported by the results of analyses using the homeostasis model assessment (Matthews *et al.* 1985) in fasting subjects (Whincup *et al.* 1997); the findings were consistent with recent reports in adults (Phillips *et al.* 1994; Lithell *et al.* 1996) suggesting that low birth weight is related to insulin resistance rather than pancreatic β cell dysfunction.

Other measures of size at birth

Birth weight is clearly a crude measure of size at birth. In studies of adults it has been suggested that more specific measures of size at birth, perhaps indicating fetal under-nutrition at critical periods of gestation, are more important (Barker, 1994, 1995). Among the markers implicated have been thinness at birth (thought to reflect undernutrition in the second trimester), shortness in relation to head circumference (third trimester undernutrition) and placental ratio (placental weight : birth weight; Barker *et al.* 1990, 1992). However, the evidence that any of these markers is more strongly related to blood pressure, glucose tolerance or insulin resistance than birth weight is weak in children. Although two studies have suggested that childhood blood pressure may increase with placental weight (Law *et al.* 1991; Moore *et al.* 1996), other studies have reported that the relationship between placental size and blood pressure, like that of birth weight and blood pressure, tends to be inverse (Williams *et al.* 1992; Whincup *et al.* 1995; Taylor *et al.* 1997). Similarly, although single dimensions of size at birth (head circumference, crown-rump length) may be inversely related to blood pressure and insulin level in childhood (Forrester *et al.* 1996; Taylor *et al.* 1997;

Whincup *et al.* 1997), there is no evidence that thinness at birth or length:head circumference are related to blood pressure or insulin level in children. Thus, in studies of childhood to date there is no strong evidence to suggest that any marker of size at birth is making a stronger contribution to the development of later cardiovascular risk than birth weight.

Size at birth and cardiovascular risk factors in childhood: the importance of childhood size

Childhood size: confounder or mediator of birth-weight relationships?

In childhood the inverse relationships between birth weight, blood pressure and insulin are only apparent after adjustment for current childhood size, carried out in most studies using current weight (Law & Shiell, 1996). Such adjustment would be appropriate if current body size were a confounder of the birth weight–risk factor relationship. However, if current size were a mediator, adjustment might be misleading (Paneth & Susser, 1995). So does the unadjusted or the adjusted model provide a better guide to the long-term influence of birth weight on blood pressure? Since the association between birth weight and current weight tends to weaken with increasing age (although a residual association persists in adulthood; Kuh & Wadsworth, 1989), it might be argued that current body size is a confounder and adjustment is, therefore, appropriate. However, a more refined approach might be to separate current weight into two components, height and weight-for-height, and consider these separately. Birth weight is related to both variables in childhood. However, height, although strongly related to blood pressure and insulin level in childhood, shows no such relationships in adult life (Walker *et al.* 1989; Perry *et al.* 1996), suggesting that height may be a reasonably pure confounder of the birth weight–risk factor relationships. On the other hand, weight-for-height is strongly related to blood pressure and insulin levels both in childhood and in adult life, and adjustment is, therefore, less appropriate. In more conservative analyses of the relationships between birth weight, blood pressure and insulin, adjusted for height alone, the inverse relationships between birth weight, blood pressure and insulin in childhood are still present and statistically significant, although weaker in strength (Taylor *et al.* 1998).

Relative importance of childhood size

It is important to assess the relative contributions of birth weight and current factors to the development of blood pressure and insulin levels. In childhood, body size is an important determinant of blood pressure and insulin levels. Weight-for-height in childhood is a particularly important marker in this context, because it continues to influence risk factors into adult life, and because childhood obesity is an important contemporary health problem. The relative contribution of birth weight and childhood ponderal index (weight/length³) to levels of blood pressure and insulin at 10–11 years have been reviewed recently (Taylor *et al.* 1997; Whincup *et al.* 1997). The influence of a standard

increase (one standard deviation or interquartile range) in childhood ponderal index was associated with an increase in childhood blood pressure and insulin level about three times greater than that of an equivalent decrease in birth weight (adjusted both for childhood height and ponderal index; Taylor *et al.* 1997; Whincup *et al.* 1997). In analyses adjusted for childhood height alone, the imbalance between birth weight and current size becomes still more marked. A review of data from other studies suggests that the same pattern is likely to apply (Whincup & Cook, 1997). Thus, the results of studies in childhood suggest that, while fetal factors may have a continuing influence on blood pressure and insulin level, the effects are dominated by the influence of childhood obesity. However, two important questions then remain. First, the influence of fetal factors on blood pressure and insulin might be particularly strong in a subgroup of the population (particularly those developing later obesity). Second, the associations might become stronger with increasing age. These questions are addressed in the following sections.

Are the effects of fetal factors stronger in obese children?

In adults, findings from studies examining cardiovascular events, blood pressure and insulin levels have suggested that the influence of size at birth on blood pressure and insulin may be particularly concentrated among subjects who are obese in adult life (Frankel *et al.* 1996; Leon *et al.* 1996; Lithell *et al.* 1996). Among studies of birth weight and blood pressure in childhood, relatively few have reported studying this issue and the findings so far reported do not suggest that the effects are stronger in obese children (Whincup *et al.* 1989, 1992). Among studies of birth weight and insulin resistance in childhood, the study by Whincup *et al.* (1997; who found the most consistent birth weight–insulin relationships) also provided some evidence that the relationship between birth weight and fasting insulin level was particularly strong in the most-obese children.

Birth weight–risk factor associations: will they be amplified between childhood and adulthood?

It is clearly important to establish the natural history of the relatively weak associations between birth size, blood pressure and insulin level observed in childhood. Apart from the possibility that the associations will become increasingly independent of later body size, it has been suggested that the associations might be ‘amplified’ with increasing age (Law *et al.* 1993), a phenomenon which might be consistent with the occurrence of ‘programming’. This possibility has been examined for blood pressure, but not so far for other risk factors. Evidence for the possible amplification of the birth weight–blood pressure relationship was first provided by Law *et al.* (1993), who examined one cross-sectional and three longitudinal studies relating birth weight and blood pressure and different ages and suggested that the birth weight–blood pressure relationship appeared to become stronger with increasing age from childhood onwards. However, the comparison, based mainly on cross-sectional data rather than longitudinal

data, provided only indirect evidence of amplification. Moreover, the extent of amplification has appeared less dramatic as more data have become available (Law & Shiell, 1996). Undoubtedly some amplification of the inverse birth weight–blood pressure relationship must occur in early childhood, because it is not present at birth, when the relationship between weight and blood pressure is positive (Whincup *et al.* 1992), but the inverse relationship has been described in 3- and 4-year olds (Law *et al.* 1991; Hashimoto *et al.* 1996). Some direct evidence for the possibility of amplification in later childhood was provided by a longitudinal study of 540 children followed between 5–7 and 9–11 years, in whom the relationship between birth weight and blood pressure almost doubled in strength (Whincup *et al.* 1995). However, this effect was seen predominantly in girls and has not yet been further substantiated. Moreover, despite the evidence of an absolute increase in the strength of the birth weight–blood pressure relationship, this study did not provide evidence that the relative strengths of the associations between birth weight and childhood obesity had changed.

There is little direct evidence of the natural history of the birth weight–blood pressure relationship passing through adolescence into adult life. This is an important period to study, because blood pressure and insulin levels both rise rapidly at this time (Orchard *et al.* 1980; Jiang *et al.* 1995). Among cross-sectional studies carried out at this time, some, but not all, have observed the presence of inverse birth weight–blood pressure relationships (Law & Shiell, 1996). The only reported follow-up study between childhood and adolescence failed to find an inverse association between birth weight and blood pressure at 17 years, but with only 121 subjects had very limited power to do so (Williams *et al.* 1992). Follow-up of larger cohorts of children through to adult life will be needed to address this issue.

Are blood pressure and insulin level the best markers of cardiovascular risk development in children?

The choice of blood pressure and insulin levels as outcomes for studies in children reflects their status as established cardiovascular risk factors in adult life (MacMahon *et al.* 1990; Perry *et al.* 1996), the consistency of their relationships with size at birth in adult life (Barker, 1994), and the evidence that they track between childhood and adult life (Andre *et al.* 1986; Jiang *et al.* 1995). However, it is possible that the conclusions drawn about the strength of evidence for the ‘fetal origins’ hypothesis may depend on the particular outcome marker studied. In adults, studies of the relationship between size at birth and cardiovascular outcome have focused not only on risk factors, but also directly on vascular structure, demonstrating, for example, that low birth weight is related to diminished arterial compliance in middle age (Martyn *et al.* 1995a), although it is difficult to be certain whether the effect is a direct one or perhaps mediated by changes in blood pressure. In children, studies have suggested that low birth weight may be related to increased left ventricular mass (Vijayakumar *et al.* 1995). More recently, there has been considerable interest

in indicators of endothelial function as possible markers of early atherosclerosis. In one recent population-based study, the relationships between birth weight, childhood size, childhood risk factors and endothelial function were examined in 333 9–11-year-old children using flow-mediated dilatation as a marker of endothelial function (Leeson *et al.* 1997). In that study, birth weight showed a consistent graded relationship with flow-mediated dilatation in the brachial artery (low birth weight, therefore, being associated with diminished endothelial function), while childhood size and childhood risk factor levels (including blood lipids and blood pressure) showed no relationship at all with flow-mediated dilatation. These findings require substantiation, and their interpretation depends on the validity of flow-mediated dilatation as a long-term marker of vascular risk. However, they emphasize that the apparent influence of fetal factors may depend on the outcome measure used, and that valid markers of early changes in vascular structure or function occurring as a result of early vascular disease are urgently needed.

Conclusions and areas for further research

The data presented suggest that in contemporary children, as in adults, small size at birth is related to higher levels of risk factors such as blood pressure and insulin, and possibly to measures of endothelial function. Among the measures of size at birth studied to date, birth weight remains the factor most consistently related to blood pressure in offspring. However, the influence of birth weight on blood pressure and insulin level is relatively small compared with that of later body size, particularly childhood obesity. Future research needs to focus on three aspects. First, longitudinal studies examining the development of cardiovascular risk between childhood and adult life are needed to examine whether the birth weight–risk factor relationships do become amplified in the transition from childhood to adulthood, and how their strength compares with that of contemporary factors (body build, diet, physical fitness and activity). Second, more direct markers of the early development of cardiovascular risk need to be identified for study in relation to birth weight and other potential determinants of early risk development. Third, the extent to which the relationships between size at birth and later cardiovascular risk reflect maternal undernutrition needs to be established, and the nutritional factors responsible identified.

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