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*Invited Review*

# The developmental origins of adult disease (Barker) hypothesis

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**Abstract**

Many studies have provided evidence for the hypothesis that size at birth is related to the risk of developing disease in later life. In particular, links are well established between reduced birthweight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. These relationships are modified by patterns of postnatal growth. The most widely accepted mechanisms thought to underlie these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure. It is suggested that the fetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life. These changes may include epigenetic modification of gene expression. Less clear at this time are the relevance of fetal programming phenomena to twins and preterm babies, and whether any of these effects can be reversed after birth. Much current active research in this field will be of direct relevance to future obstetric practice.

**Key words:** coronary heart disease, developmental origins of adult disease, diabetes, hypertension, programming.

## The developmental origins of adult disease

The 'developmental origins of adult disease' hypothesis, often called the 'Barker hypothesis' after one of its leading proponents, states that adverse influences early in development, and particularly during intrauterine life, can result in permanent changes in physiology and metabolism, which result in increased disease risk in adulthood. This hypothesis originally evolved from observations by Barker and colleagues that the regions in England that had the highest rates of infant mortality in the early twentieth century also had the highest rates of mortality from coronary heart disease decades later.[1] As the most commonly registered cause of infant death at the start of the twentieth century was low birthweight, these observations led to the hypothesis that low birthweight babies who survived infancy and childhood might be at increased risk of coronary heart disease later in life.

Two large studies of men born in Sheffield and Hertfordshire in the first quarter of the 20th century showed a strong relationship between death from coronary heart disease and decreasing birthweight, head circumference or ponderal index.[2,3] It was particularly people who were born growth restricted rather than premature who were at risk.[2] These results have since been replicated in other studies from many different countries,[4–6] as well as in women.[7]

Initially, it seemed likely that both low birthweight and coronary heart disease were caused by environmental or lifestyle factors, and that people who suffered poor growth early in life would continue to be exposed to these factors. However, although changes in western diet and lifestyle during the last century have contributed to the increase in incidence of coronary heart disease, adult lifestyle risk factors for coronary heart disease are not predictive of who will develop the disease and who will not. Furthermore, correction for known risk factors such as diet, smoking and exercise did not have a major effect on the relationships between birth size and subsequent disease risk.[4,5,8]

Relationships have now been described between reduced size at birth and other diseases that are known risk factors for coronary heart disease, including hypertension, type 2 diabetes mellitus and hyperlipidaemia. A recent systematic review reported that the majority of 80 studies on adults and children showed that there is a 2-mmHg decrease in systolic blood pressure per kilogram increase in birthweight.[9] This relationship is less well defined in adolescence, possibly because 'tracking' of blood pressure with age is disturbed at the time of the adolescent growth spurt.

The many reports of relationships between birth size and disadvantageous glucose and insulin metabolism have also recently been reviewed.[10] In particular, lower birthweight has been associated with increased insulin resistance, higher fasting insulin concentrations and increased incidence of type 2 diabetes mellitus. There is also some evidence of a relationship between lower birthweight and impaired insulin secretion, but this is less consistent.[11–13]

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Neonatal abdominal circumference has been shown to predict plasma cholesterol and fibrinogen levels in men later in life. Both of these are risk factors for the development of coronary heart disease.[14,15] It has been suggested that abdominal circumference at birth is at least partly reflecting liver size, growth of which may be impaired in babies born small, perhaps as a result of blood flow redistribution to vital organs such as the heart and brain at the expense of abdominal organs such as the liver. However, there is not yet any direct evidence of such a causal link.

Many other outcomes in adult life have been linked to size at birth. Reduced birthweight has been associated with an increased incidence of chronic lung disease,[16] and psychological outcomes,[17] and with characteristic changes in fingerprint patterns,[18,19] while larger birthweight has been associated with increased risk of polycystic ovarian disease and the hormone-related cancers: breast, prostate and testicular cancer.[20] However, only the diseases that have been confirmed in studies across many different populations and are widely accepted as related to small birth size will be discussed further in this review (Table 1).

It is important to note that these relationships between size at birth and later disease risk are continuous across the range of birth sizes, and are not merely confined to those infants born extremely small or recognised as growth restricted. This suggests that, whatever the mechanisms underlying these relationships, they must act within the normal physiological processes regulating intrauterine development, rather than involving pathological mechanisms applying only to abnormal pregnancy.

**Table 1** Diseases linked with birthweight

| | Reference |
|---|---|
| **Replicated and widely accepted association with small birth size** | |
| Hypertension | 9 |
| Coronary artery disease | 2–7 |
| Non-insulin dependent diabetes | 10 |
| Stroke | 145,146 |
| Dislipidaemia | 147–149 |
| Elevated clotting factors | 149 |
| Impaired neurodevelopment | 150–154 |
| **Described but less well replicated and accepted association with small birth size** | |
| Chronic lung disease | 16 |
| Depression | 155,156 |
| Schizophrenia | 157 |
| Behavioural problems | 17,158 |
| Marriage | 159 |
| Fingerprint patterns | 18,19 |
| Left handedness | 160,161 |
| Reduced uterine and ovarian size | 93 |
| Precocious pubarche | 162–165 |
| Breast cancer | 166 |
| Testicular cancer | 167 |
| **Described association with large birth size** | |
| Polycystic ovary disease | 168 |
| Breast cancer | 169 |
| Prostate cancer | 170 |
| Testicular cancer | 171 |
| Childhood leukaemia | 172 |

### *Early childhood growth and disease in later life*

The effect of small size at birth is modulated by patterns of childhood growth. Children born in Helsinki between 1934 and 1944 who went on to develop coronary heart disease, hypertension and diabetes as adults were generally short and thin at birth, had poor growth in the first year of life, but then accelerated weight gain in later childhood.[21–24] Thus, it appears that the increased risk of these diseases in adulthood in individuals with impaired growth before birth can be aggravated by growth failure in the first year after birth, and by rapid weight gain in childhood. However, it is not yet clear whether intervention at either of these times will alter these outcomes.

### *Links with placental weight*

Increased risk of various adult diseases has been described not only in babies born small, but also in those with unusual relationships between birthweight and placental weight. Babies born small in relation to the size of their placenta have an increased risk of developing hypertension.[23,25] It is interesting in this regard to note that low birthweight in relation to placental weight has also been associated with failure of catch-up growth in the first 18 months in babies born growth restricted.[26] On the other hand, babies who later developed type 2 diabetes, sometimes in combination with hypertension, were reported to have small placentas in relation to their birthweight.[23,27] This may indicate that there are different underlying mechanisms in the development of the different disorders.

## Possible mechanisms

The most widely accepted phenomenon proposed to underlie the developmental origins hypothesis is that of programming. This is the process whereby a stimulus or insult during a sensitive or critical period has irreversible long-term effects on development. Well-recognised mechanisms include altered fetal nutrition and increased glucocorticoid exposure. However, there may also be genetic and epigenetic links.

### *Altered fetal nutrition*

Fetal nutrition is a key regulator of fetal growth, and thus an obvious candidate as a possible programming influence.[28] It has proved remarkably easy in experimental animals to permanently alter postnatal physiology in a way analogous to that seen in the human studies by manipulation of maternal diet during pregnancy. In rats, both global maternal undernutrition and specific protein restriction result in reduced birthweight,[29,30] increased blood pressure[31,32] and impaired glucose tolerance[33] in the offspring. Similar effects have been reported in guinea pigs[34,35] and sheep.[36,37]

It is less straightforward to demonstrate such relationships with global nutrition in human pregnancy. However, both birthweight and placental weight are affected by the balance of macronutrients in the maternal diet.[38,39] Imbalance of protein and carbohydrate intake during pregnancy has been associated with reduced birthweight and increased blood pressure in the offspring.[40,41] Micronutrients may also play an important role in programming of postnatal pathophysiology. In an Indian study, maternal intake of fruit and green vegetables during pregnancy was positively associated with birth size and glucose tolerance in the offspring.[42,43] Higher calcium intake during pregnancy has been associated with lower blood pressure in the offspring in childhood.[44,45]

Fetal overnutrition may be an increasingly common programming stimulus in many communities. Rats that overeat during pregnancy because of experimentally induced impairment of hypothalamic satiety control give birth to offspring that have impaired glucose tolerance in later life.[46] Similarly, the offspring of rats fed a high-fat diet during pregnancy show impaired glucose homeostasis and hypertension as adults.[47,48] Infants of diabetic mothers also experience fetal overnutrition, as they are exposed to increased glucose and fatty acid concentrations before birth. There is now good evidence that these babies are at increased risk of glucose intolerance and type 2 diabetes in later life.[49–51]

There are many possible mechanisms by which altered fetal nutrition might lead to increased risk of disease in the offspring.[52] However, as a general schema, it is useful to think of altered fetal nutrition as leading, directly or indirectly, to altered growth and maturation of various fetal organ systems (Fig. 1). Permanent changes in the homeostatic regulation of these systems could then lead to increased risk of subsequent disease, especially when placed under increased stress after birth by additional risk factors such as ageing and obesity.

### *Glucocorticoids*

Another mechanism by which adult cardiovascular and metabolic disease may be programmed is via exposure to excess glucocorticoids. This may occur *in utero* if maternal

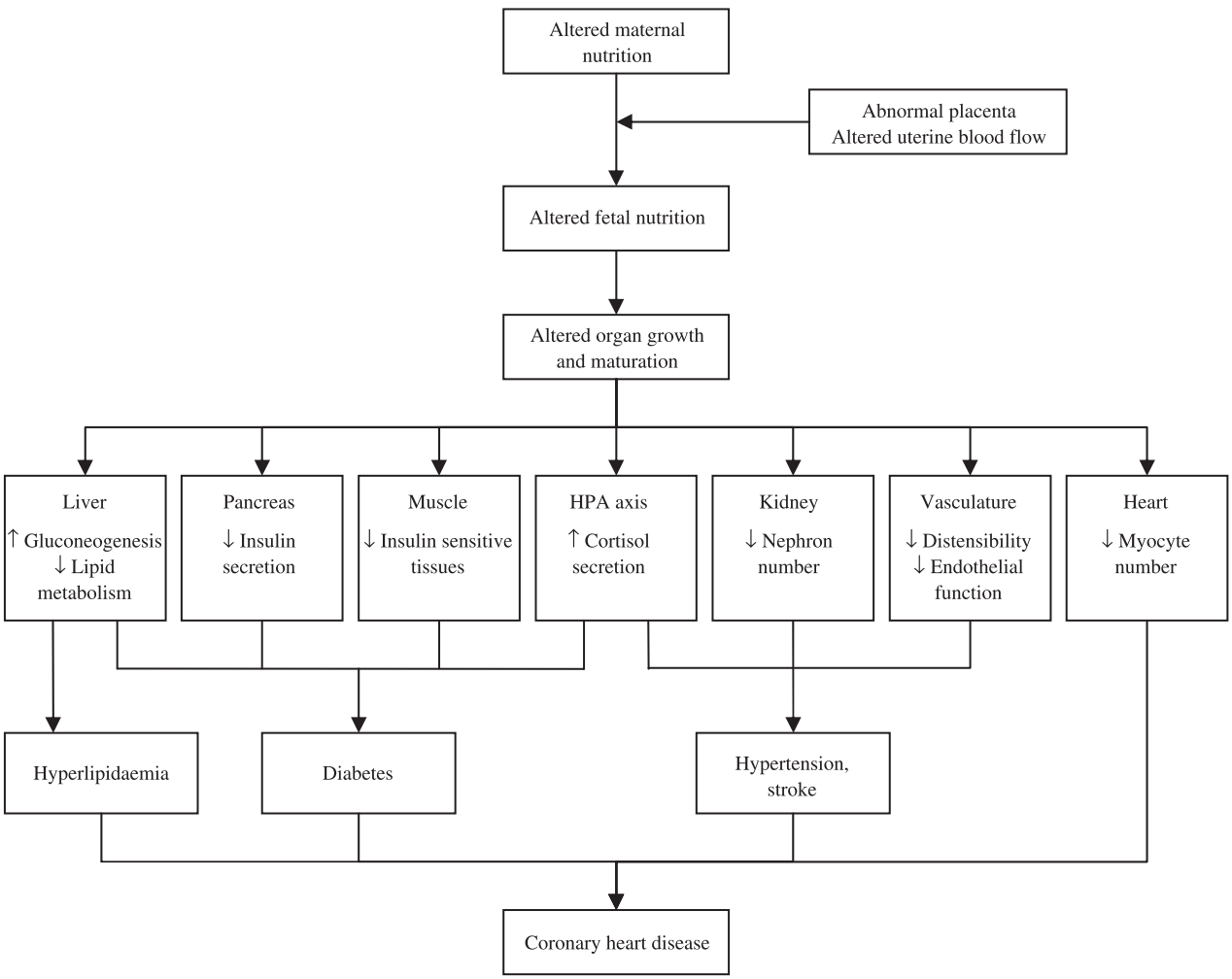


**Figure 1** Described effects of altered fetal nutrition on growth and maturation of fetal organ systems and their links with adult disease.

  

glucocorticoid levels are elevated, if exogenous synthetic glucocorticoids are administered, or if the placental barrier that protects the fetus from high levels of maternal glucocorticoids is impaired. Elevated levels of cortisol of either maternal[53] or fetal origin[54] are associated with elevated blood pressure in the sheep fetus. In rats, offspring of dams given dexamethasone during pregnancy have reduced birthweight and increased blood pressure[55] and glucose intolerance[56] in adulthood. Repeat doses of betamethasone given to pregnant sheep have similar effects.[57] Similar effects are seen in rats after inhibition of placental 11βhydroxysteroid dehydrogenase type 2 (11βHSD-2), the enzyme that inactivates cortisol in the placenta.[58,59] These effects appear to be mediated at least in part via permanent changes in the regulation of the hypothalamo-pituitary–adrenal axis in the offspring. Intrauterine glucocorticoid exposure leads to reduced numbers of glucocorticoid receptors in the hypothalamus, resulting in impaired negative feedback and hence long-term up-regulation of the hypothalamo–pituitary–adrenal axis after birth.[60] This, in turn, could contribute to increased blood pressure and glucose intolerance in the offspring.

There are intriguing data suggesting that similar mechanisms may pertain in human pregnancy. Babies born small tend to have higher basal plasma cortisol levels as adults.[61] Smaller babies also tend to have lower activity of 11βHSD-2 in their placentas.[62] Repeated administration of betamethasone or dexamethasone during pregnancy has been associated with reduced size at birth,[63,64] but no data are yet available regarding any possible long-term effects of such exposure. On the other hand, administration of a single course of betamethasone to women at risk of preterm birth has no effect on size at birth,[65] blood pressure in childhood[66] or on body size, blood pressure or plasma cortisol levels of the offspring at 30 years.[67] There is, however, a small increase in the insulin response to a glucose tolerance test, suggesting possible mild insulin resistance.[67] This finding is of no clinical significance at age 30, and is certainly not a reason to avoid giving steroids to women at risk of preterm birth, given the large and well established benefits of this treatment for the preterm infant. However, it does provide the first direct human evidence of a programming effect of prenatal glucocorticoid exposure. Only much longer follow up will show whether this has any clinical implications as this cohort ages.

It should be noted that in some circumstances, altered nutrition and glucocorticoid exposure may overlap as programming influences. Maternal dietary restriction increases maternal glucocorticoid secretion in rats,[68] reduces placental 11β-HSD-2 activity[69] and alters neonatal hypothalamo-pituitary–adrenal axis function.[70] Prevention of the rise in maternal glucocorticoid levels by maternal adrenalectomy abolishes the effect of a low protein diet on the outcomes of interest in the offspring.[71] Maternal undernutrition in sheep also alters hypothalamo–pituitary–adrenal axis function in the offspring before and after birth.[72–74] Thus, the effects of nutrition and glucocorticoids as programming stimuli may act via similar pathways to produce long-term changes in homeostatic regulation leading to increased risk of adult disease.

### *The thrifty phenotype hypothesis and predictive adaptive responses*

The 'thrifty phenotype' hypothesis first proposed by Hales and Barker suggested that adult insulin resistance and type 2 diabetes could result from the persistence of a fetal glucose-conserving adaptation in response to intrauterine hypoglycaemia.[75] During periods of maternal undernutrition the fetus reduces insulin secretion and increases peripheral insulin resistance, thus directing more glucose to the brain and heart and less to insulin-dependent tissues such as skeletal muscle.[61] When nutrient availability is abundant in postnatal life, this pancreatic β-cell defect and peripheral insulin resistance could then cause glucose intolerance and eventually diabetes. This would explain why it is mainly thin babies who then become overweight during childhood who are prone to developing type 2 diabetes later in life.[24,76]

Gluckman and Hanson have recently revised and extended this hypothesis.[77] They propose that when there is a change in the intrauterine environment, for example, nutrient restriction or high glucocorticoid levels, the fetus will make adaptations to improve its immediate chances of survival. These adaptations are often reversible. However, if the environmental changes persist, the fetus is forced to make irreversible adaptations that may or may not be immediately beneficial, but that will manifest themselves in later life. In this way the fetus is preparing itself for life in an extrauterine environment with, for example, low food availability or high levels of stress. Gluckman and Hanson coined the term 'predictive adaptive response' (PAR) for this phenomenon.[78] There are many examples of PARs from the animal world. For example, the meadow vole pup is born with a thicker coat in autumn than in spring. In this case changes in day length, signalled to the pup *in utero* by maternal melatonin levels, result in adaptive changes in coat thickness in anticipation of the extrauterine environment being cold or warm.[79] Successful adaptation to the predicted environment (a thick coat in a pup who must survive the winter) improves biological fitness. Disparities between the predicted environment and the actual environment into which the fetus is born may result in disease. This might occur if undernutrition *in utero* is followed by an abundant diet postnatally, such as a small baby born into a food-rich western society. Intriguingly, there is some evidence that the converse may also occur. Rat dams fed a high-fat diet in pregnancy have offspring with altered endothelial function and hypertension as adults.[47,80] If the offspring are also fed a high-fat diet after birth, the endothelial dysfunction, although not the hypertension, is prevented.[80]

### *Fetal insulin hypothesis*

Hattersley proposed that the relationship between small size at birth and impaired glucose tolerance in adulthood could be explained by inherited deficits in insulin secretion or action.[81] Since insulin is an important regulator of fetal growth, affected individuals with impaired insulin secretion would have impaired growth before birth, and would also go

on to have impaired glucose tolerance in adulthood. Isolated genetic polymorphisms have been described that clearly support this hypothesis.[82] However, these relatively rare changes seem unlikely to explain the very widespread relationships between birth size and later glucose tolerance described in many different populations and across the range of normal birthweights. Intriguingly, two recent studies have reported lower birthweight in the offspring of diabetic fathers.[83,84] Furthermore, fathers of low birthweight infants, who were not diabetic at the time of the birth of their child, had a nearly twofold increase in the risk of developing diabetes later in life.[83] These data suggest a link between birthweight and diabetes that is not dependent on the intrauterine environment.

### *Genetic and epigenetic links*

The link between fetal growth and adult onset disease must ultimately involve changes in gene expression, which are very likely to involve epigenetic phenomena. During early embryogenesis, DNA undergoes demethylation and remethylation; a process that involves 'labelling' of some genes as of maternal or paternal origin, and marks these genes for subsequent inactivation.[85] This epigenetic process of imprinting is thought to particularly affect many of the genes regulating fetal and placental growth.[85] In the mouse, methylation of DNA in the offspring has been shown to be altered by the level of methyl donors in the maternal diet.[86] Methylation of DNA in the fetal liver is also altered by low-protein diet during pregnancy in rats.[87] Thus, changes in the intrauterine environment may ultimately lead to altered gene expression via alterations in DNA methylation and other epigenetic mechanisms, resulting in an increased susceptibility to chronic disease in adulthood.[88]

### *Intergenerational effects*

It is now becoming clear that adverse events during pregnancy can affect not only the offspring of that pregnancy but also the next generation. It has long been recognised that the birthweight of the mother is related to the birthweight of her children.[89,90] A colony of rats fed a low-protein diet for several generations and then re-fed took three generations for fetal growth and development to return to normal.[91] A similar effect was seen during the Dutch hunger winter of 1944–1945; a 5-month period of severe famine at the end of the Second World War. Women who were severely undernourished during the first trimester of pregnancy gave birth to babies who were on average of normal birthweight, but those babies themselves then went on to give birth to smaller babies in the next generation.[92]

There are several possible explanations for these intergenerational effects on birthweight. First, the hormonal environment of the uterus of undernourished mothers may affect the developing reproductive tract of the fetus. Indeed, mothers who were small at birth have reduced uterine and ovarian size.[93] It is proposed that smaller uterine size may impose a greater 'maternal constraint' on the fetus, thereby reducing its growth, although there is not yet any direct evidence for such an effect. Second, any epigenetic changes to the genome may be passed on to the second generation.[94]

There are also intergenerational effects on risk factors for cardiovascular disease.[95] Lower maternal birthweight is associated with an increased risk of hypertension during pregnancy,[96] which in turn is associated with lower birthweight of the offspring.[97] Furthermore, maternal birthweight is negatively related to blood pressure in the offspring, regardless of maternal blood pressure during adult life.[98] This effect may be mediated by exposure to excess glucocorticoids. Second generation offspring of rats exposed to dexamethasone during pregnancy not only have reduced birthweight, but also impaired glucose tolerance.[99]

### *Periconceptional events*

Birthweight is a very crude measure of fetal growth and changes in the intrauterine environment that lead to altered risk of adult disease may not necessarily result in altered birthweight. Several studies both in experimental animals and in human pregnancy suggest that altered risk of adult disease may be linked with the maternal nutritional status around conception and implantation in the absence of altered size at birth.

In sheep, maternal undernutrition only around the time of conception is associated with preterm birth,[100] premature maturation of the fetal hypothalamo–pituitary–adrenal axis,[73] altered fetal growth trajectory and altered insulin secretion in the fetus.[101] In rats, maternal protein malnutrition only during the preimplantation period has also been shown to reduce cell numbers in the developing blastocyst, reduce birthweight and increase adult blood pressure in the offspring.[102]

Human evidence about the importance of nutrition in the periconceptional period again comes from the Dutch hunger winter studies. The offspring of women exposed to famine mid and late gestation were born smaller than unexposed babies[103] and had an increased risk of impaired glucose tolerance as adults.[104] However, the offspring of women exposed to famine in early gestation, although of normal birthweight, had a three fold increased risk of coronary heart disease as adults,[105] increased risk of obesity[106] and raised plasma fibrinogen levels.[107]

Although exposure to severe famine is rare in Western societies, maternal undernutrition around the time of conception may be more common than previously recognised. One study of an unselected series of low birthweight babies in Sydney reported that one third of mothers of the small for gestational age babies had been previously diagnosed with an eating disorder.[108] A doubling in the risk of preterm, low birthweight and small for gestational age babies have also been reported for women whose eating disorder had been treated before the beginning of pregnancy.[109,110]

## Current controversies

### *Size of the effect*

Although many studies have confirmed Barker's original description of the link between size at birth and risk of adult

  

disease, there have also been many criticisms. It has been suggested that recent systematic reviews of the link between birthweight and blood pressure are biased due to the small sample size of many of the studies.[111] Smaller studies were more likely to report more negative effects than larger studies, suggesting publication bias. However, although controlling for publication bias lessened the relationship between systolic blood pressure and birthweight, the relationship did remain significant.

The reported 2-mmHg increase in systolic blood pressure per kilogram decrease in birthweight appears to be a very small effect. However, a distinction needs to be made between physiological and pathological effects. In the American Nurses Study, the relationship with birthweight was present but weak for blood pressure, a physiological measure, and much stronger for the incidence of diagnosed hypertension, a pathological measure of much greater clinical significance.[112] Similarly, in a study of treated hypertensives, blood pressure was markedly higher in those of lower birthweight (6.4–9.4 mmHg per kilogram birthweight), although there was no relationship between blood pressure and birthweight in normotensive subjects from the same cohort.[113]

### *Twins*

Twins generally have lower birthweights than singletons,[114] so the fetal origins hypothesis might predict a higher incidence of adult disease in this population. However, mortality rates from coronary heart disease were not found to be increased in twins compared to singletons.[115–117] Furthermore, adult blood pressure did not differ between twins and their singleton siblings.[118] In contrast, there is some evidence for an increased incidence of diabetes in the twin population,[119,120] and twins have been found to have increased insulin resistance compared to singletons independent of birthweight.[121]

Studies on the relationship between birthweight and blood pressure in twins have been inconclusive. Some have shown that low birthweight is linked with elevated blood pressure[122–125] but others could not find this relationship.[126,127] However, most studies have reported an association between birthweight and glucose intolerance or type 2 diabetes in twins.[128–130] In twins discordant for glucose tolerance or diabetes the affected twin was found to have a lower birthweight than the unaffected twin,[128,129] although again, not all studies found this connection.[131]

It has been argued that twin studies can be used to separate the effects of genes and environment on the development of disease. This is based on the premise that monozygotic twins share both their genes and their uterine environment while dizygotic twins share their uterine environment but only part of their genes. However, the uterine environment may not be the same for monozygotic and dizygotic twins. The possible effects of sharing different proportions of a common placenta on fetal growth and development are well recognised, as are the effects of placental anastomoses leading to partially shared circulations, and these effects may also have long-term consequences.[132]

Finally, it has been argued that the regulation of fetal growth in twins may be fundamentally different from that in singletons. The relationship between birthweight and later disease may therefore also be different from that in singletons. Some support for this has been found in the fact that birthweight-specific mortality is lower in twins than in singletons.[133] Furthermore, the offspring of twins are generally of average birthweight while the offspring of growth restricted singletons are themselves at increased risk of being born growth restricted.[134] Few studies have compared long-term outcomes of twins with appropriate singleton controls. Thus, studies on the fetal origins of adult disease in twins need to be interpreted with caution.

### *Prematurity*

An important but as yet unanswered question is to what extent the associations with low birthweight may be influenced by gestation length rather than fetal growth. Many of the early epidemiological studies had quite limited data on gestational age of the subjects, and survival of large numbers of preterm babies is a relatively recent phenomenon so that long-term outcome studies are extremely limited. Furthermore, most of the experimental work has focused on impaired fetal growth, largely because of the lack of suitable animal models of prematurity. Nevertheless, there are now a number of studies suggesting that prematurity itself may increase the risk of several of the diseases of interest, although the relative contributions of fetal growth and gestational age remain uncertain. Blood pressure is elevated in some cohorts of young adults born preterm[135,136] and is reported to be inversely related to gestational age in some larger population studies.[137,138] Insulin resistance,[139] elevated fasting insulin levels,[135] and elevated plasma cortisol levels[140] have also been reported in young adults born preterm. If a relationship between adult disease risk and gestation length is confirmed, then this may provide some interesting new challenges for obstetric practice, since elective early delivery, even close to term, may have implications for life-long health of the baby.

### *Reversibility*

If the risk of many common diseases of adulthood in our communities is largely determined before birth, then a critical question to be addressed is the extent to which these risks may be aggravated or ameliorated by subsequent events. Since poor fetal growth is most commonly diagnosed in late gestation or even after birth, and since there are not yet any effective intrauterine treatments for the baby who is growing poorly, there has not yet been an opportunity to test directly if reversing the intrauterine growth deficit may or may not also reverse the physiological changes, although work in this area is continuing.[141]

There is some exciting new evidence that some of the programming effects of intrauterine undernutrition may be reversible after birth. The adult offspring of rats that were undernourished during pregnancy developed hyperinsulinaemia and obesity as a result of reduced locomotor activity

and overeating.[142,143] These animals also had low plasma concentrations of leptin, a hormone released by adipocytes, which is involved in the regulation of food intake, energy balance and reproduction. When they were treated with leptin in the early postnatal period, the physiological changes caused by *in utero* undernutrition were completely reversed.[144] Many more studies are needed to fully understand the biology of this and other potential treatment approaches.

## References


1 Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986; **1**: 1077–1081.

2 Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *Br Med J.* 1993; **306**: 422–426.

3 Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; **2**: 577–580.

4 Rich-Edwards JW, Stampfer MJ, Manson JE *et al.* Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *Br Med J.* 1997; **315**: 396–400.

5 Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet* 1996; **348**: 1478–1480.

6 Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ. Foetal growth and coronary heart disease in south India. *Lancet* 1996; **348**: 1269–1273.

7 Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. *Br Med J.* 1993; **307**: 1519–1524.

8 Leon DA, Lithell HO, Vagero D *et al.* Reduced foetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *Br Med J.* 1998; **317**: 241–245.

9 Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens.* 2000; **18**: 815–831.

10 Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism? – A systematic review. *Diabet Med.* 2003; **20**: 339–348.

11 Van Assche FA, Aerts L. The foetal endocrine pancreas. *Contrib Gynecol Obstet.* 1979; **5**: 44–57.

12 Beringue F, Blondeau B, Castellotti MC, Breant B, Czernichow P, Polak M. Endocrine pancreas development in growth-retarded human foetuses. *Diabetes* 2002; **51**: 385–391.

13 Veening MA, van Weissenbruch MM, Heine RJ, Delemarre-van de Waal HA. Beta-cell capacity and insulin sensitivity in prepubertal children born small for gestational age: influence of body size during childhood. *Diabetes* 2003; **52**: 1756–1760.

14 Barker DJ, Martyn CN, Osmond C, Wield GA. Abnormal liver growth in utero and death from coronary heart disease. *Br Med J.* 1995; **310**: 703–704.

15 Barker DJ, Meade TW, Fall CH *et al.* Relation of foetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *Br Med J.* 1992; **304**: 148–152.

16 Lal MK, Manktelow BN, Draper ES, Field DJ. Chronic lung disease of prematurity and intrauterine growth retardation: a population-based study. *Pediatrics* 2003; **111**: 483–487.

17 Hack M, Youngstrom EA, Cartar L *et al.* Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. *Pediatrics.* 2004; **114**: 932–940.

18 Wheeler T, Godfrey K, Atkinson C *et al.* Disproportionate fetal growth and fingerprint patterns. *Br J Obstet Gynaecol.* 1998; **105**: 562–564.

19 Godfrey KM, Barker DJ, Peace J, Cloke J, Osmond C. Relation of fingerprints and shape of the palm to foetal growth and adult blood pressure. *Br Med J.* 1993; **307**: 405–409.

20 Samaras TT, Elrick H, Storms LH. Birthweight, rapid growth, cancer, and longevity: a review. *J Natl Med Assoc.* 2003; **95**: 1170–1183.

21 Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. *Br Med J.* 2001; **322**: 949–953.

22 Forsen T, Osmond C, Eriksson JG, Barker DJ. Growth of girls who later develop coronary heart disease. *Heart* 2004; **90**: 20–24.

23 Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Foetal and childhood growth and hypertension in adult life. *Hypertension* 2000; **36**: 790–794.

24 Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia* 2003; **46**: 190–194.

25 Barker DJ, Bull AR, Osmond C, Simmonds SJ. Foetal and placental size and risk of hypertension in adult life. *Br Med J.* 1990; **301**: 259–262.

26 Harding JE, McCowan LM. Perinatal predictors of growth patterns to 18 months in children born small for gestational age. *Early Hum Dev.* 2003; **74**: 13–26.

27 Phipps K, Barker DJ, Hales CN, Fall CH, Osmond C, Clark PM. Foetal growth and impaired glucose tolerance in men and women. *Diabetologia* 1993; **36**: 225–228.

28 Harding JE. The nutritional basis of the foetal origins of adult disease. *Int J Epidemiol.* 2001; **30**: 15–23.

29 Widdowson EM, McCance RA. A review: new thoughts on growth. *Pediatr Res.* 1975; **9**: 154–156.

30 Desai M, Crowther NJ, Lucas A, Hales CN. Organ-selective growth in the offspring of protein-restricted mothers. *Br J Nutr.* 1996; **76**: 591–603.

31 Woodall SM, Johnston BM, Breier BH, Gluckman PD. Chronic maternal undernutrition in the rat leads to delayed postnatal growth and elevated blood pressure of offspring. *Pediatr Res.* 1996; **40**: 438–443.

32 Langley-Evans SC, Welham SJ, Sherman RC, Jackson AA. Weanling rats exposed to maternal low-protein diets during discrete periods of gestation exhibit differing severity of hypertension. *Clin Sci.* 1996; **91**: 607–615.

33 Ozanne SE, Hales CN. The long-term consequences of intra-uterine protein malnutrition for glucose metabolism. *Proc Nutr Soc.* 1999; **58**: 615–619.

34 Kind KL, Clifton PM, Grant PA *et al.* Effect of maternal feed restriction during pregnancy on glucose tolerance in the adult guinea pig. *Am J Physiol.* 2003; **284**: R140–R152.

35 Kind KL, Simonetta G, Clifton PM, Robinson JS, Owens JA. Effect of maternal feed restriction on blood pressure in the adult guinea pig. *Exp Physiol*. 2002; **87**: 469–477.

36 Gardner DS, Tingey K, Van Bon BW *et al*. Programming of glucose-insulin metabolism in adult sheep after maternal undernutrition. *Am J Physiol*. 2005; **289**: R947–R954.

37 Gopalakrishnan GS, Gardner DS, Rhind SM *et al*. Programming of adult cardiovascular function after early maternal undernutrition in sheep. *Am J Physiol*. 2004; **287**: R12–R20.

38 Godfrey K, Robinson S, Barker DJ, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and foetal growth. *Br Med J*. 1996; **312**: 410–414.

39 Moore VM, Davies MJ, Willson KJ, Worsley A, Robinson JS. Dietary composition of pregnant women is related to size of the baby at birth. *J Nutr*. 2004; **134**: 1820–1826.

40 Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: relation to adult blood pressure in the offspring. *Hypertension* 2001; **38**: 1282–1288.

41 Roseboom TJ, van der Meulen JH, van Montfrans GA *et al*. Maternal nutrition during gestation and blood pressure in later life. *J Hypertens*. 2001; **19**: 29–34.

42 Rao S, Yajnik CS, Kanade A *et al*. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. *J Nutr*. 2001; **131**: 1217–1224.

43 Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *J Nutr*. 2004; **134**: 205–210.

44 Gillman MW, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Lipshultz SE. Maternal calcium intake and offspring blood pressure. *Circulation* 2004; **110**: 1990–1995.

45 Belizan JM, Villar J, Bergel E *et al*. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial. *Br Med J*. 1997; **315**: 281–285.

46 Buckley AJ, Keseru B, Briody J, Thompson M, Ozanne SE, Thompson CH. Altered body composition and metabolism in the male offspring of high fat-fed rats. *Metabolism* 2005; **54**: 500–507.

47 Khan IY, Taylor PD, Dekou V *et al*. Gender-linked hypertension in offspring of lard-fed pregnant rats. *Hypertension* 2003; **41**: 168–175.

48 Taylor PD, McConnell J, Khan IY *et al*. Impaired glucose homeostasis and mitochondrial abnormalities in offspring of rats fed a fat-rich diet in pregnancy. *Am J Physiol*. 2005; **288**: R134–R139.

49 Van Assche FA, Holemans K, Aerts L. Long-term consequences for offspring of diabetes during pregnancy. *Br Med Bull*. 2001; **60**: 173–182.

50 Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. *J Pediatr Endocrinol Metab*. 2001; **14**: 1085–1091.

51 Sobngwi E, Boudou P, Mauvais-Jarvis F *et al*. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet* 2003; **361**: 1861–1865.

52 Buckley AJ, Jaquiery AL, Harding JE. Nutritional programming of adult disease. *Cell Tissue Res*. 2005; **2005**: 73–79.

53 Jensen EC, Gallaher BW, Breier BH, Harding JE. The effect of a chronic maternal cortisol infusion on the late-gestation foetal sheep. *J Endocrinol*. 2002; **174**: 27–36.

54 Tangalakis K, Lumbers ER, Moritz KM, Towstoless MK, Wintour EM. Effect of cortisol on blood pressure and vascular reactivity in the ovine foetus. *Exp Physiol*. 1992; **77**: 709–717.

55 Levitt NS, Lindsay RS, Holmes MC, Seckl JR. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. *Neuroendocrinology* 1996; **64**: 412–418.

56 Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J Clin Invest*. 1998; **101**: 2174–2181.

57 Moss TJ, Sloboda DM, Gurrin LC, Harding R, Challis JR, Newnham JP. Programming effects in sheep of prenatal growth restriction and glucocorticoid exposure. *Am J Physiol*. 2001; **281**: R960–R970.

58 Lindsay RS, Lindsay RM, Waddell BJ, Seckl JR. Prenatal glucocorticoid exposure leads to offspring hyperglycaemia in the rat: studies with the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone. *Diabetologia* 1996; **39**: 1299–1305.

59 Saegusa H, Nakagawa Y, Liu YJ, Ohzeki T. Influence of placental 11beta-hydroxysteroid dehydrogenase (11beta-HSD) inhibition on glucose metabolism and 11beta-HSD regulation in adult offspring of rats. *Metabolism* 1999; **48**: 1584–1588.

60 Seckl JR. Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol*. 2004; **151**: U49–U62.

61 Phillips DI. Insulin resistance as a programmed response to foetal undernutrition. *Diabetologia* 1996; **39**: 1119–1122.

62 McTernan CL, Draper N, Nicholson H *et al*. Reduced placental 11beta-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. *J Clin Endocrinol Metab*. 2001; **86**: 4979–4983.

63 French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: size at birth and subsequent development. *Am J Obstet Gynecol*. 1999; **180**: 114–121.

64 Thorp JA, Jones PG, Knox E, Clark RH. Does antenatal corticosteroid therapy affect birth weight and head circumference? *Obstet Gynecol*. 2002; **99**: 101–108.

65 Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972; **50**: 515–525.

66 Dalziel SR, Liang A, Parag V, Rodgers A, Harding JE. Blood pressure at 6 years of age after prenatal exposure to betamethasone: follow-up results of a randomized, controlled trial. *Pediatrics* 2004; **114**: e373–377.

67 Dalziel SR, Walker NK, Parag V *et al*. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005; **365**: 1856–1862.

68 Lesage J, Hahn D, Leonhardt M, Blondeau B, Breant B, Dupouy JP. Maternal undernutrition during late gestation-induced intrauterine growth restriction in the rat is associated

with impaired placental GLUT3 expression, but does not correlate with endogenous corticosterone levels. *J Endocrinol.* 2002; **174**: 37–43.
69 Langley-Evans SC, Phillips GJ, Benediktsson R *et al.* Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. *Placenta* 1996; **17**: 169–172.
70 Lesage J, Blondeau B, Grino M, Breant B, Dupouy JP. Maternal undernutrition during late gestation induces foetal overexposure to glucocorticoids and intrauterine growth retardation, and disturbs the hypothalamo-pituitary adrenal axis in the newborn rat. *Endocrinology* 2001; **142**: 1692–1702.
71 Gardner DS, Jackson AA, Langley-Evans SC. Maintenance of maternal diet-induced hypertension in the rat is dependent on glucocorticoids. *Hypertension* 1997; **30**: 1525–1530.
72 Bloomfield FH, Oliver MH, Giannoulias CD, Gluckman PD, Harding JE, Challis JR. Brief undernutrition in late-gestation sheep programs the hypothalamic-pituitary-adrenal axis in adult offspring. *Endocrinology* 2003; **144**: 2933–2940.
73 Bloomfield FH, Oliver MH, Hawkins P *et al.* Periconceptional undernutrition in sheep accelerates maturation of the foetal hypothalamic-pituitary-adrenal axis in late gestation. *Endocrinology* 2004; **145**: 4278–4285.
74 Hawkins P, Hanson MA, Matthews SG. Maternal undernutrition in early gestation alters molecular regulation of the hypothalamic-pituitary-adrenal axis in the ovine foetus. *J Neuroendocrinol.* 2001; **13**: 855–861.
75 Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia.* 1992; **35**: 595–601.
76 Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 2002; **45**: 342–348.
77 Gluckman P, Hanson M (eds). *The Foetal Matrix: Evolution, Development and Disease*. Cambridge: Cambridge University Press, 2005.
78 Gluckman PD, Hanson MA. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatr Res.* 2004; **56**: 311–317.
79 Lee TM, Spears N, Tuthill CR, Zucker I. Maternal melatonin treatment influences rates of neonatal development of meadow vole pups. *Biol Reprod.* 1989; **40**: 495–502.
80 Khan I, Dekou V, Hanson M, Poston L, Taylor P. Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. *Circulation* 2004; **110**: 1097–1102.
81 Hattersley AT, Tooke JE. The foetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 1999; **353**: 1789–1792.
82 Day IN, Chen XH, Gaunt TR *et al.* Late life metabolic syndrome, early growth, and common polymorphism in the growth hormone and placental lactogen gene cluster. *J Clin Endocrinol Metab.* 2004; **89**: 5569–5576.
83 Lindsay RS, Dabelea D, Roumain J, Hanson RL, Bennett PH, Knowler WC. Type 2 diabetes and low birth weight: the role of paternal inheritance in the association of low birth weight and diabetes. *Diabetes* 2000; **49**: 445–449.
84 Hypponen E, Smith GD, Power C. Parental diabetes and birth weight of offspring: intergenerational cohort study. *Br Med J.* 2003; **326**: 19–20.
85 Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. *Science* 2001; **293**: 1089–1093.
86 Wolff GL, Kodell RL, Moore SR, Cooney CA. Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. *FASEB J.* 1998; **12**: 949–957.
87 Rees WD, Hay SM, Brown DS, Antipatis C, Palmer RM. Maternal protein deficiency causes hypermethylation of DNA in the livers of rat foetuses. *J Nutr.* 2000; **130**: 1821–1826.
88 Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. *Nutrition* 2004; **20**: 63–68.
89 Little RE, Sing CF. Genetic and environmental influences on human birth weight. *Am J Hum Genet.* 1987; **40**: 512–526.
90 Klebanoff MA, Graubard BI, Kessel SS, Berendes HW. Low birth weight across generations. *JAMA* 1984; **252**: 2423–2427.
91 Stewart RJ, Sheppard H, Preece R., Waterlow JC. The effect of rehabilitation at different stages of development of rats marginally malnourished for ten to twelve generations. *Br J Nutr.* 1980; **43**: 403–412.
92 Stein AD, Lumey LH. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. *Hum Biol.* 2000; **72**: 641–654.
93 Ibanez L, Potau N, Enriquez G, de Zegher F. Reduced uterine and ovarian size in adolescent girls born small for gestational age. *Pediatr Res.* 2000; **47**: 575–577.
94 Reik W, Santos F, Dean W. Mammalian epigenomics: reprogramming the genome for development and therapy. *Theriogenology.* 2003; **59**: 21–32.
95 Drake AJ, Walker BR. The intergenerational effects of foetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol.* 2004; **180**: 1–16.
96 Klebanoff MA, Secher NJ, Mednick BR, Schulsinger C. Maternal size at birth and the development of hypertension during pregnancy: a test of the Barker hypothesis. *Arch Intern Med.* 1999; **159**: 1607–1612.
97 Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and foetal growth. *Lancet* 1997; **349**: 7–10.
98 Barker DJ, Shiell AW, Barker ME, Law CM. Growth in utero and blood pressure levels in the next generation. *J Hypertens.* 2000; **18**: 843–846.
99 Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of foetal programming by in utero exposure to glucocorticoids in rats. *Am J Physiol.* 2005; **288**: R34–R38.
100 Bloomfield FH, Oliver MH, Hawkins P *et al.* A periconceptional nutritional origin for noninfectious preterm birth. *Science* 2003; **300**: 606.
101 Oliver MH, Hawkins P, Breier BH, Van Zijl PL, Sargison SA, Harding JE. Maternal undernutrition during the periconceptual period increases plasma taurine levels and insulin response to glucose but not arginine in the late gestational foetal sheep. *Endocrinology* 2001; **142**: 4576–4579.
102 Kwong WY, Wild AE, Roberts P, Willis AC, Fleming TP. Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. *Development* 2000; **127**: 4195–4202.

103 Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. *Reprod Toxicol.* 2005; **20**: 345–352.

104 Ravelli AC, van der Meulen JH, Michels RP *et al.* Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; **351**: 173–177.

105 Roseboom TJ, Van Der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Perceived health of adults after prenatal exposure to the Dutch famine. *Paediatr Perinat Epidemiol.* 2003; **17**: 391–397.

106 Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr.* 1999; **70**: 811–816.

107 Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Plasma fibrinogen and factor VII concentrations in adults after prenatal exposure to famine. *Br J Haematol.* 2000; **111**: 112–117.

108 Conti J, Abraham S, Taylor A. Eating behavior and pregnancy outcome. *J Psychosom Res.* 1998; **44**: 465–477.

109 Thame M, Wilks RJ, McFarlane-Anderson N, Bennett FI, Forrester TE. Relationship between maternal nutritional status and infant's weight and body proportions at birth. *Eur J Clin Invest.* 1997; **51**: 134–138.

110 Godfrey KM, Forrester T, Barker DJ *et al.* Maternal nutritional status in pregnancy and blood pressure in childhood. *Br J Obstet Gynaecol.* 1994; **101**: 398–403.

111 Schluchter MD. Publication bias and heterogeneity in the relationship between systolic blood pressure, birth weight, and catch-up growth – a meta analysis. *J Hypertens.* 2003; **21**: 273–279.

112 Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation.* 1996; **94**: 3246–3250.

113 Yliharsila H, Eriksson JG, Forsen T, Kajantie E, Osmond C, Barker DJ. Self-perpetuating effects of birth size on blood pressure levels in elderly people. *Hypertension* 2003; **41**: 446–450.

114 Wilson RS. Growth standards for twins from birth to four years. *Ann Hum Biol.* 1974; **1**: 175–188.

115 Hrubec Z, Neel JV. Familial factors in early deaths: twins followed 30 years to ages 51–61 in 1978. *Hum Genet.* 1981; **59**: 39–46.

116 Vagero D, Leon D. Ischaemic heart disease and low birth weight: a test of the foetal-origins hypothesis from the Swedish Twin Registry. *Lancet* 1994; **343**: 260–263.

117 Christensen K, Vaupel JW, Holm NV, Yashin AI. Mortality among twins after age 6: foetal origins hypothesis versus twin method. *Br Med J.* 1995; **310**: 432–436.

118 de Geus EJ, Posthuma D, Ijzerman RG, Boomsma DI. Comparing blood pressure of twins and their singleton siblings: being a twin does not affect adult blood pressure. *Twin Res.* 2001; **4**: 385–391.

119 Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study. *Diabetologia* 1999; **42**: 139–145.

120 Saydah SH, Eberhardt MS, Loria CM, Brancati FL. Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol.* 2002; **156**: 714–719.

121 Jefferies CA, Hofman PL, Knoblauch H, Luft FC, Robinson EM, Cutfield WS. Insulin resistance in healthy prepubertal twins. *J Pediatr.* 2004; **144**: 608–613.

122 Dwyer T, Blizzard L, Morley R, Ponsonby AL. Within pair association between birth weight and blood pressure at age 8 in twins from a cohort study. *Br Med J.* 1999; **319**: 1325–1329.

123 Levine RS, Hennekens CH, Jesse MJ. Blood pressure in prospective population based cohort of newborn and infant twins. *Br Med J.* 1994; **308**: 298–302.

124 Loos RJ, Fagard R, Beunen G, Derom C, Vlietinck R. Birth weight and blood pressure in young adults: a prospective twin study. *Circulation* 2001; **104**: 1633–1638.

125 Poulter NR, Chang CL, MacGregor AJ, Snieder H, Spector TD. Association between birth weight and adult blood pressure in twins: historical cohort study. *Br Med J.* 1999; **319**: 1330–1333.

126 Williams S, Poulton R. Twins and maternal smoking: ordeals for the foetal origins hypothesis? A cohort study. *Br Med J.* 1999; **318**: 897–900.

127 Zhang J, Brenner RA, Klebanoff MA. Differences in birth weight and blood pressure at age 7 years among twins. *Am J Epidemiol.* 2001; **153**: 779–782.

128 Bo S, Cavallo-Perin P, Scaglione L, Ciccone G, Pagano G. Low birthweight and metabolic abnormalities in twins with increased susceptibility to type 2 diabetes mellitus. *Diabetic Med.* 2000; **17**: 365–370.

129 Poulsen P, Vaag AA, Kyvik KO, Moller Jensen D, Beck-Nielsen H. Low birth weight is associated with NIDDM in discordant monozygotic and dizygotic twin pairs. *Diabetologia* 1997; **40**: 439–446.

130 Iliadou A, Cnattingius S, Lichtenstein P. Low birthweight and type 2 diabetes: a study on 11 162 Swedish twins. *Int J Epidemiol.* 2004; **33**: 948–953.

131 Kyvik KO, Bache I, Green A, Beck-Nielsen H, Buschard K. No association between birth weight and type 1 diabetes mellitus – a twin-control study. *Diabetic Med.* 2000; **17**: 158–162.

132 Cheung YF, Taylor MJ, Fisk NM, Redington AN, Gardiner HM. Foetal origins of reduced arterial distensibility in the donor twin in twin–twin transfusion syndrome. *Lancet* 2000; **355**: 1157–1158.

133 West CR, Adi Y, Pharoah PO. Foetal and infant death in mono- and dizygotic twins in England and Wales 1982–91. *Arch Dis Child Foetal Neonatal Ed.* 1999; **80**: F217–F220.

134 Magnus P, Berg K, Bjerkedal T. No significant difference in birth weight for offspring of birth weight discordant monozygotic female twins. *Early Hum Dev.* 1985; **12**: 55–59.

135 Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies. *Lancet* 2000; **355**: 2135–2136.

136 Keijzer-Veen MG, Finken MJ, Nauta J *et al.* Is blood pressure increased 19 years after intrauterine growth restriction and preterm birth? A prospective follow-up study in the Netherlands. *Pediatrics* 2005; **116**: 725–731.

137 Leon DA, Johansson M, Rasmussen F. Gestational age and growth rate of foetal mass are inversely associated with systolic blood pressure in young adults: an epidemiologic study of 165136 Swedish men aged 18 years. *Am J Epidemiol.* 2000; **152**: 597–604.

138 Siewert-Delle A, Ljungman S. The impact of birth weight and gestational age on blood pressure in adult life: a population-based study of 49-year-old men. *Am J Hypertens*. 1998; **11**: 946–953.
139 Hofman PL, Regan F, Jackson WE *et al*. Premature birth and later insulin resistance. *N Engl J Med*. 2004; **351**: 2179–2186.
140 Szathmari M, Vasarhelyi B, Reusz G, Tulassay T. Adult cardiovascular risk factors in premature babies. *Lancet* 2000; **356**: 939–940.
141 Harding JE, Bloomfield FH. Prenatal treatment of intrauterine growth restriction: lessons from the sheep model. *Pediatr Endocrinol Rev*. 2004; **2**: 182–192.
142 Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Foetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol*. 2000; **279**: E83–E87.
143 Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol*. 2003; **285**: R271–R273.
144 Vickers MH, Gluckman PD, Coveny AH *et al*. Neonatal leptin treatment reverses developmental programming. *Endocrinology*. 2005; **146**: 4211–4216.
145 Rich-Edwards JW, Kleinman K, Michels KB *et al*. Longitudinal study of birth weight and adult body mass index in predicting risk of coronary heart disease and stroke in women. *Br Med J*. 2005; **330**: 1115.
146 Hypponen E, Leon DA, Kenward MG, Lithell H. Prenatal growth and risk of occlusive and haemorrhagic stroke in Swedish men and women born 1915–29: historical cohort study. *Br Med J*. 2001; **323**: 1033–1034.
147 Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Bleker OP. Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. *Am J Clin Nutr*. 2000; **72**: 1101–1106.
148 Barker DJ. The intra-uterine origins of disturbed cholesterol homeostasis. *Acta Paediatr*. 1999; **88**: 483–484.
149 Henry JA, Bolla M, Osmond C, Fall C, Barker DJ, 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**: 553–558.
150 McCarton CM, Wallace IF, Divon M, Vaughan HG Jr. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. *Pediatrics* 1996; **98**: 1167–1178.
151 Low JA, Handley-Derry MH, Burke SO *et al*. Association of intrauterine foetal growth retardation and learning deficits at age 9–11 years. *Am J Obstet Gynecol*. 1992; **167**: 1499–1505.
152 Robertson CM, Etches PC, Kyle JM. Eight-year school performance and growth of preterm, small for gestational age infants: a comparative study with subjects matched for birth weight or for gestational age. *J Pediatr*. 1990; **116**: 19–26.
153 Smedler AC, Faxelius G, Bremme K, Lagerstrom M. Psychological development in children born with very low birth weight after severe intrauterine growth retardation: a 10-year follow-up study. *Acta Paediatr*. 1992; **81**: 197–203.
154 Sung IK, Vohr B, Oh W. Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. *J Pediatr*. 1993; **123**: 618–624.
155 Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. *Br J Psychiatry*. 2004; **184**: 28–33.
156 Thompson C, Syddall H, Rodin I, Osmond C, Barker DJ. Birth weight and the risk of depressive disorder in late life. *Br J Psychiatry*. 2001; **179**: 450–455.
157 Kunugi H, Nanko S, Murray RM. Obstetric complications and schizophrenia: prenatal underdevelopment and subsequent neurodevelopmental impairment. *Br J Psychiatry*. 2001; **40**: S25–S29.
158 Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Brubakk AM. Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires. *Eur Child Adolesc Psychiatry*. 2005; **14**: 226–236.
159 Phillips DI, Handelsman DJ, Eriksson JG, Forsen T, Osmond C, Barker DJ. Prenatal growth and subsequent marital status: longitudinal study. *Br Med J*. 2001; **322**: 771.
160 James WH. Handedness, birth weight, mortality and Barker's hypothesis. *J Theor Biol*. 2001; **210**: 345–346.
161 Powls A, Botting N, Cooke RW, Marlow N. Handedness in very-low-birthweight (VLBW) children at 12 years of age: relation to perinatal and outcome variables. *Dev Med Child Neurol*. 1996; **38**: 594–602.
162 Ibanez L, Ferrer A, Marcos MV, Hierro FR, de Zegher F. Early puberty: rapid progression and reduced final height in girls with low birth weight. *Pediatrics* 2000; **106**: E72.
163 Ibanez L, Valls C, Miro E, Marcos MV, de Zegher F. Early menarche and subclinical ovarian hyperandrogenism in girls with reduced adult height after low birth weight. *J Pediatr Endocrinol Metab*. 2002; **15**: 431–433.
164 Bhargava SK, Ramji S, Srivastava U *et al*. Growth and sexual maturation of low birth weight children: a 14 year follow up. *Indian Pediatr*. 1995; **32**: 963–970.
165 Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. *Br J Obstet Gynaecol*. 1996; **103**: 814–817.
166 Elias SG, Peeters PH, Grobbee DE, van Noord PA. Breast cancer risk after caloric restriction during the 1944–45 Dutch famine. *J Natl Cancer Inst*. 2004; **96**: 539–546.
167 English PB, Goldberg DE, Wolff C, Smith D. Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). *Cancer Causes Control*. 2003; **14**: 815–825.
168 Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI, Fraser RB. Foetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet*. 1997; **350**: 1131–1135.
169 Michels KB, Trichopoulos D, Robins JM *et al*. Birthweight as a risk factor for breast cancer. *Lancet* 1996; **348**: 1542–1546.
170 Nilsen TI, Romundstad PR, Troisi R., Vatten LJ. Birth size and subsequent risk for prostate cancer: a prospective population-based study in Norway. *Int J Cancer* 2005; **113**: 1002–1004.
171 Richiardi L, Askling J, Granath F, Akre O. Body size at birth and adulthood and the risk for germ-cell testicular cancer. *Cancer Epidemiol Biomarkers Prev*. 2003; **12**: 669–673.
172 Hjalgrim LL, Rostgaard K, Hjalgrim H *et al*. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. *J Natl Cancer Inst*. 2004; **96**: 1549–1556.