

Birth weight, infant growth and insulin resistance

Ken K Ong and David B Dunger

Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital Box 116, Cambridge CB2 2QQ, UK

(Correspondence should be addressed to K K Ong; Email: Ko224@cam.ac.uk)

Abstract

Size at birth and early postnatal growth rates are important determinants of human perinatal survival; they also predict the tempo of growth, adult height and long-term risks for obesity, type 2 diabetes and cardiovascular disease.

Results from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) show that fetal growth is influenced by both fetal genes and maternal–uterine–placental factors. Important maternal–placental factors include parity, smoking and weight gain, but also maternal genetic factors in the mother or fetal placenta, including the mitochondrial DNA 16189 variant and *H19*. These maternal genetic factors particularly influence smaller, growth-restrained infants, as in first pregnancies. Fetal genes include the insulin gene (*INS*) VNTR (variable number of tandem repeat), which we recently confirmed to be associated with birth size and cord blood IGF-II levels; these fetal gene effects are more evident in the absence of maternal–uterine growth restraint.

During postnatal life, the *INS* VNTR III/III genotype remains associated with body size, including body mass index and waist circumference, and also lower insulin sensitivity among girls. However, as at birth, significant gene–environment interactions are seen. Rapid 'catch-up' early postnatal weight gain follows maternal–uterine restraint, and strongly predicts later childhood obesity and insulin resistance; among these children, those with *INS* VNTR class I alleles are more obese.

Genetic factors that influence early growth may have conferred some early survival advantage in human history during times of undernutrition. With abundant nutrition and rising obesity rates, these genetic factors and their interactions with maternal and childhood environmental factors that influence childhood growth may now contribute to the early development of adult disease risk. Their recognition may help the development of targeted early interventions to prevent the progression towards adult disease.

European Journal of Endocrinology 151 U131–U139

Introduction

Size at birth and early infancy growth have long been recognised to be important indicators of maternal and offspring health, and of early childhood survival (1, 2). Rapid early weight gain or large size in early childhood has also been linked to earlier sexual maturation (3–5). In recent years, the significance of perinatal and childhood growth patterns has been further extended by studies that show links with much longer term risks of diseases in adult life, such as type 2 diabetes and cardiovascular disease (6, 7). More recent studies, with postnatal growth data, show that the most common growth pattern related to later disease risk is the combination of relatively lower birth weights and subsequently becoming overweight or obese either during childhood or adult life (8, 9). These findings led Hales and Barker to suggest the 'thrifty phenotype' hypothesis, where early exposure of the fetus to poor nutrition leads to permanent changes in insulin metabolism and body fat distribution (10, 11).

Size at birth for gestational age is a marker of fetal growth rate; it is influenced by a wide range of factors

that act on the maternal–uterine environment, such as maternal parity and smoking during pregnancy, and also by factors that are familial or heritable (12, 13). These inherited and environmental factors may be complexly interrelated. For example, the contribution of parental inheritance to birth weight, as estimated by the strength of correlation between parent and offspring birth weights, is reduced in conditions where fetal growth is restrained, such as by maternal smoking in pregnancy or in first pregnancies (13). Therefore both environmental and genetic factors, and their interactions, may contribute to both fetal and early childhood growth and its links with long-term disease risks.

Size at birth and adult disease risk

The early reports in historical birth cohorts of association between smaller size at birth, and cardiovascular disease and adult onset diabetes, have since been replicated in diverse populations from different countries (14, 15). The findings persist when differences in gestational age are taken into account, and they appear to be independent of selection bias or potential confounding

factors due to social class or smoking (16). Importantly, the birth weight associations are not confined to differences between the smallest versus the other infants, but rather relate to a continuum of variable risk throughout the whole range of birth weights. For example, the original studies in men born in Hertfordshire, UK between 1911 and 1930 found that those with above average birth weight had 24% lower standardised mortality rates from coronary artery disease compared with those with average birth weights (6). In some populations the birth weight–adult disease association appears to be ‘U-shaped’, with the heaviest-born babies also having an increased long-term risk for disease (17, 18). Recent longitudinal growth data, including early childhood growth, in subjects from Finland who went on to develop type 2 diabetes in adult life showed that both larger and smaller birth weight patterns are associated with increased disease risk (19). It is likely that the long-term disease associations with larger birth weight may reflect the influence of maternal diabetes in promoting both larger birth size and conferring offspring diabetes risk (20).

Epidemiological studies indicate that size at birth and early weight gain predict the long-term risks for obesity and abnormal fat distribution. In a study of 300 000 19-year-old men exposed to the Dutch famine between 1944 and 1945, there was a nearly twofold increase in obesity risk in those subjects whose mothers were exposed to famine during the first trimesters of pregnancy (21). Gale *et al.* (22) showed that, among 70–75-year-old men studied by dual-energy x-ray absorptiometry scanning, low birth weight was associated with reduced lean tissue mass and greater body fat relative to current weight. The predisposition to adult disease conferred by low birth weight may therefore be related to excess fat deposition, in particular central fat, and the development of insulin resistance. One study, using the gold standard euglycaemic–hyperinsulinaemic clamp assessment of insulin sensitivity in 70-year-old men showed that the association between low birth weight and insulin resistance was only seen in the highest body mass index (BMI) tertile group (23). Thus, it appears to be the transition from relatively lower birth weight to larger postnatal body size that confers disease risk. With increasing abundance of nutrition and rising rates of obesity such transition may occur at younger ages (24, 25), and the effects of these factors (nutrition, obesity and transition) are currently being explored in contemporary birth cohort studies.

Rapid ‘catch-up’ early postnatal weight gain

Growth data from large contemporary birth cohorts, such as the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) (26), confirm much earlier observations in smaller studies (27) that around 25%

of all newborn infants will show a significant degree of postnatal rapid or ‘catch-up’ growth (28). Such babies tend to be longer at birth with a larger head circumference relative to their birth weight, and therefore show reduced adiposity at birth compared with other babies of the same birth weight. A further 25% of all newborn infants have relatively increased adiposity at birth and will show postnatal slow or ‘catch-down’ growth (28). The remaining infants who do not show postnatal catch-up or catch-down growth are those who grow along the same weight and length centile positions, and appear to more closely follow their genetic growth trajectory from birth as indicated by consistent strength of correlation with their mid-parental target heights (29). Catch-up and catch-down postnatal growth are most marked in terms of changes in adiposity, and are largely seen within the first 12 months of life, although they may take up to 2 years to complete (30).

The large extent of early postnatal catch-up and catch-down growth suggests that wide variations in gains in adiposity may also occur during late pregnancy. In the ALSPAC birth cohort we have shown that early postnatal catch-up and catch-down growth are closely related to maternal factors during pregnancy, such as mother’s pregnancy weight gain, smoking during pregnancy and parity (birth order). The effect of parity is particularly striking in that first babies are more likely to be restrained *in utero*, are thinner at birth and show early postnatal catch-up growth, whereas offspring of subsequent pregnancies are more likely to show *in utero* growth enhancement with postnatal catch-down growth (30). There is some evidence to suggest that these postnatal patterns of weight gain are driven by satiety, as indicated by early feeding studies in infants by Ounsted & Sleight (31), and by the finding of significant relationships between the levels of the satiety hormone leptin in cord blood at birth and subsequent patterns of weight gain (32). By the time early postnatal catch-up and catch-down growth are completed, the infants are closer to their genetic target size, as predicted by their parents’ heights (27, 29). Thus, during the early months of life, when feeding patterns are strongly influenced by the infant, and growth is regulated by nutrition, inherent patterns of increased or decreased appetite and satiety may return the infant towards its genetic growth trajectory.

However, these patterns of early postnatal growth also appear to have more long lasting effects. In the ALSPAC cohort, subjects who showed early catch-up growth became the heaviest of all children at the age of 5 years (28). This excess weight has persisted in ALSPAC catch-up children at their recent 8-year follow-up (Fig. 1), and similar observations have been made in large cohort studies in the US and in the Seychelles (33, 34). In addition to BMI (weight for height), in our studies those ALSPAC children who showed early catch-up growth also had increased abdominal circum-

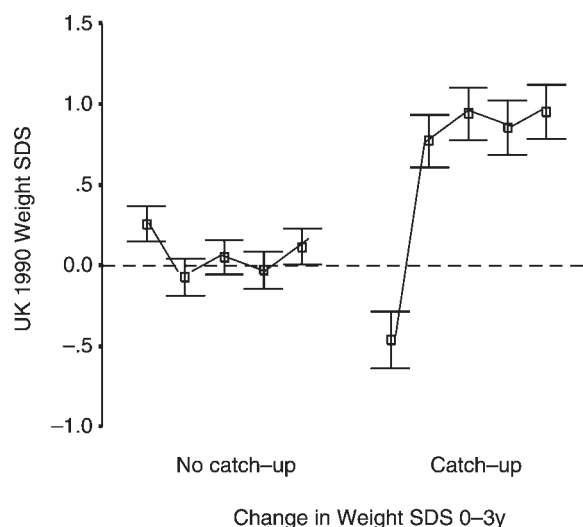


Figure 1 Persisting effects of early postnatal catch-up weight gain (gain in weight s.d. score (SDS) between 0 and 3 years greater than 0.67 SDS) on body weight at 5–8 years old. Data from the ALSPAC cohort.

ference at age 5 years. In other populations the transition from low birth weight to a normal or increased BMI during childhood has been associated with alterations in body composition: low birth weight has been associated with increased central fat deposition in children and adults (35, 36). In the Third National Health and Nutrition Examinations Survey (NHANES 3) 1988–1994, children born small for gestational age showed reduced lean tissue mass without reduction in fat mass and thus they had a higher percentage body fat (37). Studies from Australia have also reported this association between low birth weight, increased current weight and increased central fat deposition (38).

In a study from Pune, Indian children with relatively lower birth weights had increased fasting insulin levels at age 8 years and similar findings have been reported in other populations (39). Girls from Barcelona, Spain who had relatively lower birth weights and who showed postnatal catch-up growth become insulin resistant with increased central adiposity, although they may not necessarily be obese as assessed by standard BMI cut-offs (40). In the ALSPAC cohort, we recently reported that postnatal catch-up growth is associated with insulin resistance at 8 years of age, and that for this outcome the critical timing of catch-up is within the first 2–3 years of life (41). In a recent case-control study from Chile, infants with low birth weight for gestational age who showed early postnatal catch-up growth already had higher fasting insulin levels by the age of 1 year than infants of higher birth weights, even though the low birth weight infants had not yet attained the same weight at 1 year as the other infants (42).

These data suggest that low birth weight followed by early postnatal catch-up could be a risk factor for later

obesity and disease risk, and that the development of insulin resistance and increased central adiposity may be a very early feature of this growth pattern. These findings are comparable with results generated by animal models where prenatal growth restriction, followed by postnatal *ad libitum* feeding can result in insulin resistance and diabetes (11).

Genetic determinants of early growth and adult disease risk

Gene knock-out animal models have shown that the genes encoding insulin, the insulin-like growth factors (IGF-I and IGF-II), their receptors and regulatory proteins, and the insulin receptor substrate-1 have major effects on fetal growth and size at birth (43–45). Birth weights in mice homozygous for null mutations in either *Igf1* or *Igf2* were reduced to around 60% compared with wild-type mice (46, 47), and knock-out of the gene encoding the type 1 IGF receptor (*Igf1r*), which signals the anabolic actions of both IGF-I and IGF-II, resulted in even more severe fetal growth retardation with birth weights 45% of normal (43). In contrast knock-out of *Igf2r*, which encodes the non-signalling IGF-II/mannose 6-phosphate receptor, resulted in fetal overgrowth (48).

In humans, rare genetic mutations in the genes that influence insulin action, such as the insulin receptor (49) and glucokinase, which regulates fetal insulin secretion, result in small size at birth (50), and underline the importance of insulin in the regulation of human fetal growth (51). Partial *IGF1* deletion has been reported in one subject who showed severe intra-uterine and postnatal growth failure (52), and recently mutations in *IGF1R* have been reported in two children who also had retarded intra-uterine and postnatal growth (53). In addition, the Beckwith–Wiedemann fetal overgrowth syndrome has been associated with mutations and genetic variants that lead to *IGF2* overexpression (54–56). Common genetic variants in these genes could contribute to variations in birth size, and to their links with long-term disease risks.

Genetic factors could also underlie population differences in risks for obesity-related disease. Although obesity rates have increased dramatically in developed countries and urban populations, the risk of obesity-related disease appears to be disproportionately distributed, with very high rates among subjects from ethnic populations who had experienced poor nutrition until relatively recently in their history (57, 58). Thus, rates of obesity-related type 2 diabetes are particularly high in Native Americans and Hispanics and similar patterns have emerged in Australian aborigines and the Indonesian islanders (58). In children of south Asian descent, the move from rural to urban environments or migration to the US, UK and other European countries has been associated with a greatly increased prevalence of obesity-related disease and, in particular, type 2 diabetes (59). The thrifty genotype hypothesis

was originally proposed by Neel in 1962 to explain the remarkably high prevalence of type 2 diabetes in recently Westernised, previously undernourished populations (60). He suggested that there may be common genetic polymorphisms which conferred some survival advantage during earlier times of undernutrition, and through the process of selection are now over-represented in certain populations who have adapted to conditions of poor or intermittent nutrient supply.

The original thrifty genotype hypothesis and subsequent debate has been centred on how genetic variations might enhance survival during adult life (61). We would suggest that, in view of the relatively high mortality rates during perinatal life (1), and in particular during times of nutritional debilitation (62), thrifty genotypes that evolved to enhance early perinatal survival may have a larger effect on reproductive fitness and selection advantage than genotypes that promote adult survival. Such 'fetal thrifty genotypes' could now underlie current links between birth weight and adult disease risk.

The mean birth weight in any population is always slightly less than the optimal for perinatal survival of the infant (2), and as Moore and Haig (63) pointed out there is a complex paradigm where the interests of the mother may conflict with those of the father over fetal growth rates. Whereas it is in the interests of the father to have a larger baby, which achieves higher rates of perinatal survival and transmission of the father's genes to subsequent generations, fetal overgrowth may be dangerous to the mother by making greater nutrient demands and by resulting in prolonged or obstructed labour. These conflicting interests of the mother and the father may have underpinned the evolution of genetic imprinting, a mechanism whereby only those genes transmitted from either the mother or the father are expressed, and the others are silenced (64). A large proportion of those genes that are known to be imprinted are involved in the regulation of fetal growth; in general, genes that are exclusively paternally expressed enhance fetal growth, whereas exclusively maternally expressed genes are associated with reduced fetal growth (63, 65).

In infants who are smaller at birth, such as first-born infants who tend to be relatively restrained *in utero*, birth weight is more closely related to the birth weight of the mother, and of the offspring of the mother's female relatives, suggesting a specific maternal line transmission of genetic factors that restrain fetal growth (66). We have reported genetic associations between size at birth and the mitochondrial DNA 16189 variant (67) which is maternally inherited, and also with a common polymorphism in the maternally expressed *H19* gene (68). *H19* is a regulator of imprinting of the insulin-like growth factor-2 gene (*Igf2*), and its deletion in mice results in *IGF2* overexpression and larger birth size (69). In the ALSPAC birth cohort, we observed that, particularly

among restrained first pregnancies, a common *H19* genotype in the mother or offspring was associated with higher cord blood IGF-II protein levels and larger birth size (68).

In average and larger birth weight babies, such as second- and third-born infants where fetal growth restraint is less evident, a more Mendelian pattern of birth weight inheritance is observed (66). In these pregnancies, a variable number of tandem repeat (VNTR) polymorphism adjacent to the insulin gene (*INS*), which regulates both *INS* and *IGF2* expression (70, 71), has been repeatedly associated with size at birth, in particular with head circumference at birth and also with IGF-II protein levels in cord blood at birth (29, 72). While *IGF2* is paternally expressed in most tissues, the birth size association with *INS* VNTR showed no parent-of-origin effect and class III allele transmission from either parent was significantly associated with larger offspring birth size (Fig. 2). Thus, with regard to human pregnancy, there is some evidence that maternal genes may restrain fetal growth, however the role of exclusively paternally expressed genes in enhancing fetal growth has not yet been demonstrated.

Although we may be able to identify common genetic variations that are associated with size at birth, it is yet to be established whether these are thrifty, or survival-enhancing, genotypes that could underpin future disease risk. The case is strongest for the *INS* VNTR, as this genetic polymorphism has been associated with postnatal weight gain, insulin resistance, central fat deposition and type 2 diabetes (73–76). One could argue that larger size at birth, conferred by the *INS* VNTR class III/III genotype, might improve fetal survival, but at the expense of increased subsequent risks for increased central adiposity, insulin resistance and, ultimately, type 2 diabetes. Other genes that promote the development of adiposity during early postnatal life could also have had selective advantages in promoting early survival. The development of central adiposity, although now

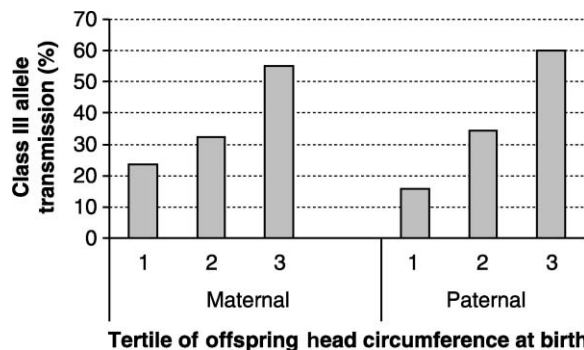


Figure 2 Increasing size of offspring birth head circumference is associated with increasing proportion of *INS* VNTR class III allele transmission from mothers ($P = 0.02$) or fathers ($P = 0.004$). Data from 551 validated ALSPAC parent-offspring trios (41).

linked with disease in today's overweight populations, could be considered as a survival advantage when nutrition was poor, as this central fat store provides a much more readily accessible source of nutrients during prolonged fasting or starvation compared with other body fat depots (77). These hypotheses relating candidate thrifty genotypes to perinatal survival and long-term disease risks could be studied in African populations where there is considerable genetic diversity (78), and particularly in some rural populations where variable nutrient supply still has an important impact on survival (62).

Interactions between phenotype, genotype and obesity risk

Experimental studies exploring the thrifty phenotype hypothesis in animal models have indicated that long-term obesity and disease risk markers can indeed be programmed by alterations in maternal nutrition such as protein restriction (79, 80), or by reduced nutritional supply to the fetus by uterine artery ligation in late pregnancy (81).

However, the implications of these observations that improving maternal nutrition may prevent future disease risk may not be true for humans. In contemporary populations, no clear relationship is seen between decreased maternal food intake and smaller size at birth (82–84), yet 25% of all infants still show fetal growth restriction and postnatal catch-up growth which are known to be risk factors for the development of obesity and insulin resistance. In rural African populations where there is extremely poor maternal nutrition, maternal restraint of fetal growth may be further exaggerated and could contribute to increased long-term disease risks (85). However, even in such populations, although improved maternal nutrition may benefit perinatal survival and reduce disease burden associated with poor nutrition in postnatal life (62), improved nutrition is unlikely to obviate long-term disease risks associated with insulin resistance, as these nutritional changes lead quickly to maternal obesity (86). Maternal weight gain is associated with increased risk for gestational diabetes, and this could underlie the associations between large birth weight and type 2 diabetes risk (20, 87). Thus, against a genetic background that predisposes to obesity and gestational diabetes, the shift from poor to improved maternal nutrition could accelerate type 2 diabetes risk rather than reduce it.

In addition to obesity and type 2 diabetes, the prevalence of polycystic ovary syndrome (PCOS) is also increased in populations where there has been, until recently, relatively poor nutrition (88). PCOS is associated with increased androgen production, which could contribute to increased central adiposity (89), and it is associated with increased risk for type 2 diabetes, and gestational diabetes (90). In UK populations, PCOS is

associated with larger birth weight (91, 92), perhaps reflecting the effects of gestational diabetes, or even high-normal glucose levels in the mother.

Genetic factors associated with PCOS include the *INS* VNTR class III/III genotype (74), and shorter CAG repeat length in the androgen receptor gene which confers greater receptor sensitivity (93). These genetic factors increase insulin resistance and androgen activity and thus may themselves be seen as risk factors for increased central adiposity. Therefore, in populations with a long history of undernutrition, and a possible background genetic predisposition to PCOS, type 2 diabetes and gestational diabetes, a sudden change to abundant nutrition and obesity could rapidly lead to a vicious cycle of increasing childhood weight gain, increased risk of ovarian hyperandrogenism, central adiposity and gestational diabetes, which, in turn, would increase the risk of type 2 diabetes in the next generation.

Relevance of perinatal factors to the current increase in childhood obesity

The disease risks associated with obesity are not uniformly distributed (57). Although the numbers of obese children who show impaired glucose tolerance or other risk markers for cardiovascular disease during adolescence may be alarming (94), there are still a large number of overweight or obese children who appear to have a low risk for the development of these diseases, at least in the short term. Increased understanding and more specific prediction in each individual of the disease risks associated with obesity could result from studies of interaction between early environmental and genetic factors, such as between early postnatal weight gain and *INS* VNTR genotype (72). In the presence of abundant nutrition and reduced energy expenditure, such interactions could determine the site of fat deposition and the associated development of insulin resistance. Furthermore, while insulin resistance may be a major risk factor for cardiovascular disease and type 2 diabetes (95), the ultimate development of type 2 diabetes is determined by the ability of the β cell to sustain compensatory hyperinsulinaemia (96). In recent studies in the ALSPAC birth cohort we were able to show that early weight gain was the major determinant of insulin resistance, however insulin secretion was more closely related to early height gain (41). Thus, an understanding of early growth patterns and their associations with central adiposity and insulin resistance, and how these, in turn, may be modified by the genetic background, will be important in developing appropriate targeted interventions to prevent disease risks associated with obesity during childhood (Fig. 3). Studies that combine early growth patterns and genetic factors to predict obesity and disease risks may also provide an opportunity to apply such targeted interventions at a much earlier stage.

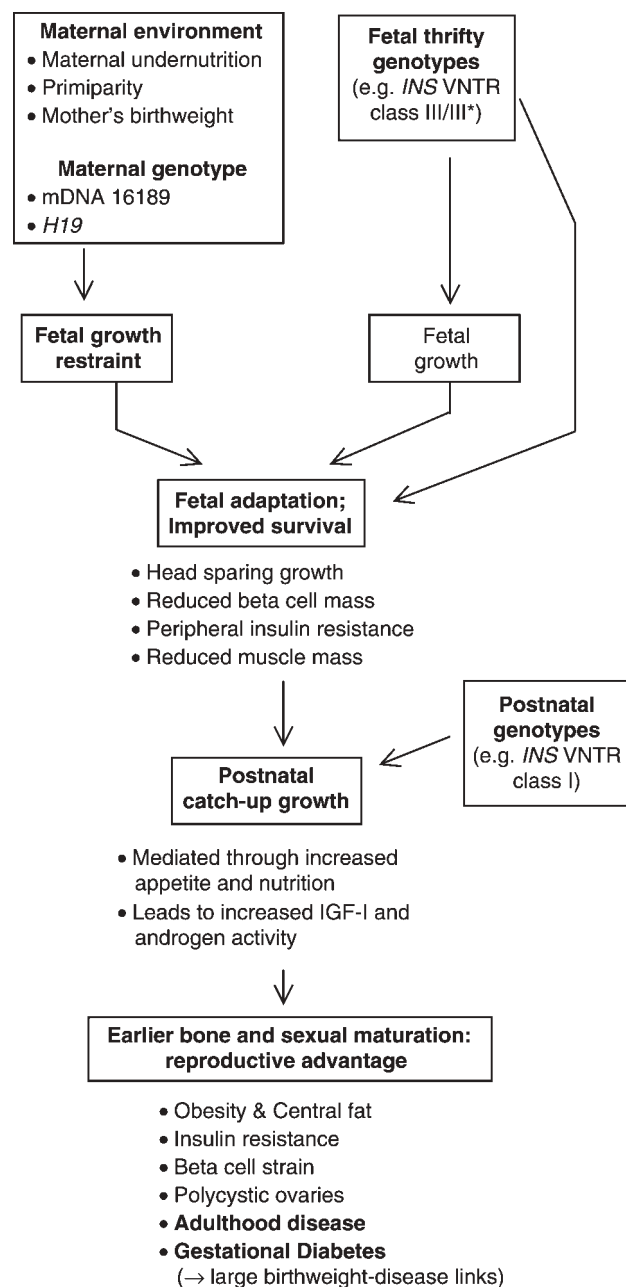


Figure 3 Schematic diagram summarising the proposed interaction between fetal thrifty genotypes and fetal growth restraint, resulting in a thrifty phenotype that enhances perinatal survival, postnatal growth and reproductive advantage, but leads to increased risks for disease in adulthood. *In the absence of fetal growth restraint and postnatal catch-up growth, the III/III genotype leads to larger size at birth, and postnatal increased adiposity and insulin resistance.

Acknowledgements

We are extremely grateful to the ALSPAC study team, and to all the children and parents who took part. ALSPAC is supported by the Medical Research Council, the Wellcome Trust, the UK Department of Health,

the Department of the Environment, the National Institutes of Health, a variety of medical research charities and commercial companies. D B D is supported by the Wellcome Trust and the Juvenile Diabetes Research Foundation.

References

- Karn MN & Penrose LS. Birth weight and gestation time in relation to maternal age, parity and infant survival. *Annals of Eugenics* 1951 **16** 147–158.
- Alberman E. Are our babies becoming bigger? *Journal of the Royal Society of Medicine* 1991 **84** 257–260.
- Mills JL, Shiono PH, Shapiro LR, Crawford PB & Rhoads GG. Early growth predicts timing of puberty in boys: results of a 14-year nutrition and growth study. *Journal of Pediatrics* 1986 **109** 543–547.
- Stark O, Peckham CS & Moynihan C. Weight and age at menarche. *Archives of Disease in Childhood* 1989 **64** 383–387.
- Ibanez L, Potau N, Marcos MV & de Zegher F. Exaggerated adrenarache and hyperinsulinism in adolescent girls born small for gestational age. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 4739–4741.
- Barker DJ, Winter PD, Osmond C, Margetts B & Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989 **2** 577–580.
- Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C & Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *British Medical Journal* 1991 **303** 1019–1022.
- Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C & Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *British Medical Journal* 1999 **318** 427–431.
- Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C & Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. *Annals of Internal Medicine* 2000 **133** 176–182.
- Hales CN & Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992 **35** 595–601.
- Hales CN & Barker DJ. The thrifty phenotype hypothesis. *British Medical Bulletin* 2001 **60** 5–20.
- Pritchard CW, Sutherland HW & Carr Hill RA. Birthweight and paternal height. *British Journal of Obstetrics and Gynaecology* 1983 **90** 156–161.
- Little RE & Sing CF. Genetic and environmental influences on human birth weight. *American Journal of Human Genetics* 1987 **40** 512–526.
- Stein CE, Fall CH, Kumaran K, Osmond C, Cox V & Barker DJ. Fetal growth and coronary heart disease in south India. *Lancet* 1996 **348** 1269–1273.
- Forsen T, Eriksson JG, Tuomilehto J, Teramo K, Osmond C & Barker DJ. Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. *British Medical Journal* 1997 **315** 837–840.
- Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R & Berglund L. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *British Medical Journal* 1998 **317** 241–244.
- McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC & Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *British Medical Journal* 1994 **308** 942–945.
- 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.

- 19 Eriksson JG, Forsen TJ, Osmond C & Barker DJ. Pathways of infant and childhood growth that lead to type 2 diabetes. *Diabetes Care* 2003 **26** 3006–3010.
- 20 Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH & Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000 **49** 2208–2211.
- 21 Ravelli GP, Stein ZA & Susser MW. Obesity in young men after famine exposure *in utero* and early infancy. *New England Journal of Medicine* 1976 **295** 349–353.
- 22 Gale CR, Martyn CN, Kellingray SD, Eastell R & Cooper C. Intrauterine programming of adult body composition. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 267–272.
- 23 McKeigue PM, Lithell HO & Leon DA. Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. *Diabetologia* 1998 **41** 1133–1138.
- 24 Reilly JJ, Dorosty AR & Emmett PM. Prevalence of overweight and obesity in British children: cohort study. *British Medical Journal* 1999 **319** 1039.
- 25 Bundred P, Kitchiner P & Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. *British Medical Journal* 2001 **322** 326–328.
- 26 Golding J, Pembrey ME & Jones R. ALSPAC—the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatric and Perinatal Epidemiology* 2001 **15** 74–87.
- 27 Tanner JM. Growth as a target-seeking function: catch-up and catch-down growth in man. In *Human Growth: A Comprehensive Treatise*, pp 167–179. Ed. F Falkner. New York and London: Plenum Press, 1986.
- 28 Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB & The ALSPAC Study Team. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *British Medical Journal* 2000 **320** 967–971.
- 29 Dunger DB, Ong KK, Huxtable SJ, Sherriff A, Woods KA, Ahmed ML, Golding J, Pembrey ME, Ring S, Bennett ST & Todd JA. Association of the *INS VNTR* with size at birth. *Nature Genetics* 1998 **19** 98–100.
- 30 Ong KK, Preece MA, Emmett PM, Ahmed ML & Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. *Pediatric Research* 2002 **52** 863–867.
- 31 Ounsted M & Sleigh G. The infant's self-regulation of food intake and weight gain. Difference in metabolic balance after growth constraint or acceleration *in utero*. *Lancet* 1975 **1** 1393–1397.
- 32 Ong KK, Ahmed ML, Sherriff A, Woods KA, Watts A, Golding J, Dunger DB & The ALSPAC Study Team. Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1145–1148.
- 33 Stettler N, Zemel BS, Kumanyika S & Stallings VA. Infant weight gain and childhood overweight status in a multicenter cohort study. *Pediatrics* 2002 **109** 194–199.
- 34 Stettler N, Bovet P, Shamlaye H, Zemel BS, Stallings VA & Paccaud F. Prevalence and risk factors for overweight and obesity in children from Seychelles, a country in rapid transition: the importance of early growth. *International Journal of Obesity Related Metabolic Disorders* 2002 **26** 214–219.
- 35 Law CM, Barker DJ, Osmond C, Fall CH & Simmonds SJ. Early growth and abdominal fatness in adult life. *Journal of Epidemiology and Community Health* 1992 **46** 184–186.
- 36 Yajnik CS. Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease. *Proceedings of the Nutrition Society* 2000 **59** 257–265.
- 37 Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR & Davis WW. Muscularity and fatness of infants and young children born small- or large-for-gestational-age. *Pediatrics* 1998 **102** E60.
- 38 Garnett SP, Cowell CT, Baur LA, Fay RA, Lee J, Coakley J, Peat JK & Boulton TJ. Abdominal fat and birth size in healthy prepubertal children. *International Journal of Obesity Related Metabolic Disorders* 2001 **25** 1667–1673.
- 39 Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhav S, Kellingray SD & Joglekar C. Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes* 1999 **48** 2422–2429.
- 40 Ibanez L, Ong K, de Zegher F, Marcos MV, del Rio L & Dunger DB. Fat distribution in non-obese girls with and without precocious pubarche: central adiposity related to insulinaemia and androgenaemia from preperty to postmenarche. *Clinical Endocrinology* 2003 **58** 372–379.
- 41 Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, Ness AR, ALSPAC Study Team & Dunger DB. Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. *Diabetologia* 2004 **47** 1064–1070.
- 42 Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G, Ong KK, Dunger DB & Mericq MV. Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3645–3650.
- 43 Baker J, Liu JP, Robertson EJ & Efstratiadis A. Role of insulin-like growth factors in embryonic and postnatal growth. *Cell* 1993 **75** 73–82.
- 44 Liu JP, Baker J, Perkins AS, Robertson EJ & Efstratiadis A. Mice carrying null mutations of the genes encoding insulin-like growth factor I (*Igf-1*) and type 1 *IGF* receptor (*Igf1r*). *Cell* 1993 **75** 59–72.
- 45 Tamemoto H, Kadowaki T, Tobe K, Yagi T, Sakura H, Hayakawa T, Terauchi Y, Ueki K, Kaburagi Y, Satoh S, Sekihara H, Yoshioka S, Horikoshi H, Furuta Y, Ikawa Y, Kasuga M, Yazaki Y & Aizawa S. Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. *Nature* 1994 **372** 182–186.
- 46 DeChiara TM, Efstratiadis A & Robertson EJ. A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. *Nature* 1990 **345** 78–80.
- 47 Powell Braxton L, Hollingshead P, Warburton C, Dowd M, Pitts Meek S, Dalton D, Gillett N & Stewart TA. *IGF-I* is required for normal embryonic growth in mice. *Genes and Development* 1993 **7** 2609–2617.
- 48 Ludwig T, Eggenschwiler J, Fisher P, D'Ercole AJ, Davenport ML & Efstratiadis A. Mouse mutants lacking the type 2 *IGF* receptor (*IGF2R*) are rescued from perinatal lethality in *Igf2* and *Igf1r* null backgrounds. *Developmental Biology* 1996 **177** 517–535.
- 49 Wertheimer E, Lu SP, Backeljauw PF, Davenport ML & Taylor SI. Homozygous deletion of the human insulin receptor gene results in leprechaunism. *Nature Genetics* 1993 **5** 71–73.
- 50 Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R & Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nature Genetics* 1998 **19** 268–270.
- 51 Fowden AL. The role of insulin in prenatal growth. *Journal of Developmental Physiology* 1989 **12** 173–182.
- 52 Woods KA, Camacho Hubner C, Savage MO & Clark AJ. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *New England Journal of Medicine* 1996 **335** 1363–1367.
- 53 Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klamm J, Kratzsch J, Osgood D, Pfaffle R, Raile K, Seidel B, Smith RJ & Chernausk SD. *IGF-I* receptor mutations resulting in intrauterine and postnatal growth retardation. *New England Journal of Medicine* 2003 **349** 2211–2222.
- 54 Forne T, Oswald J, Dean W, Saam JR, Bailleul B, Dandolo L, Tilghman SM, Walter J & Reik W. Loss of the maternal H19

- gene induces changes in Igf2 methylation in both cis and trans. *PNAS* 1997 **94** 10243–10248.
- 55 Murrell A, Heeson S, Cooper WN, Douglas E, Apostolidou S, Moore GE, Maher ER & Reik W. An association between variants in the IGF2 gene and Beckwith-Wiedemann syndrome: interaction between genotype and epigenotype. *Human Molecular Genetics* 2004 **13** 247–255.
 - 56 Maher ER & Reik W. Beckwith-Wiedemann syndrome: imprinting in clusters revisited. *Journal of Clinical Investigation* 2000 **105** 247–252.
 - 57 WHO Expert Consultation, Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004 **363** 157–163.
 - 58 Zimmet PZ. Diabetes epidemiology as a tool to trigger diabetes research and care. *Diabetologia* 1999 **42** 499–518.
 - 59 McKeigue PM, Shah B & Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991 **337** 382–386.
 - 60 Neel JV. Diabetes mellitus: a thrifty genotype rendered detrimental by 'progress'? *American Journal of Human Genetics* 1962 **14** 353–362.
 - 61 Reaven GM. Hypothesis: muscle insulin resistance is the ('not-so') thrifty genotype. *Diabetologia* 1998 **41** 482–484.
 - 62 Ceasay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM & Whitehead RG. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *British Medical Journal* 1997 **315** 786–790.
 - 63 Moore T & Haig D. Genomic imprinting in mammalian development: a parental tug-of-war. *Trends in Genetics* 1991 **7** 45–49.
 - 64 Reik W & Walter J. Genomic imprinting: parental influence on the genome. *Nature Reviews Genetics* 2001 **2** 21–32.
 - 65 Reik W & Walter J. Evolution of imprinting mechanisms: the battle of the sexes begins in the zygote. *Nature Genetics* 2001 **27** 255–256.
 - 66 Ounsted M, Scott A & Ounsted C. Transmission through the female line of a mechanism constraining human fetal growth. *Annals of Human Biology* 1986 **13** 143–151.
 - 67 Casteels K, Ong KK, Phillips DI, Bednarsz A, Bendall H, Woods KA, Sherriff A, Team TAS, Golding J, Pembrey ME, Poulton J & Dunger DB. Mitochondrial 16189 variant, thinness at birth and type 2 diabetes. *Lancet* 1999 **353** 1499–1500.
 - 68 Ong KK, Barratt B, Kratzsch J, Kiess W, Pembrey ME, Team TAS, Todd JA & Dunger DB. Associations between cord blood IGF-II levels and common polymorphisms at *INS* VNTR and *H19*—genetic determinants of size at birth in humans. *Pediatric Research* 2001 **49** 18A.
 - 69 Leighton PA, Ingram RS, Eggenschwiler J, Efstratiadis A & Tilghman SM. Disruption of imprinting caused by deletion of the *H19* gene region in mice. *Nature* 1995 **375** 34–39.
 - 70 Bennett ST, Wilson AJ, Cucca F, Nerup J, Pociot F, McKinney PA, Barnett AH, Bain SC & Todd JA. *IDDM2*-VNTR-encoded susceptibility to type 1 diabetes: dominant protection and parental transmission of alleles of the insulin gene-linked minisatellite locus. *Journal of Autoimmunity* 1996 **9** 415–421.
 - 71 Paquette J, Giannoukakis N, Polychronakos C, Vafiadis P & Deal C. The *INS* 5' variable number of tandem repeats is associated with *IGF2* expression in humans. *Journal of Biological Chemistry* 1998 **273** 14158–14164.
 - 72 Ong KK, Petry CJ, Barratt BJ, Ring S, Cordell HJ, Wingate DL, Pembrey ME, Todd JA & Dunger DB. Maternal–fetal interactions and birth order influence insulin variable number of tandem repeats allele class associations with head size at birth and childhood weight gain. *Diabetes* 2004 **53** 1128–1133.
 - 73 Bennett ST & Todd JA. Human type 1 diabetes and the insulin gene: principles of mapping polygenes. *Annual Reviews in Genetics* 1996 **30** 343–370.
 - 74 Waterworth DM, Bennett ST, Gharani N, McCarthy MI, Hague S, Batty S, Conway GS, White D, Todd JA, Franks S & Williamson R. Linkage and association of insulin gene VNTR regulatory polymorphism with polycystic ovary syndrome. *Lancet* 1997 **349** 986–990.
 - 75 Ong KK, Phillips DI, Fall C, Poulton J, Bennett ST, Golding J, Todd JA & Dunger DB. The insulin gene VNTR, type 2 diabetes and birth weight. *Nature Genetics* 1999 **21** 262–263.
 - 76 Huxtable SJ, Saker PJ, Haddad L, Walker M, Frayling TM, Levy JC, Hitman GA, O'Rahilly S, Hattersley AT & McCarthy MI. Analysis of parent-offspring trios provides evidence for linkage and association between the insulin gene and type 2 diabetes mediated exclusively through paternally transmitted class III variable number tandem repeat alleles. *Diabetes* 2000 **49** 126–130.
 - 77 Frayn KN. Macronutrient metabolism of adipose tissue at rest and during exercise: a methodological viewpoint. *Proceedings of the Nutrition Society* 1999 **58** 877–886.
 - 78 Stead JD & Jeffreys AJ. Structural analysis of insulin minisatellite alleles reveals unusually large differences in diversity between Africans and non-Africans. *American Journal of Human Genetics* 2002 **71** 1273–1284.
 - 79 Ozanne SE, Lewis R, Jennings BJ & Hales CN. Early programming of weight gain in mice prevents the induction of obesity by a highly palatable diet. *Clinical Science* 2004 **106** 141–145.
 - 80 Petry CJ, Dorling MW, Pawlak DB, Ozanne SE & Hales CN. Diabetes in old male offspring of rat dams fed a reduced protein diet. *International Journal of Experimental Diabetes Research* 2001 **2** 139–143.
 - 81 Simmons RA, Templeton LJ & Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. *Diabetes* 2001 **50** 2279–2286.
 - 82 Rogers I, Emmett P, Baker D & Golding J. Financial difficulties, smoking habits, composition of the diet and birthweight in a population of pregnant women in the South West of England. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *European Journal of Clinical Nutrition* 1998 **52** 251–260.
 - 83 Godfrey KM, Barker DJ, Robinson S & Osmond C. Maternal birthweight and diet in pregnancy in relation to the infant's thinness at birth. *British Journal of Obstetrics and Gynaecology* 1997 **104** 663–667.
 - 84 Mathews F, Yudkin P & Neil A. Influence of maternal nutrition on outcome of pregnancy: prospective cohort study. *British Medical Journal* 1999 **319** 339–343.
 - 85 Prentice AM, Whitehead RG, Watkinson M, Lamb WH & Cole TJ. Prenatal dietary supplementation of African women and birthweight. *Lancet* 1983 **1** 489–492.
 - 86 van der Sande MA, Ceasay SM, Milligan PJ, Nyan OA, Banya WA, Prentice A, McAdam KP & Walraven GE. Obesity and undernutrition and cardiovascular risk factors in rural and urban Gambian communities. *American Journal of Public Health* 2001 **91** 1641–1644.
 - 87 Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F & Gautier JF. Effect of a diabetic environment *in utero* on predisposition to type 2 diabetes. *Lancet* 2003 **361** 1861–1865.
 - 88 Rodin DA, Bano G, Bland JM, Taylor K & Nussey SS. Polycystic ovaries and associated metabolic abnormalities in Indian subcontinent Asian women. *Clinical Endocrinology* 1998 **49** 91–99.
 - 89 Ibanez L, Ong KK, Ferrer A, Amin R, Dunger DB & de Zegher F. Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 2600–2606.
 - 90 The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction* 2004 **19** 41–47.

- 91 Michelmore KF, Balen AH, Dunger DB & Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. *Clinical Endocrinology* 1999 **51** 779–786.
- 92 Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI & Fraser RB. Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet* 1997 **350** 1131–1135.
- 93 Ibanez L, Ong KK, Mongan N, Jaaskelainen J, Marcos MV, Hughes IA, De Zegher F & Dunger DB. Androgen receptor gene CAG repeat polymorphism in the development of ovarian hyperandrogenism. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3333–3338.
- 94 Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS & Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *New England Journal of Medicine* 2002 **346** 802–810.
- 95 Facchini FS, Hua N, Abbasi F & Reaven GM. Insulin resistance as a predictor of age-related diseases. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 3574–3578.
- 96 Kahn SE. Clinical review 135: the importance of beta-cell failure in the development and progression of type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4047–4058.

Received 18 May 2004

Accepted 10 August 2004