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Symposium on 'Nutrition in early life: new horizons in a new century'

Session 7: Early nutrition and later health
Early developmental pathways of obesity and diabetes risk

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Size at birth and patterns of postnatal weight gain have been associated with adult risk for the development of type 2 diabetes in many populations, but the putative pathophysiological link remains unknown. Studies of contemporary populations indicate that rapid infancy weight gain, which may follow fetal growth restriction, is an important risk factor for the development of childhood obesity and insulin resistance. Data from the Avon Longitudinal Study of Pregnancy and Childhood shows that rapid catch-up weight gain can lead to the development of insulin resistance, as early as 1 year of age, in association with increasing accumulation of central abdominal fat mass. In contrast, the disposition index, which reflects the β-cells ability to maintain insulin secretion in the face of increasing insulin resistance, is much more closely related to ponderal index at birth than postnatal catch-up weight gain. Infants with the lowest ponderal index at birth show a reduced disposition index at aged 8 years associated with increases in fasting NEFA levels. The disposition index is also closely related to childhood height gain and insulin-like growth factor-I (IGF-I) levels; reduced insulin secretory capacity being associated with reduced statural growth, and relatively short stature with reduced IGF-I levels at age 8 years. IGF-I may have an important role in the maintenance of β-cell mass, as demonstrated by recent studies of pancreatic β-cell IGF-I receptor knock-out and adult observational studies indicating that low IGF-I levels are predictive of subsequent risk for the development of type 2 diabetes. However, as insulin secretion is an important determinant of IGF-I levels, cause and effect may be difficult to establish. In conclusion, although rapid infancy weight gain and increasing rates of childhood obesity will increase the risk for the development of insulin resistance, prenatal and postnatal determinants of β-cell mass may ultimately be the most important determinants of an individual's ability to maintain insulin secretion in the face of increasing insulin resistance, and thus risk for the development of type 2 diabetes.

Childhood obesity: Insulin resistance: Catch-up growth: Insulin-like growth factor-I

It is over 15 years since Barker and Hales (Hales *et al.* 1991; Hales & Barker, 1992) first published their observations of the relationship between size at birth and adult risk for the development of impaired glucose tolerance and type 2 diabetes (T2D). Through study of historical birth records they noted a continuous increase in risk for impaired glucose tolerance and T2D with decreasing birth weight; the smallest babies having an OR of 6·6 compared with those with the highest birth weight (Hales *et al.* 1991). These observations have been replicated in other

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; IGF-I, insulin-like growth factor-I; T2D, type 2 diabetes.

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populations and do not appear to be confounded by socio-economic and other environmental factors. Eriksson *et al.* (2003) have studied a large Finnish birth cohort and have described size at birth and early postnatal growth patterns for 290 adults with T2D. It was found that 66% of the subjects with T2D were born smaller than average, and they showed rapid weight gain during the first 2 years of life and continued to gain weight rapidly. Furthermore, 34% of subjects with T2D had relatively large birth weights, possibly as a result of gestational diabetes, and these subjects demonstrated initial losses in weight and length centile position; but again from the age of 2 years these children gained in weight centile progressively and became obese. Several other studies (Pettitt *et al.* 1987; Silverman *et al.* 1991; Dabelea *et al.* 2000; Sobngwi *et al.* 2003) have shown that offspring of mothers with gestational diabetes, type 1 diabetes or T2D are at increased risk for the development of obesity and T2D.

These epidemiological data have been gathered largely through the retrospective study of birth records of subjects who had subsequently developed T2D. Thus, they are robust in relation to the outcome measures, but the birth and growth data are limited and pathophysiological mechanisms underlying these associations remain unclear. A considerable amount of information has become available from a variety of animal models showing that prenatal fetal undernutrition can lead to reductions in β-cell mass and confer risk of diabetes, particularly if the animals are overfed in the early postnatal period (Reusens & Remacle, 2006). In human subjects the study of contemporary birth cohorts, such as the Avon Longitudinal Study of Parents and Children (ALSPAC; Ness, 2004; Ong & Dunger, 2004), has provided detailed information on pregnancy and follow-up measurements through early infancy into adolescent years. Other population studies (Ibanez *et al.* 2006; Iniguez *et al.* 2006) have compared children born small-for-gestational age with subjects who were appropriate-for-gestational age. It is the purpose of the present article to review what has been learned about how the pathways from smaller size at birth through rapid infancy weight gain lead to future risk of T2D.

Prenatal exposures

The critical windows of prenatal and early postnatal life proposed by Widdowson & McCance (1975) appear to be important in determining the long-term risk for diabetes. In human subjects, in addition to fetal genes, the maternal uterine environment is an important determinant of size at birth (Ong *et al.* 2000). The growth of first-born babies appears to be restrained as they are smaller at birth and then show postnatal rapid catch-up weight gain (Ong *et al.* 2002). In these first-borns birth weight correlations with maternal and grand-maternal birth weights are particularly strong (Ounsted *et al.* 1986, 1988). The nature of this maternal inheritance of birth weight is unclear. Associations between birth weight and common genetic variation in mitochondrial genes, which are inherited only from the mother, and imprinted genes, where only the maternal copy is expressed, have been described (Casteels *et al.*

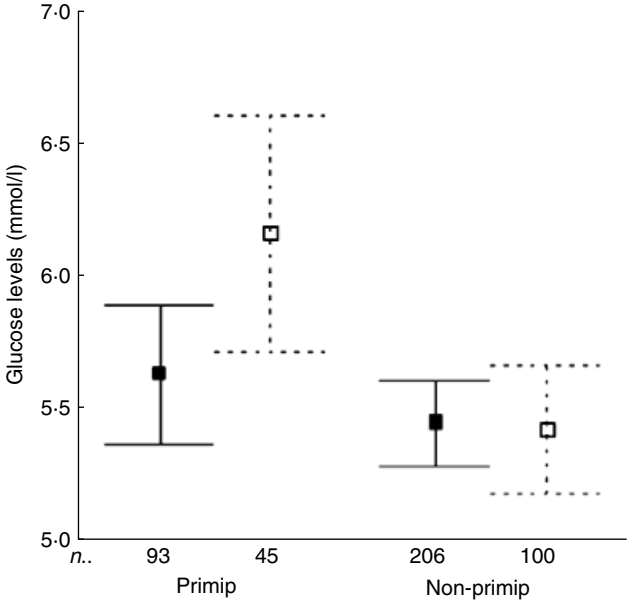

Fig. 1. Maternal glucose levels at 1 h after an oral glucose load at 27–32 weeks of gestation in the Cambridge Birth Cohort, by mother's *H19* 2992 genotype (CC, (■); T* (CT or TT), (□)) and stratified by birth order (primip, mother's first child; non-primip, second or subsequent child). Values are means and 95% CI represented by vertical bars. Associations with mother's genotype (CC *v.* T*) were only seen in first pregnancies ($P = 0{\cdot}01$). (Reproduced from Petry *et al.* 2005, with the permission of *BMC Genetics*.)

1999; Petry *et al.* 2005). More recently, attention has turned to epigenetic mechanisms whereby the maternal uterine environment could permanently alter methylation marks on the genome and therefore later gene expression (Engel *et al.* 2004). Curiously, low birth weight in the mother is also associated with an increased risk of gestational diabetes in the offspring (Seghieri *et al.* 2002). This observation brings forth the paradox of associations between both low and high birth weights and increased risks for T2D. In the Cambridge Birth Cohort mothers of first-born babies were found to have higher blood glucose levels than others who were having their second or third baby (Petry *et al.* 2005), and it is possible that the mechanisms for maternal restraint of fetal growth could also, in genetically-susceptible individuals, lead to gestational diabetes (Fig. 1). The mechanisms underlying programming of diabetes risk *in utero* are likely to be complex and probably involve an interaction between fetal genes and the maternal uterine environment. It is becoming clearer that these prenatal interactions increase the subsequent risk for the development of insulin resistance and obesity, and may be associated with reduced β-cell mass and thus risk for T2D.

Catch-up weight gain and insulin sensitivity

In the ALSPAC cohort about 25% of infants were found to show postnatal rapid catch-up weight gain (they crossed

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centiles upwards over the first 6–12 months), with approximately 25% exhibiting relative catch-down in weight relative to their birth centile (Ong *et al*. 2000). The remaining infants grew steadily along the weight centile on which they were born. It has been debated whether this realignment of growth patterns represents true 'catch-up' and 'catch-down' growth; observations in the ALSPAC cohort (Ong *et al*. 2000) would indicate that they are clearly related to prenatal factors such as parity, maternal smoking and maternal birth weight, indicating reversal of the effects of restraint or enhancement of fetal growth. Catch-up weight gain seems to be driven by satiety, as it can be predicted from cord blood leptin and ghrelin levels (Ong *et al*. 1999; Gohlke *et al*. 2005), and is associated with increased levels of nutrient intake at age 4 months (Ong *et al*. 2006). Catch-up in height also occurs in these infants, but is generally completed by the age of 6–12 months and growth then continues along a centile appropriate for mid-parental height. In contrast, the rapid weight gain may continue, and in the ALSPAC cohort the early-'catch-up' group was found to have the greatest BMI, percentage body fat and fat mass at age 5 years when compared with the no change or 'catch-down' groups (Ong *et al*. 2000). In addition, 'catch-up' infants were found to have an increased waist circumference at 5 years, which may be critical in relation to future metabolic risk.

Central adiposity and accumulation of visceral fat in particular are important risk factors for the development of insulin resistance (Garnett *et al*. 2001), and in a study of small-for-gestational-age infants *v*. appropriate-for-gestational-age infants an accretion of excess central fat in small-for-gestational-age infants between ages 2 and 4 years has been described (Ibanez *et al*. 2006). Garnett *et al*. (2001) have shown that for each tertile of weight at 8 years infants with low birth weight have the greatest percentage of abdominal fat. In the ALSPAC cohort it was found (Ong *et al*. 2004) that 'catch-up' infants are the most insulin resistant at age 8 years, and it is the overweight children aged 8 years with the lowest birth weight who are the most insulin resistant, but the effect of size at birth is only evident in those in the highest tertile of weight at 8 years (Fig. 2).

Rapid postnatal weight gain also appears to lead to more rapid maturation and earlier age at the onset of puberty (dos Santos Silva *et al*. 2002). This outcome has also become evident in the ALSPAC cohort, and there appears to be a strong trans-generational effect. The offspring of mothers with early age at menarche are relatively small at birth and show the classical catch-up weight gain growth pattern. In contrast, the offspring of mothers who had a late menarche are slighter larger at birth and show postnatal catch-down in weight (KK Ong and DB Dunger, unpublished results). This trans-generational effect again indicates the importance of maternal genes and may suggest epigenetic modulation of fetal genes.

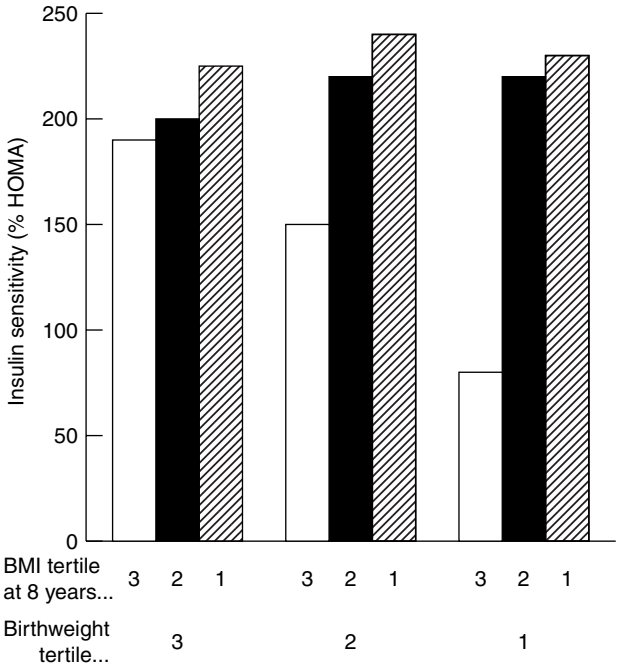

Fig. 2. Fasting insulin sensitivity (homeostasis model assessment; HOMA) at 8 years of age by tertiles of birth weight and current BMI in the Avon Longitudinal Study of Parents and Children cohort. There was a significant interaction between birth weight and current BMI on insulin sensitivity at 8 years ($P<0{\cdot}05$), such that lower birth weight was related to lower insulin sensitivity only among children with the highest BMI at age 8 years (BMI tertile 3; $P=0{\cdot}006$ for trend). (Reproduced from Ong *et al*. 2004, with the permission of *Diabetologia*.)

Height gain and insulin secretion

Catch-up growth appears to be driven by decreased satiety (Ounsted & Sleigh, 1975), and it is a risk factor for the development of central adiposity and insulin resistance (Ong *et al*. 2004). However, insulin resistance *per se* only leads to diabetes if there is failure of β-cell compensation.

The relationship between insulin resistance and insulin secretion is parabolic and β-cell capacity is best described by the product of the two; the 'disposition index' (Stumvoll *et al*. 2005). In ALSPAC this index was assessed at age 8 years in >800 children using a short oral glucose-tolerance test with measurements of glucose and insulin at 0 and 30 min, in which insulin secretion was estimated by calculating the insulinogenic index and homeostasis model assessment gave an estimate of insulin sensitivity. A lower disposition index was shown to be associated with lower ponderal index at birth, but not with the rate of postnatal weight gain (Ong *et al*. 2004). It was also found to be closely related to height, mid-parental height and insulin-like growth factor-I (IGF-I) levels; the children showing the least gains in postnatal height and with the lowest IGF-I levels were found to have the lowest disposition index (Ong *et al*. 2004). Similar data have been reported from a Chilean cohort of small-for-gestational-age and appropriate-for-gestational-age infants studied at a much earlier age (Iniguez *et al*. 2006). The difference in height gain between children in the highest and lowest tertiles of insulin secretion adjusted for sensitivity and IGF-I levels at 8 years is striking. The children with relatively poor insulin secretion aged 8 years show a pronounced loss in height SD

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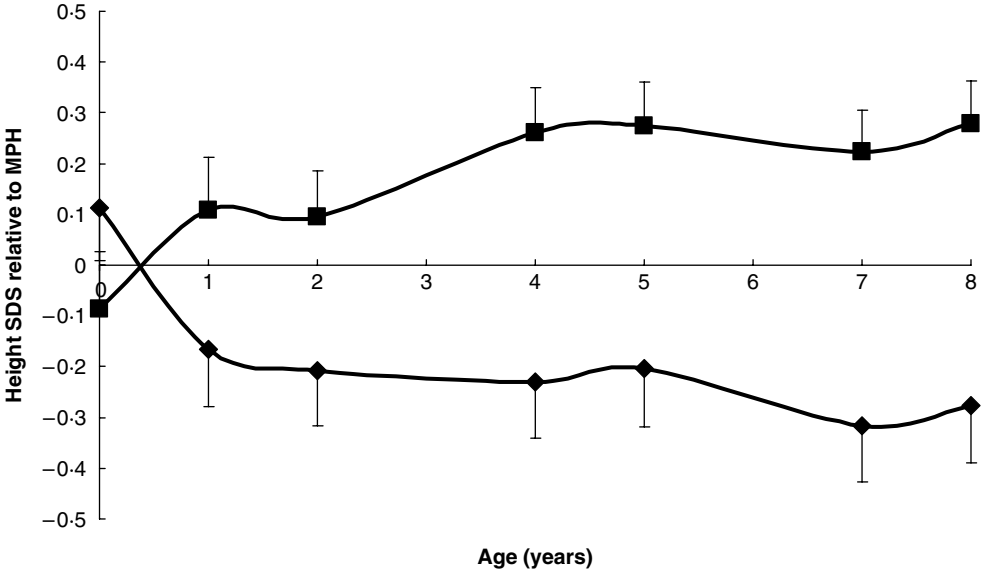

Fig. 3. Height SD score (SDS) relative to mid-parental height (MPH) from birth to age 8 years by extreme tertiles of IGF-I levels at 8 years in the Avon Longitudinal Study of Parents and Children cohort. Values are means with 1 SE represented by vertical bars. (◆), Lowest tertile; (■), highest tertile. There were significant differences in height SDS over time ($P<0{\cdot}0001$; repeated-measures analysis).

score and reduced levels of IGF-I between ages 6 months to 1 year (Fig. 3). This period is critical for determining height trajectory (Widdowson & McCance, 1975), which in early infancy is regulated by insulin and IGF-I (Silbergeld *et al*. 1989; Low *et al*. 2001; Ong *et al*. 2006).

Thus, following prenatal growth restraint catch-up growth driven by reduced satiety can lead to insulin resistance and visceral fat accumulation, but height gain and IGF-I levels may be more important markers of β-cell mass and the subsequent risk for the development of T2D. ALSPAC has shown that children with the least height gain by 8 years have the lowest insulin secretion, despite being relatively insulin sensitive. Indeed, the insulin sensitivity may be an adaptive response to poor insulin secretion. However, the children who probably give the greatest concern are those with the lowest insulin sensitivity, and although they show compensatory hyperinsulinaemia, their insulin secretion is less than that seen in the other subjects (B Salgin, KK Ong, CJ Petry, P Emmett and DB Dunger, unpublished results). The same relationship between height and IGF-I levels has been observed in adults who go on to develop T2D. The relationship between short stature and T2D risk was first observed in the MRC Ely cohort of adults aged 45–65 years (Williams *et al*. 1995), and it has subsequently been shown (Sandhu *et al*. 2002) that adults with normal glucose tolerance but low IGF-I levels are the most likely to progress to impaired glucose tolerance and T2D over the following 5 years.

Maintenance of β-cell mass

What is remarkable about these data linking size at birth, childhood gains in height and weight and risk for T2D is that the exposure occurs in early life yet the disease outcome may be delayed by 30–60 years. β-Cell mass increases continuously with growth and is known to accelerate in obese subjects and during pregnancy (Van Assche *et al*. 1978; Bonner-Weir *et al*. 1989; Bruning *et al*. 1997). Thus, β-cell mass is not a fixed entity and how early developmental influences could become 'hard-wired' needs to be understood. Fetal insulin secretion *in utero* is an important determinant of size at birth and it has been proposed (Fowden, 1989; Hattersley *et al*. 1998) that genetic defects affecting insulin secretion could explain both size at birth and disease outcome. However, studies of genetic defects associated with T2D in relation to size at birth (Hattersley *et al*. 1998) give variable results, with either no association or an association between genetic markers of T2D risk and larger, rather than smaller, size at birth. An alternative hypothesis is that the *in utero* environment effects epigenetic changes in transcription factors that regulate β-cell development and mass (Engel *et al*. 2004). A further proposal (Jensen *et al*. 2003) is that the *in utero* environment may programme hormonal axes that are important in maintaining β-cell mass.

A particular interest has been in the relationship between IGF-I levels, height gain and β-cell mass, which has been investigated in the ALSPAC cohort. Higher IGF-I levels at 5 years predict greater β-cell function at age 8 years (Ong *et al*. 2004), paralleling the observations made in the MRC Ely adult cohort (Sandhu *et al*. 2002). β-Cell function is closely related to height and lean body mass, which are regulated by IGF-I. Experimental knock-out studies of the IGF-I and insulin receptor genes in the β-cell leads to failure of β-cell development and loss of insulin secretion (van Haeften & Twickler, 2004; Ueki *et al*. 2006). Furthermore, IGF-I deficiency in adults is associated with

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gains in abdominal adiposity, insulin resistance and T2D risk (Sandhu *et al*. 2002; Dunger *et al*. 2003). Thus, impaired IGF-I production throughout childhood and adult life could be one element in explaining links between size at birth and adult T2D risk. However, as IGF-I levels are determined by insulin secretion (Holly *et al*. 1989), cause and effect may be difficult to identify, yet IGF-I may be a determinant of insulin secretion (Kulkarni *et al*. 2002; Xuan *et al*. 2002). This hypothesis can be tested and aetiological trials are currently being carried out in the MRC Ely cohort to look at the effects of low-dose growth hormone, which lead to small increases in IGF-I levels (Yuen *et al*. 2005), on insulin secretion and the risk for the development of impaired glucose tolerance (Yuen *et al*. 2004).

Conclusion

Understanding the mechanisms underlying links between size at birth and risk for T2D has important implications for public health. In countries such as India, where nutrition has recently improved, particularly with population migration from rural to urban environments or emigration, babies born small are at high risk for developing T2D (McKeigue *et al*. 1991; World Health Organization Expert Consultation, 2004). In contemporary Western countries the risks associated with low birth weight as a result of poor maternal nutrition during pregnancy are much lower (Godfrey *et al*. 1997; Rogers *et al*. 1998; Mathews *et al*. 1999); however, the risks related to increasing rates of maternal obesity and gestational diabetes are of greater concern (Reilly *et al*. 1999; Dabelea *et al*. 2000; Bundred *et al*. 2001). A recent study of women in Eastern Europe (Hesse *et al*. 2003) has shown that an increase in maternal pregnancy weight gain is one of the first responses to socio-economic improvement. Data from the Pima Indians (Franks *et al*. 2006) demonstrate that even borderline increases in maternal blood glucose levels during pregnancy may increase risk of T2D in the offspring.

The complex interaction between the maternal uterine environment and fetal genes has evolved over many thousands of years to optimise maternal and fetal survival (Neel, 1962; Haig, 1996). The recent changes in the nutritional status of mothers and offspring may not just be associated with obesity, but could also alter the balance of risk for adult disease such as T2D.

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