Insulin resistance in childhood: The EarlyBird Diabetes Study (12)

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Introduction

Insulin resistance, which underpins the modern epidemic of diabetes, may be acquired early in life, when it is potentially reversible. EarlyBird is a prospective, non-interventional, longitudinal study that focuses on the natural evolution of insulin resistance in a cohort of healthy children. It plans to follow these children until the age of 16, closely observing their development and lifestyles. Its aim is to explain the process that leads some, but not others, to develop type 2 diabetes. This report (the twelfth in a series for the EarlyBird study) highlights some results from the first phase of the study.

Once virtually unrecognised in adolescents, type 2 diabetes is rapidly becoming a significant global paediatric problem and now accounts for up to half of all new diagnoses of diabetes in children (Fagot-Campagna, 2000). Type 2 diabetes is characterised by the presence of three major defects: insulin resistance, beta cell dysfunction and elevated hepatic glucose production.

Insulin resistance is present when an abnormally large amount of insulin (endogenous or exogenous) is required for a normal biological response – that is, when the tissues are 'resistant' to the effect of insulin. Insulin resistance can be triggered by many conditions, including pregnancy, ageing and infection, but obesity is the single most important determinant (Montague and O'Rahilly, 2000).

Initially, hypersecretion of insulin compensates for insulin resistance and glucose levels remain normal. However, this hypersecretion of insulin places abnormal demands on the beta cells of the pancreas, which become increasingly unable to respond to demand after meals (impaired glucose tolerance). As insulin resistance and beta cell failure progress, fasting glucose also becomes elevated. Eventually, the beta cells become exhausted, insufficient insulin is produced to meet demand, and type 2 diabetes is diagnosed. Hyperglycaemia per se can further impair insulin sensitivity and beta cell function (glucotoxicity). The high insulin levels cause secondary disturbances that affect lipids, blood pressure, coagulation factors and urates – first described by Reaven (1988) as the metabolic syndrome.

The EarlyBird study

The EarlyBird study is a prospective, non-interventional cohort study of 300 randomly recruited, healthy children and their parents, based in Plymouth, UK. The majority are white Caucasian, with a wide socio-economic mix.

Local research ethics committee approval for the study was obtained in 1999. Details of recruitment and methodology have been described by Voss et al (2003). Mean age at recruitment was 4.9 years.

EarlyBird plans to follow these children until the age of 16, closely observing their development and lifestyles. Its aim is to explain the process that leads some, but not others, to go on to develop type 2 diabetes.

Anthropometric and blood pressure measurements are repeated at 6-month intervals, and all other tests annually. Detailed socio-economic, medical and family history questionnaires are completed annually. A limited number of anthropometric measurements, and fasting blood samples were taken at baseline from the parents.

The main outcome measures were as follows.

- *Candidate factors:* birth weight, height, body weight, body mass index (BMI),

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1 The gestational environment is important in the 'programming' of insulin resistance.

2 Gender differences in insulin resistance are present as early as 5 years of age.

3 Higher levels of physical activity are associated with improved metabolic profile in children from 6 years of age.

4 Adiposity increases between the ages of 5 and 7 years, whereas insulin resistance decreases.

5 Many parents fail to recognise when their child is overweight.

KEY WORDS

- **Type 2 diabetes**
- **Insulin resistance**
- **Children**
- **Obesity**
- **EarlyBird Diabetes Study**

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1 Type 2 diabetes is strongly associated with a family history, and work to identify genetic mutations has been extensive.

2 Insulin resistance in contemporary children appears to be a function of excess weight rather than low birth weight or change in weight.

3 The EarlyBird girls at 5 years were 33% more insulin resistant than the boys and had higher levels of markers of metabolic risk.

4 If energy intake is not matched by energy expenditure, an excess of only 2% will lead to obesity over a small number of years.

skinfolds at five sites, circumferences, body composition analysis by dual-energy X-ray absorptiometry (DEXA) and bio-impedance, resting energy expenditure, physical activity and diet.

- *Insulin resistance:* Homeostasis Model Assessment insulin resistance (HOMA-IR).
- *Markers of metabolic impact:* blood pressure, full blood count, HbA_{1c}, lipids, insulin-like growth factor 1, gonadotrophins and sex hormone binding globulin (SHBG).

Results

Nature or nurture?

Type 2 diabetes is strongly associated with a family history, and work to identify genetic mutations has been extensive. Hattersley and Tooke (1999) identified the genes responsible for maturity-onset diabetes of the young (MODY) – a relatively rare condition – and predicted that a genetic cause for insulin resistance will ultimately be found.

The association between maternal diabetes and high birthweight, caused by the mother's hyperglycaemia, is well known. Even a mild degree of hyperglycaemia can produce considerable variation in birthweight, as demonstrated by Hattersley and Tooke (1999). Pregnancy is a time of naturally increased insulin resistance; when combined with insulin resistance due to obesity, it may lead to gestational diabetes and lasting effects on the offspring. EarlyBird demonstrated the important influence of maternal pre-conception BMI on the gestational environment, with heavier women tending to have higher glucose levels and heavier babies (Jeffery et al, 2004).

The fetal programming hypothesis suggests that insulin resistance is programmed by a poor gestational environment, for which low birthweight is a surrogate (Barker et al, 1990). We tested this hypothesis on data from the EarlyBird cohort at baseline and found no relationship between birthweight and insulin resistance at age 5 years (Wilkin et al, 2002). However, insulin resistance correlated with weight at age 5, with heavier children being more insulin resistant. Early weight change (between birth and 5 years of age) did not improve on – but merely co-correlated with – current weight in the prediction of insulin resistance at 5 years. Insulin resistance in contemporary children therefore appears to be a function of excess weight rather than low birth weight or change in weight (catch-up).

Gender differences

Globally, reports of type 2 diabetes in children show a consistent female preponderance (Murphy et al, 2004). The EarlyBird girls at 5 years were 33% more insulin resistant than the boys, even after adjustment for differences in anthropometry, physical activity, body composition and energy expenditure (Murphy et al, 2004). Furthermore, compared with boys, the girls had higher fasting triglycerides and lower high-density lipoprotein (HDL)-cholesterol and SHBG – all markers of metabolic risk.

At 5 years of age the girls had similar waist circumferences to the boys (51.3 vs 51.1 cm, p=0.59), but among their parents the fathers were significantly fatter (92.2 vs 80.8 cm, p=0.001) and were 7% more insulin resistant than the mothers. Once adjusted for waist circumference, however, mothers were again more insulin resistant, by approximately 25%, suggesting that females are intrinsically more insulin resistant than males throughout life. Adult males develop diabetes more frequently than adult females, but this can be explained almost entirely by the acquisition of visceral fat – the so-called 'beer belly'.

Physical activity

Body weight is highly regulated and reflects the cumulative balance between calories consumed and calories expended. If intake is not matched by energy expenditure, an excess of only 2% will lead to obesity over a small number of years (Goran and Gower, 2001). Energy expenditure is made up of three components: resting energy expenditure, which is fixed; thermic response to feeding; and free-living energy expenditure (physical activity), which is voluntary.

Resting energy expenditure is measured annually in the EarlyBird cohort by

indirect calorimetry (gaseous exchange measurement), and early results have been published (Kirkby et al, 2004). Physical activity is also assessed annually by the use of electronic accelerometers. EarlyBird uses the MTI (formerly CSA) accelerometer (MTI, Fort Walton, Florida) (*Figure 1*), which samples movement 600 times a minute in the vertical plane and integrates the data into 1-minute epochs, storing it on a chip that can be downloaded (Metcalf et al, 2002a). The accelerometer records clock time, intensity and duration of movement.

Such accelerometers are precise (Metcalf et al, 2002b) and correlate well with activity-related energy expenditure measured by room respiration calorimetry (Puyau et al, 2002). In the EarlyBird study they are set to record continuously throughout a 7-day period (*Figure 2*).

At 5 and 6 years of age, there was no relationship between physical activity and insulin resistance in the EarlyBird children of either gender (Metcalf et al, 2003). However, when controlled for BMI, weak but significant inverse relationships became apparent between physical activity and triglycerides in 6-year-old boys and girls, and between physical activity and the total cholesterol : HDL-cholesterol ratio in boys only.

The effect of physical activity on these markers of metabolic health was present in a second cohort of older children (7–11 years of age; Mallam et al, 2003a). In the girls of this cohort, there was also a negative correlation between insulin resistance and physical activity; that is, the more active the child, the lower her insulin resistance. This trend is likely to strengthen as the children mature.

A further, remarkable finding by Mallam et al (2003b) was that the variation in physical activity between children was attributable to the child, and not to his or her environment. Mallam et al (2003b) compared total physical activity over 1 week between children from three very different schools, where the timetabled physical activity varied from 9 hours per week in a private preparatory school to 1.8 hours per week in an inner-city school. Although children in the first school recorded the most activity during school time, children in the other schools apparently made up for it by undertaking more activity out of school. Less than 3% of the variation in physical activity undertaken by these primary school children was attributable to differences in their school environment.

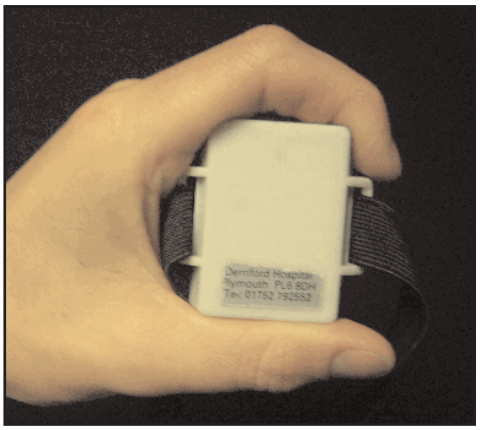

Figure 1. MTI accelerometer. Samples changes in acceleration 10 times per second. Records clock time, duration and intensity of movement.

Figure 2. Jack wearing his 'busy box' (activity monitor).

These findings suggest that physical activity in young children may be centrally regulated: EarlyBird has found a five-fold variation between children, but remarkable consistency within them year on year. Central appetite control – the so-called 'appestat' – is an accepted concept (Joliffe, 1952), and the presence of a corresponding mechanism (activitystat) to control energy expenditure seems likely.

Dissociation between fat mass and insulin resistance in young children

A major factor in the development of insulin resistance in adults is accumulation of body fat (Kahn et al, 2001), although this

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1 Physical activity is assessed annually in the EarlyBird study by the use of the MTI electronic accelerometer.

2 Associations between lipid levels and physical activity become apparent from the age of 6 years.

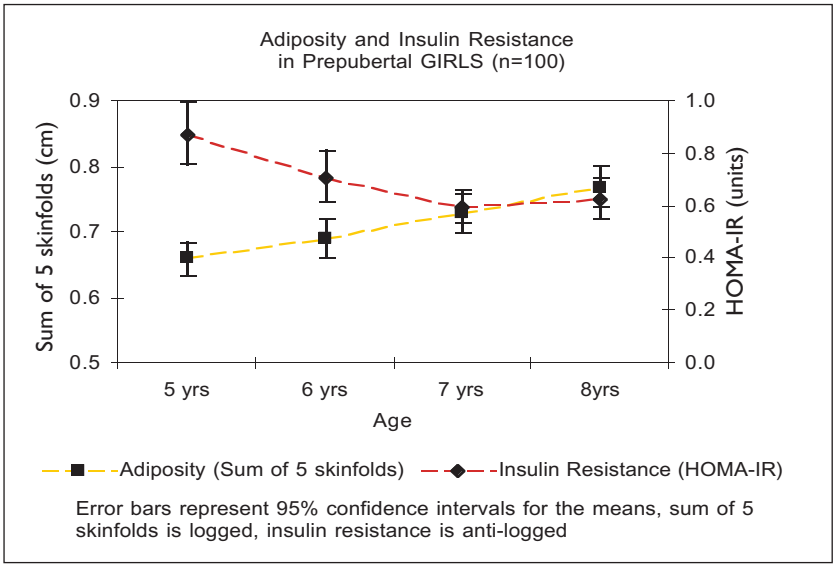
3 Variation in physical activity between children was attributable to the child, and not to his or her environment.

4 Although children in a private preparatory school recorded the most activity during school time, children in other schools apparently made up for it by undertaking more activity out of school.

has not been studied closely in young children. EarlyBird explored emerging relationships between body fat, insulin resistance and cardiovascular risk variables in the cohort tested at 5, 6, 7 and 8 years (Alba et al, 2004).

As expected, indices of body fat (mean skinfold thickness, BMI and percentage fat by DEXA) all rose progressively and significantly between 5 and 7 years (skinfold mean rise +18%, $p<0.001$). Insulin levels and HOMA-IR, on the other hand, fell substantially (mean fall 24%, $p<0.05$). Consistent with the reduction in insulin resistance, HDL-cholesterol rose (17%, $p<0.001$) and triglycerides fell (8%, not significant; *Figure 3*).

This dissociation – rising fat but falling insulin resistance – was unexpected and previously unreported. However, these data are consistent with Frayn's (2002) lipid flux hypothesis, which proposes that adipose tissue buffers the flux of fatty acids in the circulation by 'trapping' them, and by increasing triglyceride clearance. The growth deceleration and fall in growth hormone that characterises pre-puberty could also be implicated. These findings are important in the potential they offer for misinterpretation of health interventions designed to improve metabolic profile in this age group.



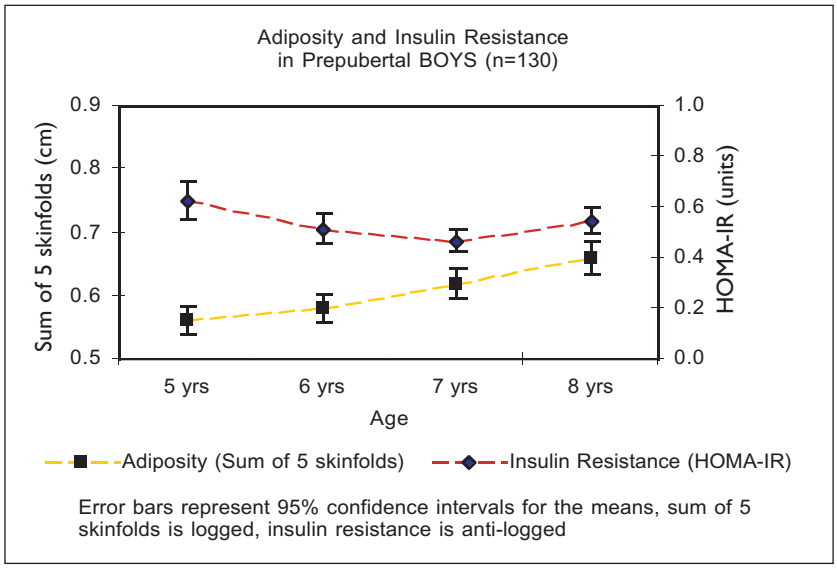


Figure 3. Dissociation of adiposity and insulin resistance in EarlyBird girls (top) and boys (above).

Parental perceptions of children's weight

Interventions to prevent obesity should begin early in life, and parents play a key role in shaping early eating habits and establishing patterns of regular physical activity in children's lives. For parents to engage actively in efforts to prevent obesity, they must first be aware that their children are becoming overweight, and concerned about the potential consequences.

EarlyBird studied parental perceptions of their own and their child's weight at age 7 (Jeffery et al, 2005). The parents completed a written questionnaire asking them, first, 'which statement best describes (a) your own, (b) your child's weight?' Possible answers on a five-point scale ranged from 'very underweight' to 'very overweight'. They were then asked whether they ever worried about their own or their child's weight, with possible answers ranging from 'very worried about underweight' to 'very worried about overweight'. Following completion of the questionnaire, both parents and children were weighed and measured and their BMI was calculated.

Overweight and obesity were defined as BMI >25 kg/m^2 and >30 kg/m^2, respectively, in adults (World Health Organization, 1998), and BMI >91st and >98th age- and gender-specific centiles, respectively, in children (Cole et al, 1995). We found that 51.6% of mothers, 71.7% of fathers and 20.4% of the children at age 7 (16.6% of boys and 25.0% of girls) were overweight or obese.

The following points summarise the

findings from this study.

- Forty per cent of overweight parents both underestimated and were unconcerned about their own weight.
- Only a quarter of parents recognised and were concerned about overweight in their child (*Figure 4*).
- Parents were less likely to identify overweight in their sons than in their daughters.
- None of parental weight status, socio-economic status and level of education had any effect on the parents' awareness of their child's weight status.
- There was no difference in prevalence of overweight and obesity by social class in parent or child.

There was a clear divergence between lay and clinical definitions of overweight in the EarlyBird families, with the majority of the parents unaware that the child was overweight. Parents, understandably, appeared to be judging their child's size in relation to contemporary children, and not according to UK norms, which have been 'pegged' at 1990 values and do not reflect the rapid increase in BMI seen in today's children.

These findings appear to confirm the growing acceptance of a higher BMI in society, despite the fact that the metabolic risks remain the same. Ways of facilitating parental awareness need to be explored, and should include regular weighing and measuring of all children, plotting these measurements on growth charts and explaining these to parents. The perceived risk that raising awareness of overweight could lead to depression, anxiety and eating disorders has to be put in context: the prevalence of bulimia nervosa among young females in the US is 1%, and of anorexia nervosa is 0.3% (Hoek and van Hoeken, 2003); both prevalences are negligible among boys; and the prevalences are hardly comparable to the prevalence of obesity.

Methodological issues

Attrition is a major threat to longitudinal cohort studies, but to date it has been minimal. After the first 4 years, EarlyBird retains 90% of the original children and can claim compliance of more than 85% for all tests. The low attrition rate has been achieved by a small team of research nurses in close contact with the families. Every effort is made for the children to attend with friends, and appointments are flexible. A telephone call the day before has been particularly successful in reducing missed appointments.

Transport and expenses are provided to enable families to get to the hospital. Toys, videos and computer games are provided, along with refreshments for the parents. The children are fasting but are given breakfast when the tests are completed. Social events such as the Christmas party and Summer Fun Day are very popular. The children are able to collect EarlyBird T-shirts, baseball caps, badges and stationery, as well as stickers, stamps and certificates, and these help them to feel valued members of the study. As they grow older, their changing needs and expectations will have to be anticipated and met.

The EarlyBird cohort is 98% Caucasian, with five children of mixed race. This is representative of the local population, but it limits generalisability to populations with a greater ethnic mix. All socio-economic groups, however, are represented in equal proportions.

Conclusions

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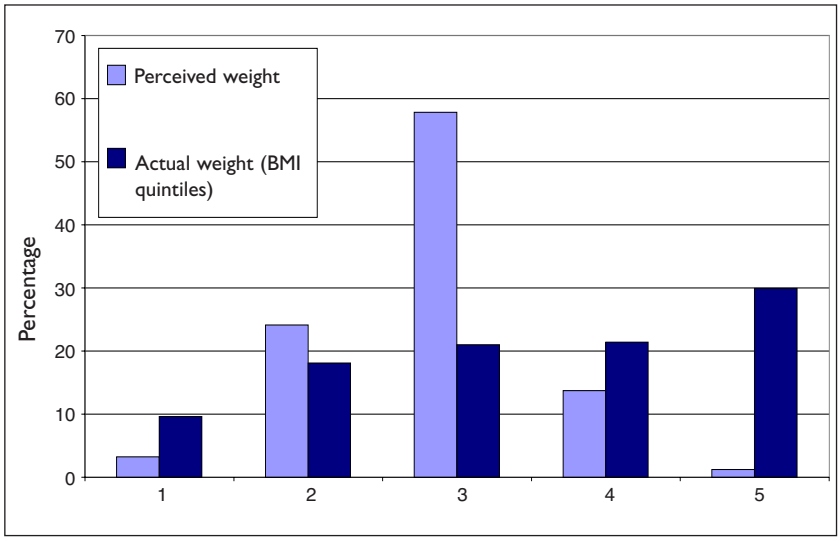

Figure 4. Mothers' perceptions of their child's weight compared with the BMI quintile. Fathers' perceptions were very similar. Key – Perceived weight according to written question 'Which statement best describes your child's weight?' 1=Very underweight; 2=A little underweight; 3=About right; 4=A little overweight; 5=Very overweight. BMI shown in quintiles of age- and gender-specific centiles: 1=0–19.9; 2=20–39.9; 3=40–59.9; 4=60–79.9; 5=80–100.

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1 Only a quarter of parents recognised and were concerned about overweight in their child.

2 Fears that raising awareness of overweight can lead to eating disorders need to be put into context: their prevalence is hardly comparable to that of obesity.

3 Retention and compliance in the EarlyBird study cohort are high.

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1 Prospective cohort studies are the most powerful in epidemiology.

2 The EarlyBird study addresses a cause of morbidity and mortality that is of major concern to the health of the nation.

3 Data from the EarlyBird study are potentially of major value to health education.

powerful in epidemiology, and the EarlyBird study addresses a cause of morbidity and mortality that is of major concern to the health of the nation. There is still much to be learned about the development of obesity and insulin resistance in children, and there is fundamental value in understanding the mechanisms responsible.

Clarification of the relationships between adiposity, visceral fat mass, physical activity and insulin resistance is the first step in formulating educational strategies for the prevention of diabetes and its associated metabolic disturbances. Data from this study are potentially, therefore, of major value to health education. ■

For more information please visit:
www.earlybirddiabetestrust.org

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