Obesity-linked insulin resistance in children – an emerging problem

The EarlyBird Study (31)

AN Jeffery, BS Metcalf, J Hosking, LD Voss, TJ Wilkin*

Summary

Once virtually unheard of in adolescents and children, type 2 diabetes is rapidly becoming a significant paediatric problem. However, insulin resistance may precede the onset of diabetes by several years, and may be acquired early in life, when it is potentially reversible. The EarlyBird Study is following a group of healthy young children as they grow, aiming to establish why some children, but not others, will go on to develop insulin resistance. A total of 300 children and their parents were recruited into a prospective cohort study at the age of five years (2000/2001). Annual measures include height, weight, body composition, physical activity, resting energy expenditure, blood pressure, fasting insulin, glucose and lipids. Insulin resistance is calculated by HOMA-IR. Annual follow up is planned for twelve years, until the children are aged 16 years.

Results in this paper are reported on the first four study years (children aged five to eight years): (1) The proportion of overweight and obese children rose with age, reaching almost one in five children at age eight. (2) Relationships between BMI and insulin resistance were evident from five years old, and strengthened over time, reaching a correlation value of r=0.51 ($p<0.001$) in eight-year-old girls. (3) Boys had a higher resting energy expenditure than girls. (4) Relationships between physical activity and metabolic health were inconsistent and varied with age and gender.

This study presents evidence that excess weight is a key factor in early development of insulin resistance. EarlyBird is unique in its longitudinal design, which will help determine what combination of factors drives the development of childhood insulin resistance, their relative contribution and, importantly, how that contribution changes as children grow and mature.

Eur Diabetes Nursing 2006; 3(1): 41–45.

Key words

Type 2 diabetes, insulin resistance, children, birth weight, BMI, body composition, physical activity, resting energy expenditure

Introduction

Type 2 diabetes accounts for 75% to 90% of all cases of diabetes, depending on ethnic background. Worldwide prevalence has risen exponentially over recent years; the World Health Organization has predicted that the total number of people with diabetes will rise from 171 million in the year 2000 to 366 million in 2030.[1]

Type 2 diabetes is said to account for as many as half of all new diagnoses of diabetes in children in some populations,[2] and the prevalence among adolescents in the USA has been estimated at 4.1/1000.[3] The first UK children with type 2 diabetes were reported in 2000.[4] The early age of onset of type 2 diabetes will significantly increase the risk of microvascular complications – known to be related to the duration of diabetes – as well as to the level of hyperglycaemia. Treatment of type 2 diabetes and the metabolic syndrome poses a growing challenge for paediatric endocrinologists and is potentially a major public health issue.

Diagnosis and classification of diabetes in children and adolescents is not always straightforward because of the increasing incidence of both types of diabetes in young people.[5,6] The Accelerator Hypothesis[7] asserts that insulin resistance underlies both types of diabetes, set against different genetic backgrounds, and predicts that heavier children develop diabetes earlier in life than they would do otherwise, as confirmed by Kibirige *et al.*[8] Children with type 2 diabetes tend to be overweight with insidious onset of symptoms. They may have mild or absent polyuria and polydipsia, often present with glycosuria without ketonuria, and little or no recent weight loss.[9] However, many children presenting with type 1 diabetes are also overweight at diagnosis, and

Authors

AN Jeffery, MSc, RGN, Senior Research Nurse
BS Metcalf, BSc, Data Manager and Statistician
J Hosking, PhD**,** Assistant Data Manager
LD Voss, PhD, Study Co-ordinator
TJ Wilkin, MD, Study Director and Professor of Endocrinology & Metabolism, Peninsula Medical School, Plymouth Campus, UK

***Correspondence to:**
AN Jeffery, EarlyBird Research Centre, Children's Day Beds, Level 12, Derriford Hospital, Plymouth, PL6 8DH, UK
e-mail: alison.jeffery@pms.ac.uk
Tel: +44 1752 763472
Fax +44 1752 763471

Received: 29 December 2005
Accepted in revised form: 19 January 2006

	Boys BMI (n=148)	% overweight or obese	Girls BMI (n=116)	% overweight or obese
Age 5	15.97	13.5	16.51	17.5
Age 6	15.91	12.7	16.56	16.7
Age 7	16.13	12.7	16.97	19.8
Age 8	16.55	17.6	17.51	23.1

* BMI≥91st centile. Centiles derived from age and gender-specific norms.[23]

Table 1. BMI of EarlyBird children with percentage of children overweight or obese* at each age

antibody and c-peptide testing is often inconclusive.[9]

Type 2 diabetes represents one outcome of insulin resistance, the metabolic syndrome, with other components including hyperlipidaemia, hypertension and coagulation disorders. Insulin resistance is present when abnormally large volumes of insulin are required for a normal biological response – that of maintaining a normal glucose level, where the tissues have become 'resistant' to the action of insulin. Insulin resistance can be triggered by pregnancy, ageing and infection, but the single most important determinant is obesity.[10] Insulin resistance is measured on a continuum and there is no cut-off point to denote a pathological level, which will vary from person to person, and is suggested by the development of the overt signs of metabolic disturbance. These signs include glucose intolerance, hypertension, hyperlipidaemia, hyperuricaemia and coagulation disorders. Impaired glucose tolerance was diagnosed in 25% of obese children in the USA.[11] In another US study,[12] the prevalence of components of the metabolic syndrome increased with the severity of obesity, and reached 50% in severely obese youngsters, with each half-unit increase in body mass index (BMI) being associated with an increase in the risk of metabolic syndrome among overweight and obese children.

The EarlyBird Study

The rationale behind this study is that insulin resistance may be acquired early in life, at a time when it is potentially reversible. EarlyBird is a non-intervention study following a cohort of healthy children from the ages of five through to 16 years, closely observing their development and lifestyles, and aiming to explain the process that will lead some, but not others, to develop insulin resistance and type 2 diabetes.

EarlyBird commenced recruitment of healthy five-year-old children in 2000 from randomly selected schools in Plymouth, UK. The cohort comprises 300 children, closely grouped in age, with a standard deviation of 0.3 years. The majority are white Caucasian, with a wide socio-economic mix. Local research ethics committee approval was granted in 1999, informed written consent was obtained from the parents at recruitment, and verbal assent is given by the child at each visit. Full details of recruitment and methodology were described by Voss *et al.*[13]

Briefly, annual measures include detailed anthropometry: sum of five skinfolds, body composition analysis (bioimpedence and dual-energy x-ray absorpimetry), resting energy expenditure (gaseous exchange measurement), 7-day physical activity monitoring (accelerometry), blood pressure and fasting blood tests (including glucose, insulin, lipids). Insulin resistance is calculated by the homeostasis model method (HOMA-IR).[14] The use of this method in epidemiologic studies has been validated in both adults[15] and children.[16]

Questionnaire data includes data on diet, socio-economic details, medical and family history. A limited number of anthropometric and blood tests were made on the parents at baseline. Participant attrition to date has been low: full data sets were available from 83% of the children at age eight years, and 79% of the children had complete data sets for every study year. Variables with a non-normal distribution were logged to achieve a normal distribution for parametric analyses.

EarlyBird is a longitudinal study, and its unique contribution to understanding the pathological processes behind insulin resistance in young people will become apparent in later stages of the study as the children reach maturity. However, interesting interim results have already emerged, some of which are summarised below.

Programming: gestation, birthweight, early feeding

Recently, there has been considerable interest in the idea that very early life factors might affect metabolic health later in life. The first programming hypotheses were formulated by Barker *et al*[17–19] in the early 1990s, and were based on observations of men and women born in the early years of the twentieth century. Those born relatively light and thin showed higher incidences of diabetes and cardiovascular disease in adulthood, and it was deemed that suboptimal

	BMI		SSF		Waist	
	Boys	Girls	Boys	Girls	Boys	Girls
Age 5	0.21 (0.01)	0.23 (0.02)	0.12 (0.16)	0.07 (0.46)	0.27 (0.001)	0.24 (0.01)
Age 6	0.16 (0.06)	0.24 (0.01)	0.07 (0.39)	0.19 (0.05)	0.16 (0.07)	0.22 (0.03)
Age 7	0.38 (<0.001)	0.51 (<0.001)	0.31 (<0.001)	0.54 (<0.001)	0.38 (<0.001)	0.49 (<0.001)
Age 8	0.37 (<0.001)	0.51 (<0.001)	0.34 (<0.001)	0.57 (<0.001)	0.39 (<0.001)	0.61 (<0.001)
Boys n=134, girls n=103 (children who had all tests at all ages)						

Table 2. Pearson's correlations (r[p]) between insulin resistance and BMI, sum of skinfolds and waist circumference at each age

nutrition at key stages of intrauterine development was the culprit. This was combined with subsequent observations that those who were born light, but who subsequently gained excess weight, were most at risk from adult disease. Growth acceleration at critical periods of post-natal development has also been implicated by Lucas' team[20,21] in the subsequent development of obesity and metabolic disease.

EarlyBird is ideally placed to look for evidence of early 'programming' on the health of its children. As expected, birth weight was related to the child's weight at age eight years (r=0.32, p<0.001), as weight generally tracks through childhood. However, there was no relationship between birth weight and insulin resistance at age eight years (partial correlation r=-0.02). We also investigated the importance of excess early weight gain in the children by looking for correlations between weight change from birth to three weeks of age and outcome measures at age eight years. Again, we found no relationships between early weight change and later weight (r=0.03), adiposity (measured by skinfolds r=0.02) or insulin resistance (partial correlation with current BMI r=-0.09) (all p>0.05).

It appears that in contemporary UK children, lifestyle factors operating throughout childhood may be more important than the legacy of the fetal and early infant environments, and that excess weight is acquired gradually throughout childhood, as reported by Kinra *et al*,[22] rather than at 'critical periods'.

Weight and adiposity

The importance of obesity in the development of insulin resistance in both adults and children is generally accepted[12] but further questions remain to be answered regarding the importance of fat distribution, length of time spent as an obese individual, the contribution of inherited tendencies to diabetes, and whether cut points exist that are predictive of the subsequent development of disease.

The mean BMI of the EarlyBird children at each age is shown in Table 1. Overweight was defined as BMI≥91st gender-specific centile, according to 1990 norms.[23] The proportion of overweight boys remained relatively stable from age five to seven years, but increased sharply at age eight years. The girls had higher mean BMI at age five years, and this increased steadily throughout the four year period. At age eight years, 18% of boys and 23% of girls were overweight or obese. Adiposity (measured by mean of five skinfold measurements) rose from five to eight years (skinfold mean rise +18%, p<0.001).

BMI, adiposity measured by skinfolds, and waist circumference correlated with insulin resistance in both boys and girls at most ages, with the heavier and fatter children having higher insulin resistance (see Table 2). These correlations strengthened with age. Simple regression models were used to determine the contribution made by each of these variables at age five years towards insulin resistance at age eight years (Table 3). BMI, adiposity and waist circumference explained 10%, 11% and 16% of the variation in insulin resistance respectively. Waist circumference is thus the most useful single measure for predicting insulin resistance at this age, although there are obviously other contributory factors.

Despite the increase in adiposity described above, insulin resistance fell substantially over the four year period (mean fall 24%, p<0.05). This unexpected fall comprised both a fall in insulin of 27.1% and a rise in glucose of 8.1%. The improvement in insulin resistance was supported by a corresponding fall in triglycerides and rise in HDL-cholesterol, suggesting a true improvement in metabolic health despite increasing fatness. The increase in fatness could be due to generation of a wave of new adipocytes, acting as powerful buffers for postprandial lipid fluxes, with a subsequent improvement in insulin resistance, as described by Frayn.[24] The rise in adiposity and improvement in metabolic health was consistent in the lightest and the heaviest children, and thus may indicate physiological metabolic remodelling prior to the onset of

	R^2	df	F	Beta	Sig
BMI 5y	0.10	236	33.22	0.35	<0.001
SSF 5y	0.12	235	32.11	0.35	<0.001
Waist 5y	0.16	236	45.80	0.40	<0.001

Table 3. Simple regression analyses. Prediction of insulin resistance at age 8 years from anthropometric variables age 5 years (n=237)

puberty, when insulin resistance is known to rise.

These findings have important implications for interpretation of intervention studies designed to reduce insulin resistance in this age group, but they also make interpretation of measures of body size and adiposity difficult for clinicians to interpret. Although adiposity is related to insulin resistance at all ages, adiposity at age five years does not necessarily equate to an increased insulin resistance at age eight years.

Energy expenditure

Energy expenditure is a combination of the basal metabolic rate, which is closely related to resting energy expenditure, the energy expenditure involved in thermogenesis, and voluntary energy expenditure (physical activity). Resting energy expenditure is fixed, and comprises 60% to 80% of total energy expenditure,[25] and is known to be an independent determinant of insulin resistance in adults with type 2 diabetes.[26] However, little is known about its relationships to insulin resistance in children.

Resting energy expenditure (REE) is measured annually in the EarlyBird children by indirect calorimetry in the fasting state, and the measure is robust (year on year correlations r=0.4 to 0.6, p<0.001). We have demonstrated a weak correlation between REE and insulin resistance in the boys at age five years (r=-0.21, p=0.03) but not the girls (r=0.12, p=0.34),[27] which was independent of both fat mass and fat free mass. Thus, boys with a higher REE tended to have a lower insulin resistance. We also demonstrated a gender difference: although their BMI was significantly higher, the REE of the girls was significantly lower than that of the boys. Even after adjusting for anthropometric variables, the mean value in the girls was 6.7% lower than that of the boys (1060 versus 1131 respectively, p=0.04). This gender difference may be intrinsic and may have implications for future weight gain in girls.

Studies in adults have shown that regular physical activity (PA) can lower insulin resistance, improve glucose tolerance and reduce the risk of type 2 diabetes.[28] This effect may act through selective reduction in visceral fat, improvements in peripheral insulin resistance, or improvement in cardiovascular fitness. Less is known in children. Wareham *et al* recently reviewed the literature[29] and found inconsistent evidence for the metabolic benefit of PA in children: of the eight cross sectional studies, four found negative and two positive relationships between PA and insulin resistance, and the remaining two studies found no relationship at all.

EarlyBird is also ideally placed to study the effects of PA over the course of childhood, using a robust and well-validated tool, the accelerometer (MTI, Fort Walton Beach, Florida). The accelerometer samples movement 600 times a minute in the vertical plane, and integrates the data into one minute epochs, storing it onto a chip which can be downloaded at the end of the week-long sampling period. The accelerometer records clock time, intensity and duration of movement. EarlyBird records physical activity for a week every year. Year-on-year correlations are between r=0.33 and r=0.55 (p<0.001), suggesting that the activity level of a child is reasonably consistent over time.

Relationships between physical activity and body size in EarlyBird children to date are unclear. There were early indications that boys who did more PA were leaner (at age five years, the correlation between high intensity PA and skinfolds was 0.40, p=0.02). A similar correlation was evident in seven-year-old boys (correlation between PA and skinfolds r=-0.21, p=0.01). However, such relationships were absent in boys at ages six and eight years, and in the girls at all ages.

Relationships between physical activity and metabolic variables such as blood pressure, insulin resistance and lipids are also weak and inconsistent in these young children. Blood pressure was inversely related to PA in eight-year-old boys (r=-0.33, p<0.001), suggesting that boys who undertook more activity recorded significantly lower blood pressures. However, this relationship was absent in girls of the same age.

Relationships between physical activity and health are thus unclear at present, but may emerge as the EarlyBird children mature. By gathering detailed physical activity data on each child every year for 12 years, we will be in a strong position to determine the contribution made by physical activity over time to a child or adolescent's metabolic health.

Conclusions

Obesity-associated diseases such as type 2 diabetes and cardiovascular disease are emerging problems in the paediatric population. The link between increased body fat and disease risk is well known. However, despite numerous studies, there is much yet to be learned about the

aetiology of insulin resistance and diabetes in children. The notions of over-nutrition and under-activity alone are too simplistic.

A longitudinal study such as EarlyBird, following an unselected group of healthy children as they grow, should provide a unique insight into one of the most serious threats to health that exists today. Importantly, these findings will form a basis for formulating educational strategies for the prevention of diabetes and its associated metabolic disturbances.

Acknowledgements:
The authors gratefully acknowledge the staff of the EarlyBird Study including nurses Rosemary Snaith and Karen Brookes and the EarlyBird children and their families.

Conflict of interest:
EarlyBird has been supported by Diabetes UK, Smith's Charity, Roche Products, The Child Growth Foundation, Eli Lilly, London Law Trust and the EarlyBird Diabetes Trust.

References

1. Wild S, Roglic G, Green A, *et al.* Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**(5):1047–1053.
2. Fagot-Campagna A, Pettitt DJ, Engelgau MM, *et al.* Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000; **136**(5): 664–672.
3. Fagot-Campagna A. Emergence of type 2 diabetes mellitus in children: epidemiological evidence. *J Pediatr Endocrinol Metab* 2000; **13:** 1395–1402.
4. Ehtisham S, Barrett TG, Shaw NJ. Type 2 diabetes mellitus in UK children – an emerging problem. *Diabet Med* 2000; **17**(12): 867–871.
5. Mauny F, Grandmottet M, Lestradet C, *et al.* Increasing trend of childhood type 1 diabetes in Franche-Comte (France): analysis of age and period effects from 1980 to 1998. *Eur J Epidemiol* 2005; **20**(4): 325–329.
6. Rosenbloom AL, Joe JR, Young RS, *et al.* Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 1999; **22**(2): 345–354.
7. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* 2001; **44**(7): 914–922.
8. Kibirige M, Metcalf B, Renuka R, *et al.* Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care* 2003; **26**(10): 2865–2870.
9. Bricker LA, Draznin MB, Hare JD, *et al.* Diabetes in adolescent patients: diagnostic dilemmas. *Indian J Pediatr* 2001; **68**(3): 223–227.
10. Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. *Diabetes* 2000; **49**(6): 883–888.
11. Sinha R, Fisch G, Teague B, *et al.* Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002; **346**(11): 802–810.
12. Weiss R, Dziura J, Burgert TS, *et al.* Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004; **350**(23): 2362–2374.
13. Voss LD, Kirkby J, Metcalf BS, *et al.* Preventable factors in childhood that lead to insulin resistance, diabetes mellitus and the metabolic syndrome: the EarlyBird diabetes study 1. *J Pediatr Endocrinol Metab* 2003; **16**(9): 1211–1224.
14. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**(7): 412–419.
15. Bonora E, Targher G, Alberiche M, *et al.* Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; **23**(1): 57–63.
16. Gungor N, Saad R, Janosky J, *et al.* Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 2004; **144**(1): 47–55.
17. Barker DJ, Bull AR, Osmond C, *et al.* Fetal and placental size and risk of hypertension in adult life. *BMJ* 1990; **301**(6746): 259–262.
18. Hales CN, Barker DJ, Clark PM, *et al.* Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991; **303**(6809): 1019–1022.
19. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992; **35**(7): 595–601.
20. Singhal A, Fewtrell M, Cole TJ, *et al.* Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet* 2003; **361**(9363): 1089–1097.
21. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004; **363**(9421): 1642–1645.
22. Kinra S, Baumer JH, Davey SG. Early growth and childhood obesity: Historical cohort study. *Arch Dis Child* 2005; **90**(11):1122–1127.
23. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995; **73**(1): 25–29.
24. Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002; **45**(9): 1201–1210.
25. Goran MI. Energy metabolism and obesity. *Med Clin North Am* 2000; **84**(2): 347–362.
26. Blonk MC, Jacobs MA, Friedberg CE, *et al.* Determinants of insulin sensitivity and consequences for lipoproteins and blood pressure in subjects with non-insulin-dependent diabetes mellitus. *Metabolism* 1994; **43**(4): 501–508.
27. Kirkby J, Metcalf BS, Jeffery AN, *et al.* Sex differences in resting energy expenditure and their relation to insulin resistance in children (EarlyBird 13). *Am J Clin Nutr* 2004; **80**(2): 430–435.
28. Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**(6): 393–403.
29. Wareham NJ, Brage S, Franks PW, *et al.* Relationship between physical activity and insulin resistance. In: *Insulin Resistance: Insulin Action and its Disturbances in Disease.* Kumar S, O'Rahilly S (eds). Chichester: John Wiley & Sons Ltd, 2004; 317–400.