# Testing the Accelerator Hypothesis

## The relationship between body mass and age at diagnosis of type 1 diabetes

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**OBJECTIVE** — Previous reports have predicted greater risk of type 1 diabetes among people who were heavier as young children. The Accelerator Hypothesis predicts earlier onset in heavier people, without necessarily a change in risk, and views type 1 and type 2 diabetes as the same disorder of insulin resistance, set against different genetic backgrounds. Insulin resistance is a function of fat mass, and increasing body weight in the industrialized world has been accompanied by earlier presentation (i.e., acceleration) of type 2 diabetes. We wanted to establish whether increasing body weight was also asociated with the earlier presentation of type 1 diabetes, as the Accelerator Hypothesis would predict.

**RESEARCH DESIGN AND METHODS** — The relationships between fatness and age at diagnosis were examined in context of birth weight, weight change since birth, weight at diagnosis, BMI at diagnosis, and BMI 12 months later in 94 children aged 1–16 years (49 boys and 45 girls) presenting for management of acute-onset type 1 diabetes.

**RESULTS** — BMI standard deviation score (SDS) at diagnosis, weight SDS change since birth, and BMI SDS 12 months later were all inversely related to age at presentation ($r = -0.39$ to $-0.40$, $P < 0.001$). The boys were significantly fatter than the girls (BMI SDS 0.56 vs. $-0.08$, respectively; $P = 0.006$) and presented with diabetes at a significantly younger age (6.74 vs. 8.32 years, respectively; $P < 0.05$). The sex difference in age at diagnosis, however, disappeared when corrected for BMI ($P = 0.31$), suggesting that fatness or something related to it was the responsible factor.

**CONCLUSIONS** — The data are consistent with the hypothesis that the age at presentation of type 1 diabetes is associated with fatness. The implications for prevention of type 1 diabetes may be important.

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The prevalence of diabetes is increasing rapidly in industrialized countries. Although most attention has focused on the increase in type 2 diabetes, there has been a parallel increase in type 1 diabetes, which requires explanation (1). Type 2 diabetes is believed to result from the loss of β-cell function in association with insulin resistance (2). The Accelerator Hypothesis regards type 1 diabetes in the same way (3).

Awareness of overlap between type 1 and type 2 diabetes is not new. There has long been interest in insulin resistance in type 1 diabetes, although related more to its implications for management and outcome than to its pathogenesis (4–8). The term "type one-and-a-half" diabetes, referring to the progression in some from type 2 to type 1 diabetes, was coined years ago and remains an area of lively debate (9). In a modern context, the increasing difficulty in distinguishing type 1 from type 2 diabetes in obese young people has given rise to the designation "double diabetes," in which recognition is given to the coexistence of autoimmunity and insulin resistance (10).

The insulin resistance that underlies type 2 diabetes seems to result mainly from lifestyle factors: weight increase and physical inactivity (11,12). Insulin resistance upregulates the β-cells metabolically and accelerates their loss through glucotoxicity (13). The tempo is normally slow. The Accelerator Hypothesis argues that people in whom type 1 diabetes develops are subject to the same weight increase, the same insulin resistance, the same metabolic upregulation, and the same acceleration in β-cell loss as those with type 2 diabetes. They are, in addition, genetically susceptible to mounting an aggressive immune response to metabolically upregulated β-cells (14,15). Depending on the genotype, this further accelerator can greatly increase the tempo of β-cell loss. Those with type 1 diabetes nevertheless remain a subset of type 2 diabetes, sharing the same basic accelerator: insulin resistance. Indeed, the Accelerator Hypothesis predicts that if people in whom type 1 diabetes would develop lacked the immunogenetic accelerator, they would still be at risk for type 2 diabetes at a later time.

One of the issues currently surrounding type 2 diabetes is the relative contribution of birth weight, weight change, and current weight to the insulin resistance that underlies it (16). The "fetal origins" (17) and subsequent "thrifty phenotype" (18) and weight "catch-up" (19,20) hypotheses examine populations of low birth weight, arguing that poor nutrition during gestation leads both to low birth weight and insulin resistance. However, it is no longer possible to demonstrate a relationship between birth weight and insulin resistance in contemporary

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**Abbreviations:** SDS, standard deviation score.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**See accompanying editorial, p. 2954.**

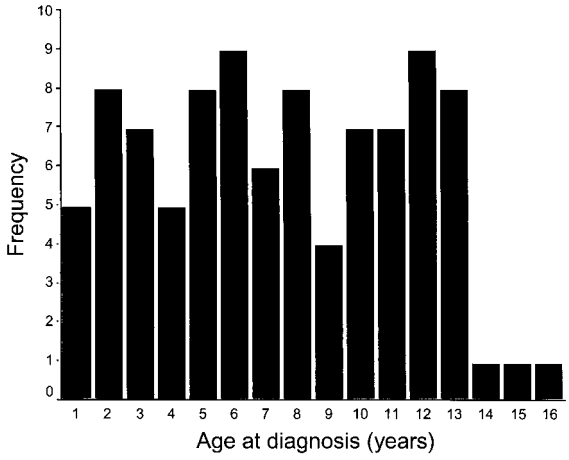


**Figure 1**—*Histogram illustrating the frequency distribution of type 1 diabetes presentation according to age.*

children, in whom low birth weight is unusual (21). Current weight, on the other hand, correlates with insulin resistance whatever the birth weight, whereas weight change seems to be merely a cocorrelate of current weight (21).

It is already known that people in whom type 1 diabetes develops are heavier in early childhood than nondiabetic people (22–26) and tend to be taller (27). Moreover, the prevalence and titer of GAD antibodies are also related to BMI both in first-degree relatives of type 1 diabetic subjects (28) and in the normal population (29). The Accelerator Hypothesis goes further and predicts that, among those who develop type 1 diabetes, the heavier children will do so at a younger age, in the same way that greater body mass accelerates the onset of type 2 diabetes (30). It goes on to suggest a mechanism whereby insulin resistance could interact with the type 1 diabetes susceptibility genotype to further accelerate β-cell loss. Because only a defined subgroup of the population is genetically susceptible, the Accelerator Hypothesis predicts that increasing obesity in children would cause the age at presentation to decrease without necessarily changing lifetime risk. Recent epidemiological data suggest that this may be the case (31,32). In this study, we test the Accelerator Hypothesis in a group of type 1 diabetic children of widely varying age and body mass. We asked the question "Do fatter children become type 1 diabetics at a younger age?"

## RESEARCH DESIGN AND METHODS

— The study was conducted retrospectively on 94 children (49 boys and 45 girls) aged 1–16 years presenting for management of acute-onset type 1 diabetes to the James Cook University Hospital, Middlesbrough, U.K., during the period 1980–2000. All but two patients were white, and twin births ($n$ = 4) were excluded. The criteria for inclusion were those diagnostic of type 1 diabetes: high blood glucose, presence of ketoacidosis, and/or requirement of insulin. Islet-related antibodies were not tested. The relationships between fatness and age at diagnosis of diabetes were examined in the context of birth weight, weight change since birth, weight at diagnosis, and BMI at diagnosis, all expressed as the standard deviation score (SDS) adduced from the 1990 U.K. growth standards (33,34). Measurements were made by a single clinic team on cantilever scales and a Harpenden stadiometer. The children were reviewed weekly after presentation for 6 weeks, and "at diagnosis" relates to height and weight recorded at week 6, when rehydration is likely to have been complete. We also compared the data "at diagnosis" with BMI SDS recorded 12 months later, when stable growth trajectories are likely to have been reestablished. We also recorded the duration of symptoms and identified those presenting with ketoacidosis.

### Statistical analysis

The study had sufficient power to show a correlation of $r = 0.29$ with 80% power and 95% certainty. Proportions were compared using the $\chi^2$ test. Simple correlations were calculated between age at diagnosis and birth weight SDS, weight change SDS, weight SDS, height SDS, and BMI SDS at diagnosis and 12 months later. Stepwise regression was performed to determine which combination of independent variables best predicted age at diagnosis (the dependent variable). Partial correlations (correlations controlled for the effect of the model variables) were also calculated for variables not selected in the regression model. The children were grouped into age-at-diagnosis quartiles. Mean birth weight SDS, weight SDS change since birth, weight SDS, and BMI SDS at diagnosis were calculated for each age-at-diagnosis quartile and were compared using ANOVA. Correlations and comparisons were also conducted on BMI recorded 12 months after diagnosis.

## RESULTS

— All ages at onset from 1 to 16 years were represented in this study (Fig. 1). A total of 22 of the 94 children were ketoacidotic at presentation. The proportion of diabetic ketoacidosis in the youngest quartile (10 of 23) was significantly higher than the second (3 of 25), third (4 of 23), and oldest (5 of 23) quartiles ($P < 0.05$). Importantly, there were no differences between the quartiles in the duration of symptoms recorded and year of diagnosis ($P = 0.95$).

The mean weight SDS at birth, weight SDS and BMI SDS at diagnosis, and weight SDS change since birth according to age-at-diagnosis quartile are shown in Table 1. Change in weight SDS since birth and BMI SDS at diagnosis were each greater in those who developed diabetes at a younger age. Putting the two observations together, it might be concluded that those who gained the most weight developed diabetes at the youngest ages. However, weight SDS change was highly correlated with weight SDS at diagnosis ($r = 0.73$, $P < 0.001$); those who gained the most weight also ended up among the heaviest.

Table 2 shows the correlations between age at diagnosis, birth weight SDS, weight SDS change since birth, weight SDS at diagnosis, height SDS at diagnosis, and BMI SDS at diagnosis and 1 year later. There were inverse and statistically significant relationships for weight SDS change since birth, weight SDS at diagnosis, and BMI SDS at diagnosis but not birth weight. The inverse relationship between age at diagnosis and BMI SDS remained when the boys and girls were analyzed separately (boys $r = -0.44$, $P = 0.002$; girls $r = -0.33$, $P = 0.025$). Stepwise regression selected BMI SDS at diagnosis

**Table 1—*Relationship of body weight to age-at-diagnosis quartile***

| Age quartile | *n* | Age at diagnosis | Weight SDS at birth | Weight SDS at diagnosis | BMI SDS at diagnosis | Weight SDS change |
|---|---|---|---|---|---|---|
| Q1 | 23 | 2.5 ± 0.9 | −0.15 ± 0.81 | 0.71 ± 1.12 | 0.79 ± 1.23 | 0.86 ± 1.31 |
| Q2 | 25 | 5.8 ± 1.0 | 0.04 ± 0.96 | 0.44 ± 0.87 | 0.42 ± 0.93 | 0.40 ± 1.14 |
| Q3 | 23 | 9.2 ± 1.1 | 0.23 ± 0.96 | 0.11 ± 1.16 | 0.03 ± 1.02 | −0.12 ± 1.58 |
| Q4 | 23 | 12.6 ± 1.2 | 0.25 ± 1.09 | 0.04 ± 1.13 | −0.26 ± 1.16 | −0.21 ± 1.36 |
| All | 94 | 7.5 ± 3.9 | 0.09 ± 0.96 | 0.33 ± 1.09 | 0.25 ± 1.14 | 0.23 ± 1.40 |
| *P* value | 94 | <0.001 | 0.46 | 0.13 | <0.01 | 0.03 |

Data are means ± SD. *P* values are based on the *F* statistic derived from ANOVA.

only for the group as a whole ($r = -0.43$, $P < 0.001$). The multiple regression analysis shown in Table 3 indicates that the other variables were all either co-correlates of BMI SDS or less predictive of age at diagnosis. None of these variables, singly or in combination, better predicted age at diagnosis, although the partial correlation of birth weight SDS with age at diagnosis, controlling for BMI SDS, became closer to significance ($r = 0.20$, $P = 0.06$).

The boys presented at a significantly younger age than the girls (6.74 years in boys, 8.32 years in girls; $P = 0.049$). However, the boys were significantly fatter than the girls at diagnosis (BMI SDS 0.56 in boys, −0.08 in girls; $P = 0.006$), and the difference in age at presentation was lost when corrected for BMI SDS (boys 7.12, girls 7.90, $P = 0.31$).

We compared the data at diagnosis with recordings of BMI made 12 months later. The correlation between the BMI SDS of individuals on the two occasions was strong ($r = 0.76$, $P < 0.001$), despite a substantial increase in mean BMI SDS from +0.18 at diagnosis to +0.94 12 months later ($P < 0.001$). Importantly, we also looked at the weight gain according to age to infer whether the younger children may simply have lost less weight before diagnosis. The change in BMI SDS between diagnosis and 12 months later was not related to the age of the subject, whether analyzed by age-at-diagnosis quartile ($P = 0.16$) or by regression ($r = 0.16$, $P = 0.14$). The gradient from regression was small: an increase of 0.03 SDS in the difference between the BMI at diagnosis and the BMI 12 months later for every 1-year increase in age at diagnosis. Finally, the relationship between age at diagnosis and BMI SDS at 12 months remained unchanged from what it had been at 6 weeks ($r = -0.40$, $P < 0.001$).

**CONCLUSIONS** — The data suggest that the age at diagnosis of type 1 diabetes is a function of body mass. Three lines of evidence presented here lead to that conclusion. First, weight SDS and BMI SDS, whether analyzed for differences in distribution according to age-at-onset quartile, or in a simple regression, are significantly related to age at presentation. Second, the relationship between age at diagnosis and weight SDS change since birth was almost as strong. All children gain weight, but weight SDS change is a measure of the excess weight gained or centiles crossed (21). Third, the boys were significantly fatter than the girls and presented with diabetes at a significantly younger age. The difference in age at diagnosis disappeared, however, when adjusted for body weight, suggesting that weight or something related to it was the factor responsible.

However, the study has a number of weaknesses. First, there was a lack of genetic and serological data with which to type the children immunogenetically. Nevertheless, we believe the children were likely to have been type 1 diabetic (autoimmune) for three reasons. All required insulin to normalize blood sugar levels, none of the children were particularly obese at presentation (maximum BMI SDS 2.73), and type 2 diabetes presenting before 16 years of age has been rare in the U.K. Second, it is possible that greater weight loss because of a longer prodrome in the older child could be mis-



**Table 2—*Simple correlation matrix***

| *n* = 94 | Birth weight SDS | Weight SDS at diagnosis | Weight SDS change | Height SDS at diagnosis | BMI SDS at diagnosis | BMI SDS 1 year after diagnosis |
|---|---|---|---|---|---|---|
| Age at diagnosis | 0.15 (0.16) | −0.29 (<0.01) | −0.33 (<0.01) | 0.06 (0.58) | −0.39 (<0.001) | −0.40 (<0.001) |
| Birth weight SDS | — | 0.07 (0.49) | −0.63 (<0.001) | 0.00 (0.99) | 0.09 (0.39) | 0.07 (0.50) |
| Weight SDS at diagnosis | — | — | 0.73 (<0.001) | 0.64 (<0.001) | 0.69 (<0.001) | 0.52 (<0.001) |
| Weight change SDS | — | — | — | 0.50 (<0.001) | 0.48 (<0.001) | 0.35 (<0.001) |
| Height SDS at diagnosis | — | — | — | — | −0.09 (0.39) | −0.04 (0.71) |
| BMI SDS at diagnosis | — | — | — | — | — | 0.76 (<0.001) |
| BMI SDS 1 year after diagnosis | — | — | — | — | — | — |

Data are *r* (*P* value). The far right column relates to the 87 of 94 children in whom BMI SDS was recorded 12 months after diagnosis.

**Table 3—*Multiple regression model***

| Model | *r* | *P* |
|---|---|---|
| BMI SDS at diagnosis | −0.39 | <0.001 |
| Excluded variables | Partial *r* | *P* |
| Birth weight SDS | 0.20 | 0.06 |
| Weight change SDS | −0.18 | 0.09 |
| Weight SDS at diagnosis | −0.04 | 0.74 |

Partial *r* is the correlation that remains between the nonselected variables and age at diagnosis after the effect of BMI SDS at diagnosis has been removed.

construed as weight-driven acceleration of the disease in those of younger onset. Type 1 diabetes is certainly associated with weight loss, and the prodrome is often more aggressive and of shorter duration in the younger child. Predisease growth charts would have provided the best evidence of true growth trajectory but were not available. Instead, we compared the data at diagnosis with recordings made 12 months later, when it is likely that metabolic health would have been restored and growth trajectories reestablished. There was a strong correlation in BMI SDS between diagnosis and 12 months later, despite a substantial mean weight adjustment. More importantly, age had no significant impact on the adjustment in BMI SDS, suggesting that, had a longer prodrome been associated with diabetes in older children, it was not responsible for the younger onset of diabetes in heavier children. Indeed, age at diagnosis was correlated as well with BMI SDS at 12 months as it was at diagnosis, suggesting that, although there are substantial weight changes around diabetes onset, children tend to retain their growth trajectories relative to each other, much as they do after chronic illness. It seems likely that BMI SDS after diagnosis is a sufficiently reliable index of premorbid body mass for group analysis. We also lacked direct measures of insulin resistance at and before development of diabetes. Insulin resistance is a well-known feature of type 1 diabetes at presentation (4–8), but the premorbid measures related to body mass, i.e., 1 year before onset, would provide the strongest evidence of cause and effect. Finally, the numbers in this study were small by epidemiological standards but nevertheless had sufficient power to reveal with clear statistical significance the relationships on which its conclusions were based.

Earlier studies reporting a higher risk of type 1 diabetes in children who were heavier as toddlers needed a control group with which to compare the diabetic children (22–26). Although such reports predicted greater risk among heavier infants, the Accelerator Hypothesis goes further and predicts earlier onset, without necessarily a change in lifetime risk (35). Here, the analysis is one of intragroup correlation, rather than intergroup comparison, and a control group was not needed.

Contrary to the present series, many studies have recorded an earlier diagnosis of type 1 diabetes in girls. However, there is no inconsistency here, as girls are generally fatter (and more insulin-resistant) than boys (21). Puberty is associated with a sharp increase in insulin resistance, occurs earlier in girls than in boys, and has to be considered in the relationship between body mass and age at onset of diabetes. Tanner staging for pubertal development is not routine in the diabetes clinic, but sexual maturity is unlikely to have had a material impact on the question we addressed in this study. We used sex-specific SDS charts for height and weight with which to adjust for the differences between boys and girls, and the youngest (prepubertal) children contributed as much to the relationship between body mass and age at onset as the older (pubertal) ones. Importantly, the relationship remained true for both boys and girls when analyzed separately, and BMI, which can overestimate fatness in younger (shorter) children (36), did not seem to be an artifact because the relationship applied as much to simple weight SDS as to BMI SDS.

We did not find this cohort of diabetic children to be systematically heavier at birth, as might have been expected from the reports referred to above where type 1 diabetic people were heavier than their peers as young children. Only the birth weights of those in age-at-diagnosis quartiles 3 and 4, in whom onset of diabetes was least accelerated, lay above the mean for the whole group. Indeed, the younger the age at diagnosis, the lower the birth weight. Those in quartiles 1 and 2, in whom diabetes was most accelerated, lay at or below mean birth weight, not above. The combined influence on insulin resistance of lower birth weight and rapid weight gain in early childhood has been attributed to so-called "catch-up" growth (16,19,20,37). However, as we have shown previously in the EarlyBird study (21), weight "catch-up" is closely correlated with current weight and probably not, as such, a mechanism for insulin resistance. Indeed, the children from quartiles 1 and 2 in the present study were close to mean birth weight, and it is arguable that the group in whom the onset of diabetes was most accelerated were not so much children of low birth weight as those who had gained most during their early years to reach the highest BMI.

Diabetes is the outcome of a process; it is not the process itself. The process is one of progressive β-cell loss that may take years. Although insulin resistance is widely regarded to be the factor responsible in pre–type 2 diabetes, epidemiologists have until now viewed pre–type 1 diabetes as a separate process and have searched in vain for separate immunologic triggers. Among those suggested are viruses, dietary nitrosamines, and cow's milk protein (38). During the ~35 years since diabetes was first perceived histologically to be of two types, the one metabolic and the other autoimmune (39), the prevalence of obesity in the industrialized world has more than doubled (40). So has that of type 2 and type 1 diabetes (41). Indeed, wherever in the world there has been an increase in type 2 diabetes, there has been a parallel increase in childhood type 1 diabetes (42).

The data reported here are not proof that the increasing prevalence of obesity in childhood is the cause of the increasing incidence of type 1 diabetes. It is indeed possible that the increase in weight is a maladaptation to pre-diabetes accelerated by another cause. The data are only consistent with a hypothesis that will ultimately best be tested by intervention with either weight reduction or insulin-sensitizing medication. It is now possible to predict type 1 diabetes with some precision (43), and given the encouraging data from lifestyle prevention studies in pre–type 2 diabetes (44,45), it may arguably be worth considering lifestyle intervention trials to reduce insulin resistance in people with pre–type 1 diabetes before embarking on further immunomodulatory drug trials. Insulin resistance is the predictable and inevitable result of weight increase to which whole populations are now subject, and the data reported here lend support to the hypothesis that type 1 and type 2 diabetes are one and the same

disorder of insulin resistance set against different genetic backgrounds.

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**References**


1. EURODIAB ACE Study Group: Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 355:873–876, 2000
2. Dostou J, Gerich J: Pathogenesis of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 109 (Suppl. 2):S149–S156, 2001
3. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
4. Ginsberg HN: Investigation of insulin sensitivity in treated subjects with insulin-dependent diabetes mellitus. *Diabetes* 26:278–283, 1977
5. DeFronzo RA, Hendler R, Simonson D: Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 31:795–801, 1982
6. Linn T, Ebener K, Raptis G, Laube H, Federlin K: Natural course of insulin sensitivity and insulin reserve in early insulin-dependent diabetes mellitus. *Metabolism* 44:617–623, 1995
7. Leslie RD, Taylor R, Pozzilli P: The role of insulin resistance in the natural history of type 1 diabetes. *Diabet Med* 14:327–331, 1997
8. Greenbaum CJ: Insulin resistance in type 1 diabetes. *Diabete Metab Res Rev* 18:192–200, 2002
9. Juneja R, Palmer JP: Type 1 1/2 diabetes: myth or reality? *Autoimmunity* 29:65–83, 1999
10. Libman I, Arslanian S: Type 2 diabetes in childhood: the American perspective. *Horm Res* 59 (Suppl. 1):69–76, 2003
11. Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winter K, Pederson O: Insulin sensitivity index, acute insulin response and glucose effectiveness in a population-based sample of 380 young healthy Caucasians: analysis of the impact of gender, body fat, physical fitness and lifestyle factors. *J Clin Invest* 98: 1195–1209, 1996
12. Prentice AM, Jebb SA: Obesity in Britain: gluttony or sloth? *BMJ* 311:437–39
13. Maedler K, Spinas GA, Lehmann R, Sergeev P, Weber M, Fontana A, Kaiser N, Donath MY: Glucose induces beta-cell apoptosis via upregulation of the Fas receptor in human islets. *Diabetes* 50: 1683–1690, 2001
14. Bjork E, Kampe O, Karlsson FA, DG, Andersson A, Hellerstrom C, Eizirik DL: Glucose regulation of the autoantigen GAD65 in human pancreatic islets. *J Clin Endocrinol Metab* 75:574–576, 1992
15. Wilkin T: Autoimmunity: attack or defence? (The case for a primary lesion theory). *Autoimmunity* 3:57–73, 1989
16. 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. *BMJ* 318:427–431, 1999
17. Barker DJ: The fetal and infant origins of adult disease. *BMJ* 301:1111–1116, 1990
18. Hales CN, Barker DJ. Type 2 (non-insulin-dependent): diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35:595–601, 1992
19. Cianfarani S, Germani D, Branca F: Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. *Arch Dis Child Fetal/Neonatal Ed* 81:F71–F73, 1999
20. Bavdekar A, Yajnik CS, Fall CHD, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C: Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes* 48:2422–2429, 1999
21. Wilkin TJ, Metcalf BS, Murphy MJ, Kirkby J, Jeffery AN, Voss LD: The relative contributions of birth weight, 'catch-up' weight and current weight to insulin resistance in contemporary five-year-olds: (EarlyBird 2). *Diabetes* 51:3468–3472, 2002
22. Baum JD, Ounsted M, Smith MA: Weight gain in infancy and subsequent development of diabetes mellitus in childhood. *Lancet* 2:866, 1975
23. Johansson C, Samuelsson U, Ludvigsson J: A high weight gain in early life is associated with an increased risk of type 1 (insulin-dependent) diabetes. *Diabetologia* 37:91–94, 1994
24. Hypponen E, Kenward MG, Virtanen SM, Piitulainen A, Virta-Autio P, Tuomilehto J, Knip M, Akerblom HK: Infant feeding, early weight gain and risk of type 1 diabetes. *Diabetes Care* 22:1961–1965, 1999
25. Bruining GJ: Association between infant growth before onset of juvenile type 1 diabetes and autoantibodies to IA-2. *Lancet* 356:655–656, 2000
26. Hypponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK, The Childhood Diabetes in Finland Study Group: Obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes Care* 23:1755–1760, 2000
27. Blom L, Persson LA, Dahlquist G: A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 35:528–533, 1992
28. Weets I, Van Autreve J, Van der Auwera BJ, Schuit FC, Du Caju MV, Decochez K, De Leeuw IH, Keymeulen B, Mathieu C, Rottiers R, Dorchy H, Quartier E, Gorus FK; Belgian Diabetes Registry: Male-to-female excess in diabetes diagnosed in early adulthood is not specific for the immune-related form, nor is it HLA-DQ restricted: possible relation to increased body mass index. *Diabetologia* 44:40–47, 2001
29. Rolandsson O, Hagg E, Hampe C, Sullivan EP Jr, Nilsson M, Jansson G, Hallmans G, Lernmark A: Glutamate decarboxylase (GAD 65) and tyrosine phosphatase-like protein (IA-2) autoantibody index in a regional population is related to glucose intolerance and body mass index. *Diabetologia* 42:555–559, 1999
30. Ehtisham S, Barrett TG, Shaw NJ: Type 2 diabetes mellitus in UK children–an emerging problem. *Diabet Med* 17:867–871, 2000
31. Gorus FK, Pipeleers DG, the Belgian Diabetes Registry: Prospects for predicting and stopping beta cell destruction. *Best Pract Res Clin Endocrinol Metab* 15:371–389, 2001
32. Pundziute-Lycka A, Dahlquist G, Nysstrom L, Arnqvist H, Bjork E, Blohme G, Bolinder J, Eriksson JW, Sundqvist G, Ostman J, the Swedish Childhood Diabetes Group: The incidence of type 1 diabetes has not increased, but has shifted to a younger age-at-diagnosis in the 0–34 years group in Sweden 1983 to 1998. *Diabetologia* 45:783–791, 2002
33. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA: Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 73:17–24, 1995
34. Cole TJ, Freeman JV, Preece MA: Body mass index reference curves for the UK. *Arch Dis Child* 73:25–29, 1995
35. Weets I, De Leeuw IH, Du Caju MV, Rooman R, Keymeulen B, Mathieu C, Rottiers R, Daubresse JC, Rocour-Brumioul D, Pipeleers DG, Gorus FK, The Belgian Diabetes Registry: The incidence of type 1 diabetes in the age group 0–39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation. *Diabetes Care* 25: 840–846, 2002
36. Voss LD, Mulligan J: Child obesity and body-mass index. *Lancet* 353:2070, 1990
37. Crowther NJ, Cameron N, Trusler J, Gray IP: Association between poor glucose tolerance and rapid post-natal weight gain in seven-year-old children. *Diabetologia* 41: 1163–1167, 1998
38. Dahlquist G: The aetiology of type 1 diabetes: an epidemiological perspective. *Acta Paediatr* 425 (Suppl.):5–10, 1998
39. Gepts W: Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes* 14:619–633, 1965
40. Zimmet P: Globalisation, coca-colonisation and the chronic disease epidemic:

can the Doomsday scenario be averted? *J Intern Med* 247:301–310, 2000
41. Akerblom HK, Reunanen A: The epidemiology of insulin-dependent diabetes mellitus (IDDM) in Finland and in northern Europe. *Diabetes Care* 8 (Suppl. 1):10–16, 1985
42. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J: Worldwide increase of type 1 diabetes: analysis of the data on published incidence trends. *Diabetologia* 42: 1395–1403, 1999
43. Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, Eisenbarth GS: Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. *Diabetes* 47:1857–1866, 1998
44. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group: prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
45. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002