Obesity, Increased Linear Growth, and Risk of Type 1 Diabetes in Children

ELINA HYPPÖNEN, MSC, MPH
SUVI M. VIRTANEN, MD, DMSC, MSC
MIKE G. KENWARD, PHD
MIKAEL KNIP, MD, DMSC
HANS K. ÅKERBLOM, MD, DMSC
THE CHILDHOOD DIABETES IN FINLAND STUDY GROUP

OBJECTIVE — The purpose of the present study was to evaluate the effect of obesity and linear growth on the risk of developing type 1 diabetes in children.

RESEARCH DESIGN AND METHODS — The study population consists of all diabetic children <15 years of age diagnosed from September 1986 to April 1989 in Finland and their birth date– and sex-matched population-based control subjects. Growth data were obtained from well-baby clinics and school health care units for 586 diabetic and 571 control subjects, resulting in a total of 18,823 paired weight-height observations.

RESULTS — Both boys and girls who developed type 1 diabetes were heavier and taller throughout childhood than control children. A 10% unit increment in relative weight was associated with a 50–60% increase in the risk of type 1 diabetes before 3 years of age and a 20–40% increase from 3 to 10 years of age. The increase in risk of type 1 diabetes for 1 SD score increment in relative height was 20–30%. Obesity (relative weight >120%) after 3 years of age was associated with a more than twofold risk of developing type 1 diabetes.

CONCLUSIONS — The present observation that obesity and rapid linear growth are risk factors for type 1 diabetes in children indicates that the increase in the prevalence of obesity and secular growth that has occurred in most industrialized countries over the last decades may be involved in the increase in type 1 diabetes incidence simultaneously observed in many countries.

Diabetes Care 23:1755–1760, 2000

The annual incidence of type 1 diabetes in Finland was found to be 50/100,000 children under 15 years of age in 1998 (A. Reunanen, personal communication), which is more than four times higher than that reported in the first nationwide survey (12/100,000) in 1953 (1), and a steep increase has also been observed in other countries over the past decades (2). Obesity is a well-established risk factor for type 2 diabetes, whereas no differences were observed in weight between children who developed type 1 diabetes and control children in the only study published so far evaluating weight gain from birth until the diagnosis of type 1 diabetes (3). Enhanced weight gain in infancy has, however, been associated with an increased risk of type 1 diabetes (4,5). Hyperinsulinemia is known to be associated with obesity both in children (6) and in adults (7). Insulin functions also as a permissive growth factor (8). Children with type 1 diabetes have been reported to be taller than control children even several years before clinical presentation (3,9). The association between obesity or accelerated height gain before the diagnosis and an increased risk of type 1 diabetes could be due to enhanced insulin secretion, since active β-cells have been shown to be more susceptible to cytokine-induced damage than resting cells in in vitro studies (10). We have previously reported an association between greater weight gain in infancy and the development of type 1 diabetes (5), and the purpose of the present study was to investigate whether obesity, relative weight, and relative height were related to the risk of development of type 1 diabetes later in childhood.

RESEARCH DESIGN AND METHODS

Subjects

All children under the age of 15 years with newly diagnosed type 1 diabetes were invited to participate in the nationwide Childhood Diabetes in Finland case-control study from September 1986 to April 1989 (11). Of 801 affected children invited, 94% took part in the study. Blood samples from the identified index children were analyzed for type 1 diabetes–associated autoantibodies (islet cell antibodies, insulin autoantibodies, antibodies to GAD, and antibodies to the protein tyrosine phosphatase related IA-2 antigen), and 98% of the diabetic patients were found to be positive for at least one of the four antibodies (12), confirming that they had autoimmune, i.e., type 1, diabetes. Birth date– and sex-matched nondiabetic control children were randomly selected from the Finnish national population registry. After three attempts at matching, 85% of diabetic children had matched control subjects.

Among both the diabetic and the control subjects, 53% were boys. The median age at the diagnosis of type 1 diabetes was 8.1 years (range 1.0–14.9): <5 years for 133 (23%), 5–9 years for 248 (42%), and ≥10 years for 205 (35%) children. Neonatal data (date of birth, birth weight, premature birth, and birth order) and sociodemographic data (place of residence, maternal education, and maternal age) were collected using structured questionnaires. Length of maternal education was ≥13 years for 37% of the diabetic patients and

From the School of Public Health (E.H., S.M.V.), the Tampere Diabetes Research Center (E.H., S.M.V., M.K.), the Medical School (M.K.), University of Tampere, and the Department of Pediatrics (S.M.V., M.K.), Tampere University Hospital, Tampere; the Hospital for Children and Adolescents (M.K., H.K.Å.), University of Helsinki, Helsinki, Finland; and the Department of Epidemiology and Public Health (M.G.K.), London School of Hygiene and Tropical Medicine, London, U.K.

Address correspondence and reprint requests to Elina Hyppönen, School of Public Health, FIN-33014 University of Tampere, Tampere, Finland. E-mail: elina.hypponen@uta.fi.

Received for publication 3 May 2000 and accepted in revised form 25 August 2000.

Abbreviations: OR, odds ratio; SDS, SD score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Proportion of obese children (relative weight >120%) and the risk of type 1 diabetes associated with obesity*

	Boys		Girls		
Age (years)	Diabetic	Control	Diabetic	Control	OR (95% CI)
2	0.8 (268)	0.7 (295)	1.7 (240)	0.4 (253)	2.35 (0.58–9.52)
4	2.8 (217)	1.3 (302)	5.6 (215)	2.7 (263)	2.37 (1.07–5.26)
6	5.8 (172)	4.0 (303)	9.9 (161)	5.3 (264)	2.10 (1.11–3.98)
8	9.3 (118)	6.8 (278)	16.3 (98)	6.9 (232)	2.36 (1.25–4.46)
10	13.3 (75)	9.9 (233)	13.2 (53)	7.9 (202)	2.25 (1.06–4.80)
12	16.7 (24)	8.8 (182)	13.3 (15)	8.5 (164)	2.96 (0.90–9.75)

Data are % (total number of interpolated observations). ORs are adjusted for corresponding height, sex, and birth year.

for 40% of the control subjects ($P = 0.19$). Maternal age at the time of birth of the child was >30 years for 34% of the diabetic patients and 32% of the control subjects ($P = 0.50$). An equal proportion of the diabetic and control children lived in rural areas outside population centers (25 vs. 23%, $P = 0.44$). Of the diabetic patients, 12%, and of the control subjects, 13% had been born at least 2 weeks before the expected time ($P = 0.60$) and were considered to be premature. The proportion of the diabetic and control subjects born as the first child in the family did not differ (46 vs. 49%, $P = 0.36$).

Growth assessments

Copies of growth charts and records were obtained from well-baby clinics and school health care units for the 586 diabetic patients and 571 control subjects who form the present study population. Data on the heights of both parents were available for 457 patients and 440 control subjects, for whom the target height could be calculated.

To avoid more acute effects of the metabolic derangement on relative height and weight, immediately prior to diagnosis, growth data for up to 1 year preceding the diagnosis were considered from the diabetic children. From the control subjects, all measurements taken under the age of 14 years were included, making the estimates for control children more accurate. This is analogous to a situation in which several control subjects are chosen for one study patient, as is routinely used in epidemiological studies. The total number of paired weight-height measurements was 8,344 for the diabetic patients and 10,479 for the control subjects. For the patients, 5,505 (66%), and for the control subjects, 5,139 (49%) measurements were taken when the child was <2 years of age: 2,578 (31%) for the patients and 4,060 (39%) for the control subjects from 2 to 9 years, and 261 (3%) for the patients and 1,280 (12%) for the control subjects when the child was ≥10 years of age. The mean number of paired weight and height observations was 14.2 ± 5.3 for the diabetic patients and 18.4 ± 5.7 for the control subjects, ranging from 1 to 43 observations. Most of the measurements were obtained as numerical data, but for 12% of the patients and 9% of the control subjects, all measurements were read from the growth charts.

The ethical committees of all participating hospitals approved the study protocol.

Statistical analyses

Relative weight was calculated as weight in relation to the mean weight for height and sex (100%), and relative height as a deviation of height in SD scores (SDSs) from the mean height for age and sex. Relative weight, relative height, and target height were computed using Finnish growth standards (13–16). None of the children in the present study exceeded the height limits for determination of the relative weight (180 cm for boys and 170 cm for girls). The parent-specific target height (16) was corrected for secular growth as previously described (17).

The main statistical analysis was based on models for relative weight and relative height in relation to age. To account for the serial nature of the measurements and the lack of balance with respect to the times of measurement and the numbers of subjects, random coefficient regression models were used in which the parameters of the underlying growth curves are allowed to vary among individuals (18). The PROC MIXED procedure (SAS/STAT software; SAS Institute, Cary, NC) was used to fit these models (19). To allow the use of simple polynomial models to represent the age trajectories of individuals, the age scale was divided into three periods: from 2 weeks of age to 1.9 years, 2–9.9 years, and ≥10 years. Separate models were used for each period. Having allowed for variability among individual trajectories, the matching variable had no additional effect on the fit of the models and was therefore omitted. Initially, a cubic response was fitted to each average trajectory, and this was simplified to a quadratic, linear, or constant trajectory if the higher order terms were found to be nonsignificant ($P \geq 0.05$).

A separate cubic spline smoother was fitted to the observations from each individual and used to interpolate at the appropriate ages (20). The interpolation was carried out only if the child provided measurements both above and below that age. The number of interpolated observations for diabetic and control children at different ages are presented in Table 1. Logistic regression was used to assess the effect of interpolated relative weight (per 10% unit increase), relative height (per 1 SDS increase), and obesity (relative weight >120 vs. ≤120%) on the risk of type 1 diabetes. To maximize the precision of the final risk estimates, the results from boys and girls were combined. Equality of odds ratios (ORs) between sexes was tested using a conventional likelihood ratio test. Since no confounding was observed by the known neonatal (birth weight, premature birth, and birth order) or sociodemographic (place of residence, maternal education, and maternal age) characteristics, all ORs have been presented by controlling for the matching factors and the corresponding value of the other anthropometric measure. All OR calculations were carried out using the STATA package (Version 6).

RESULTS — The mean relative weight or relative height at birth did not differ between the diabetic and control subjects: relative weight was 100.3 vs. 99.3% ($P = 0.16$) for boys and 99.9 vs. 100.2% ($P = 0.72$) for girls, and relative height was 0.21 vs. 0.07 SDS ($P = 0.13$) for boys and −0.05 vs. −0.09 SDS ($P = 0.70$) for girls, respectively. Both boys and girls who developed type 1 diabetes were heavier than control children from early infancy onward (Fig. 1*A*). In the longitudinal data analysis, the fitted difference in relative weight was 1.0% (−0.2 to 2.1; $P = 0.09$) between the diabetic and control boys and 1.5% (0.3 to 2.6; $P = 0.01$) between the diabetic and control girls before the age of 2 years. From 2 to 9.9

years of age, the estimated difference in relative weight between the diabetic and control boys was 2.7% (1.4–4.1), $P < 0.001$. Among girls, diabetic patients were, over the same period, consistently significantly heavier than control subjects, and the difference in relative weight ranged from a minimum of 2.0% (0.5–3.6), $P = 0.01$, at 3 years of age to a maximum of 5.6% (2.9–8.2), $P < 0.001$, at 8 years of age.

For relative height, there was a clear difference between diabetic and control boys from early infancy onward (Fig. 1*B*): 0.26 SDS (0.12–0.41), $P < 0.001$, before 2 years of age and 0.23 SDS (0.08–0.38), $P = 0.003$, between 2 and 9.9 years of age. Among the girls, there was a significant difference in relative height in the longitudinal analysis from 6 months to 1.9 years (difference at 6 months 0.19 SDS [0.01–0.37], $P = 0.03$) and also between 2 and 9.9 years of age (difference 0.28 SDS [0.12–0.44], $P < 0.001$). There was a limited amount of information available from the age of 10 years onward, especially for girls, and only the difference in relative height between the diabetic and control boys was found to be statistically significant (difference 0.31 SDS [0.06–0.57], $P = 0.01$). Adjustment for the neonatal or sociodemographic characteristics or for target height had only a negligible effect on the differences in relative weight or relative height between the diabetic and control children (data not shown).

Both higher relative weight and greater relative height were associated with an increased risk of developing type 1 diabetes when adjusted for each other (Fig. 2) or for neonatal and sociodemographic characteristics. The magnitude of the effect of greater relative weight on the risk of developing type 1 diabetes seemed to be somewhat stronger in infancy and early childhood, whereas the effect of relative height seemed to remain constant throughout the age range. There was some indication that the effect of greater weight on the risk of developing type 1 diabetes would be stronger in girls than in boys at 6 months of age (likelihood ratio test for interaction, $P = 0.05$), but there was no evidence for a sex-related difference in the effect of relative weight or relative height at any other time point, and therefore only the ORs for all the children are presented. The number of very young children classified as obese (relative weight >120%) was small, but after 3 years of age, obesity was significantly associated with an increased risk of developing type 1 diabetes

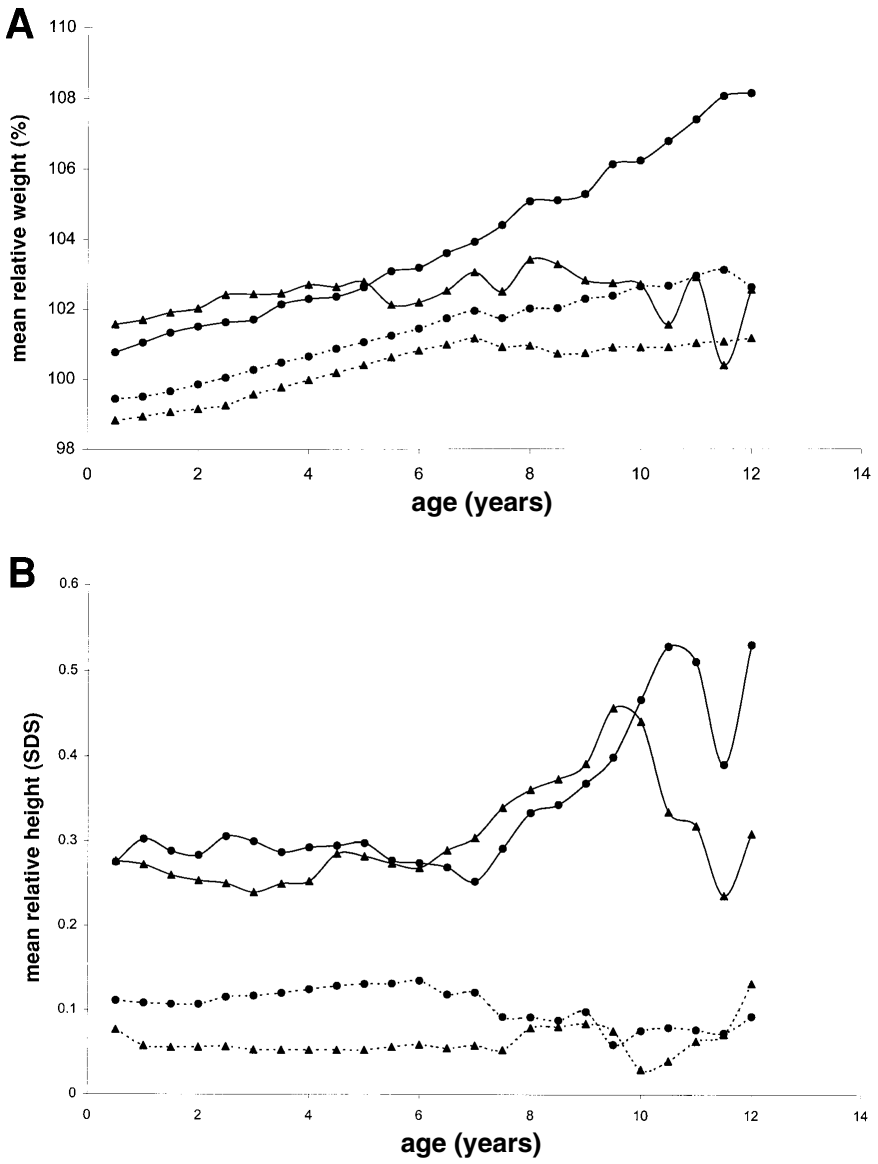

Figure 1—*Cross-sectional mean relative weights (A) and heights (B) for diabetic and control groups, calculated from the interpolated values.* —●—, *Diabetic boys;* - - ●- - -, *control boys;* —▲—, *diabetic girls;* - - ▲ - -, *control girls.*

(Table 1). Adjustment for corresponding height or for sociodemographic or neonatal factors did not affect these associations.

There was no significant difference between diabetic and control children in target height calculated from the heights of the parents (0.14 vs. 0.04 SDS, $P = 0.08$, for boys; 0.06 vs. 0.01 SDS, $P = 0.42$, for girls), and the adjustment for the target height did not affect the association between relative height and the risk of type 1 diabetes. There was a suggestion of a positive association between target height and the risk of type 1 diabetes (OR 1.23 [0.99–1.52], $P = 0.06$), but no association was evident after adjustment for the child's current height (OR 1.01 [0.76–1.34], $P = 0.97$). No evidence was found for an interaction between relative weight and relative height or between relative height and target height in relation to the risk of type 1 diabetes.

CONCLUSIONS — Obesity is a well-known risk factor for type 2 diabetes, yet we are the first to show an association between childhood obesity and an increased risk of type 1 diabetes. In the present study, children who developed type 1 diabetes were consistently heavier and taller than control

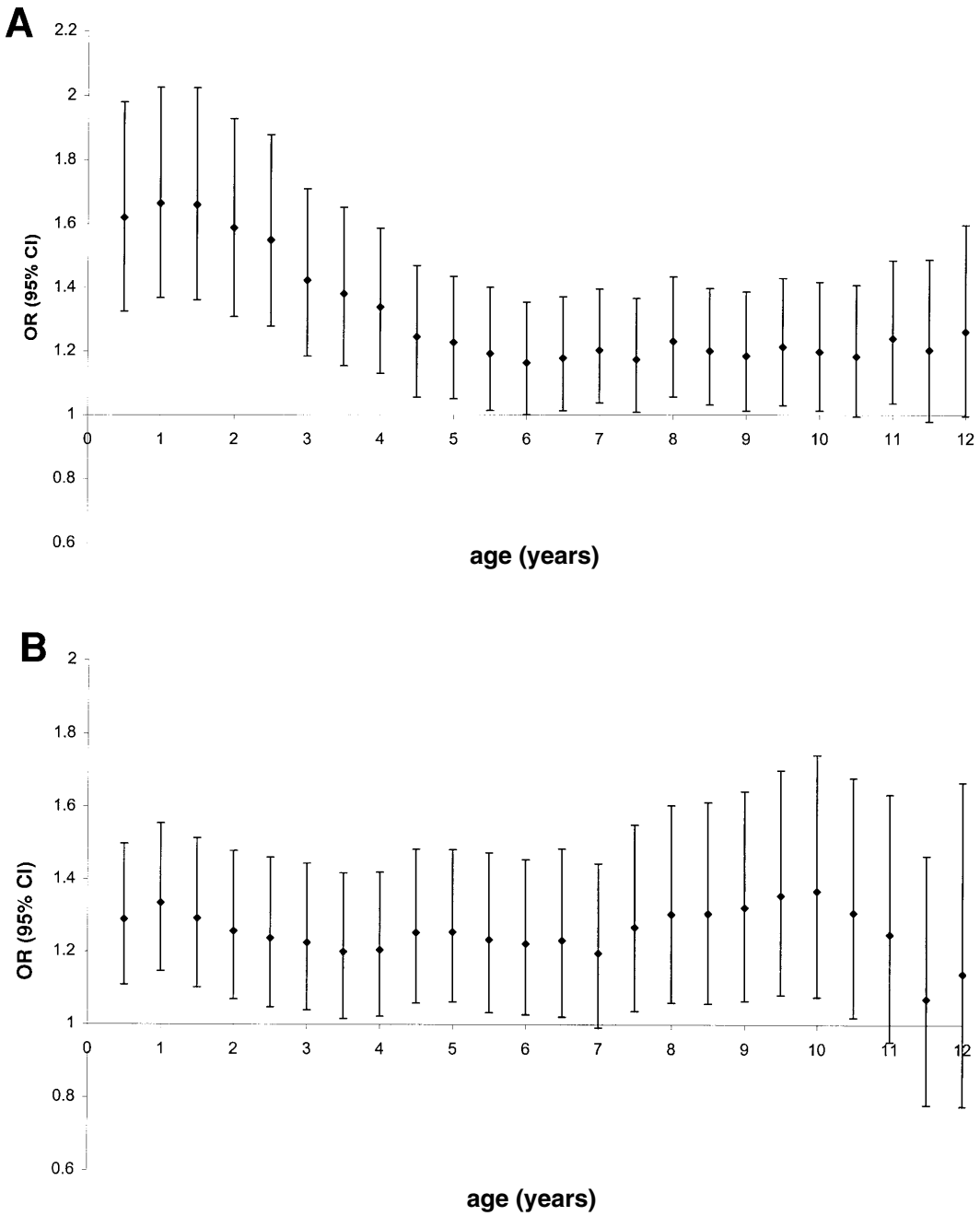

Figure 2—*Risk of type 1 diabetes for an increase of 10% units in relative weight* (A) *and for a 1 SDS increase in relative height* (B)*. Data are adjusted for sex, date of birth, and the corresponding value of the other anthropometric measure. Error bars indicate the 95% CIs for the OR.*

children, even after adjustment for several sociodemographic factors. Our finding that Finnish children who developed type 1 diabetes are taller than control children before the diagnosis of type 1 diabetes is consistent with earlier reports from Sweden (3) and England (9). Children who develop type 1 diabetes have been observed to be heavier than control children in infancy (4,5), and the present study shows a persistent difference in weight between the affected and the control children later in childhood.

The prevalence of obesity in the control children was of the same magnitude in the present study as that seen in the large Cardiovascular Risk in Young Finns study in the 1980s (21), being slightly higher than expected in young boys and slightly lower in girls when using the same reference values (data not shown). The prevalence of obesity in children who developed type 1 diabetes was consistently higher than that earlier observed in unaffected children (21). The significant association between obesity and an increased risk of type 1 diabetes remained unchanged after adjustment for several potential confounders. This suggests that the selection of control subjects was not biased in our study and that the increase in the risk of type 1 diabetes associated with obesity is true.

The association of accelerated weight and height gain in childhood and an increased risk of type 1 diabetes could be explained by increased insulin secretion and β-cell stress, since hyperfunctioning β-cells have been shown to be more susceptible to the cytotoxic effect of various cytokines (10). If the basic mechanism is a genetic susceptibility to hyperinsulinemia that increases the vulnerability of the β-cell or a possible overcompensated β-cell function triggered by early lesions of the β-cells (3), then both increased weight and height gain could be considered as risk markers of type 1 diabetes. It is possible, however, that a genetic tendency toward accelerated growth may be of decisive importance in inducing hyperinsulinemia and thus in increasing the risk of type 1 diabetes. Also, hyperinsulinemia induced by overweight may be a primary event in some children. Obese children are known to grow faster than nonobese children (22). In the present study, greater height before the diagnosis of type 1 diabetes was associated with an enhanced risk of type 1 diabetes independent of the weight of the child. It is interesting to note, however, that higher weight seemed to have the most pronounced effect on the risk of type 1 diabetes during the period when growth velocity is known to be most rapid. Unfortunately, because of a lack of data from mid-puberty, it was not possible in the present study to evaluate the effect of fast growth in puberty on the risk of type 1 diabetes.

We found no convincing evidence for an association between genetic target height and the risk of type 1 diabetes, which is in accordance with an earlier observation that the mid-parental height of children with type 1 diabetes is not higher than expected (23). Information on the growth velocity of the parents, however, was not available in either of the studies; it is therefore not possible to rule out genetically determined rapid growth as a factor associated with the development of type 1 diabetes in children.

The incidence of type 1 diabetes in Finland has increased more than four times since the early 1950s (1), and a continuous increase has also been reported in several other countries (2). A secular increase in the final height has been observed in Finland (24), as well as in almost all other developed countries (25), over the last century. Although the total energy intake has not been reported to have increased in Finnish children during the past decades, the observation of a decrease in the level of physical activity and an increase in the prevalence of obesity in childhood and adolescence (26) indicates an excess of energy intake. This may contribute to the secular changes in growth and induce β-cell hyperfunction. In addition, obesity and lack of physical activity are known to be associated with a decreased peripheral insulin sensitivity (27). Insulin resistance leads to β-cell stress, making these cells even more vulnerable to cytotoxic actions.

Taken together, these observations suggest that there may be a link between the secular changes in linear growth, the increase in the prevalence of childhood obesity, and the rising incidence of childhood type 1 diabetes observed in many developed countries. We suggest that the common denominator is increased insulin secretory demands that cannot be met by the stressed β-cells, resulting in the manifestation of type 1 diabetes in an increasing number of genetically susceptible individuals.

Acknowledgments — This study was supported by the National Institutes of Health (DK-37957 to H.K.Å. and J. Tuomilehto), the National Research Council for Agriculture and Forestry and Medical Research of the Academy of Finland, the Finnish Diabetes Research Foundation, the Association of Finnish Life Insurance Companies, the University of Helsinki, the Yrjö Jahnsson Foundation, the Reino Lahtikari Foundation, the Juho Vainio Foundation, and the University of Tampere.

We express our gratitude to the children, parents, and diabetes nurses who participated in the study. We thank Paula Virta-Autio, MSc, Ari Piitulainen, MB, and Elina Tanner for assistance with data management.

APPENDIX

The Childhood Diabetes in Finland (DiMe) Study Group — Principal investigators: H.K. Åkerblom and J. Tuomilehto; coordinators: R. Lounamaa and L. Toivanen; data management: J. Pitkäniemi and E. Virtala; local investigators: A. Fagerlund, M. Flittner, B. Gustafsson, C. Häggqvist, A. Hakulinen, L. Herva, P. Hiltunen, T. Huhtamäki, N.-P. Huttunen, T. Huupponen, M. Hyttinen, T. Joki, R. Jokisalo, M.-L. Käär, S. Kallio, E.A. Kaprio, U. Kaski, M. Knip, L. Laine, J. Lappalainen, J. Mäenpää, A.-L. Mäkelä, K. Niemi, A. Niiranen, P. Ojajärvi, T. Otonkoski, K. Pihlajamäki, S. Pöntynen, J. Rajantie, J. Sankala, J. Schumacher, M. Sillanpää, M.-R. Ståhlberg, C.-H. Stråhlmann, T. Uotila, M. Väre, P. Varimo, and C. Wetterstrand; special investigators: A. Aro, M. Hiltunen, H. Hurme, H. Hyöty, J. Ilonen, J. Karjalainen, M. Knip, P. Leinikki, A. Miettinen, T. Petäys, L. Räsänen, H. Reijonen, A. Reunanen, T. Saukkonen, E.Savilahti, E. Tuomilehto-Wolf, P. Vähäsalo, and S.M. Virtanen.

References

1. Somersalo O: Studies of childhood diabetes. I. Incidence in Finland. *Annals Paediatrica Fennica* 1:239–249, 1955
2. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J: Worldwide increase in incidence of type I diabetes: the analysis of the data on published incidence trends. *Diabetologia* 42:1395–1403, 1999
3. Blom LG, Persson LÅ, Dahlquist GG: A high linear growth is associated with an increased risk of childhood diabetes. *Diabetologia* 35:528–533, 1992
4. Johansson C, Samuelsson U, Ludvigsson J: A high weight gain early in life is associated with an increased risk of type I (insulin dependent) diabetes mellitus. *Diabetologia* 37:91–94, 1994
5. Hyppönen E, Kenward MG, Virtanen SM, Piitulainen A, Virta-Autio P, Tuomilehto J, Knip M, Åkerblom HK, the Childhood Diabetes in Finland (DiMe) Study Group: Infant feeding, early weight gain, and risk of type 1 diabetes. *Diabetes Care* 22:1961–1965, 1999
6. Drash A: Relationship between diabetes mellitus and obesity in the child. *Metabolism* 22:337–344, 1973
7. DeFronzo RA, Ferranini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
8. Hill DJ, Milner RDG: Insulin as a growth factor. *Pediatr Res* 19:879–886, 1985
9. Price DE, Burden AC: Growth of children before onset of diabetes. *Diabetes Care* 15: 1393–1395, 1992
10. Nerup J, Mandrup-Poulsen T, Molvig J, Helquist S, Wogensen L, Egeberg J: Mechanisms of pancreatic β-cell destruction in type 1 diabetes. *Diabetes Care* 11 (Suppl. 1): 16–23, 1988
11. Tuomilehto J, Lounamaa R, Tuomilehto-Wolf E, Reunanen A, Virtala E, Kaprio EA, Åkerblom HK: Epidemiology of childhood diabetes mellitus in Finland: background of a nationwide study of type I (insulin-dependent) diabetes mellitus. *Diabetologia* 35:70–76, 1992
12. Savola K, Bonifacio E, Sabbah E, Kulmala P, Vähäsalo P, Karjalainen J, Tuomilehto-Wolf E, Meriläinen J, Åkerblom HK, Knip M, the Childhood Diabetes in Finland Study Group: IA-2 antibodies: a sensitive marker of IDDM with clinical onset in childhood and adolescence. *Diabetologia* 41:424–429, 1998
13. Sorva R, Tolppanen EM, Perheentupa J: Variation of growth in length and weight of children. I. Years 1 and 2. *Acta Paediatr Scand* 79:490–497, 1990
14. Sorva R, Lankinen S, Tolppanen EM, Perheentupa J: Variation of growth in height

and weight of children. II. After infancy. *Acta Paediatr Scand* 79:498–506, 1990
15. Pere A: Comparison of two methods for transforming height and weight to normality. *Ann Hum Biol* 27:35–45, 2000
16. Sorva R, Tolppanen EM, Lankinen S, Perheentupa J: Growth evaluation: parent and child specific height standards. *Arch Dis Child* 64:1483–1487, 1989
17. Pere A, Perheentupa J, Peter M, Voutilainen R: Follow up of growth and steroids in premature adrenarche. *Eur J Pediatr* 154:346–352, 1995
18. Longford NT: *Random Coefficient Models*. Oxford, Oxford University Press, 1993
19. SAS Institute: SAS/STAT software: the mixed procedure. In *Changes and Enchangements Through Release 6.12*. Cary, NC, SAS Institute, 1997, p. 571–702
20. Green PJ, Silverman BW: *Nonparametric Regression and Generalized Linear Models*. London, Chapman and Hall, 1994
21. Nuutinen EM, Turtinen J, Pokka T, Kuusela V, Dahlstrom S, Viikari J, Uhari M, Dahl M, Kaprio EA, Pesonen E, Pietikäinen M, Salo MK, Åkerblom HK: Obesity in children, adolescents and young adults. *Ann Med* 23: 41–46, 1991
22. Vignolo M, Naselli A, Di Battista E, Mostest M, Aicardi G: Growth and development in simple obesity. *Eur J Pediatr* 147:242–244, 1988
23. Songer TJ, LaPorte RE, Tajima N, Orchard TJ, Rabin BS, Eberhardt MS, Dorman JS, Cruickshanks KJ, Cavender DE, Becker DJ, Drash AL: Height at diagnosis of insulin-dependent diabetes in patients and their non-diabetic family members. *BMJ* 292: 1419–1422, 1986
24. Rimpelä M, Rimpelä A, Vikat A, Herman-son E, Kaltiala-Heino R, Kosunen E, Savolainen A: Miten nuorten terveys on muuttunut 20 vuoden kuluessa [How the health of adolescents has changed during the past 20 years; in Finnish]. *Suomen Lääkärilehti* 52:2705–2712, 1997
25. Hauspie RC, Vercauteren M, Susanne C: Secular changes in growth. *Horm Res* 45:8–17, 1996
26. Porkka KVK, Raitakari OT, Leino A, Laitinen S, Räsänen L, Rönnemaa T, Marniemi J, Lehtimäki T, Taimela S, Dahl M, Uhari M, Åkerblom HK, Viikari JS: Trends in serum lipid levels during 1980–1992 in children and young adults: the Cardiovascular Risk in Young Finns Study. *Am J Epidemiol* 146: 64–77, 1997
27. Tremblay A: Nutritional determinants of the insulin resistance syndrome. *Int J Obes Metab Disord* 19:S60–S68, 1995