Rapid Early Growth Is Associated With Increased Risk of Childhood Type 1 Diabetes in Various European Populations

THE EURODIAB SUBSTUDY 2 STUDY GROUP

OBJECTIVE — To confirm that early growth is associated with type 1 diabetes risk in European children and elucidate any role of infant feeding.

RESEARCH DESIGN AND METHODS — Five centers participated, each with a population-based register of type 1 diabetes diagnosed at <15 years of age. Control subjects were randomly chosen from population registers, schools, or polyclinics. Growth data were obtained from routine records and infant feeding information from parental questionnaire or interview. Patient/control subject differences in mean standard deviation score (SDS) were obtained for each center and pooled. Odds ratios (ORs) were pooled by the Mantel-Haenszel method, and logistic regression was used to adjust for confounders.

RESULTS — Growth data were available for 499 patients and 1,337 control subjects. Height and weight SDS were significantly increased among patients from 1 month after birth, the maximum differences of 0.32 (95% CI 0.14–0.50) and 0.41 (0.26–0.55), respectively, occurring between 1 and 2 years of age. Significant excesses in BMI SDS were observed from 6 months of age, with the largest difference of 0.27 (0.10, 0.44) evident between 1 and 2 years. Breast-feeding was associated with reduced disease risk, OR 0.75 (0.58–0.96). Introduction of cow's milk, formula, or solid foods before 3 months was not associated with significant risk elevation.

CONCLUSION — Increased early growth is associated with disease risk in various European populations. Any role of infant feeding in this association remains unclear.

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In 1975, it was reported that the incidence of childhood type 1 diabetes peaks at about 11 years for both boys and girls (1), and it has subsequently been suggested that this is due to the high growth rate during puberty causing an increased demand on the insulin-producing β-cells, thus precipitating disease occurrence (2,3). Two decades later, a large population-based study using routinely recorded data showed that a high growth rate many years before disease onset was also a risk factor (4). No clear association with weight for height was shown, but later studies reported greater weight gains during the first year of life in children who later developed diabetes compared with control subjects (5,6), as well as increased BMI in the first year of life and an increased height in the next 2 years (7). Recently an increased relative weight has been reported in such children throughout childhood (8). It has been speculated that the key factor behind these observations is the overfeeding of children, which will accelerate growth as measured by both increased weight and height (9).

It has also been suggested that the greater weight gain in childhood observed in diabetic children before the onset of disease may be linked with higher rates of bottle-feeding in these children, explaining the frequently observed association between diabetes and a short duration of breast-feeding (and the consequent early introduction of cow's milk) (10). However, one study has concluded, to the contrary, that the introduction of formula feeding before 3 months of age and rapid growth in infancy are independent risk factors for childhood type 1 diabetes (6).

We have collected data on infant feeding practices and routine growth measurements for children before being diagnosed with childhood type 1 diabetes and for age-matched control children in a large, population-based, case-control study of environmental risk factors for this disease in different European populations with a wide range of incidence rates. In this report, we wanted to confirm in different European settings the association between various measures of growth in early childhood and subsequent risk of type 1 diabetes and to explore any role of infant feeding.

RESEARCH DESIGN AND METHODS

— Each of the eight centers that participated in EURODIAB Substudy 2 had a population-based register of childhood-onset diabetes operating in accordance with the methodology used by the EURODIAB ACE (Aetiology of Childhood Diabetes on an Epidemiological Basis) Group (11), ensuring that patients were obtained from a temporally and geographically defined study base in each center. After consultation with the study coordinators, a population-based sample of control children, matched to the patients in age distribution, was obtained in each center using sources that depended on local circumstances as previously described (12). An agreed-on set of core variables, including information about infant feeding (duration of breast-feeding,

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Abbreviations: OR, odds ratio; SDS, standard deviation score.

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

age at introduction of formula feeding, dairy milk, foods containing fruit, vegetable, fish, meat, and egg), was then collected from parents by interview or questionnaire. Growth data were obtained from routine assessments recorded in the child's health care booklet or clinic record; however, three of the eight centers (Bulgaria, Romania, and Leeds) had difficulty in complying with this element of the study and are not included in this report. All information was transferred to a standardized coding sheet and records (stripped of identifying features) were dispatched to a single center for data entry and analysis.

Height and weight measurements were used in the analysis only if the measurements were taken before the date of diagnosis for the patients or a corresponding qualifying date for control subjects, the midpoint of the center's period of patient recruitment. Because separate growth standards were not available for all the participating centers, the height, weight, and BMI (weight divided by height squared) values were adjusted for age and sex by converting to standard deviation score (SDS) using the computerized 1990 British standard (13). The score represents the number of standard deviations that a child's growth measurement differs from the mean of the distribution in British children of the same age and sex. Birth scores were adjusted for gestational age. To ensure that a child with multiple measurements available in a period contributed only once to the analysis for the period, scores for the child were averaged before analysis to give a result that was representative of the child's growth status in the period. The statistical efficiency of this simple approach was subsequently investigated using an alternative, more complex approach based on general estimating equations. Patient/control subject differences in mean SDS were calculated within each center, and these differences were then weighted and pooled. A test of the pooled difference was obtained by multiple regression analysis, and a test of heterogeneity in these differences between centers was obtained by adding an interaction term between center and patient/control status to the multiple regression (14). Children were designated as being overweight between the ages of 2 and 6 years if BMI exceeded an age- and sex-specific cutoff defined according to a recently proposed international standard (15). These cutoff values range from 18.41 and 18.02 kg/m^2 for boys and girls aged 2 years to 17.55 and 17.34 kg/m^2 for boys and girls aged 6 years. The Mantel-Haenszel approach was used to pool odds ratios (ORs) for exposures (e.g., breast-feeding, early introduction of solid foods, overweight) obtained from each center, to test the significance of the combined OR, and to test for heterogeneity in the ORs between centers (16). To adjust for potential confounders, logistic regression analysis was used with terms included in the model to represent centers. Statistical analyses were performed using the SPSS (SPSS, Chicago, IL) and Stata (Stata, College Station, TX) packages.

RESULTS — In the five participating centers, 683 children with diabetes onset before the age of 15 years and 2,167 age-matched control subjects were selected to take part in the study. The parents of 610 (89.3%) of the patients and 1,616 (74.6%) of the control subjects responded to a questionnaire or invitation to interview; growth data were available for 499 (81.8%) of the responding patients and 1,337 (82.7%) of responding control subjects (Table 1).

The differences in mean height, weight, and BMI SDS between patients and control subjects are shown in Table 2 for various periods after birth. Significant differences in height and weight SDS were evident even at birth, and these differences increased in magnitude to a maximum between ages 1 and 2 years. There were only slight differences in BMI at birth, but these differences also increased in magnitude with increasing age and were significant after 6 months. Differences showed a similar pattern for boys and girls, although they tended to be larger for boys at most ages. Figure 1 presents the results between the ages of 1 and 2 years by study center. Tests for heterogeneity showed that differences between centers were not significant. In terms of the original variables, these differences in SDS between 1 and 2 years of age correspond roughly to differences of 1 cm, 0.5 kg, and 0.4 kg/m^2 for height, weight, and BMI, respectively. To demonstrate that such apparently small differences may nevertheless translate to meaningful increases in disease risk, childhood obesity (as defined by a recently proposed international standard), based on the first available BMI measurement after the age of 2 years, was associated with an increased disease risk: OR 1.73 (95% CI 1.19–2.52), with no evidence of heterogeneity between centers.

When growth data were examined in relation to the number of years before diagnosis (or the corresponding qualifying date for control subjects), weight and height scores were significantly larger in patients than in control subjects for up to 6 years before diagnosis and BMI scores for up to 4 years before diagnosis (Table 3). In the year directly preceding diagnosis, all three scores were still larger in patients, but only the comparison of weight scores attained significance.

Breast-feeding of any duration was associated with a reduction in risk, with a pooled OR of 0.75 (95% CI 0.58–0.96) and no evidence of heterogeneity between centers. The age at which various foods were introduced to the diet was also examined; the introduction before 3 months of age of cow's milk (OR 1.15, 95% CI 0.74–1.81), cow's milk or formula (OR 1.01, 95% CI 0.81–1.25), or solid foods (OR 0.74, 95% CI 0.57–0.95) was not associated with any significant elevation in risk. Indeed the finding for solid foods suggested a reduced risk, although there was significant heterogeneity between centers ($P < 0.001$), with the Lithuanian center showing a significantly increased risk and the Latvian and Luxembourg centers significantly reduced risks. None of these results were altered by adjustment for several potential confounding variables (maternal age at delivery, neonatal jaundice, neonatal respiratory infection, vitamin D supplementation, and asthma).

When these infant feeding indicators were examined in relation to growth data, the early introduction of solids was associated only with significantly higher height SDS at the age of 6–12 months. The early introduction of cow's milk or formula was associated with lower weight and BMI SDS between 1 and 6 months, but there was evidence of heterogeneity, indicating that this finding was not consistent across centers.

Both height SDS and BMI SDS between 1 and 2 years were independently predictive of diabetes when simultaneously included in a logistic regression analysis: OR 1.36 (95% CI 1.17–1.58) and 1.35 (95% CI 1.15–1.57), respectively. These results were little altered by

Table 1—*Summary of participants in the five study centers*

Center and status	Source	Number eligible	Number responding to questionnaire or interview	Availability of at least one height or weight measurement among responders*	Mean number of measurement times in subjects with at least one measurement*
Austria (Vienna)					
Patient	1989–94 registrations	117	104 (88.9)	78 (75.0)	5.2
Control subject	Schools	477	380 (79.7)	312 (82.1)	5.2
Latvia (one region excluded)					
Patient	1989–94 registrations	143	141 (98.6)	117 (83.0)	5.4
Control subject	Population register	410	324 (79.0)	259 (79.9)	5.1
Lithuania (whole nation)					
Patient	1989–94 registrations	124	117 (94.4)	116 (99.1)	8.1
Control subject	Polyclinics	369	269 (72.9)	263 (97.8)	7.2
Luxembourg (whole nation)					
Patient	1989–95 registrations	59	59 (100.0)	33 (55.9)	4.7
Control subject	Schools/preschools	188	178 (94.7)	124 (69.7)	4.5
United Kingdom (Northern Ireland)					
Patient	1990-92 registrations	240	189 (78.8)	155 (82.0)	2.9
Control subject	General practitioner registers	723	465 (64.3)	379 (81.5)	3.1
Total					
Patient		683	610 (89.3)	499 (81.8)	5.2
Control subject		2,167	1,616 (74.6)	1,337 (82.7)	4.9

Data are *n* or *n* (%). *Between age of 1 month and age at diagnosis (patients) or qualifying date (control subjects).

adjustment for a range of possible confounders (maternal age at delivery, neonatal jaundice, neonatal respiratory infection, vitamin D supplementation, and asthma). Furthermore when the various indicators of infant feeding were included in the model, similar results were obtained, thus providing no evidence to support the hypothesis that the infant feeding factors played a role in explaining the excess risk associated with increased growth. The OR associated with breast-feeding, in particular, in this analysis remained significant, OR 0.59 (95% CI 0.35–0.97), indicating that a high early growth rate and failure to breast-feed are independent predictors of disease risk.

CONCLUSIONS — As standards for growth were not available for each of the centers participating in our study, we chose to use the British growth standard to perform our analyses. The appropriateness of this standard could be questioned, and we therefore repeated our analyses using a standard derived from the U.S. Health Examination Survey (17,18). Although individuals' scores differed between the two standards in their absolute values, we found that the differences in mean scores (Tables 2 and 3) were robust to the choice of standard.

In contrast to some recent studies (7,8), growth measurements for many of the children in our study were too sparse to permit more sophisticated longitudinal analysis methods to be employed. However, we did investigate if there was much loss of statistical efficiency through the simple averaging of scores within each time period for each subject. When we repeated the analyses in Table 2 using a general estimating equation approach to analyze all growth measurements in each time period, we obtained similar estimates, with no obvious gain in efficiency as judged by the width of the 95% CIs. The high levels of statistical significance attained in many of our cross-sectional comparisons mean that, even if a correction were employed to allow for analyses of multiple time periods, the interpreta-

Table 2—*Patient/control subject differences in SDS for growth measurements taken at different ages pooled over five centers*

Age	*n* (patients, control subjects)*	Height SDS		Weight SDS		BMI SDS	
		Difference (95% CI)	*P*	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Birth	478, 1257	0.14 (0.01–0.27)	0.04	0.11 (0.01–0.21)	0.03	0.05 (−0.06 to 0.17)	0.36
1–6 months	309, 825	0.23 (0.06–0.39)	0.007	0.24 (0.12–0.36)	<0.001	0.08 (−0.06 to 0.23)	0.33
6 months to 1 year	304, 799	0.32 (0.17–0.48)	<0.001	0.36 (0.23–0.49)	<0.001	0.16 (0.00–0.31)	0.05
1–2 years	214, 593	0.32 (0.14–0.50)	<0.001	0.41 (0.26–0.55)	<0.001	0.27 (0.10–0.44)	0.002
2–4 years	178, 441	0.19 (−0.01 to 0.39)	0.06	0.24 (0.07–0.41)	0.007	0.21 (0.03–0.40)	0.03
4–6 years	164, 397	0.26 (0.07–0.44)	0.006	0.29 (0.11–0.47)	0.002	0.20 (−0.01 to 0.41)	0.06

*Refers to subjects with both height and weight measurements. No evidence of center-to-center heterogeneity was found in any analysis ($P > 0.05$).

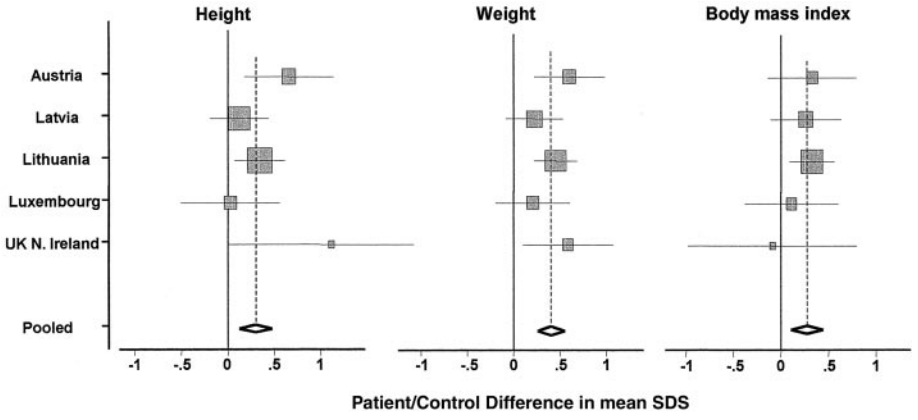

Figure 1—*Differences in means (95% CI) between patients and control subjects in height, weight, and BMI SDS at age 1–2 years, pooled over centers. The box size indicates the weight contributed by each center to the pooling.*

tion of our findings would remain clear. We confirm that, as early as the first few years of life, height, weight, and BMI SDS are risk determinants for childhood-onset type 1 diabetes in different areas of Europe. Also, by looking at periods before diagnosis, an increased weight, height, and BMI can be seen from 1 year and up to 5–6 years before the onset of clinical disease.

Because adequate insulin supply is a fundamental prerequisite for normal growth in children, measurements taken around the time of disease onset may be blurred by the duration and magnitude of insulin deficiency. This may explain why the patient/control subject differences were reduced in the year before diagnosis (Table 3) even though we omitted measurements taken within a month of diagnosis. Although this could also explain why a review of early studies on children's height at the time of diagnosis of type 1 diabetes noted conflicting results (19), more recent studies that have incorporated appropriate control groups have more consistently reported that diabetic children are taller at diagnosis (4,20–22), although often the results were not consistent in all age-groups. Interestingly, when we examined our results by age-group, a significant excess in height SDS in the year before diagnosis was observed only for those with onset in the 5- to 9-year-age-group, a finding that supports two of these studies (20,21).

Birth weight has also been studied as a possible indicator of subsequent type 1 diabetes risk. In many of the smaller studies, no consistent association has been found (5,23–27). However, two large register-based studies have reported a weak but uniformly increasing risk with increasing birth weight (28,29), and a previous analysis of our own data suggested a reduced risk associated with having a birth weight under 2,500 g (30). We were not able to confirm reports that onset before 5 years of age was associated with low birth weight (5,31).

Growth depends on genetic, nutritional, and hormonal factors, and we cannot exclude the possibility that the association between a high growth rate and childhood diabetes is due to a common genetic trait. However, the slightly stronger association between diabetes and the gain in weight as opposed to height found in our study and others (5,8) might suggest that nutritional factors are responsible. As in another recent study (6), we could not confirm a previous suggestion that an early introduction of solid foods, defined by the authors as occurring before 3 months of age (32), was associated with an increased risk. Indeed, pooled over all centers, our results suggested a reduction in risk, but there was evidence of heterogeneity in the findings between centers, possibly suggesting that early exposure to solid foods may not be a primary risk factor. Limitations and biases in parental recall of infant feeding practices may also explain these contradictory results, and ideally, overfeeding would be measured by a prospective evaluation of energy intake during childhood.

A relationship between growth and childhood diabetes risk is central to the accelerator hypothesis (33), which argues that the distinction between type 1 and type 2 diabetes is becoming increasingly blurred and that physical inactivity and weight gain lead to insulin resistance, which is responsible for the rising incidence of both type 1 and type 2 diabetes in industrially developed societies. The association between growth and childhood diabetes risk described in this study is also consistent with the ecological association between gross national product and diabetes incidence in different countries (34), since childhood growth is known to reflect population wealth (35).

Table 3—*Patient/control subject differences in SDS for growth measures taken in periods before diagnosis (patients) or qualifying date (control subjects) pooled over five centers*

Period before diagnosis	*n* (cases, control subjects)*	Height SDS		Weight SDS		BMI SDS	
		Difference (95% CI)	*P*	Difference (95% CI)	*P*	Difference (95% CI)	*P*
1 month to 1 year	141, 380	0.12 (−0.10 to 0.34)	0.28	0.25 (0.05–0.44)	0.01	0.16 (−0.07 to 0.38)	0.17
1–2 years	170, 416	0.17 (−0.01 to 0.36)	0.07	0.37 (0.19–0.55)	<0.001	0.30 (0.07–0.53)	0.01
2–3 years	152, 420	0.23 (0.02–0.44)	0.03	0.32 (0.14–0.50)	<0.001	0.22 (0.02–0.42)	0.03
3–4 years	144, 376	0.30 (0.09–0.51)	0.004	0.37 (0.18–0.55)	<0.001	0.34 (0.12–0.55)	0.002
4–5 years	151, 358	0.38 (0.13–0.63)	0.003	0.27 (0.07–0.46)	0.007	0.19 (−0.03 to 0.40)	0.09
5–6 years	126, 292	0.37 (0.14–0.59)†	0.001	0.28 (0.07–0.49)	0.01	0.06 (−0.18 to 0.29)	0.64

*Refers to subjects with both height and weight measurements. †Significant center-to-center heterogeneity ($P < 0.05$).

Some part of the association between growth and childhood diabetes risk could be attributable to socioeconomic circumstances, but these are difficult to measure, especially in a multicenter study such as ours.

In conclusion, our population-based patient/control subject study confirms previous reports showing that rapid growth in early childhood measured by height, weight, or BMI is a risk factor for childhood-onset diabetes in various European populations.

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APPENDIX

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