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Clinical genetics of Type 1 Diabetes Genetic correlates of early growth and disease progression

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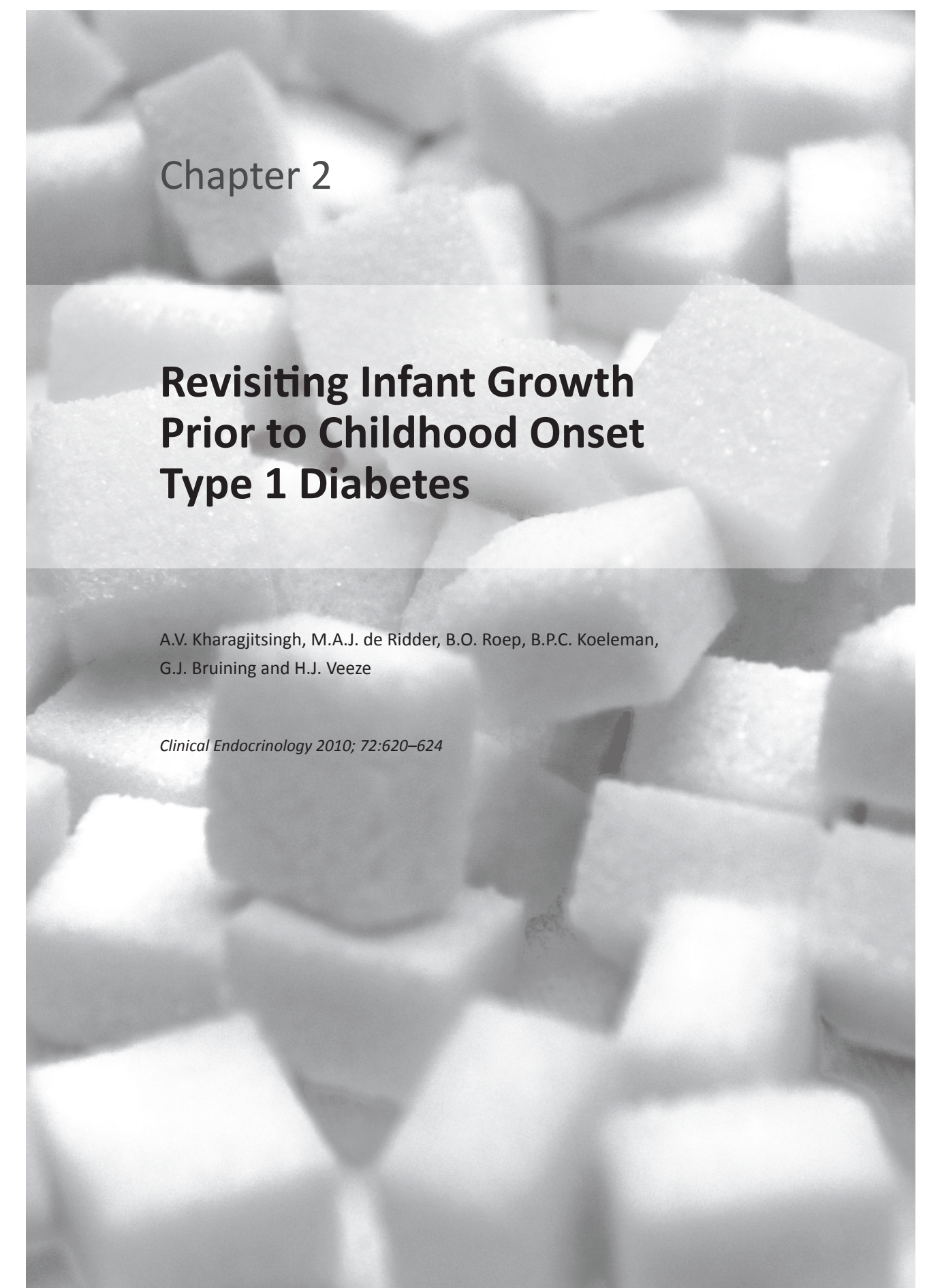
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A close-up, black and white photograph of numerous sugar cubes. The cubes are piled together, with some in sharp focus in the foreground and others blurred in the background, creating a sense of depth. The lighting highlights the crystalline texture of the sugar.

Chapter 2

Revisiting Infant Growth Prior to Childhood Onset Type 1 Diabetes

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Summary

Objective: Accelerated early growth prior to childhood type 1 diabetes onset is associated with an increased risk for type 1 diabetes (T1D). We aimed to study early growth correcting for the previously neglected confounder of familial effects.

Design: Infant growth was studied in a retrospective family case control study of diabetic children in which siblings acted as matched familial controls allowing correction for confounders related to family particulars.

Patients: Weight and height data were collected from 213 juvenile onset type 1 diabetic children and their 255 healthy siblings. Growth in the first four years of life was studied using repeated measurement. The degree of early overgrowth was correlated with age of clinical onset.

Results: Birth weight and length did not differ between later diabetic children and their siblings. In the first year of life, weight standard deviation score (SDS) differed between patients and sibs ($P = 0.0001$). After the first year, both diabetic children and sibs showed parallel enhanced weight and height gain SDS until age 4 years. Earlier onset diabetes was associated with a higher weight SDS at 6 months of age.

Conclusion: In this family case-control study the association of increased growth with development of T1D is limited to the first year of life implying that increased growth beyond the first year can be attributed to familial growth patterns, rather than predisposition to T1D per se. Age at disease onset correlated with increased weight in the first 6 months of life, indicating importance of features very early in life on later development of T1D.

Introduction

In 1975, increased postnatal weight gain in children was noted to precede the onset of diabetes.¹ Studies have confirmed as the finding of accelerated growth, expressed as height, weight or BMI gain prior to clinical onset of childhood diabetes. Almost all studies used growth data from the infant (background) population at large as controls.^{2–5} These control groups do not take familial factors into account. Our previous study used siblings as ‘nested’ controls and had infant growth data analysed by repeated measurement analysis.⁶ Growth measures differ uniquely between height and weight very early in life: infants triple their birth weight during the first year, while their height requires 4 years to double. Furthermore, infants grow with mini-spurts and -delays. In retrospective surveys, growth data may inevitably be missing. Using available time points, missing data may be estimated at different ages, which has to be taken into account in the growth analysis.

Here, we revisited and extended our earlier study, employing repeated measurements and appropriate analytical methods, and including infants who developed diabetes as early as 1 year of age, rather than after 4 years of age.⁶

Subjects and Methods

Study design and subjects

Families with diabetic children with ages of onset 1–15 (inclusive) years were recruited from the five childhood diabetes clinics in the Rotterdam area. Weight and height data were collected from Caucasoid non-immigrant families. Children from

immigrant parents were not invited to join, as insufficient standard growth data for comparison are available for each of their multiple origins. We selected families with two or more children: one diabetic patient and at least one unaffected healthy sibling. The subjects and controls were comparable concerning age (or date of birth; Table 1). In cases of more than one healthy sibling, the one with the closest date of birth was included in the study.

Growth data including height and weight during infancy and early childhood, i.e., the first 4 years of life was retrieved from each child’s health care record; this is a booklet distributed to every child in the Netherlands at birth to register anthropometric measurements in a standardized way, including gestational age, information on infant feeding, vaccinations, and advice given by health professionals at each baby clinic visit. One or more healthy siblings served as reference. Exclusion criteria were diabetes in the mother, i.e., either during pregnancy or with known diabetes, birth outside gestational ages 37–42 weeks, diagnosis of diabetes of the proband <1-year old or any condition or medication possibly influencing growth.

All diabetic children were diagnosed between 1989 and 2006 and were on insulin treatment since clinical diagnosis of diabetes according to the criteria of the International Society for Pediatric and Adolescent Diabetes (ISPAD). The study was approved by the Erasmus University Medical Center Ethical Committee and written consent for participation was obtained from each parent and child if older than 12 years.

Table 1 | Characteristics growth cohort

	Families	Diabetes children	Siblings
Numbers	213	213	255
Number of observations per child	average: 9 P10-P90: 6 - 12	idem	idem
Height father (SD)	181.6 (6.4)		
Height mother (SD)	168.9 (6.0)		
Targeted height SDS (SD)	0.01 (0.72)		
Boys/girls		105 / 108 49% / 51%	130 / 125 51% / 49%
Birth weight boys (SD)		3658 (618)	3746 (651)
Birth weight girls (SD)		3521 (571)	3556 (660)
Age at onset diabetes (SD) n=197		7.5 (4.1)	
Birth length boys		51.4 (2.5)	50.9 (2.7)
Birth length girls		50.4 (2.4)	50.5 (2.7)
BMI at birth boys (kg/m ²)		13.2 (1.1)	13.4 (1.4)
BMI at birth girls (kg/m ²)		13.3 (1.4)	13.5 (1.5)
Ponderal Index (g/cm ³) at birth boys		2.58 (0.24)	2.64 (0.26)
Ponderal Index (g/cm ³) at birth girls		2.64 (0.28)	2.67 (0.34)

Growth Parameters

Weight and height were retrieved from each child's health care record booklet. This records the child's development and measurements monthly during the first year, and then twice a year up to the age of four. The offices provide and check 95% of all infant vaccinations and use the same special equipment to measure weight and length in infants at every visit. Weight and height measurements were used from the patients up to 6 months before the date of diagnosis.

Statistical Analyses

Weight, height and BMI (weight divided by height squared) were converted to standard deviation scores (SDSs) on the basis of contemporary Dutch Caucasoid growth data.⁷ The SDSs represent the number of standard deviations that a child's

anthropometric measurement differs from the mean of the distribution in Dutch children of the same age and sex. Absence of changes in growth pattern in a group is reflected by a mean SDS of zero, while increase in SDS implies accelerated (more than normal) longitudinal growth (i.e., height or weight) gain.

Growth data in the first 4 years of life were analysed using repeated measurements analysis,⁸ specifying two levels with repetitions: (1) children within a family, (2) anthropometric measurements within a child. We used the PROC MIXED repeated measurement analysis as implemented in SAS. This method takes into account the dependency of measurements within individuals as well as in groups (e.g., families) by specifying random intercepts and random slopes for both family and

individuals, allowing for the correlation between serial measurements from each child. Given the unique growth pattern in the first year of life, a model allowing for different growth rates in the first 12 months and afterwards was employed. The structure of the correlations between serial measurements of a child was specified in this model. Repeated measurements analysis deals with variation in measurement times between subjects without loss of validity of the results. This type of analysis allows all available data to be used, even in cases of additional siblings linked to one patient, as well as data of children with incomplete follow up. Our approach differs from methods analysing pairs (one control per patient) or methods analysing growth data at fixed time points in terms of precision. Repeated measurements analysis allows all follow-up data of an outcome measurement to be used in one analysis, unaffected by missing data. Thus, all available outcome data contribute to the analysis.

In the patient group, we also studied the relationship between age of diagnosis and growth pattern in the first year of life, i.e., Pearson correlation coefficients were computed for age at clinical presentation of diabetes and averaged weight and height SDS in the first year of life.

Statistical analyses were performed using SPSS (SPSS 11, Chicago, IL, USA) and SAS (SAS Institute Inc., Cary, NC, USA, version 9) software programs. P-values <0.05 were considered significant.

Results

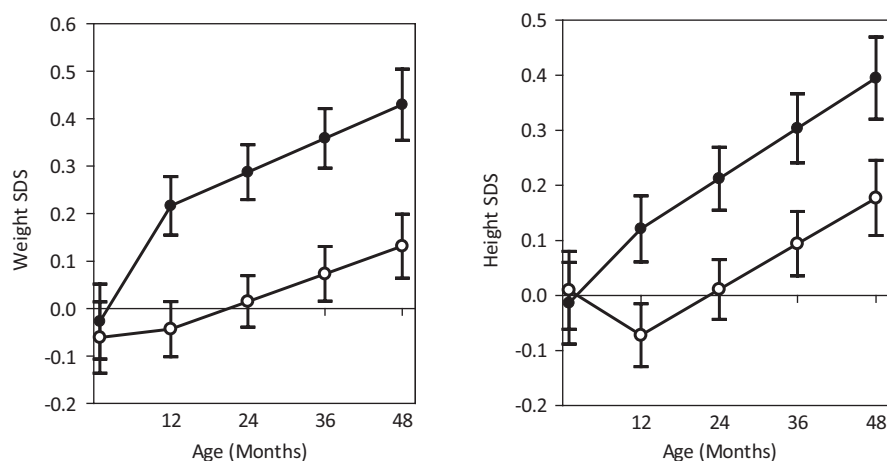
A total of 213 Caucasian families, each with one child with juvenile onset type 1 diabetes and their respective 255 healthy siblings were included

in our study (Table 1). The average number of recorded anthropometric measurements per child was 9. Of the 213 diabetic children, 197 had a known age of clinical presentation of diabetes. The average age of diagnosis was 7.5 years (range: 1.0-15.7 years). Birth size (height or weight SDS) did not differ between patients and siblings. Change in height and weight SDS, and absolute weight and height SDS were compared between patients and siblings in the studied time frame (first 4 years of life; Table 2).

Repeated measurements analysis showed differences for weight gain (=delta weight SDS) in the first year of life between patients and sibs ($P = 0.04$, Figure 1). The delta weight SDS for T1D patients was 0.27 (95% CI: 0.09-0.44), while for the sibs there was no increase. No difference in increase in weight SDS from the age of 1 year onwards was observed (1-4 years, $P = 0.63$), suggesting that increased growth associated to T1D is confined to the first year of life. The mean weight SDS of patients was significantly greater compared to their siblings, at age 6 months, 1 and 4 years ($P = 0.03$, 0.0001 and 0.0007, respectively). A similar pattern was observed for height SDS: a significant difference in increase in height SDS during the first year was revealed between patients and sibs ($P = 0.02$), with an increase for T1D patients of 0.15 (95% CI: 0.00-0.29), compared with no increase for the siblings. Similar to the weight parameter, there was no difference in increase in height SDS between probands and siblings after the age of 1 year ($P = 0.75$). Again, patients were taller than their unaffected siblings after year one and remained so up to age four. Patients and siblings did not differ for delta BMI SDS in the first 4 years (Table 2).

Table 2 | Repeated measurements analysis: mean (SE) weight, height and BMI SDS cases *versus* siblings in their first four years of life

	CASES (n=213)	SIBS (n=255)	P-value
Birth weight SDS	-0.03 (0.08)	-0.06 (0.07)	0.71
Δ weight 1 st year	0.27 (0.09)	0.02 (0.08)	0.04
Δ weight >1 st year	0.07 (0.02)	0.06 (0.02)	0.63
Weight SDS at age 1	0.22(0.06)	-0.04(0.06)	0.0001
Weight SDS at age 4	0.43(0.07)	0.13(0.07)	0.0007
Δ height 1 st year	0.15 (0.07)	-0.09 (0.07)	0.02
Δ height >1 st year	0.09 (0.02)	0.08 (0.02)	0.75
Height SDS at age 1	0.12 (0.06)	-0.07 (0.06)	0.003
Height SDS at age 4	0.39 (0.07)	0.18 (0.07)	0.007
Δ BMI 1 st year	0.18 (0.10)	0.14 (0.09)	0.76
Δ BMI >1 st year	-0.02 (0.03)	-0.03 (0.02)	0.74
BMI SDS at age 1	0.24 (0.07)	0.07 (0.06)	0.02
BMI SDS at age 4	0.18 (0.08)	-0.03 (0.07)	0.04
Weight SDS at age 6 months	0.08 (0.06)	-0.05 (0.06)	0.03
Height SDS at age 6 months	0.05 (0.06)	-0.03 (0.06)	0.23
BMI SDS at age 6 months	0.15 (0.06)	-0.004 (0.06)	0.01

**Figure 1** | Weight (left) and height (right) SDS in the first four years of life in patients (filled circles) and their siblings (open circles). Mean SDS $\pm$ SE are depicted. A weight SDS of zero equals that of the background population (corrected for age and gender).

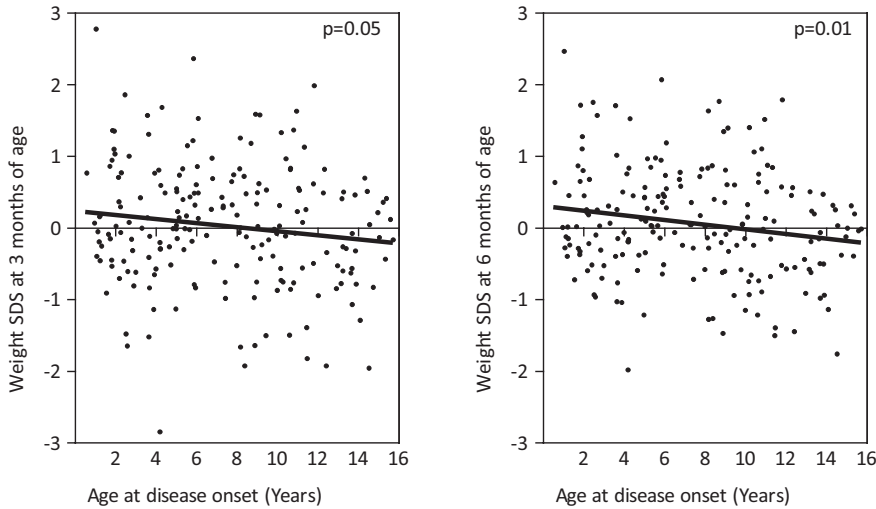


Figure 2 | Correlation between age at onset of clinical disease versus weight SDS at age 3 months (left) and 6 months (right). A weight SDS of zero equals that of the background population (corrected for age and gender). Positive weight SDS is correlated with earlier diabetes onset. (n=198; Pearson correlation $R = -0.138$ and $R = -0.176$, respectively.)

Earlier onset of diabetes, i.e., a younger age of diagnosis, was associated with higher weight SDS at 3 and 6 months of age ($P = 0.05$ and $P = 0.01$, respectively; Figure 2). A similar pattern for BMI SDS was seen.

Discussion

In this retrospective family case-control study of early infant growth prior to juvenile onset diabetes, we found that early growth, i.e., weight and height gain in the first year of life is significantly higher in patients than their unaffected siblings whilst their birth weight or length did not differ. We further report that a younger age of type 1 diabetes manifestation is associated with higher weight SDS and BMI SDS during the first half year.

Contrary to most other studies on growth and diabetes, we compared data from children with T1D and their healthy siblings. This enabled us to correct for confounders who are related to family particulars such as feeding habits, physical exercise and socio-economic status. As the contribution of increased growth is confined to the first year of life we speculate that after the age of 1 year, familial growth patterns may act as a confounding factor. Our findings of an earlier age of disease presentation correlating positively with higher weight and BMI SDS in the first year of life confirm earlier reports, in spite of differences in their experimental design.^{3,5,9–15} A single earlier study using healthy siblings as part of the control group tested for height prior to disease presentation and analysed anthropometric measurements at certain ages separately. However, they recorded measurements starting at 3.5 years of age.¹⁶ We previously used anthropometric measurements

at fixed time points analysing conditional SD scores and repeated measurements, matched with siblings as reference, where cases with missing data were excluded from analysis.⁶ This analysis was restricted by the fact that data were adjusted for those of a previous time point, rather than with the full range of longitudinal data as analysed in our current report. Furthermore, data collection was limited to one sibling for each T1D patient analysed pair-wise (sib-proband). In our opinion, it is pivotal to stress the differences in growth pattern between patients and siblings as done in our current study, rather than comparing actual growth data with those of possibly biased population controls (due to e.g. out-of-date and/or geographical influences).

Given our sample size we could not confirm earlier large cohort studies reporting a positive association between high birth weight and diabetes risk.^{11,17–19} It is conceivable that overweight in newborns later developing type 1 diabetes as documented in large series elsewhere was masked in the present study by the closeness of the siblings used for controls. Yet, the gradual progression of differences from their siblings in weight and height with age, in fact as early as from 3 to 6 months of age onwards, underscores the significance of this finding.

The data were collected in a period of approximately 18 months. As a consequence, families that have all progeny affected have been excluded whilst unaffected offspring may have been born within these families later on, after our period of data collection.

Overfeeding may play a role in the tendency of overgrowth prior to T1D,^{1,20,21} although compelling evidence for this as a primary mechanism

for earlier clinical manifestation of disease preceded by overgrowth is still lacking. Lending support to the possibility of overfeeding is a Swedish matched-case referent study showing that increased weight for age, although in 7- to 14-year olds, was associated with later type 1 diabetes.^{20,22} The authors speculate that betacells become sensitized to immune damage and apoptosis by their 'overloading' through a variety of mechanisms, ultimately leading to their accelerated destruction.²⁰ Increased insulin requirement as a result of an increased growth rate is one of several environmental determinants exerting this destructive overload effect, which by overfeeding children, may contribute to juvenile onset T1D. Without data on food history, we cannot establish whether overfeeding contributed to our findings, but the current data from our family study are concordant with this hypothesis.

While most of the studies looking at early growth prior to clinical diagnosis of T1D in comparable Caucasian populations analysed their data by t-tests (e.g., the largest international Eurodiab study⁹), Hyponen and colleagues employed repeated measurements analysis in comparable growth studies.²³ They evaluated whether the increased T1D risk conferred by early introduction of cow milk supplements is mediated via accelerated growth in the first year of life which they confirmed in a (nonfamilial) casecontrol setting and inferred rapid growth, and weight gain in particular, in infancy (as early introduction of formula feeding) to be an independent risk factor for later T1D.²⁴ They suggested secular trends in increased growth as seen elsewhere to be contributing in the parallel increase of T1D incidence which they further substantiated recently.²⁵

Our findings concur with a widely debated ‘accelerator hypothesis’ postulating a shared basis for T1D and T2D by three accelerators: genetic predisposition, insulin resistance caused by rapid growth (i.e., weight gain), and islet autoimmunity leading to beta-cell insufficiency.²¹ This hypothesis would predict an inverse relationship between age at onset of disease and body mass index standard deviation score (BMI-SDS), as corroborated by our findings and those of others.^{5,12-15} However, opposing studies have been reported.^{26,27}

Our study showed that increased growth prior to the clinical onset of juvenile T1D patients is already manifested in, but also limited to, the first year of life. This may present an intervention point for therapeutic strategies. An ongoing prospective study that will provide more definite insight in food intake as an early exposure risk factor, like the Trial to Reduce T1D in the Genetically at Risk (TRIGR) will be welcomed in this context²⁸ and may guide future interventions in health programs aiming to counter the globally reported increase of T1D.

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