ARTICLE

Children developing type 1 diabetes before 6 years of age have increased linear growth independent of HLA genotypes

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Abstract

Aims/hypothesis High birthweight and increased childhood growth are risk factors for type 1 diabetes. Relative birthweight is associated with HLA genotypes that confer a high risk of diabetes. Our aims were to test whether young children prior to clinical onset of type 1 diabetes have increased: (1) birthweight or birth length standard deviation scores (SDS); (2) height development SDS; or (3) BMI SDS during first 18 months of life and whether these parameters are related to HLA genotypes or mid-parental height (MPH).

Methods Birthweight, birth length, weight and height were obtained from 58 type 1 diabetes children and 155 controls matched for HLA or not in the Diabetes Prediction in Skåne study.

Results Birth length SDS corrected for MPH was increased in children developing diabetes compared with all ($p<$ 0.048) and with non-HLA- ($p<0.050$) but not with HLA-matched controls. Children developing diabetes had increased height gain at 0 to 18 months of age ($p<0.005$). Diabetic children were significantly taller from 6 to 18 months of age when correcting for MPH compared with non-HLA-matched as well as HLA-matched controls, but BMI was not increased.

Conclusions/interpretation Birth length SDS was associated with diabetes risk HLA. When corrected for MPH, children developing diabetes were taller at birth than non-HLA- but not taller than HLA-matched controls. Diabetic children had increased MPH-corrected height up to 18 months of age compared with both HLA- and non-HLA-matched controls. High-risk HLA affects prenatal growth, but other factors may explain the increased postnatal linear growth in children developing diabetes.

Keywords Birth length · Birthweight · BMI · Mid-parental height · Standard deviation score · Type 1 diabetes

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Abbreviations
DiPiS   Diabetes Prediction in Skåne
MPH   mid-parental height
SDS   standard deviation score

Introduction

Type 1 diabetes, a serious chronic autoimmune disease, is due to immune-mediated destruction of the pancreatic islet beta cells resulting in loss of insulin production. Children developing type 1 diabetes will depend on lifelong treatment with insulin and have a high rate of complications. The incidence of type 1 diabetes in children is increasing [1, 2], especially in children below 4 years of age [3-5]. The cause of this increasing incidence is still unknown, as is the cause of the disease itself. Genetic factors, mainly HLA DR-DQ genotypes, are strong susceptibility factors [6]. However, among newly diagnosed type 1 diabetes patients only 10 to 15% have a first-degree relative with the disease [7] and the concordance rate between monozygotic twins is low [8, 9], underlining the importance of environmental factors.

High birthweight has been reported as a risk factor for type 1 diabetes [10-13]. We have demonstrated that children born with type 1 diabetes high-risk HLA genotypes had an increased risk of high birthweight corrected for gestational age (i.e. relative birthweight) [14]. This relationship between HLA genotypes and birthweight was recently confirmed in a study of children born to mothers with diabetes [15]. We also found that infections with fever, gastroenteritis or both during pregnancy increased the risk of high relative birthweight [16]. The possible consequences of these interactions for postnatal growth and development of type 1 diabetes are unknown.

Retrospective studies of children with diabetes have reported increased linear growth up to 7 years before onset of disease [17] as well as increased height and weight standard deviation scores (SDS) from 1 month of age [18] and increased growth in length between 1 and 3 years of age [19, 20]. The authors of the latter study corrected growth for mid-parental height (MPH), which is known to correlate with both birthweight and birth length [21], and with postnatal growth of the child [21, 22].

Increased weight and BMI in children who have developed diabetes have been reported in some studies [18–20, 23, 24], but were not found in others [25–27]. The results in some of these studies [23, 26, 27] are complicated by the use of data collected from patients after diagnosis of diabetes, when insulin therapy had already been introduced. In the Diabetes Prediction in Skåne (DiPiS) study [14, 28, 29], children are followed from birth. As 60 children below the age of 6 years have already developed type 1 diabetes, we wanted to examine whether any of these children showed deviation in growth. Our aims were to test whether children prior to their clinical diagnosis of type 1 diabetes have increased: (1) birthweight or birth length SDS; (2) height development SDS; and (3) BMI SDS during the first 18 months of life, and whether any of these parameters are related to the HLA genotype of the child or MPH.

Methods

Population In this descriptive prospective study, we analysed data from children developing diabetes in Skåne, the most southern part of Sweden. Of 48,000 children born from September 2000 to August 2004, 60 had developed diabetes as of December 2006. These children were all born during the screening years of the DiPiS study, a population-based prospective investigation of diabetes in children [14, 28, 29], allowing us to select a total of 155 matched control children.

The aim of the DiPiS is to determine the positive predictive value for type 1 diabetes of genetic risk combined with islet cell autoantibody markers and to identify factors during and after pregnancy that may trigger the disease [28]. Cord blood from more than 35,000 children was genotyped for HLA and analysed for islet autoantibodies. Participating parents filled in questionnaires when the child was 2 months of age [28]. Children with increased risk of type 1 diabetes, according to a scoring based upon HLA genotype, cord blood islet autoantibodies or other risk factors such as high birthweight, infections during pregnancy and first-grade relative with diabetes, are followed annually from 2 years of age with blood samples for islet autoantibodies and questionnaires. Children developing two to three islet autoantibodies are followed every 3 months by a paediatrician, including performance of blood tests for islet autoantibodies, glucose and HbA$_{1c}$. The Lund University Ethics Committee approved the DiPiS study.

Type 1 diabetic children The 60 children (35 boys, 25 girls) developing diabetes before the end of December 2006 (Fig. 1) were between 9 months and 5 years and 10 months old (median 2.75, range 0.75–5.84 years) at diagnosis. Seven boys and four girls developed diabetes before 18 months of age. A cord blood sample for the DiPiS study was obtained at delivery from 50 of the children. Gestational age ranged from 30 to 42 weeks, with 3/60 children born prematurely (one at 30 weeks, two at 36 weeks). An additional three children were born to mothers with gestational diabetes, but none of the children had a mother with type 1 diabetes. Growth curves were available for 58/60 children.

Control children We randomly selected 155 controls, all born to non-diabetic mothers, but matched for sex, gestational week and date of birth (year and month and as near date as possible), from the 25,378 children participating in the DiPiS. Among the control children, 51 were also matched for HLA.

Fig. 1 Children developing diabetes participating and not participating in the Diabetes Prediction in Skåne (DiPiS) study. Since children at high risk of type 1 diabetes were offered follow-up from 2 years of age, 14 children participating in the DiPiS who developed diabetes below this age were excluded from the follow-up
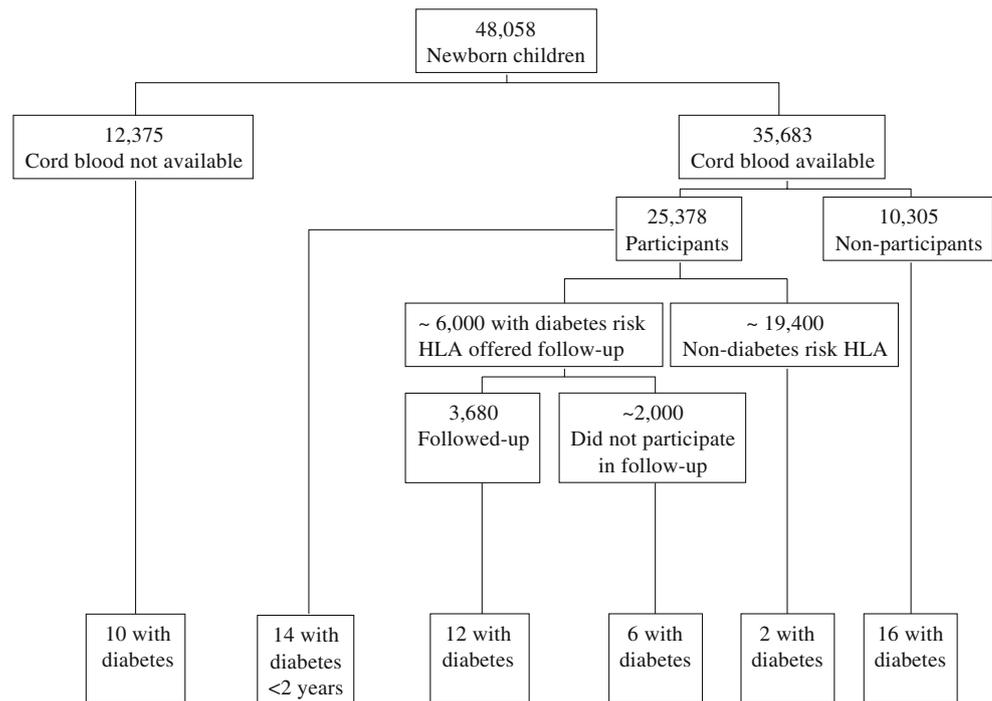
Growth Swedish children are regularly examined by Child Health Services (Barnavårdscentraler) before starting school. At these visits, weight and height of the child are recorded, and a growth chart completed. These growth charts, which contain birthweight, birth length, parental height and growth in infancy compared with standard Swedish normograms [30], were obtained with parental consent. Information on both parents' heights was available for 95% of the children.

HLA The genotypes *HLA-DQA1* and *HLA-DQB1* were determined by PCR and sequence-specific probes as previously described [14, 31, 32]. HLA genotypes were available from 55 diabetic children, either from cord blood or from samples obtained at the diagnosis of diabetes. *HLA-DQA1*-B1** genotypes were ranked according to the risk designation criteria used to identify newborns at risk of type 1 diabetes in the DiPiS as described previously [14]. A 'risk code' was established as an arbitrary numeric description of the risk designation (Table 1).

Statistics Birthweight and birth length SDS were calculated as described [33]. Height and weight SDS after birth were calculated from the Swedish reference population [30]. MPH was calculated according to the following previously described formula [34]: SDS MPH=(height SDS of father+ height SDS of mother)/1.61. BMI SDS was calculated according to Karlberg et al. [35]. Difference from MPH was calculated as SDS birth length or height minus SDS MPH.

Parametric tests were used. If, in tests of between-group differences, unequal variances were observed, the number

of degrees of freedom were corrected according to Sattherwaite [36].

In post hoc tests following ANOVA, correction for multiple testing was performed with Dunnett's test. Using multiple regression analysis we tested whether gestational age, diabetes, MPH or HLA high-risk genotypes were associated with birth length SDS, birthweight SDS and gain in height SDS. In the regression analyses, HLA risk code genotypes 3 and 4 were combined and used as a dummy variable, and compared with all other genotypes (Table 1).

We considered p values less than 0.05 to be significant. In children developing diabetes before 18 months of age, values of height and BMI were not included at diabetes onset and thereafter.

Results

HLA genotypes in diabetic children Among 55 HLA-typed diabetic children, 50 (91%) had high or moderate type 1 diabetes HLA risk, whereas five had genotypes with neutral (n=4) or low (n=1) risk of diabetes (Table 1).

Birth length and birthweight standard deviation scores Birth length or birthweight SDS did not differ between children who developed diabetes and either non-HLA-matched or HLA-matched controls. However, when birth length SDS was corrected for MPH, children developing diabetes had a higher score than either non-HLA-matched controls ($p<$ 0.031) or all controls ($p<$0.048) (Table 2). There was no

Table 1 *HLA-DQB1* risk designation, genotype, risk code and HLA genotype in 55/60 children developing diabetes before 6 years of age

Diabetes risk designation[a]	HLA		Risk code[c]	HLA genotype
	DQA1*-B1* genotype			*n*=55 (%)
	Allele 1	Allele 2		
Very high	0501-0201	0301-0302	4	28 (51)
High	0301-0302	0102-0604	3	4 (7)
High	0301-0302	X	3	8 (15)
Moderate	0501-0201	0102-0604	2	
Moderate	0501-0201	X	2	10 (18)
Neutral	0201-0201	0102-0604	1	
Neutral	0201-0201	X, 0501-0201	1	1 (1.8)
Neutral	0201-0201	0301-0302	1	1 (1.8)
Neutral	0102-0604	X	1	
Neutral	X	X	1	
Neutral	0301-0301	0301-0302	1	1 (1.8)
Neutral	0301-0301	0501-0201, 0201-0201	1	1 (1.8)
Low	0301-0301	0102-0604	0	
Low	0301-0301	X	0	
Low	0103-0603	0301-0302	0	1 (1.8)
Low	0103-0603	0501-0201, 0201-0201	0	
Low	0103-0603	0301-0301	0	
Low	0103-0603, 0102-0602[b]	0102-0602, 0102-0604[b], X	0	
Low	0102-0602	0301-0302	0	
Low	0102-0602	0501-0201, 0201-0201	0	
Low	0102-0602	0301-0301	0	
Low	0102-0602	X	0	

X is not *DQA1*-B1** *0501-0201, 0201-0201, 0301-0301, 0301-0302, 0102-0602, 0103-0603* and *0102-0604*, but includes potential homozygosity
[a] Risk designation criteria used to identify newborns at risk of type 1 diabetes as previously described [14]
[b] Genotypes *DQA1*-B1** *0103-0603/0102-0602, 0103-0603/0102-0604, 0103-0603/X* or *0102-0602/0102-0604*
[c] Risk code is an arbitrary numeric description of the risk designation

significant difference in birth length SDS corrected for MPH when comparing diabetic children with their HLA-matched controls (Table 2). The parents of children with diabetes were slightly shorter than parents of all control children ($p<0.012$) and of HLA-matched controls ($p<0.042$; Table 2).

When analysing the multivariate association of birth length and birthweight SDS with gestational age, diabetes, MPH and HLA genotypes, both birth length SDS ($p<0.001$) and birthweight SDS ($p<0.029$) were positively associated with MPH (Table 3). Moreover, birth length SDS was correlated to HLA genotypes. Using the HLA genotype risk code in Table 1, a high HLA risk for diabetes was seen to be correlated to an increased birth length SDS ($p<0.010$) (Table 3). There were no significant associations between birth length SDS or birthweight SDS and gestational age or diabetes (Table 3).

Height development standard deviation scores Height development SDS was calculated for the children at 3, 6, 12 and 18 months of age. In children developing diabetes before 18 months of age, the height SDS at diagnosis and thereafter was not included. Height SDS in children developing diabetes did not differ from that in the non-HLA or the HLA-matched controls, except at 18 months when diabetic children were taller than non-HLA-matched controls (Electronic supplementary material [ESM] Table 1). In contrast, analysis of height gain SDS, i.e. delta height SDS, showed that the children who later developed diabetes had an increased growth rate from birth to 18 months of age compared with their HLA-matched controls, but not with non-HLA-matched controls ($p<0.008$; ESM Table 1).

In the next analysis, height development SDS was corrected for MPH SDS to demonstrate that the children who later developed diabetes were significantly taller than all controls, non-HLA-matched controls and HLA-matched controls from 6 to 18 months of age (ESM Table 2). When testing this in a regression analysis (Table 4), the children developing diabetes had increased height velocity from 0 to 18 months of age ($p<0.005$), controlling for gestational age, MPH SDS, HLA risk code and birth length SDS. A high MPH (i.e. tall parents) increased the height gain from birth to 18 months of age. However, HLA with risk for diabetes did not significantly affect height gain (Table 4).

Table 2 Standard deviation scores of birth length, birthweight and BMI at birth in children developing diabetes as compared with all controls, non-HLA-matched controls and HLA-matched controls

Parameter	A		B		C		D		D vs A	D vs B	D vs C
	All controls	n	Non-HLA-matched controls	n	HLA-matched controls	n	Diabetes	n	p value	p value	p value
Birth length SDS	0.34 (0.17 to 0.52)	155	0.22 (0.00 to 0.44)	104	0.58 (0.30 to 0.87)	51	0.39 (0.17 to 0.60)	58	<0.76	<0.31	<0.27
Birthweight SDS	0.60 (0.43 to 0.77)	155	0.52 (0.31 to 0.73)	104	0.75 (0.47 to 1.04)	51	0.49 (0.27 to 0.72)	58	<0.51	<0.87	<0.15
BMI SDS birth	0.27 (0.10 to 0.44)	155	0.30 (0.10 to 0.50)	104	0.21 (−0.15 to 0.57)	51	0.09 (−0.22 to 0.40)	58	<0.30	<0.24	<0.61
Diff. MPH, birth	−0.11 (−0.32 to 0.09)	147	−0.18 (−0.45 to 0.08)	100	0.03 (−0.30 to 0.36)	47	0.27 (−0.01 to 0.54)	55	<0.048	<0.031	<0.28
SDS MPH	0.45 (0.29 to 0.62)	147	0.41 (0.20 to 0.63)	100	0.54 (0.26 to 0.81)	47	0.10 (−0.11 to 0.32)	55	<0.012	<0.042	<0.013

Values are mean (95% CI) unless stated otherwise

Children with diabetes had a significantly lower MPH than all controls and HLA-matched controls

Diff. MPH = SDS birth length or height−SDS MPH

Diff., difference from

Body mass index standard deviation scores BMI SDS was calculated for the children at 0, 3, 6, 12 and 18 months of age. In children developing diabetes before 18 months the BMI SDS was not included at diabetes onset or thereafter. There were no significant differences in BMI SDS between children who later developed diabetes and non-HLA-matched or all the controls (data not shown). Comparison of BMI SDS in children who later developed diabetes with that in their HLA-matched controls showed that the children developing diabetes had a significantly lower BMI at 6 months of age ($p<0.011$) (ESM Table 3). Furthermore, the children developing diabetes had a significantly lower BMI SDS than the Swedish standard population both at 12 months ($p<0.009$) and at 18 months ($p<0.003$) of age (ESM Table 3).

Discussion

The major finding in our study was that children developing diabetes before 6 years of age had increased height development at 0 to 18 months of age ($p<0.005$), when controlling for gestational age, MPH SDS, HLA genotypes and birth length SDS. In the children developing diabetes, the age-dependent trend of increased difference between the height of the child and MPH underscores the accelerated height development. Furthermore, the novel finding that birth length SDS was increased in children with high-risk HLA, regardless of whether they developed diabetes or not, confirms our previous finding [14] that HLA genotypes conferring risk of diabetes were associated with increased intrauterine growth. However, due to the limited sample,

we were unable to confirm our previous finding of an association between birthweight SDS and HLA. In addition, we failed to support the hypothesis that children developing diabetes before 6 years of age had a higher birthweight SDS, but found that birth length SDS corrected for MPH was increased in diabetic children as compared with their non-HLA-matched children. The fact that this difference was not observed when compared with HLA-matched children suggests that diabetes high-risk HLA may not only affect birthweight but also birth length. Finally, in these children developing diabetes before 6 years of age, the analysis of BMI SDS suggested a trend towards a reduced rather than an increased BMI.

The present study represents all of the children who were born in Skåne County during the period September 2000 to August 2004 and subsequently developed type 1 diabetes by December 2006 [14, 28]. The 60 children developing diabetes before 6 years of age represent an incidence rate as high as about 40/100,000 children per year. In addition, a notably high number of children (11) developed diabetes before 18 months of age. Our study is therefore a population-based investigation of type 1 diabetes in children below the age of 6 years in a high-incidence cohort. Our ongoing investigation of all the children in this cohort will be needed to establish whether an accelerated height development will also be observed in those children who develop diabetes at a later age. In addition, it cannot be excluded that some of the HLA-matched controls will also develop diabetes in the future.

A potential weakness in studies on newborn children is the risk of recall bias if the values on birth length and birthweight are obtained from the parents. In the present

Table 3 Multiple regression analysis of birth length SDS and birthweight SDS as dependent variables in relation to gestational age, diabetes, MPH and HLA genotypes with high risk of type 1 diabetes

Parameter	Birth length SDS			Birthweight SDS		
	β	SE (β)	p value	β	SE (β)	p value
Intercept	0.87	1.65	<0.60	2.80	1.67	<0.10
Gestational age	−0.02	0.42	<0.64	−0.06	0.04	<0.17
Diabetes	−0.03	0.18	<0.89	−0.04	0.18	<0.84
MPH	0.29	0.08	<0.001	0.18	0.08	<0.029
HLA risk code 3 or 4[a]	0.42	0.16	<0.010	0.14	0.16	<0.38

[a] HLA risk codes 3 or 4 were combined and used as a dummy variable (=1) vs codes 0, 1 and 2 (=0)

study, care was taken to obtain the birth length and birthweight data from the growth curves maintained for each child by the Child Health Services. Several epidemiological studies have reported that type 1 diabetic children have a higher birthweight [10–13]. This was not observed in the present group of children developing diabetes before 6 years of age. On the other hand, when birth length was corrected for MPH, we found that our children were taller than the controls, which is consistent with a previous finding that short birth length decreased the risk of type 1 diabetes in children up to 15 years of age [37]. The fact that birth length corrected for MPH was increased in the diabetic children compared with non-HLA-matched but not with HLA-matched controls could be due to our limited number of HLA-matched controls. Nevertheless, it is still an important novel finding, especially since we found that birth length was significantly associated with HLA genotypes.

In our study, MPH SDS were taken into consideration when we analysed intrauterine and childhood growth, since birth length, birthweight and childhood linear growth are strongly correlated with the height of the parents [21, 22, 38]. Therefore it is important to correct for MPH when

analysing growth parameters. The previously described correlation between parental height and either birthweight or birth length was also confirmed in our study. We are not aware of any other study using HLA-matched controls, which seems important, as on the basis of our [14, 16] and other [15, 39] studies, it cannot be excluded that HLA is conspicuously associated with growth development not only in utero but also after delivery.

Increased height and linear growth in childhood have been reported to be a risk factor for diabetes [17–19]. In the present study we failed to confirm an increased height based on SDS in children developing diabetes. In contrast, the increased height development in relation to birth length in the diabetic children compared with HLA-matched controls suggests that children on their way to clinical diabetes may be exposed to factors that affect growth. This was also confirmed by the finding that children developing diabetes were significantly taller than expected from MPH compared with both non-HLA-matched and HLA-matched controls. We had hypothesised that HLA genotypes conferring risk of diabetes were responsible for the increased growth in children who later develop diabetes, as reported by us earlier for high-risk HLA genotypes and

Table 4 Regression analysis of SDS of height gain

Parameter	Height gain SDS at age											
	0–3 months			0–6 months			0–12 months			0–18 months		
	b	SE (b)	p value	b	SE (b)	p value	b	SE (b)	p value	b	SE (b)	p value
Intercept	−12.73	1.26	<0.001	−6.53	1.26	<0.001	−3.13	1.39	<0.025	−1.94	1.28	<0.131
Gestational age	0.33	0.03	<0.001	0.17	0.03	<0.001	0.09	0.04	<0.017	0.05	0.03	<0.120
MPH SDS	0.19	0.06	<0.001	0.27	0.06	<0.001	0.32	0.07	<0.001	0.41	0.06	<0.001
Diabetic	0.10	0.13	<0.431	0.22	0.14	<0.110	0.23	0.16	<0.142	0.42	0.15	<0.005
HLA risk code 3 or 4	−0.01	0.12	<0.937	0.01	0.13	<0.955	−0.04	0.14	<0.779	0.04	0.13	<0.753
Birth length SDS	−0.31	0.05	<0.001	−0.51	0.06	<0.001	−0.51	0.06	<0.001	−0.55	0.06	<0.001
Adjusted R^2 (%)	44			38			31			41		

Children developing diabetes had increased height gain at 0–18 months of age. A high MPH (i.e. tall parents) and a low birth length SDS also increased height gain in the child. Gestational age was important for height up to 12 months of age, while diabetes risk HLA did not significantly affect the height gain

birthweight [14]. However, our data did not support this hypothesis and indicate that factors other than high-risk HLA are responsible for this increased growth rate in children developing diabetes.

In this prospective study we examined the growth pattern of a cohort of children developing diabetes before 6 years of age compared with controls matched for HLA genotypes and corrected for MPH since this is strongly associated with the linear growth of children [21, 22, 38]. Previous studies have reported a relationship between high birthweight and both low-risk [39] and high-risk [14, 15] HLA genotypes. Our finding that birth length SDS was associated with HLA genotypes supports the hypothesis that HLA affects intrauterine growth. The association between birth length SDS and HLA is a novel finding, consistent with our previous result that HLA is associated with birthweight. The question of how HLA genotypes affect intrauterine growth remains to be answered. It is possible that they could influence the way the body handles infections, with or without subsequent temporary hyperglycaemias [16].

In conclusion, we report that children developing diabetes before 6 years of age had increased height development at 0 to 18 months of age, independently of gestational age, MPH SDS, HLA genotypes and birth length SDS. Thus, HLA did not explain the previously described height gain in infancy. We therefore speculate that height gain is related to the type 1 diabetes disease process. We also confirmed our earlier association between HLA genotypes and intrauterine growth, but were unable to confirm previous reports of increased BMI in children developing type 1 diabetes.

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