Helena Elding Larsson,[1] Kendra Vehik,[2] Michael J. Haller,[3] Xiang Liu,[2] Beena Akolkar,[4] William Hagopian,[5] Jeffrey Krischer,[2] Åke Lernmark,[1] Jin-Xiong She,[6] Olli Simell,[7] Jorma Toppari,[7,8] Anette-G. Ziegler,[9] and Marian Rewers,[10] for the TEDDY Study Group*

Growth and Risk for Islet Autoimmunity and Progression to Type 1 Diabetes in Early Childhood: The Environmental Determinants of Diabetes in the Young Study

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PATHOPHYSIOLOGY

Increased growth in early childhood has been suggested to increase the risk of type 1 diabetes. This study explored the relationship between weight or height and development of persistent islet autoimmunity and progression to type 1 diabetes during the first 4 years of life in 7,468 children at genetic risk for type 1 diabetes followed in Finland, Germany, Sweden, and the U.S. Growth data collected every third month were used to estimate individual growth curves by mixed models. Cox proportional hazards models were used to evaluate body size and risk of islet autoimmunity and type 1 diabetes. In the overall cohort, development of islet autoimmunity (*n* = 575) was related to weight *z* scores at 12 months (hazard ratio [HR] 1.16 per 1.14 kg in males or per 1.02 kg in females, 95% CI 1.06–1.27, *P* < 0.001, false discovery rate [FDR] = 0.008) but not at 24 or 36 months. A similar relationship was seen between weight *z* scores and development of multiple islet autoantibodies (1 year: HR 1.21, 95% CI 1.08–1.35, *P* = 0.001, FDR = 0.008; 2 years: HR 1.18, 95% CI 1.06–1.32, *P* = 0.004, FDR = 0.02). No association was found between weight or height and type 1 diabetes (*n* = 169). In conclusion, greater weight in the first years of life was associated with an increased risk of islet autoimmunity.

Type 1 diabetes is one of the most common chronic pediatric diseases in which a progressive autoimmune process destroys the β-cells of pancreatic islets, resulting in loss of insulin secretion. Islet autoimmunity (IA) precedes the clinical onset of disease by months to years and is detected by the presence of islet autoantibodies against GAD, insulinoma-associated protein 2, and insulin (1). An estimated 70% of children with multiple islet autoantibodies progress to diabetes within 10 years (2–4).

The incidence of type 1 diabetes in children has increased 3–5% annually since the 1960s (5,6). The cause of this secular trend remains unknown, but environmental factors are assumed to trigger IA in genetically susceptible children who carry specific HLA-DR and -DQ genotypes (7,8). Infant overfeeding and accelerated infant/toddler growth have been proposed as a potential trigger (9). According to the accelerator hypothesis, excessive weight gain and resulting insulin resistance accelerate β-cell apoptosis and autoimmunity in the presence of the susceptibility HLA genotypes (10,11).

Although several retrospective studies have reported associations between higher birth weight (12) or childhood

[1]Department of Clinical Sciences, Lund University, Malmö, Sweden
[2]Health Informatics Institute, Morsani College of Medicine, University of South Florida, Tampa, FL
[3]Department of Pediatrics, University of Florida, Gainesville, FL
[4]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD
[5]Pacific Northwest Diabetes Research Institute, Seattle, WA
[6]Center for Biotechnology and Genomic Medicine, Medical College of Georgia, Georgia Regents University, Augusta, GA
[7]Department of Pediatrics, Turku University Hospital, Turku, Finland
[8]Departments of Physiology and Pediatrics, University of Turku, Turku, Finland
[9]Institute of Diabetes Research, Helmholtz Zentrum München, Klinikum rechts der Isar, Technische Universität München, and Forschergruppe Diabetes e.V., Neuherberg, Germany
[10]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, CO

Corresponding author: Helena Elding Larsson, helena.larsson@med.lu.se.

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H.E.L. and K.V. contributed equally to this study.

*Members of the TEDDY Study Group are listed in the Supplementary Data online.

height and weight (13–17) and type 1 diabetes, prospective studies of IA have found less evidence for the accelerator hypothesis (18). The German BABYDIAB study found no relationship between BMI or insulin resistance in 135 children with IA (19); however, an earlier infant BMI peak predicting IA was subsequently reported (20). In the U.S. Diabetes Autoimmunity Study in the Young (DAISY) of children aged >2 years (n = 143), an increased height growth velocity but not weight or BMI growth velocity predicted the development of IA (21). Of note, higher weight z scores at ages 2 and 4 years predicted the development of IA (n = 46) in a cohort of 548 Australian children followed from birth (22).

We tested the hypotheses that higher weight and, separately, height in the initial 4 years of life predict *1*) the development of IA and *2*) progression to type 1 diabetes. The Environmental Determinant of Diabetes in the Young (TEDDY) cohort (23) provided an opportunity to test the generalizability of evidence across four diverse populations.

RESEARCH DESIGN AND METHODS

Design and Settings

TEDDY is a prospective cohort study funded by the National Institutes of Health with the primary goal of identifying environmental causes of type 1 diabetes. The study includes six clinical research centers: three in the U.S. (Colorado, Georgia/Florida, and Washington) and three in Europe (Finland, Germany, and Sweden). The detailed study design and methods have been published previously (23). The study was approved by local institutional review boards and is monitored by an external evaluation committee formed by the National Institutes of Health.

Participants

Participants were identified at birth by screening for high-risk HLA genotypes (24). Starting in 2004, TEDDY included 8,676 children with an increased genetic risk of type 1 diabetes who are to be followed from birth to 15 years of age. Height (length before age 2 years and standing height after age 2 years) and weight are obtained at TEDDY clinics by trained TEDDY personnel, and blood samples are drawn for measurements of islet autoantibodies every 3 months from 3 months up to 4 years of age and every 3–6 months after 4 years of age, depending on autoantibody status. Children were excluded from these analyses if *1*) their HLA eligibility could not be confirmed at a repeated genotyping at the age of 9 months, *2*) their islet autoantibody results were indeterminate, *3*) they had been followed for <12 months without IA or type 1 diabetes developing, or *4*) they had more than five consecutive growth measures missing (Fig. 1).

Main Outcome Measures

Any IA was defined as confirmed persistent presence of one or more islet autoantibodies on two or more sequential clinic visits. Islet autoantibodies against GAD, insulinoma-associated protein 2, and insulin were measured by radiobinding assays (25,26) in two reference laboratories (Barbara Davis Center for Childhood Diabetes, University of Colorado Denver and University of Bristol, U.K.). All positive samples and 5% of negative samples were retested in the other reference laboratory and deemed confirmed if concordant. Multiple islet autoantibodies were defined as two or more islet autoantibodies at two consecutive clinic visits. Type 1 diabetes was diagnosed by using American Diabetes Association criteria (27).

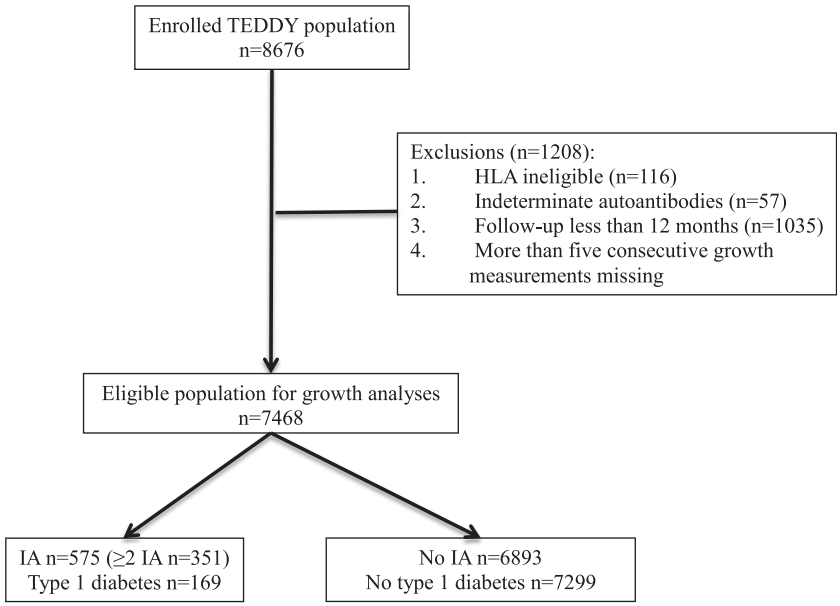

Figure 1—Flowchart of the children included in TEDDY and the children for whom a full set of growth data was available for analysis. IA developed in 575 children, multiple IA in 351 children, and type 1 diabetes in 169 children.

Statistical Analyses

The age at development of persistent confirmed IA was that at the initial two or more consecutive positive tests. In analyses of multiple islet autoantibodies, age at the second persistent confirmed autoantibody finding was used. Only growth data up to the date of seroconversion to IA or to the date of diagnosis of type 1 diabetes were used. The analyses of progression to type 1 diabetes included only the children in whom persistent IA developed before the onset of type 1 diabetes.

Individual growth curves were developed for each child by using mixed models with fixed and random effects of the height and weight on age for each sex. Best-fitting mixed models were used to produce estimates of mean growth curves and best linear unbiased predictors (BLUPs) for individual participants' growth curves for weight and height throughout childhood. Quadratic polynomial splines were applied to model the nonlinear growth curve (weight and height) from birth to 4 years of age. The models were examined by using several potential combinations of knots from the set (0.5, 1, 1.5, 2, 3). According to Akaike information criteria and Bayesian information criterion, four knots (at 0.5, 1, 2, and 3 years) were used in the fitting of weight on age, and five knots (at 0.5, 1, 1.5, 2, and 3 years) were used in the fitting of height on age. Standardized growth measures (weight *z* score and height *z* score) were derived from Centers for Disease Control and Prevention standardized growth charts (28) and use of SAS programs. These were best represented in 0–93 months by second-degree polynomials in fixed effects and first-degree in random effects. BLUPs of individual growth curves were assessed at each time point, including those when height and weight were missing, resulting in an interpolation of ~18% of the height and weight measurements. Plots of the raw data and BLUP curves were similar. Cox proportional hazards models were used to assess specific identified periods by fixed measures (birth to 12 months, birth to 24 months, and birth to 36 months) and over time by repeated measures (time-varying covariate to 4 years and 3, 6, 9, and 12 months prior) for association with IA and type 1 diabetes. All models were adjusted for the presence of the HLA-DR3/4 genotype (yes, no), presence of a family history of type 1 diabetes (mother, father, or sibling), sex, birth size, and country of residence. Evidence of nonproportional hazards related to country of residence in the Cox models existed; therefore, the country of residence was adjusted for by using the strata statement in SAS. The strata statement allowed for the fitting of separate baseline hazard functions for each country in the Cox models. Weight models were adjusted for birth weight *z* scores and height models for birth length *z* scores (28). The heterogeneity by country was tested by assessing the interaction between country and body size (weight and height *z* score) in the Cox regression models. Multiple comparisons were conducted with a false discovery rate (FDR) ≤ 0.05 considered significant.

RESULTS

TEDDY children (n = 8,676) were followed prospectively for a median of 60 months (quarters 1–3: 29–79 months). Among the 7,468 children with sufficient growth data, persistent IA developed in 575 (7.7%) and multiple IA in 351 (4.7%), and 169 (2.3%) progressed to type 1 diabetes (Fig. 1 and Table 1). Mean age at seroconversion to persistent IA was 31 (SD 21) months, multiple IA 34 (SD 20) months, and onset of type 1 diabetes 45 (SD 23) months. A total of 109 (19%) children developed islet autoimmunity before 12 months of age and 265 (46%) before 24 months of age. Five (3%) children progressed to type 1 diabetes before 12 months of age and 44 (26%) before 24 months of age. Table 1 summarizes the demographic characteristics of the study participants. The history of type 1 diabetes in a first-degree relative and the HLA-DR3/4 genotype predicted development of IA and type 1 diabetes (Table 1).

Growth Parameters and Development of IA

In the overall cohort, Cox proportional hazards model analysis showed a small increase in the risk of any persistent IA with greater toddler weight or height, adjusting for birth size, HLA genotype, family history of type 1 diabetes, sex, and country of residence. After correction for multiple analyses, weight *z* score at 12 months (hazard ratio [HR] 1.16 per 1.14 vs. 1.02 kg for males vs. females, respectively; 95% CI 1.06–1.27; $P < 0.001$; FDR = 0.008) predicted IA (Fig. 2 and Table 2). With the more stringent outcome defined as positive for multiple persistent islet autoantibodies, weight *z* scores at 12 and 24 months were predictive in the overall cohort when correction for multiple analyses was performed. HRs for any IA and multiple IA were also examined in relation to weight *z* scores or height *z* scores at 3, 6, 9, or 12 months before development of IA (Fig. 2 and Table 2). Little evidence was found for excess weight or height 3–12 months before development of any IA or multiple IA.

In a time-varying model of growth up to 4 years of age, weight *z* scores were not associated with the development of any IA or multiple IA (Fig. 2 and Table 2). There was no evidence of heterogeneity on the effect of weight or height *z* scores by country on any persistent IA (all $P \geq 0.27$) or multiple persistent IA (all $P \geq 0.38$).

A sensitivity analysis was carried out that excluded children born to mothers with type 1 diabetes; this exclusion did not affect the results. Other factors related to increased weight during the first year of life were being a girl and having the HLA-DR3/3 genotype, whereas breastfeeding for >3 months was associated with lower weight. However, adjustment for these factors did not change the results.

Growth Parameters and Progression to Type 1 Diabetes

Growth over time did not affect time to progression to type 1 diabetes in children with multiple IA (Fig. 2 and Table 2). The height and weight assessed in specific intervals (birth to 12, 24, and 36 months) was also not predictive of

progression from multiple islet autoantibodies to type 1 diabetes (Fig. 2 and Table 2).

DISCUSSION

In this large, multicountry cohort of 7,468 children at high genetic risk of type 1 diabetes, we found a weak association between early weight *z* scores and the development of any IA or multiple IA. The association was also found when controlling for confounding factors and correcting for multiple analyses. No association between early growth and the progression to type 1 diabetes was found. The study tested the overload hypothesis, which states that increased weight could induce β-cell autoimmunity in genetically predisposed children (9), and the accelerator hypothesis, which proposes that insulin resistance due to weight gain accelerates the autoimmune process, leading to type 1 diabetes (10,11), but we could not conclusively confirm either hypothesis.

TEDDY is the largest prospective, longitudinal follow-up study of children at risk for type 1 diabetes to date. Because screening for IA is done every third month, the time for seroconversion to IA is easy to define. At all visits, height and weight are recorded, making it possible to evaluate growth before and after seroconversion. Therefore, TEDDY provides a unique opportunity to test the postulated overload and accelerator hypotheses. Potential confounders adjusted for or excluded through sensitivity analysis were birth size, sex, family history of type 1 diabetes, breastfeeding, and HLA-DR and -DQ genotypes. Further analyses may include non-HLA genetic markers possibly associated with both IA and infant/toddler growth and differ in allele frequencies among the participating countries in TEDDY.

In addition to breastfeeding, a number of infant/toddler dietary exposures have been linked to IA and type 1 diabetes (29–31). TEDDY has shown that some of the exposures vary significantly by country (32,33), and some are likely to increase or decrease weight gain during early childhood.

TEDDY children are still young, with a mean age at seroconversion to persistent IA of 31 months and at clinical onset of type 1 diabetes of 45 months. Insulin resistance as an accelerator of progression to type 1 diabetes may have a greater impact in older children (i.e., during puberty). Because diabetes has developed in only a fraction of the children with IA in TEDDY to date, the results may change in future analyses. The growth pattern in children with early seroconversion may also be different from that in children experiencing seroconversion later in life. The TEDDY cohort will be followed to 15 years of age, enabling further analyses of growth and development associated with both IA and type 1 diabetes.

The TEDDY cohort was selected based on the presence of HLA genotypes with increased type 1 diabetes risk. As such, the current findings may not be representative of all children in whom IA and type 1 diabetes develop. In children with low-risk HLA genotypes, aberrations of growth may be of more significant importance for the

Table 1—Characteristics of children in whom persistent IA and type 1 diabetes develop

	Developed IA (*n* = 575)	Did not develop IA (*n* = 6,893)	HR (95% CI)	Developed type 1 diabetes (*n* = 169)	Did not develop type 1 diabetes (*n* = 7,299)	HR (95% CI)
Age at first autoantibody-positive visit/diagnosis of type 1 diabetes or most recent visit (months)	31 (21)	61 (26)		45 (23)	64 (26)	
Country						
Finland	25 (144)	22 (1,513)		31 (52)	22 (1,605)	
Germany	8 (46)	7 (462)		12 (21)	7 (487)	
Sweden	34 (194)	30 (2,069)		27 (45)	30 (2,218)	
U.S.	33 (191)	41 (2,849)		30 (51)	41 (2,989)	
Family history of type 1 diabetes						
Yes	22 (124)	10 (714)	2.36 (1.92–2.91)[a]	32 (54)	11 (784)	3.70 (2.62–5.22)[a]
High-risk HLA-DR or -DQ genotype						
DR3/4	50 (290)	38 (2,642)	1.71 (1.45–2.01)[a]	55 (93)	39 (2,839)	2.15 (1.58–2.92)[a]
Sex						
Female	46 (250)	49 (3,407)	0.78 (0.66–0.92)[a]	46 (77)	49 (3,580)	0.85 (0.63–1.15)[a]

Data are % (*n*) or mean (SD). [a]HRs adjusted for relation to type 1 proband, HLA-DR or -DQ genotype, sex, and age at first persistent confirmed autoantibody and stratified by country of residence.

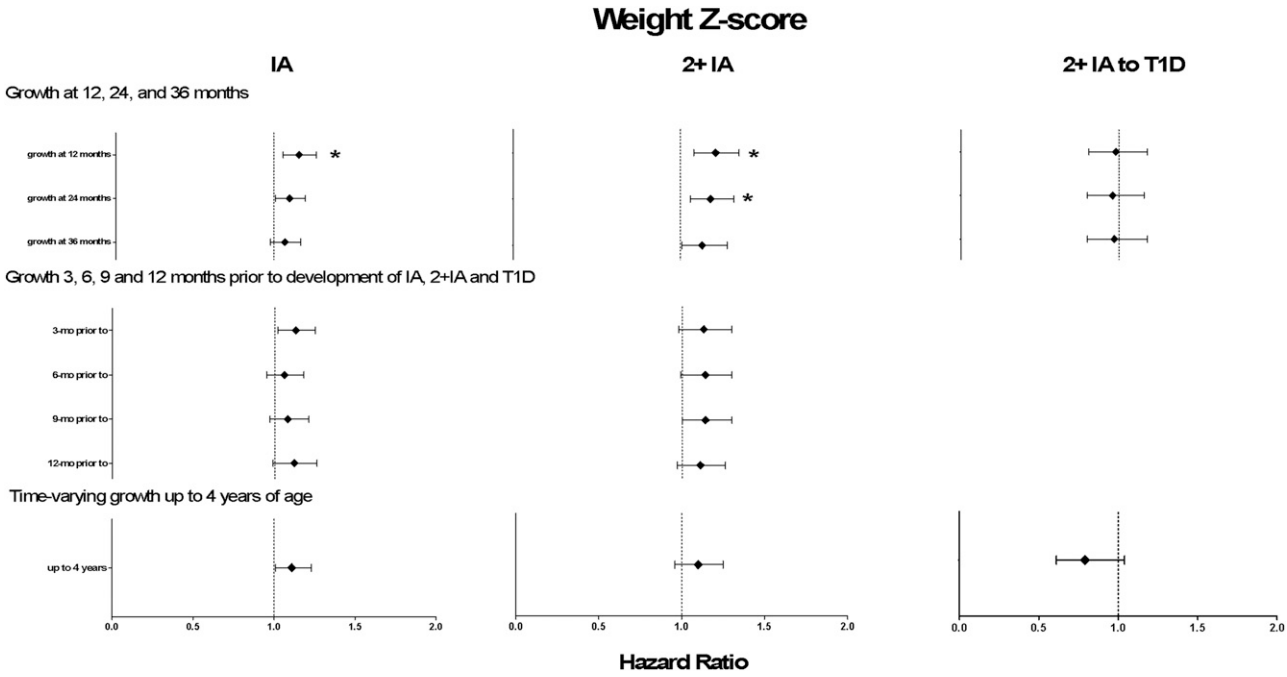

Figure 2— HRs and 95% CIs for any IA and multiple IA (2+ IA) and type 1 diabetes (T1D) in relation to weight *z* scores at 12, 24, and 36 months of age; change in weight *z* scores 3, 6, 8, or 12 months before development of IA, 2+ IA, and T1D; and time-varying growth up to 4 years of age (only events up to 4 years included). Only weight *z* scores are shown because height *z* scores were not significant. *Statistically significant, FDR < 0.05.

development of type 1 diabetes, as previously described (34). Also possible is that the impact of growth on risk for type 1 diabetes may be present only in some cases and depend on gene interactions and epigenetic factors. Because HLA genotypes associated with an increased type 1 diabetes risk are also associated with birth weight (35,36), HLA genotypes likely affect childhood growth. Nevertheless, increased early linear growth has been reported in children before the onset of type 1 diabetes independent of HLA genotypes (15).

Childhood height and linear growth are strongly correlated to both maternal and paternal height (37,38). We were not able to adjust the analyses for parental height, which may have had an impact on the analyses of height data, although it would not have affected weight data as much.

A number of previous studies have investigated height and weight growth and development of type 1 diabetes and showed that an increased growth velocity may be a risk factor for type 1 diabetes (13–17). However, only few prospective investigations among children that separated the impact of growth on seroconversion to IA and progression to type 1 diabetes in children with IA have been published, and results have been inconsistent. In the U.S. DAISY, an increased height growth velocity was associated with the risk of seroconversion (IA developed in 143 of 1,714 children), whereas weight and BMI growth velocity had no effect (21). In the current study, we could not confirm these findings. The reason for this may be that we used growth parameters from 3 months of age, whereas growth between 2 and 11 years of age was studied in DAISY. In an Australian study of first-degree relatives with type 1 diabetes, increased weight *z* score was reported as a predictor of IA independent of dietary factors in 46 children experiencing seroconversion at a young age (median 1.7 years) (22). In a study from Germany that used combined data from BABYDIAB and BABYDIET, an early age of infant BMI peak was associated with development of IA in 135 children (20). Not being able to fully confirm those findings in the current large multicenter study, we report findings similar to the Australian study. However, the weak association may indicate that growth is not the primary trigger for IA.

Insulin resistance has been suggested to accelerate the process from IA to clinically overt type 1 diabetes (39,40). On the contrary, neither weight nor BMI growth velocity could be confirmed to increase the risk for progression to type 1 diabetes (n = 21) in children with autoantibody positivity in the DAISY, whereas height growth velocity independently increased the risk (21). In the current study, we were not able to assess insulin resistance by HOMA. By using weight *z* score as an indicator of potential insulin resistance (41), we could not confirm that insulin resistance accelerates the progression from persistent IA to type 1 diabetes as in other studies (39,40,42). However, the children in the current cohort were young, and only in the Childhood Diabetes in Finland (DiME) study, where HOMA of insulin resistance/first phase insulin response predicted progression to type 1 diabetes in 77 siblings

Table 2—HRs for any IA, 2+ IA, and type 1 diabetes relative to weight or length/height *z* scores at various ages; months before IA, 2+ IA, or type 1 diabetes diagnosis; and time-varying model of growth up to 4 years of age

	Any IA				2+ IA				2+ IA to type 1 diabetes			
Time	HR	95% CI	*P* value	FDR	HR	95% CI	*P* value	FDR	HR	95% CI	*P* value	FDR
Weight												
12 months of age	**1.16**	**1.06–1.27**	**0.001**	**0.008**	**1.21**	**1.08–1.35**	**0.001**	**0.008**	0.98	0.81–1.18	0.81	0.81
24 months of age	1.10	1.01–1.20	0.03	0.091	**1.18**	**1.06–1.32**	**0.004**	**0.021**	0.96	0.80–1.16	0.69	0.69
36 months of age	1.07	0.98–1.17	0.15	0.17	1.13	1.01–1.28	0.04	0.091	0.97	0.80–1.18	0.79	0.79
Length/height												
12 months of age	1.12	1.01–1.24	0.03	0.16	1.15	1.01–1.31	0.03	0.16	0.93	0.75–1.16	0.53	0.69
24 months of age	1.07	0.97–1.18	0.20	0.39	1.11	0.98–1.26	0.12	0.39	0.96	0.79–1.18	0.69	0.69
36 months of age	1.07	0.97–1.18	0.18	0.39	1.15	1.02–1.30	0.02	0.16	0.92	0.74–1.15	0.46	0.69
Weight												
3 months prior	1.13	1.02–1.25	0.02	0.08	1.11	0.97–1.26	0.13	0.17				
6 months prior	1.06	0.95–1.18	0.29	0.29	1.14	1.00–1.30	0.05	0.096				
9 months prior	1.08	0.97–1.21	0.16	0.17	1.14	0.99–1.30	0.06	0.096				
12 months prior	1.12	0.99–1.26	0.06	0.096	1.13	0.98–1.30	0.11	0.16				
Length/height												
3 months prior	1.03	0.92–1.15	0.66	0.70	1.09	0.94–1.26	0.24	0.39				
6 months prior	1.06	0.95–1.19	0.32	0.39	1.09	0.94–1.26	0.25	0.39				
9 months prior	0.98	0.87–1.11	0.80	0.80	1.07	0.92–1.25	0.37	0.42				
12 months prior	1.07	0.94–1.22	0.32	0.39	1.11	0.95–1.31	0.19	0.39				
Weight												
Up to 4 years	1.11	1.01–1.23	0.04	0.09	1.10	0.96–1.25	0.16	0.17	0.79	0.61–1.04	0.09	0.15
Length/height												
Up to 4 years	1.08	0.97–1.21	0.17	0.39	1.08	0.94–1.25	0.28	0.39	0.80	0.59–1.07	0.13	0.52

HRs adjusted for birth weight *z* score (for weight *z* score models) and birth length *z* scores (for length/height *z* score models), relation to type 1 proband, HLA-DR or -DQ genotype, and sex and stratified by country of residence. Boldface indicates statistical significance, FDR < 0.05. 2+ IA, multiple IA.

with autoantibody positivity of type 1 diabetes patients (42), were the participants at a comparably young age.

Greater weight in early childhood appears to predict a small increase in the risk of IA. The relevance of these findings for determining risk of diabetes will require longer follow-up of the cohort and evaluation of additional factors, such as infant feeding and genetic determinants of growth.

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