



Growth and development of islet autoimmunity and type 1 diabetes in children genetically at risk

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Abstract

Aims/hypothesis We aimed to evaluate the relationship between childhood growth measures and risk of developing islet autoimmunity (IA) and type 1 diabetes in children with an affected first-degree relative and increased HLA-conferred risk. We hypothesised that being overweight or obese during childhood is associated with a greater risk of IA and type 1 diabetes.

Methods Participants in a randomised infant feeding trial ($N = 2149$) were measured at 12 month intervals for weight and length/height and followed for IA (at least one positive out of insulin autoantibodies, islet antigen-2 autoantibody, GAD autoantibody and zinc transporter 8 autoantibody) and development of type 1 diabetes from birth to 10–14 years. In this secondary analysis, Cox proportional hazard regression models were adjusted for birthweight and length z score, sex, HLA risk, maternal type 1 diabetes, mode of delivery and breastfeeding duration, and stratified by residence region (Australia, Canada, Northern Europe, Southern Europe, Central Europe and the USA). Longitudinal exposures were studied both by time-varying Cox proportional hazard regression and by joint modelling. Multiple testing was considered using family-wise error rate at 0.05.

Results In the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) population, 305 (14.2%) developed IA and 172 (8%) developed type 1 diabetes. The proportions of children overweight (including obese) and obese only were 28% and 9% at

The investigators and members of The TRIGR Investigators are listed in the electronic supplementary material.

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Research in context

What is already known about this subject?

- Increased rate of weight gain during childhood has been associated with development of type 1 diabetes and progression from islet autoimmunity to type 1 diabetes
- A higher rate of linear growth in early childhood is reported to be related to an increased risk of progression from islet autoimmunity to type 1 diabetes

What is the key question?

- In children at especially high genetic risk of type 1 diabetes (a positive family history and increased HLA-conferred risk), are growth measures and occurrence of being overweight and obese during childhood associated with a greater risk of islet autoimmunity and type 1 diabetes?

What are the new findings?

- In this large international cohort of children with genetic risk, we observed that being overweight at 2–10 years of age was associated with increased risk of developing type 1 diabetes

How might this impact on clinical practice in the foreseeable future?

- Understanding of the association between body composition and type 1 diabetes may encourage preventive weight management strategies for children at risk of type 1 diabetes

10 years, respectively. Annual growth measures were not associated with IA, but being overweight at 2–10 years of life was associated with a twofold increase in the development of type 1 diabetes (HR 2.39; 95% CI 1.46, 3.92; $p < 0.001$ in time-varying Cox regression), and similarly with joint modelling.

Conclusions/interpretation In children at genetic risk of type 1 diabetes, being overweight at 2–10 years of age is associated with increased risk of progression from multiple IA to type 1 diabetes and with development of type 1 diabetes, but not with development of IA. Future studies should assess the impact of weight management strategies on these outcomes.

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00179777) NCT00179777

Keywords Beta cell autoimmunity · Childhood growth · Genetic risk · Length · Type 1 diabetes · Weight

Abbreviations

DAISY	Diabetes Autoimmunity Study in the Young
GADA	GAD autoantibody
IA	Islet autoimmunity
IAA	Insulin autoantibody
IA-2A	Islet antigen-2 autoantibody
IOTF	International Obesity Task Force
PTP	Pathway to Prevention
TEDDY	The Environmental Determinants of Diabetes in the Young
TRIGR	Trial to Reduce IDDM in the Genetically at Risk
ZnT8A	Zinc transporter 8 autoantibody

although levelling off is seen in some [2]. The rise in the disease incidence has been reported to be due to increased rates of disease in younger age groups. A recent report from the US population observed racial differences in incidence rates, with increases occurring at 10–14 years and 0–4 years of age in white and black children, respectively [3]. The autoimmune process that results in beta cell destruction and leads to type 1 diabetes is believed to be the result of a combination of genetic predisposition and environmental or lifestyle risk factors. Environmental triggers considered to influence the expression of the disease include viruses, the intestinal microbiome, rapid growth and weight gain, and nutritional factors [4, 5].

The causes of childhood obesity are multifactorial, with predisposing genetic factors and environmental components that include excessive energy intake in relation to physical activity [6]. Observations of greater birthweight as well as increasing trends for childhood obesity worldwide have led researchers to hypothesise that accelerated childhood growth

Introduction

The incidence of type 1 diabetes in children and young adults continues to increase in most developed countries [1],

may contribute to the increasing incidence of type 1 diabetes [7–10]. Increased growth could either initiate or accelerate islet autoimmunity (IA). One possible mechanism is that excess weight gain and sedentary lifestyle could cause insulin resistance and hyperinsulinaemia and further increased beta cell metabolism [11]. These metabolically active beta cells have been shown to be more vulnerable to autoimmune attack by cytokines than cells at rest [12]. A second possibility is that obesity-related insulin resistance with associated increased insulin demand may accelerate an ongoing beta cell destructive process and/or result in earlier or accelerated presentation of type 1 diabetes [13]. Maternal diabetes during pregnancy, including type 1 diabetes, has been associated with an increased prevalence of childhood obesity largely as a result of fetal exposure to hyperinsulinaemia. This may be due partly to increased concentrations of glucose stimulating the fetal beta cells and partly as a consequence of transplacental transfer of insulin–insulin antibody complexes from the maternal circulation, increased fat deposition and macrosomia [14]. Factors associated with maternal type 1 diabetes, including shorter duration of breastfeeding and higher birth size, are believed to contribute to this observed increase in being overweight and obese in offspring during childhood [15]. Despite these risk factors for obesity, maternal type 1 diabetes increases the risk of type 1 diabetes in the offspring less than type 1 diabetes in other first-degree relatives [16].

There is some inconsistency in the literature on the effect of growth measures during the first years of life on the development of IA or type 1 diabetes [17–22]. A meta-analysis of 29 primarily European studies reported that children who have a higher birthweight have a small increase in the risk of type 1 diabetes [23]. Increased rate of weight gain during childhood has also been associated with development of type 1 diabetes [9, 17, 24] and progression from IA to type 1 diabetes [25, 26]. However, another study reported that weight, BMI, and weight and BMI velocities were not associated with development of IA or progression from IA to type 1 diabetes [27]. A recent prospective study reported that a lower rate of linear growth during infancy and higher rate of linear growth in early childhood (up to 4 years) were associated with increased risk of progression from IA to type 1 diabetes [21]. Two other studies reported that an increased rate of linear growth during the first two years of life was associated with developing multiple IA [28] and during childhood (2–11 years) was associated with earlier development of IA [27].

The association of the occurrence of being overweight and obese with the development of IA and type 1 diabetes is unknown. We examined growth measures (weight, length/height and occurrence of being overweight and obese) annually and over time (up to 10 years of age) and the risk of development of IA and type 1 diabetes in the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) population who have at least one first-degree relative with type 1 diabetes

and carry HLA-conferred susceptibility. We hypothesised that a higher weight and length/height z score and occurrence of being overweight and obese (annually and over time) during childhood are associated with islet autoantibody positivity and a greater risk of type 1 diabetes. If confirmed in this large international population, weight loss treatment programmes to slow excess weight gain should be considered in the prevention of type 1 diabetes.

Methods

Design and participants The TRIGR study is an international type 1 diabetes prevention trial designed to determine whether weaning to a hydrolysed infant formula reduces the incidence of type 1 diabetes in children with a first-degree relative with type 1 diabetes and increased HLA-defined genetic risk. The trial was approved by the Ethics Institutional Review Boards and Committees of Human Experimentation in all participating TRIGR centre institutions. Written informed consent was obtained from the family prior to enrolment and assent was obtained for underage participants during the study, if required. A full description of the TRIGR study design has been reported previously [29]. In total, 2159 children at increased risk for developing type 1 diabetes from the USA, Canada, Australia and 12 countries in Europe were recruited for the trial between May 2002 and January 2007. Children were monitored until the last child reached 10 years of age for the frequency of type 1 diabetes-associated autoantibodies and/or the development of clinical diabetes. HLA genotyping for selected DQB1 and DQA1 alleles was performed using sequence-specific oligonucleotide hybridisation. Children with the following risk genotypes were included: (1) *HLA DQB1*02/DQB1*03:02* (high risk); (2) *HLA DQB1*03:02/x* (moderate risk; x not *DQB1*02*, *DQB1*03:01* or *DQB1*06:02*); (3) *HLA DQA1*05-DQB1*02/y* (y not *DQA102:01-DQB1*02*, *DQB1*03:01*, *DQB1*06:02* or *DQB1*06:03*) or *HLA DQA1*03-DQB1*02/y* (mild risk; y not *DQA102:01-DQB1*02*, *DQB1*03:01*, *DQB1*06:02* or *DQB1*06:03*).

Variable measures As part of the TRIGR study protocol, anthropometric indices (weight in kilograms and length before 2 years of age or height beginning at 2 years of age in centimetres) were obtained at birth and at each study visit (every 3 months until 1 year of age and annually thereafter to age 10–14 years). Participants with anthropometric data are included in this secondary analysis ($N=2149$). BMI was calculated beginning at 2 years of age. The International Obesity Task Force (IOTF) cut-off points for being overweight (corresponding $BMI=25\text{ kg/m}^2$ in adults) and obese (corresponding $BMI=30\text{ kg/m}^2$ in adults) by age and sex were used (available from 2 years of age onwards) [30].

Because there were no differences in any of these measures between the two intervention groups, their data were combined. Any IA was defined as positivity for one or more of the following biochemical autoantibodies: insulin autoantibodies (IAA), islet antigen-2 autoantibody (IA-2A), GAD autoantibody (GADA) and zinc transporter 8 autoantibody (ZnT8A), on two or more sequential study visits. IAA first antibody is IAA being the first positive antibody out of GADA, IAA, IA-2A and ZnT8A. GADA first antibody is GADA being the first positive antibody out of GADA, IAA, IA-2A and ZnT8A. Multiple IA was defined as positivity for two or more autoantibodies on two or more sequential study visits. Progression from multiple IA to type 1 diabetes was defined as the development of type 1 diabetes after being positive for multiple IA. Growth data up to the date of seroconversion to IA or within 3 months of the date of diagnosis of type 1 diabetes were used in the analyses. IAA, IA-2A, GADA and ZnT8A were quantified with the use of specific radiobinding assays in the Scientific Laboratory, Children's Hospital, University of Helsinki, Helsinki, Finland [31]. Type 1 diabetes was diagnosed according to the World Health Organization criteria [32].

Statistical analysis An imputation algorithm was used to correct errant entered weight and length/height values. Missing data were ignored in the time-dependent Cox models. Twenty-nine per cent of the participants had one or more missing calculated BMI values from the time of birth to their last visit. However, joint modelling by design inputs missing data based on the longitudinal mixed modelling that was performed. Ten participants had no weight or length/height measures and were not included in the analyses.

Cox proportional hazard models were used to assess the association of fixed measures for weight z score, length/height z score and being overweight and/or obese by age with the development of any IA, IAA first antibody, GADA first antibody, multiple IA, progression from multiple IA to type 1 diabetes and type 1 diabetes. Similarly, Cox proportional hazard models with time-dependent covariates (last value carried forward) for weight z score, length/height z score and being overweight and/or obese were constructed for the development of any IA, IAA first antibody, GADA first antibody, multiple IA, from multiple IA to type 1 diabetes and type 1 diabetes. These models were adjusted for birthweight z score, birth length z score, sex, HLA risk and maternal type 1 diabetes (yes/no), and, to account for possible non-proportional hazards, were stratified by region of residence (Australia, Canada, Northern Europe [Finland, Sweden], Southern Europe [Italy, Spain], Central Europe I [Czech Republic, Estonia, Hungary, Poland], Central Europe II [Germany, Luxembourg, the Netherlands, Switzerland] and the USA) (Table 1).

Joint models (models that fit jointly generalised mixed models for longitudinal data and proportional hazard models for time-to-event response) for each measure (weight z score, length/height z score and being overweight and/or obese based on IOTF cut-off points) were constructed to predict the time to IA and type 1 diabetes. These models, likewise, were stratified by region and adjusted for birthweight z score, birth length z score, sex, HLA risk and maternal type 1 diabetes (yes/no). The joint model analysis could not be completed for obesity (IA, type 1 diabetes) and for being overweight (IA) as the joint model failed to converge.

For participants who were lost to follow-up, all information available up until the date of their last study visit was used in the time-dependent Cox models as well as in the joint modelling. To account for multiple testing, the Bonferroni method was used to control the family-wise error rate at 0.05. As such, p values less than 0.005 were considered statistically significant. All analyses were performed using Statistical Analysis Software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Of the 2149 TRIGR participants, 305 (14%) developed IA and 172 (8%) type 1 diabetes (Table 1). The median (IQR) age of seroconversion to IA was 36.4 (17.8–64.3) months and the onset of type 1 diabetes 71.5 (35.1–108.6) months. The demographic characteristics of the TRIGR study population are shown in Table 1. Sex and anthropometric measures at birth did not predict the development of IA or type 1 diabetes. Compared with the highest-risk genotype, fewer children with the moderate- and lower-risk genotypes developed IA and type 1 diabetes. The proportions of participants who were overweight and obese by sex at annual visits from 2 to 10 years of age are shown in electronic supplemental material (ESM) Fig. 1. In both female and male children, the proportions of children overweight (including obese) and obese rose steadily from ~9% and ~1.5%, respectively, at 2 years to 28% and 9%, respectively, by age 10 years.

Growth measures and development of IA The growth measures at any age point (weight z score, length/height z score and occurrence of being overweight and obese) adjusted for birthweight z score, birth length/height z score, sex, HLA risk, maternal type 1 diabetes status, mode of delivery and breastfeeding duration, and stratified by region of residence, were not associated with the development of any IA, IAA first, GADA first or multiple IA in Cox proportional hazard models when multiple testing was considered (ESM Tables 1 and 2). In the time-varying model of growth from 1 year up to 10 years of age, weight z scores, length/height z scores and being overweight and obese were not associated with the development of any IA, first antibody or multiple IA.

Table 1 Characteristics of participating children according to IA and type 1 diabetes development

Characteristic	IA ^a (n = 305)	No IA (n = 1844)	HR (95% CI)	Type 1 diabetes (n = 172)	No type 1 diabetes (n = 1977)	HR (95% CI)
Age at first autoantibody-positive visit/diagnosis of type 1 diabetes or most recent visit (months) ^b	36.4 (17.8–64.3)	120.0 (119.4–120.0)		71.5 (35.1–108.6)	142.3 (127.0–155.2)	
Country regions ^c						
Northern Europe	77 (25.3)	478 (25.9)		49 (28.5)	506 (25.6)	
Central Europe I	42 (13.8)	237 (12.9)		20 (11.6)	259 (13.1)	
Central Europe II	32 (10.5)	153 (8.3)		12 (7.0)	173 (8.8)	
Southern Europe	11 (3.6)	101 (5.5)		6 (3.5)	106 (5.4)	
USA	50 (16.4)	343 (18.6)		32 (18.6)	361 (18.3)	
Canada	83 (27.2)	441 (23.9)		45 (26.2)	479 (24.2)	
Australia	10 (3.3)	91 (4.9)		8 (4.7)	93 (4.7)	
Maternal type 1 diabetes ^c	131 (43.0)	976 (52.9)	0.71 (0.55, 0.91)	69 (40.1)	1038 (52.5)	0.67 (0.48, 0.94)
HLA ^c						
<i>HLA-DQB1*0302/DQB1*02</i>	117 (38.4)	398 (21.6)	1	73 (42.4)	442 (22.4)	1
<i>HLA-DQB1*0302/x</i>	123 (40.3)	824 (44.7)	0.54 (0.42, 0.69)	63 (36.6)	884 (44.7)	0.45 (0.32, 0.63)
<i>HLA-DQA1*05-DQB1*02/y</i> or <i>HLA-DQA1*03-DQB1*02/y</i>	65 (21.3)	622 (33.7)	0.38 (0.28, 0.52)	36 (20.9)	651 (32.9)	0.36 (0.24, 0.53)
Sex (female) ^c	136 (44.6)	879 (47.7)	0.87 (0.70, 1.10)	81 (47.1)	934 (47.2)	0.93 (0.69, 1.26)
Birthweight z score ^c	0.30 (1.02)	0.29 (1.07)	0.95 (0.82, 1.09)	0.26 (0.98)	0.29 (1.07)	0.95 (0.78, 1.14)
Birth length z score ^c	0.58 (1.01)	0.48 (0.98)	1.12 (0.97, 1.30)	0.51 (0.93)	0.49 (0.99)	1.05 (0.86, 1.28)
Mode of delivery ^c						
Vaginal delivery	174 (57.1)	1037 (56.2)	1	104 (60.5)	1107 (56.0)	1
Caesarean section	131 (43.0)	807 (43.8)	1.20 (0.94, 1.54)	68 (39.5)	870 (44.0)	1.07 (0.77, 1.50)
Breastfeeding duration ≥ 6 months ^c	190 (62.3)	1025 (55.6)	1.10 (0.87, 1.39)	109 (63.4)	1106 (55.9)	1.18 (0.86, 1.63)

HRs based on models adjusted for birthweight z score, birth length/height z score, sex, HLA risk, maternal type 1 diabetes status, mode of delivery and breastfeeding duration, and stratified by region of residence (Northern Europe: Finland, Sweden; Central Europe I: Czech Republic, Estonia, Hungary, Poland; Central Europe II: Germany, Luxembourg, the Netherlands, Switzerland; Southern Europe: Italy, Spain)

^a Antibodies include IAA, IA-2A, GADA and ZnT8A

^b Median (IQR)

^c n (%)

^d Mean (SD)

Similarly, joint modelling analysis for weight z score, length/height z score and occurrence of being overweight indicated that the measures of growth over time were not associated with the development of any IA or multiple IA.

Growth measures and development of type 1 diabetes The association of growth measures with the progression from multiple IA to type 1 diabetes and with the development of type 1 diabetes was assessed using fixed measures and longitudinal exposures. In the time-varying model of growth from 1 year up to 10 years of age, weight z score was associated with the progression from multiple IA to type 1 diabetes (HR 1.53; 95% CI 1.16, 2.03; $p = 0.003$) and with the development of type 1 diabetes (HR 1.43; 95% CI 1.20, 1.72; $p < 0.001$; ESM Table 3). In addition, the time-varying Cox regression model showed that the risk of developing type 1 diabetes was two times as high over time in children who were overweight from 2 years up to 10 years of age (HR 2.39; 95% CI 1.46,

3.92; $p < 0.001$) (Table 2). A similar result was observed according to joint modelling (HR 2.16; 95% CI 1.40, 3.21; $p = 0.004$). Cox proportional hazard regression analysis of fixed measures revealed an increase in risk of progressing from multiple IA to type 1 diabetes for weight z score at 3 years of age (HR 1.48; 95% CI 1.13, 1.92; $p = 0.004$) after adjustment for covariates and when multiple testing was considered (ESM Table 3). An increase in the risk of progression from multiple IA to type 1 diabetes was also observed at 3 years of age in children who were overweight (HR 3.61; 95% CI 1.73, 7.54; $p < 0.001$) and in children who were obese (HR 18.88; 95% CI 4.27, 83.45; $p < 0.001$) (Table 2 and Fig. 1a–d).

Discussion

In this international, large birth cohort of 2149 children with increased genetic risk of type 1 diabetes, we observed a strong

Table 2 The risk of type 1 diabetes associated with being overweight (including obese) and obese by age and time-varying model of being overweight (including obese) and obese and up to 10 years of age using IOTF BMI cut-off points ($N = 2149$)

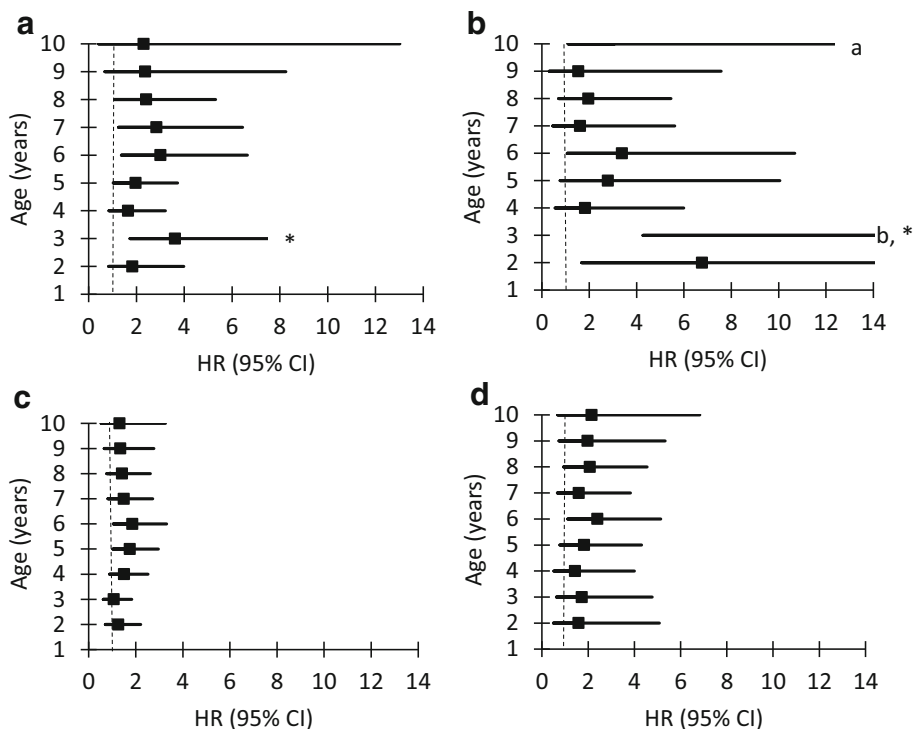
Variable	From multiple IA ^a to type 1 diabetes ($n = 133$)			Type 1 diabetes ($n = 172$)		
	HR	95% CI	p value	HR	95% CI	p value
Overweight (%)						
2 years	1.83	0.84, 3.98	0.13	1.26	0.71, 2.21	0.43
3 years	3.61	1.73, 7.54	<0.001	1.07	0.62, 1.83	0.82
4 years	1.65	0.85, 3.21	0.14	1.50	0.89, 2.52	0.13
5 years	1.96	1.03, 3.72	0.04	1.75	1.03, 2.96	0.04
6 years	3.01	1.37, 6.64	0.006	1.86	1.05, 3.31	0.03
7 years	2.84	1.25, 6.44	0.01	1.49	0.82, 2.72	0.19
8 years	2.41	1.09, 5.31	0.03	1.42	0.77, 2.62	0.26
9 years	2.36	0.68, 8.25	0.18	1.35	0.66, 2.77	0.41
10 years	2.30	0.41, 13.02	0.34	1.31	0.53, 3.26	0.56
Obesity (%)						
2 years	6.76	1.68, 27.28	0.007	1.59	0.50, 5.08	0.44
3 years	18.88	4.27, 83.45	<0.001	1.73	0.63, 4.77	0.29
4 years	1.83	0.56, 5.99	0.32	1.44	0.52, 4.00	0.48
5 years	2.79	0.77, 10.05	0.12	1.83	0.78, 4.31	0.17
6 years	3.38	1.07, 10.68	0.04	2.40	1.12, 5.14	0.02
7 years	1.61	0.46, 5.61	0.46	1.60	0.67, 3.83	0.29
8 years	1.96	0.71, 5.45	0.20	2.07	0.94, 4.55	0.07
9 years	1.54	0.31, 7.57	0.59	1.98	0.74, 5.33	0.18
10 years	70.85	1.11, 4529.89	0.04	2.15	0.68, 6.83	0.19
Overweight up to 10 years	2.17	1.12, 4.19	0.02	2.39	1.46, 3.92	<0.001
Obesity up to 10 years	0.98	0.21, 4.61	0.98	2.08	0.93, 4.64	0.07
Overweight (joint modelling)	^b	^b	^b	2.16	1.40, 3.21	0.004
Obesity (joint modelling)	^b	^b	^b	^b	^b	^b

HRs adjusted for birthweight z score and birth length z score, sex, HLA risk, maternal type 1 diabetes status, mode of delivery and breastfeeding duration, and stratified by region of residence. Presented p values are nominal (uncorrected) p values, and were considered significant if < 0.005

^a Antibodies include IAA, IA-2A, GADA and ZnT8A; the number of children with multiple IA = 190

^b Model failed to converge

Fig. 1 Risk of type 1 diabetes associated with being overweight (including children who are obese) and obese by age (2 to 10 years). Progression from multiple islet autoimmunity to type 1 diabetes associated with being overweight (a) and obese (b). Development of type 1 diabetes associated with being overweight (c) and obese (d). * $p < 0.001$; ^aactual values (HR 70.85 95% CI 1.11, 4529.89); ^bactual values (HR 18.88, 95% CI 4.27, 83.45)



positive association between being overweight over 2 to 10 years of age and development of type 1 diabetes. This association remained significant after controlling for the confounders and multiple testing, and the finding was the same using time-varying Cox proportional hazard regression and joint model analysis. Weight z score from 1 year up to 10 years of age was associated with greater risk of progression from multiple IA to type 1 diabetes. A similar association was found with weight z score and being overweight and obese at the 3 year age point. A possible explanation for this observation is that children who are heavier and taller require more insulin. If insulin secretion does not parallel an increase in growth, then insulin insufficiency results in the development of type 1 diabetes. Weight or height z scores or being overweight or obese were not significantly associated with development of IA or multiple IA. Neither did anthropometric measures at birth predict the development of IA or type 1 diabetes.

The strengths of the study include a large cohort with a carefully constructed study protocol and the use of strictly standardised and validated prospective data collection and measurement methods. Participation in the study remained excellent during the long follow-up. Compared with other prospective studies that examined associations between childhood growth measures and development of IA and type 1 diabetes, this study has a long follow-up and a relatively high number of children who developed any IA, multiple IA or type 1 diabetes. Frequent measurements of growth both before

and after seroconversion enabled us to explore the associations of the growth measures with both initiation and acceleration of the IA development.

In the TRIGR population, the proportions of children overweight (including obesity) and obese increased by age, reaching 28% and 9%, respectively, at 10 years in both sexes (from 2012 to 2017). By comparison, in the general population a systematic analysis of being overweight and obese in children from developed countries by the Global Burden of Disease 2013 Obesity Collaboration revealed a prevalence of being overweight or obese of 24% (95% CI 23%, 25%) for boys and 23% (95% CI 22%, 24%) for girls aged 2–19 years using the IOTF cut-off points, which is lower than the prevalence of being overweight (including obese) for the TRIGR population at 10 years of age [33]. The proportion of 11-year-old European children who were overweight or obese in the Health Behavior in School-Aged Children Study: International Report from the 2013–2014 Survey was 17% in girls and 27% in boys using IOTF BMI cut-off points, which is also lower than the TRIGR study population from the same time period [34].

The Diabetes Autoimmunity Study in the Young (DAISY) includes a US population of children at increased genetic risk for type 1 diabetes [24]. At 8 years of age, DAISY children were observed to have a mean \pm SD BMI of 16.83 ± 2.38 kg/m². This is approximately the 50% percentile on the Centers for Disease Control and Prevention (CDC) Clinical Growth Charts for boys and girls [35]. We previously reported

differences in early childhood growth between TRIGR regions [36]. The higher early childhood weight and length measures were consistent with the higher incidence of type 1 diabetes in Northern European TRIGR countries and Canada compared with southern countries [37], which supported a relationship but did not determine causality.

Our results are inconsistent with some previous studies that showed direct association between linear growth parameters and the development of IA in children at increased genetic risk of type 1 diabetes. Greater linear growth velocity was associated with IA and type 1 diabetes in the at-risk Colorado DAISY study population ($N=1714$) [24] and with an increased risk of progression from IA to type 1 diabetes in The Environmental Determinants of Diabetes in the Young (TEDDY) study ($N=7522$) [21], while no association between length/height and IA or type 1 diabetes risk or progression from IA to type 1 diabetes was observed in TRIGR. The difference in results may be due to differences between the study populations or in measurement techniques in the varying studies. The DAISY population includes three groups of children at risk for developing type 1 diabetes (unaffected first-degree relatives of patients with type 1 diabetes, infants screened for HLA susceptibility at birth and siblings of the newborn-screened group). The TEDDY study population includes a cohort covering four countries of genetically high-risk children, the majority selected from the general population, whereas participants in the TRIGR study were recruited from a high-risk population with affected first-degree relatives in 15 countries and additionally were screened for HLA-conferred risk genes. In both TEDDY and TRIGR studies, hazard models were adjusted for similar variables (birth measures, sex, HLA risk, family history of type 1 diabetes [TEDDY] or maternal type 1 diabetes [TRIGR], duration of exclusive breastfeeding and country of residence).

Moreover, while we observed no association between birth measures and the development of type 1 diabetes, a primarily European study meta-analysis revealed an increase in type 1 diabetes risk of 3% per 500 g increase in birthweight after adjustment for gestational age, maternal age, birth order, Caesarean section, breastfeeding and maternal diabetes [23]. In addition, children in the Diabetes Prediction in Skåne study who developed type 1 diabetes were taller at birth compared with age- and sex-matched control participants born to mothers without type 1 diabetes [38]. A systematic review and meta-analysis suggests that childhood obesity increases the risk of type 1 diabetes [17]. Weight gain rate in early childhood was directly associated with progression from IA to type 1 diabetes in the TEDDY study but only in children with GADA appearing first [21]. In the time-varying model of weight z score from 1 year up to 10 years of age, we observed an association with progression from multiple IA to type 1 diabetes but did not examine this based on appearance of first IA.

Our observation that being overweight is associated with progression from multiple IA to type 1 diabetes and with the development of type 1 diabetes is consistent with the observation of higher weight and body composition measures in a large population ($N=9248$) of young German and Austrian children (<5 years of age) diagnosed with type 1 diabetes [39]. In a subgroup ($n=1117$) of participants of the TrialNet Pathway to Prevention (PTP) study, which includes first-, second- or third-degree relatives (2 to 18 years of age) of people with type 1 diabetes, consistent elevation of BMI ≥ 85 th percentile was found to be associated with increased risk of progression from IA to type 1 diabetes [26]. This increased risk occurred at a lower level of sustained elevated BMI in children <12 years of age, particularly in female children. In the TrialNet PTP subgroup of participants ($n=706$) who were single autoantibody positive, persistently elevated BMI was found to increase the risk of developing multiple IA in children >9 years of age who did not carry high-risk HLA haplotypes but not in children <9 years of age regardless of HLA type [27]. The TrialNet PTP results are somewhat consistent with our observations. However, TrialNet examined the association between persistent excess weight in participants and risk of IA or progression to type 1 diabetes, whereas we examined being overweight and/or obese.

The lack of information on parental weight and height is a limitation of this study. Neither did we have information on puberty timing of the participating children. As the participants had a very high genetic risk of type 1 diabetes due to HLA-conferred risk genes and at least one of the first-degree relatives having type 1 diabetes, these findings are not necessarily generalisable to populations with lower genetic susceptibility. We did not assess insulin resistance by the homeostatic model of assessment. Therefore, we cannot confirm that the progression from multiple IA to type 1 diabetes was accelerated by insulin resistance. We used BMI as a measure of adiposity in our population. The assessment of excess adiposity may be strengthened in future studies by the use of objective measures of fat mass such as blood leptin level and adiponectin concentration [40].

Increased weight and consistent overweight status in young children increased the risk of developing type 1 diabetes in a large, international population of children at high genetic risk. This is the first study to examine the relationship between weight status, expressed as being overweight and obese, and the development of IA, multiple IA and type 1 diabetes in addition to the progression from multiple IA to type 1 diabetes. The World Health Organization has reported that childhood obesity is a serious global public health challenge that affects countries worldwide [41]. In comparison with children at a healthy weight, children who are overweight or obese are at higher risk for pulmonary, endocrine (insulin resistance) and cardiovascular conditions during childhood that may have long-lasting effects [42]. Treatment programmes to slow the

progress of weight gain or encourage gradual weight loss in children may be implemented based on BMI status (overweight or obese) [43]. In addition to setting targets for stopping the increase in obesity, expert committees have developed action steps and recommendations for healthcare professionals to aid with the prevention and treatment of childhood obesity [43, 44]. The results of this study support prior research that has shown an association between growth and the development of type 1 diabetes in children and expand the literature by reporting associations using standardised definitions of being overweight and obese that guide clinical practice. Future studies should assess the impact of weight management strategies on these outcomes.

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Data availability The dataset used for these analyses can be requested by emailing TRIGR@epi.usf.edu.

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References

- Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, EURODIAB Study Group (2009) Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–2020: a multicentre prospective registration study. *Lancet* 373:2027–2033. [https://doi.org/10.1016/S0140-6736\(09\)60568-7](https://doi.org/10.1016/S0140-6736(09)60568-7)
- Harjutsalo V, Sund R, Knip M, Groop PH (2013) Incidence of type 1 diabetes in Finland. *JAMA* 310:427–428. <https://doi.org/10.1001/jama.2013.8399>
- Lipman TH, Levitt Katz LE, Ratcliffe SJ et al (2013) Increasing incidence of type 1 diabetes in youth. *Diabetes Care* 36:1597–1603. <https://doi.org/10.2337/dc12-0767>
- Virtanen SM (2016) Dietary factors in the development of type 1 diabetes. *Pediatr Diabetes* 17(Suppl 22):49–55. <https://doi.org/10.1111/pedi.12341>
- Rewers M, Ludvigsson J (2016) Environmental risk factors for type 1 diabetes. *Lancet* 387(10035):2340–2348. [https://doi.org/10.1016/S0140-6736\(16\)30507-4](https://doi.org/10.1016/S0140-6736(16)30507-4)
- Institute of Medicine (2012) Accelerating progress in obesity prevention: solving the weight of the nation. The National Academies Press, Washington, DC
- Knip M, Reunanen A, Virtanen SM, Nuutinen M, Viikari J, Akerblom HK (2008) Does the secular increase in body mass in children contribute to the increasing incidence of type 1 diabetes? *Pediatr Diabetes* 9:46–49. <https://doi.org/10.1111/j.1399-5448.2007.00344.x>
- Hyponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK (2000) The Childhood Diabetes in Finland Study Group. Obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes Care* 23:1755–1760. <https://doi.org/10.2337/diacare.23.12.1755>
- Johansson C, Samuelsson U, Ludvigsson J (1994) A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 37:91–94. <https://doi.org/10.1007/BF00428783>
- Wilkin TJ (2001) The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922. <https://doi.org/10.1007/s001250100548>
- Dahlquist G (2006) Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* 49:20–24. <https://doi.org/10.1007/s00125-005-0076-4>
- Palmer JP, Helquist S, Spinas GA et al (1989) Interaction of beta-cell activity and IL-1 concentration and exposure time in isolated rat islets of Langerhans. *Diabetes* 38:1211–1216. <https://doi.org/10.2337/diab.38.10.1211>
- Libman IM, Pietropaolo M, Arslanian SA, LaPorte RE, Becker DJ (2003) Changing prevalence of overweight children and adolescents at onset of insulin-treated diabetes. *Diabetes Care* 26:2871–2875. <https://doi.org/10.2337/diacare.26.10.2871>
- Dabelea D (2007) The predisposition to obesity and diabetes in offspring of diabetic mothers. *Diabetes Care* 30(Suppl 2):S169–S174. <https://doi.org/10.2337/dc07-s211>
- Hummel S, Pfluger M, Kreichauf S, Hummel M, Ziegler AG (2009) Predictors of overweight during childhood in offspring of parents with type 1 diabetes. *Diabetes Care* 32:921–925. <https://doi.org/10.2337/dc08-1943>
- Gale EA, Gillespie KM, Diabetes and gender (2001) *Diabetologia* 44:3–15. <https://doi.org/10.1007/s001250051573>
- Verbeeten KC, Elks CE, Daneman D, Ong KK (2011) Association between childhood obesity and subsequent type 1 diabetes: a systematic review and meta-analysis. *Diabet Med* 28:10–18. <https://doi.org/10.1111/j.1464-5491.2010.03160.x>
- Couper JJ, Beresford S, Hirte C et al (2009) Weight gain in early life predicts risk of islet autoimmunity in children with a first-degree relative with type 1 diabetes. *Diabetes Care* 32:94–99. <https://doi.org/10.2337/dc08-0821>
- Beyerlein A, Thiering E, Pfluegger M et al (2014) Early infant growth is associated with the risk of islet autoimmunity in genetically susceptible children. *Pediatr Diabetes* 15:534–542. <https://doi.org/10.1111/pedi.12118>
- Larsson HE, Vehik K, Haller MJ et al (2016) Growth and risk for islet autoimmunity and progression to type 1 diabetes in early childhood: the environmental determinants of diabetes in the young study. *Diabetes* 65:1988–1995. <https://doi.org/10.2337/db15-1180>

21. Liu X, Vehik K, Huang Y et al (2020) Distinct growth phases in early life associated with the risk of type 1 diabetes: the TEDDY Study. *Diabetes Care* 43:556–562. <https://doi.org/10.2337/dc19-1670>
22. Magnus MC, Olsen SF, Granström C et al (2015) Infant growth and risk of childhood-onset type 1 diabetes in children from 2 Scandinavian birth cohorts. *JAMA Pediatr* 169:e153759. <https://doi.org/10.1001/jamapediatrics>
23. Caldwell CR, Stene LC, Joner G et al (2010) Birthweight and the risk of childhood-onset type 1 diabetes: a meta-analysis of observational studies using individual patient data. *Diabetologia* 53:641–651. <https://doi.org/10.1007/s00125-009-1648-5>
24. Antvorskov JC, Aunsholt L, Buschard K et al (2018) Childhood body mass index in relation to subsequent risk of type 1 diabetes—a Danish cohort study. *Pediatr Diabetes* 19:265–270. <https://doi.org/10.1111/pedi.12568>
25. Ferrara CT, Geyer SM, Evans-Molina C et al (2017) Excess BMI in childhood: a modifiable risk factor for type 1 diabetes development. *Diabetes Care* 40:698–701. <https://doi.org/10.2337/dc16-2331>
26. Ferrara-Cook C, Geyer SM, Evans-Molina et al (2020) Excess BMI accelerates islet autoimmunity in older children and adolescents. *Diabetes Care* 43:580–587. <https://doi.org/10.2337/dc19-1167>
27. Lamb MM, Yin X, Zerbe GO et al (2009) Height growth velocity, islet autoimmunity and type 1 diabetes development: the Diabetes Autoimmunity Study in the Young. *Diabetologia* 52:2064–2071. <https://doi.org/10.1007/s00125-009-1428-2>
28. Pacaud D, Nucci AM, Cuthbertson D et al (2021) Association between family history, early growth and the risk of beta cell autoimmunity in children at risk for type 1 diabetes. *Diabetologia* 64:119–128. <https://doi.org/10.1007/s00125-020-05287-1>
29. TRIGR Study Group (2007) Study design of the Trial to Reduce IDDM in the Genetically at Risk (TRIGR). *Pediatr Diabetes* 8:117–137. <https://doi.org/10.1007/s00125-010-1964-9>
30. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320:1240–1243. <https://doi.org/10.1136/bmj.320.7244.1240>
31. Knip M, Virtanen SM, Seppä K et al (2010) Dietary intervention in infancy and later signs of beta-cell autoimmunity. *N Engl J Med* 363:1900–1908. <https://doi.org/10.1056/NEJMoa1004809>
32. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553. [https://doi.org/10.1002/\(SICI\)1096-9136\(199807\)15:7<539::AID-DIA668>3.0.CO;2-S](https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S)
33. The Global Burden of Disease 2013 Obesity Collaboration (2014) Global, regional and national prevalence of overweight and obesity in children and adults 1980–2013: a systematic analysis. *Lancet* 384:766–781. [https://doi.org/10.1016/S0140-6736\(14\)60460-8](https://doi.org/10.1016/S0140-6736(14)60460-8)
34. Inchley J, Currie D, Young T, et al (eds) (2016) Growing up unequal: gender and socioeconomic differences in young people's health and well-being. Health Behavior in School-Aged Children (HBSC) Study: International Report from the 2013/2014 Survey. World Health Organization, Copenhagen
35. Centers for Disease Control and Prevention. Clinical growth charts. Available from https://www.cdc.gov/growthcharts/clinical_charts.htm#Set1. Last reviewed 16 June 2017. Accessed 11 Jan 2020
36. Nucci AM, Becker DJ, Virtanen SM et al (2012) Growth differences between North American and European children at risk for type 1 diabetes. *Pediatr Diabetes* 13:425–431. <https://doi.org/10.1111/j.1399-5448.2011.00840.x>
37. DIAMOND Project Group (2006) Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. *Diabet Med* 23:857–866. <https://doi.org/10.1111/j.1464-5491.2006.01925.x>
38. Larsson HE, Hansson G, Carlsson A et al (2008) Children developing type 1 diabetes before 6 years of age have increased linear growth independent of HLA genotypes. *Diabetologia* 51:1623–1630. <https://doi.org/10.1007/s00125-008-1074-0>
39. Knerr I, Wolf J, Reinehr T et al (2005) The ‘accelerator hypothesis’: relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia* 48:2501–2504. <https://doi.org/10.1007/s00125-005-0033-2>
40. Mantzoros CS, Rifas-Shiman SL, Williams CJ, Fargnoli JL, Kelesidis T, Gillman MW (2009) Cord blood leptin and adiponectin as predictors of adiposity in children at 3 years of age: a prospective cohort study. *Pediatrics* 123:682–689. <https://doi.org/10.1542/peds.2008-0343>
41. World Health Organization (2018) Taking action on childhood obesity. Available from <https://apps.who.int/iris/bitstream/handle/10665/274792/WHO-NMH-PND-ECHO-18.1-eng.pdf?ua=1>. Accessed 8 Oct 2020
42. Lobstein T, Baur L, Uauy R, for the IASO International Obesity Task Force (2004) Obesity in children and young people: a crisis in public health. *Obes Rev* 5(Suppl 1):4–85. <https://doi.org/10.1111/j.1467-789X.2004.00133.x>
43. Barlow SE, the Expert Committee (2007) Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 120(Suppl 4):S164–S192. <https://doi.org/10.1542/peds.2007-2329C>
44. World Health Organization (2017) Report of the Commission on Ending Childhood Obesity implementation plan: executive summary. Available from <https://apps.who.int/iris/bitstream/handle/10665/259349/WHO-NMH-PND-ECHO-17.1-eng.pdf?sequence=1>. Accessed 8 Oct 2020

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