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Height Growth Velocity, Islet Autoimmunity and Type 1 Diabetes Development: the Diabetes Autoimmunity Study in the Young

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Abstract

Aims/hypothesis—Larger childhood body size and rapid growth have been associated with increased type 1 diabetes risk. We analyzed height, weight, body mass index (BMI), and velocities of growth in height, weight, and BMI, for association with development of islet autoimmunity (IA) and type 1 diabetes.

Methods—Since 1993, the Diabetes Autoimmunity Study in the Young (DAISY) has followed children at increased type 1 diabetes risk, based on HLA DR,DQ genotype or family history, for development of IA and type 1 diabetes. IA was defined as presence of autoantibodies to insulin, GAD or IA2 twice in succession, or autoantibody positive on one visit and diabetic at the next consecutive visit within one year. Type 1 diabetes was diagnosed by a physician. Height and weight were collected starting at age 2 years. Of 1,714 DAISY children < age 11.5 years, 143 children developed IA, and 21 progressed to type 1 diabetes. We conducted Cox proportional hazards analysis to explore growth velocities and size measures for association with IA and type 1 diabetes development.

Results—Higher height growth velocity was associated with IA development (HR: 1.63, CI: 1.31-2.05) and type 1 diabetes development (HR: 3.34, CI: 1.73-6.42) for a 1 standard deviation difference in velocity.

Conclusions/interpretation—Our study suggests that greater height growth velocity may be involved in the progression from genetic susceptibility to autoimmunity and then to type 1 diabetes in pre-pubertal children.

Keywords

childhood height; height growth velocity; islet autoimmunity; type 1 diabetes

Introduction

Type 1 diabetes is an autoimmune disease in which the insulin-producing beta cells of the pancreas are destroyed. A long preclinical phase of islet autoimmunity (IA) often precedes the clinical diagnosis of type 1 diabetes. Children progress from islet autoimmunity to type 1 diabetes at different rates (1;2), and it is still unknown whether or not all children that develop IA will eventually develop type 1 diabetes. Identifying the predictors of IA and type 1 diabetes

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might shed light on the biologic mechanisms that influence the early stages of this autoimmune disease process.

Two recent hypotheses postulate that the current childhood obesity epidemic is driving the increasing incidence and earlier age of type 1 diabetes onset seen around the world (3-6). The Overload Hypothesis (7) suggests that the high insulin demand on the beta cell that results from the overfeeding and resultant accelerated growth of today's youth make the beta cells vulnerable to autoimmune attack and apoptosis. The Accelerator Hypothesis postulates that insulin resistance caused by excess weight gain may accelerate beta cell apoptosis in individuals at genetic risk (8).

Ecologic studies have suggested a correlation between increasing BMI, weight and height and incidence of type 1 diabetes in the population (9;10). Several studies have shown an association between higher body mass index (BMI) standard deviation (SD) scores and earlier age at diagnosis of type 1 diabetes(11-14), although others have not (15-17). In case-control studies, children with type 1 diabetes showed increased weight, height or BMI SD scores compared to non-diabetic children either in infancy or early childhood (18-26). Analysis of a birth cohort suggested that increased BMI in childhood increased risk of self-reported type 1 diabetes (27). A recent study examined this in a cohort of children at increased risk of type 1 diabetes and found that higher weight and BMI SD scores were associated with development of islet autoimmunity (28). Childhood obesity and rapid growth may trigger autoimmunity by creating higher insulin demands on the pancreas, which may make the beta cell more active and more visible to the immune system. Higher insulin demands might also exacerbate autoimmunity by stressing beta cells already under autoimmune attack. We used a prospective cohort of healthy children age 2 to 11 years who are at increased genetic risk for type 1 diabetes, to explore the association of childhood size and growth rate with two outcomes: earlier IA development, and more rapid progression to type 1 diabetes in children with evidence of IA.

Methods

DAISY is a prospective study of three groups of young children at increased risk for developing type 1 diabetes. One group consists of unaffected first-degree relatives of patients with type 1 diabetes, identified and recruited between birth and age eight years through the Barbara Davis Center for Childhood Diabetes in Denver, Colorado, other diabetes care clinics, and the Colorado IDDM Registry. The second group consists of babies born at St. Josephs Hospital in Denver, Colorado, and screened by umbilical cord blood samples for diabetes-susceptibility alleles in the HLA region. The third group is composed of siblings of the second (newborn screened) group, who are also screened and enrolled into DAISY and followed for the development of autoimmunity and type 1 diabetes. The details of the newborn screening (29) have been published elsewhere. DAISY has enrolled 2,600 children from 1993 to 2004. The Colorado Multiple Institutional Review Board approved all study protocols, and informed consent was obtained from the parents/legal guardians of all children.

HLA genotype status of the child was determined from a cord blood sample, if obtained at birth, or from a blood draw at the first clinic visit. Blood was sent to Roche Molecular Systems, Inc, Alameda, CA for PCR-based HLA class II typing. The high-risk HLA DR,DQ genotype was defined as (DRB1*03/ DRB1*04, DQB1*0302). Prospective follow-up of DAISY children included testing for autoantibodies to insulin, protein tyrosine phosphatase islet antigen 2 (IA2), and glutamic acid decarboxylase (GAD) at clinic visits at 9,15, and 24 months (if child enrolled at birth) or at enrollment visit (if child enrolled later in childhood), and annually thereafter up to age 15 years. GAD autoantibodies and IA2 autoantibodies were measured with a combined radiobinding assay (30;31). Insulin autoantibody was measured by a micro–insulin autoantibody assay as described previously (31;32).

The outcome of IA was defined as presence of autoantibodies to insulin, GAD or IA2 at two consecutive clinic visits, or autoantibody positive on one visit and diabetic on the next consecutive visit within one year. The age at the first of two consecutive IA positive visits, or the age at the IA positive visit that was followed by type 1 diabetes diagnosis within one year, was used as the age at IA development (ie, in the time to event analyses). Children who tested positive for ≥ 1 autoantibody were examined every 3-6 months, and hemoglobin A1c and random glucose were also measured. A child was referred to a physician for type 1 diabetes diagnosis if they had a random glucose >200 mg/dl and/or a hemoglobin A1c > 6.2%. The criteria used for diagnosis included typical symptoms of polyuria and/or polydipsia and a random glucose >200 mg/dl or an oral glucose tolerance test with a fasting plasma glucose of > 125 mg/dl or a 2 hour glucose >200 mg/dl. Details of intensive monitoring and diagnosis protocol were described previously (33). The age at physician diagnosis was used as the age at type 1 diabetes development (ie, in the time to event analyses).

Gender, race/ethnicity, maternal education, and household income were collected in an interview at the time of enrollment. Weight was measured at every clinic visit on a scale with precision ± 0.1 kg. Height was first measured when the child was able to stand cooperatively, around 2 years old, and at every clinic visit thereafter, using a stadiometer with a precision of ± 1 mm. Body Mass Index (BMI) was calculated as weight (kilograms) / height (meters)^2 for all clinic visits where the child was at least 2 years old.

These analyses are limited to children who developed IA or type 1 diabetes after the age of 2 years, the age at which we first obtained height measurements. Because puberty is a time of increased insulin resistance resulting from very rapid growth rate and dramatic hormonal changes (34), we analyzed records collected prior to age 11.0 for girls, and prior to age 11.5 for boys. These age cutoffs represent the median ages at which a sample of DAISY children (n=604) reported being at Tanner stage 2 on a self-Tanner staging questionnaires (35).

Cohort for the Analysis of the Development of IA

In order to explore associations between childhood size, growth rate, and time to IA development, we analyzed DAISY children for whom at least 2 height and weight measures were available (9,914 records on 1,714 children) prior to or at IA development. Seventy-five of the 1,714 children developed IA during follow-up.

Cohort for the Analysis of the Development of Type 1 Diabetes in Autoimmune Children

To explore associations between childhood body size, growth rates, and type 1 diabetes development, we analyzed 143 autoimmune children for whom at least 2 height and weight measurements were collected at least three months prior to type 1 diabetes diagnosis. Twenty-one children developed type 1 diabetes. These 143 IA positive children included 73 of the children who developed IA during the study, 32 who developed autoantibodies before age 2, and 39 who had autoantibodies at their first clinic visit.

Children often lose weight rapidly just prior to type 1 diabetes diagnosis. We did not want to include data that may have been influenced by the disease prodrome, rather than reflecting on a potential predictor of the disease. Therefore, we did not use the height and weight measurements collected within 3 months of type 1 diabetes diagnosis, and instead extrapolated these values based on our models, as described in the statistical analysis section below.

Statistical Analyses

In order to get an accurate picture of each child's overall growth experience, we first produced graphs of growth values for individual children, as well as population means, of height, weight, and BMI, at each age (in years). Next, we fit mixed models of the best-fitting polynomials for

the fixed effects and for the random effects of height, weight, and BMI on age for each gender. This method is described in Fitzmaurice et al(36) and an example of the use of this method can be found in Sontag et al. (37). The best-fitting mixed models produced estimates of the mean growth curves as well as best linear unbiased predictors (BLUPs) for individual subjects' growth curves with respect to height, weight, and BMI. BMI throughout childhood in this cohort was best represented by second degree polynomials in the fixed effects and random effects. Height and weight gain patterns in this cohort were linear in both the fixed and random effects.

BLUPs of individual subjects' growth curves were evaluated at each clinic visit, including records where height, weight, or BMI were missing. Plots indicated that the BLUP curves closely fit the raw data. Using BLUPs allowed us to disregard the height and weight measures within 3 months of type 1 diabetes diagnosis, and instead extrapolate these values for clinic visits close to diagnosis, when the disease process itself may be affecting body size. BLUPS also allowed us to interpolate body size values that were missing, as either height or weight was not measured in about 7% of the clinic visits. The first derivatives of the polynomial equations used to calculate the above growth curves gave BLUPs of the instantaneous growth velocities for height, weight, and BMI at each clinic visit. The instantaneous growth velocity of BMI varied over time, while the instantaneous growth velocities of height and weight were constant for each child. Cox proportional hazards models allowed us to examine the BLUPs of height, weight, BMI, and instantaneous velocity of BMI as time varying covariates for association with IA, and for association with type 1 diabetes in children with IA. Hazard Ratios were calculated for a 1 standard deviation (SD) difference in velocity. BLUPs of instantaneous height growth velocity and instantaneous weight growth velocity were analyzed as fixed covariates, because height and weight growth velocity remained constant over age. All models were adjusted for ethnicity (non-Hispanic White or other), HLA DR,DQ genotype (high-risk or not) and family history of type 1 diabetes. Analyses with type 1 diabetes as the outcome were also adjusted for the age at which the first autoantibody was detected. All statistical modeling and analyses were conducted using SAS version 9.1 (SAS institute, Cary, NC).

The term "instantaneous growth velocity" refers to growth velocity, ie, change in size per unit time, as the unit of time approaches zero. For ease of presentation, we refer to these variables simply as growth velocity rather than instantaneous growth velocity throughout the remainder of the manuscript.

Results

Height, Weight, BMI and Growth Velocity in the DAISY Cohort

As shown in cross sections of the DAISY cohort (Table 1), estimates of height and weight are higher in the older age groups. BMI is stable or slightly decreases between ages 3 and 5 years, and then is increased at age 8 years, suggestive of adiposity rebound(38). Growth velocity of BMI is negative in the 3 and 5-year olds, suggesting a slowdown of growth in BMI. In 8 year olds, the BMI growth velocity is positive, reflecting increasing growth in the older ages. The growth velocities of height and weight were similar in 3, 5 and 8 year olds.

Analysis of the Development of IA in Children at Increased Risk of Type 1 Diabetes

Seventy-five of the 1,714 DAISY children in this analysis developed IA, at a mean age of 6.6 years (Table 2). The minimum number of size measurements per child in this analysis was 2, the median was 5, and maximum was 16. Mean heights, weights and BMIs by age of children who did and did not become IA positive are presented in Supplemental Online Figure 1. Adjusting for ethnicity, HLA DR,DQ genotype and family history of type 1 diabetes, greater height growth velocity was strongly associated with IA development (Table 2). Height and

weight were also inversely associated with IA development, although the associations were weaker, particularly for weight. Height was inversely correlated with height growth velocity in these children (Pearson r: −0.09, p = 0.0007). When both height and height growth velocity were included in the model together, the estimates were HR: 0.01, CI: 0.002-0.02 for height, and HR: 5.26, CI: 3.77-7.33) for height growth velocity.

Analysis of the Development of Type 1 Diabetes in Autoimmune Children

This analysis included 143 children who had developed IA, of whom 21 developed type 1 diabetes. All children had at least 2 height and weight measurements at or after the development of IA. Those who developed type 1 diabetes had at least 2 height and weight measurements collected at least three months prior to type 1 diabetes diagnosis. The minimum number of size measurements per child in this analysis was 2, the median was 7, and maximum was 31. Mean heights, weights and BMIs by age of IA positive children who did and did not develop type 1 diabetes are presented in Supplemental Online Figure 2. The 21 children who developed diabetes had a mean IA development age of 2.32 years (compared with 5.29 years in those who had not developed diabetes during follow-up), and developed type 1 diabetes at a mean age of 6.86 years (Table 3).

In models adjusted for age at first autoantibody positive visit, ethnicity, HLA DR,DQ genotype, and family history of type 1 diabetes, greater height growth velocity was strongly associated with progression to type 1 diabetes (HR: 3.34, CI: 1.73–6.42) for a 1 SD difference in velocity, in children with autoimmunity. Height, weight, BMI, weight growth velocity, and BMI growth velocity were not associated with more rapid progression to type 1 diabetes in autoimmune children (Table 3).

Discussion

In this analysis of children at increased genetic risk for type 1 diabetes, greater height growth velocity was associated with earlier IA development in healthy children, and was even more strongly associated with more rapid progression to type 1 diabetes in autoimmune children. Shorter height was weakly associated with IA development, but was not associated with progression to type 1 diabetes in IA positive children. Weight, BMI, and growth velocities of weight and BMI were not associated with either IA development or progression to type 1 diabetes.

Many of the previous studies had used SD scores for height, weight, and BMI, calculated from general population data for the analysis of association with type 1 diabetes, using a case-control design. However, since the DAISY cohort is selected to be at increased genetic risk for type 1 diabetes, and therefore is not expected to be representative of the general population, and because we have an excellent comparison group embedded within our cohort (i.e., the higher risk children who did not develop the outcome), it was not necessary to calculate SD scores to examine the association between body size and the development of islet autoimmunity and type 1 diabetes. Prospective follow-up of our cohort produced longitudinal data on size, which gave us the opportunity to examine *velocity* of growth. We note that our results regarding height velocity are consistent with what has been reported, even though other studies had used other statistical approaches and had used SD scores for their measure of height. Our analyses extend the previous findings by suggesting that the *velocity* of linear growth, rather than attained height or change in height (growth), may be the operative factor.

The mean difference in height growth velocity between DAISY children who did and did not develop IA is 0.18 cm per year (Table 2). It is not clear whether an increase in growth velocity of this small of a magnitude is biologically relevant. However, the difference in height growth velocity between those autoimmune children who did and did not develop diabetes is much

larger. IA-positive children that subsequently developed type 1 diabetes had a mean height growth velocity that was 0.54 cm per year greater than IA-positive DAISY children that did not develop type 1 diabetes. The consistency of the associations between greater height growth velocity and more rapid development of both IA and type 1 diabetes is intriguing. Our findings may offer preliminary support for the Overload Hypothesis (7), which suggests that high growth rate may exacerbate the autoimmune process via beta cell overload. A causal link between rapid linear growth rate and greater risk of IA and subsequent type 1 diabetes development could be postulated. However, we acknowledge that greater height growth velocity may simply be a side effect of the underlying biologic mechanisms that drive the autoimmune disease process.

One potential explanation for our findings is that increased linear growth velocity, perhaps associated with higher levels of IGF-1, may result in greater insulin secretion and insulin resistance, which have also been shown to be associated with greater IGF-1 levels (34;39; 40). Insulin resistance may increase demands on the beta cell, and has been shown to precede type 1 diabetes development (41), especially when coupled with reduced insulin secretion (42). However, there is currently little evidence supporting a role of insulin resistance in predicting islet autoimmunity. Finally, we cannot rule out a primary increase in insulin levels as the explanation for the more rapid linear growth. Chronic hyperinsulinemia, perhaps due to a genetic tendency for hyperinsulinemia, would result both in greater growth rate (43) and greater demands for insulin from the beta cell. The class III allele of the *INS* gene, which is considered to be protective against type 1 diabetes (44), is also associated with lower BMI and lower fat mass in children with rapid infant growth (45), possibly through lower insulin secretion. Thus, exploration of the role of the insulin (*INS*) gene and its effect on insulin secretion may further our understanding of the association between rapid linear growth velocity and progression through the autoimmune disease process. In considering potential genetic influences on the observed associations between increased linear growth velocity and the autoimmune disease process, it is useful to note that statistical adjustment for HLA and family history did not materially affect these associations.

While a variety of biologic mechanisms may be responsible for greater demand on the beta cell to produce insulin, the mechanism by which increased beta cell stress may lead to IA and type 1 diabetes may be more straight-forward. Greater beta cell activity in response to high glucose concentrations has been linked with increased beta cell expression of the GAD antigen (46). Also, more active beta cells have been shown to be more susceptible to cytokine damage (47;48). Thus, increasing beta cell activity, due to any cause, may trigger or exacerbate an autoimmune disease process. We are limited in this exploration by our lack of measurements on IGF-1, growth hormone, insulin, insulin resistance and beta cell function in DAISY children.

Our finding that shorter height was a weak risk factor for IA development was unexpected in light of the previously described associations between greater height and type 1 diabetes development(19;20;22;24;25). One possible explanation of this unexpected finding is that shorter children may have experienced fetal or early life growth restriction, and may be more likely to grow more rapidly than their peers. Therefore, shorter height may simply proxy greater height growth velocity in the analysis of healthy children for the development of IA. We note that shorter height was not associated with earlier type 1 diabetes development in autoimmune children, which suggests that the biologic mechanisms represented by shorter height may only be important at the earliest stages of the disease.

Childhood obesity and rapid weight gain, as measured by childhood BMI, weight growth velocity, and BMI growth velocity, were not associated with earlier IA development in healthy children, or more rapid progression to type 1 diabetes in autoimmune children. These findings run contrary to previous reports (18;20-23;25-28) which suggested that increased height,

weight, and/or BMI may be associated with type 1 diabetes or islet autoimmunity development. It is possible that the effects of obesity (weight or BMI) on the autoimmune disease process might be more evident in children without genetic risk for type 1 diabetes, and therefore may not be detectable in DAISY's higher risk population. Also, the majority of these studies found associations with size or growth in very young ages, which was not the population of the current study. Our results suggest that the association with height velocity and type 1 diabetes is present at later ages in childhood. We are not able to make any inferences regarding the role of height growth velocity in the risk of islet autoimmunity and type 1 diabetes in children under the age of 2 years.

In conclusion, greater height growth velocity is either directly involved, or correlated with unmeasured factors involved, in the natural evolution from genetic susceptibility to autoimmunity and type 1 diabetes development in pre-pubertal children. Our results support further exploration of the biologic mechanisms underlying the association between rapid linear childhood growth rate, IA development, and progression to type 1 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BLUP	best linear unbiased predictors
DAISY	Diabetes Autoimmunity Study in the Young
IA	islet autoimmunity
IA2	protein tyrosine phosphatase islet antigen 2

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Table 1

Childhood Size and Growth Velocities in 3, 5 and 8 year old children in the Diabetes Autoimmunity Study in the Young (DAISY)

	Age 3 (Mean (SD))	Age 5 (Mean (SD))	Age 8 (Mean (SD))
	N = 1,319	N = 1,140	N = 796
Height (cm)[a]	97.06 (4.25)	110.94 (4.78)	130.86 (5.95)
Weight (kg)[a]	14.78 (1.68)	20.34 (2.95)	29.44 (5.90)
BMI (kg/m^2)[a]	16.04 (1.08)	15.85 (1.42)	16.83 (2.38)
Height growth velocity (change in cm per year)	6.84 (0.54)	6.75 (0.56)	6.63 (0.57)
Weight growth velocity (change in cm per year)	2.78 (0.84)	2.81 (0.91)	2.96 (1.01)
BMI growth velocity (change in $kg / m^2 \cdot year$)	−0.26 (0.29)	0.08 (0.32)	0.58 (0.47)

[a] Best linear unbiased predictor (BLUP) estimates of height, weight, or BMI.

Table 2

Analysis of Body Size and Growth in the Development of IA in Children at Increased Risk of Type 1 Diabetes

	Developed Islet Autoimmunity (N = 75)	Did not Develop Islet Autoimmunity (N = 1,639)	Hazard Ratio (95% Confidence Interval)
Variable	**% Yes (N)**	**% Yes (N)**	
High-risk HLA DR,DQ genotype	34.7 (26)	19.5 (319)	2.13 (1.32 – 3.42)
Family history of type 1 diabetes	57.3 (43)	48.0 (786)	1.44 (0.91 – 2.28)
Female	53.3 (40)	47.4 (777)	1.29 (0.82 – 2.04)[a]
Non-Hispanic White Ethnicity	80.0 (60)	75.6 (1,239)	1.12 (0.63 – 2.00)[a]
Maternal education > 12 years (N = 1,656)	83.8 (62)	78.6 (1,244)	1.36 (0.73 – 2.52)[a]
Annual Income ≥ $30,000 (N = 1,617)	76.4 (55)	76.9 (1,188)	1.01 (0.58 – 1.74)[a]
	Mean (SD)	**Mean (SD)**	
Age at first autoantibody positive visit or most recent visit (yrs)	6.63 (2.39)	7.91 (2.71)	N/A
Height (cm)[b]	N/A[c]	N/A[c]	0.34 (0.16–0.72) [d]
Weight (kg)[b]	N/A[c]	N/A [c]	0.61 (0.39–0.98) [d]
BMI (kg/m^2)[b]	N/A[c]	N/A[c]	0.99 (0.80–1.21) [d]
Height growth velocity (change in cm / year)	6.96 (0.45)	6.78 (0.55)	1.63 (1.31–2.05)[d]
Weight growth velocity (change in kg / year)	2.80 (0.70)	2.80 (0.87)	0.88 (0.69–1.11)[d]
BMI growth velocity (change in kg / m^2 · year)	N/A[c]	N/A[c]	0.88 (0.64–1.21) [d]

[a] Hazard ratios adjusted for HLA DR,DQ genotype and family history of type 1 diabetes

[b] Best linear unbiased predictor (BLUP) estimates of height, weight, or BMI.

[c] Not applicable due to the time-varying nature of the data. See Table 1 for details regarding these variables.

[d] Hazard ratios for a 1 standard deviation (SD) difference, adjusted for ethnicity, HLA DR,DQ genotype, and family history of type 1 diabetes. The standard deviations for height, weight, BMI, height growth velocity, weight growth velocity and BMI growth velocity were 17.84, 8.67, 1.99, 0.57, 0.93, and 0.57, respectively.

Table 3

Analysis of Body Size and Growth in the Development of Type 1 Diabetes in Autoimmune Children at Increased Risk of Type 1 Diabetes

	Progressed to Type 1 Diabetes (N = 21)	Did Not Progress to Type 1 Diabetes (N = 122)	Hazard Ratio (95% Confidence Interval)
Variable	**% Yes (N)**	**% Yes (N)**	
High-risk HLA DR,DQ genotype	52.4 (11)	27.1 (33)	2.14 (0.91 – 5.06)
Family history of type 1 diabetes	71.4 (15)	52.5 (64)	2.02 (0.78 – 5.23)
Female	47.6 (10)	48.4 (59)	1.51 (0.62 – 3.64)[a]
Non-Hispanic White Ethnicity	85.7 (18)	82.0 (100)	0.54 (0.15 – 1.90) [a]
Maternal education >12 years (N = 138)	71.4 (15)	81.2 (95)	0.81 (0.30 – 2.18) [a]
Annual Income ≥ $30,000 (N = 133)	75.0 (15)	77.9 (88)	0.60 (0.19 – 1.93) [a]
	Mean (SD)	**Mean (SD)**	
IA development age (yrs)	2.32 (1.78)	5.29 (2.97)	0.84 (0.64 – 1.09) [a]
Age at type 1 diabetes development or most recent visit (yrs)	6.86 (2.12)	8.80 (2.58)	N/A
Height (cm) [b]	N/A[c]	N/A [c]	0.98 (0.22–4.36) [d]
Weight (kg) [b]	N/A [c]	N/A [c]	0.88 (0.33–2.32) [d]
BMI (kg/m^2) [b]	N/A [c]	N/A [c]	1.12 (0.70–1.81) [d]
Height growth velocity (change in cm / year)	7.16 (0.49)	6.62 (0.64)	3.34 (1.73–6.42) [d]
Weight growth velocity (change in kg / year)	2.74 (1.34)	3.17 (1.22)	1.01 (0.58–1.77) [d]
BMI growth velocity (change in kg / m^2 · year)	N/A [c]	N/A [c]	1.28 (0.79–2.08) [d]

[a] Hazard ratios adjusted for age at first autoantibody positive visit, HLA DR,DQ genotype and family history of type 1 diabetes

[b] Best linear unbiased predictor (BLUP) estimates of height, weight, or BMI.

[c] Not applicable due to the time-varying nature of the data. See Table 1 for details regarding these variables.

[d] Hazard ratios for a 1 standard deviation (SD) difference, adjusted for age at first autoantibody positive visit, ethnicity, HLA DR,DQ genotype and family history of type 1 diabetes. The standard deviations for height, weight, BMI, height growth velocity, weight growth velocity and BMI growth velocity were 18.19, 9.26, 2.05, 0.68, 1.14, and 0.58, respectively.