# Distinct Growth Phases in Early Life Associated With the Risk of Type 1 Diabetes: The TEDDY Study

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH


## OBJECTIVE

**This study investigates two-phase growth patterns in early life and their association with development of islet autoimmunity (IA) and type 1 diabetes (T1D).**

## RESEARCH DESIGN AND METHODS

**The Environmental Determinants of Diabetes in the Young (TEDDY) study followed 7,522 genetically high-risk children in Sweden, Finland, Germany, and the U.S. from birth for a median of 9.0 years (interquartile range 5.7–10.6) with available growth data. Of these, 761 (10.1%) children developed IA and 290 (3.9%) children were diagnosed with T1D. Bayesian two-phase piecewise linear mixed models with a random change point were used to estimate children's individual growth trajectories. Cox proportional hazards models were used to assess the effects of associated growth parameters on the risks of IA and progression to T1D.**

## RESULTS

**A higher rate of weight gain in infancy was associated with increased IA risk (hazard ratio [HR] 1.09 [95% CI 1.02, 1.17] per 1 kg/year). A height growth pattern with a lower rate in infancy (HR 0.79 [95% CI 0.70, 0.90] per 1 cm/year), higher rate in early childhood (HR 1.48 [95% CI 1.22, 1.79] per 1 cm/year), and younger age at the phase transition (HR 0.76 [95% CI 0.58, 0.99] per 1 month) was associated with increased risk of progression from IA to T1D. A higher rate of weight gain in early childhood was associated with increased risk of progression from IA to T1D (HR 2.57 [95% CI 1.34, 4.91] per 1 kg/year) in children with first-appearing GAD autoantibody only.**

## CONCLUSIONS

**Growth patterns in early life better clarify how specific growth phases are associated with the development of T1D.**


Type 1 diabetes (T1D) is a common pediatric chronic disease and is preceded by a preclinical period of islet autoimmunity (IA) in the presence of islet autoantibodies against GAD (GADA), IA2 (IA2A), and/or insulin (IAA). IA commonly develops as early as infancy, with a peak incidence at ~1 to 2 years of age (1–3). The Environmental Determinants of Diabetes in the Young (TEDDY) study reported that HLA-DR-DQ and age are strongly associated with the specific islet autoantibody that appears at the initial seroconversion. The majority of children who seroconvert develop either IAA or GADA as a single first-appearing autoantibody. Over time, these children may remain single autoantibody positive, develop other autoantibody(s), or revert to autoantibody negative. IAA generally appears at an earlier age than GADA, and the order of appearance of the autoantibodies is related to HLA-DR-DQ genotypes (1).

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*A complete list of the members of the TEDDY Study Group can be found in the Supplementary Data online.

Factors in early life likely play an important role in the initiation of IA, and excess growth is a potential candidate, as proposed by the accelerator hypothesis (4) and the overload hypothesis (5). The accelerator hypothesis proposes that excess weight gain and associated insulin resistance accelerate β-cell apoptosis and thereby drive autoimmunity in genetically susceptible children. The overload hypothesis suggests that metabolic overload of the β-cell including insulin resistance might be due to a high growth rate.

Several retrospective studies have reported associations between increased linear growth and weight gain in childhood, particularly in the first 2 years of life, and later onset of T1D (6–8). Longitudinal growth data collected from birth in prospective studies provide an opportunity to study the role of growth in the initiation of IA and the progression to T1D. Several prospective studies reported associations between growth in early life and the risk of IA (9–12). The Australian Baby Diab Study reported that weight SD score (SDS) at 2 years was associated with the risk of IA (9). The U.S. Diabetes Autoimmunity Study in the Young (DAISY) of children aged >2 years showed that height growth velocity, but not weight or BMI growth velocity, was associated with the risks of IA and progression to T1D (10). Moreover, the German BABYDIAB and BABYDIET studies reported that a younger age at infant BMI peak was associated with the risk of IA (13). Previously, the TEDDY study investigated weight and height SDSs at several specific ages during the first 4 years of age and found that the weight SDS at 1 year of age was associated with the risk of IA (12). These findings give evidence that weight gain in very early life and height growth velocity in childhood are associated with the risk of IA. However, there is still no clear picture of whether or how the whole growth trajectory in early life is associated with the development of IA/T1D. This is mainly due to the lack of growth data in infancy and the lack of complex modeling techniques for longitudinal growth data in early life. By modeling of the entire growth trajectory, the growth patterns can be easily identified and help pinpoint the timing of a potential disturbance or exposure.

In this study, we investigated detailed growth data in early life and assessed their relationship with the development of IA and the progression to T1D in the TEDDY study. We modeled growth trajectories of weight and height in early life in two phases: fast growth in infancy and relatively slow growth subsequently in early childhood (Fig. 1). We used Bayesian two-phase piecewise linear mixed models with a random change point (14) to estimate a child's individual-level random effects (prechange slope, postchange slope, and change point), which correspond to the individual-specific growth parameters (growth rate in infancy, growth rate in early childhood, and age at the phase transition) (Fig. 1*B*). The estimated change point is the point or time period in which the child transitioned from the phase of rapid infancy growth to another phase of slower childhood growth. Then, we assessed whether these growth parameters were associated with the risk of IA and the risk of progression from IA to T1D.

## RESEARCH DESIGN AND METHODS

### Participants

TEDDY is a prospective cohort study with the aim to identify environmental causes of T1D. The study included six clinical research centers: three in the U.S. (Colorado, Georgia/Florida, and Washington) and three in Europe (Finland, Germany, and Sweden). Written informed consents were obtained for all study participants from a parent or a primary caretaker, separately, for genetic screening and participation in the prospective follow-up, beginning at birth. The high-risk genotypes selected for inclusion for participants screened from the general population were as follows: DRB1*04-DQA1*03-DQB1*03:02/DRB1*03-DQA1*05-DQB1*02:01 (DR3/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*03:02 (DR4/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*08-DQA1*04-DQB1*04:02 (DR4/8), and DRB1*03-DQA1*05-DQB1*02:01/DRB1*03-DQA1*

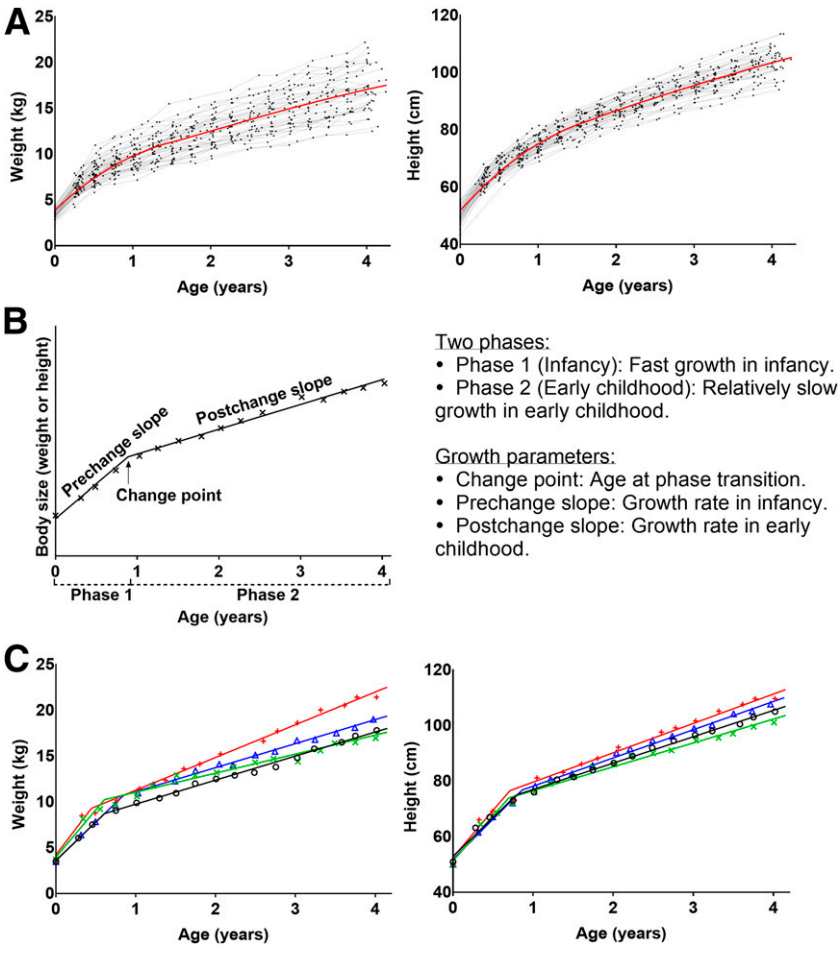


**Figure 1**—Growth in early life. *A*: Trajectories of body size measurements of 50 randomly selected TEDDY subjects and the mean (loess) curves for weight and height. *B*: Description of the two-phase piecewise linear modeling of growth in early life. *C*: Fitted growth curves of weight and height from the Bayesian two-phase piecewise linear modeling for four randomly selected subjects.

05-DQB1*02:01 (DR3/3). Additional study inclusion genotypes for first-degree relatives of a subject with T1D were: DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*02:02 (DR4/4b), DRB1*04-DQA1*03-DQB1*03:02/DRB1*01-DQA1*01-DQB1*05:01 (DR4/1), DRB1*04-DQA1*03-DQB1*03:02/DRB1*13-DQA1*01-DQB1*06:04 (DR4/13), DRB1*04-DQA1*03-DQB1*03:02/DRB1*09-DQA1*03-DQB1*03:03 (DR4/9), and DRB1*03-DQA1*05-DQB1*02:01/DRB1*09-DQA1*03-DQB1*03:03 (DR3/9) (15). The HLA-DR-DQ genotype abbreviations shown in parentheses will be used throughout this article. A total of 8,676 children were enrolled and followed prospectively from 3 months to 15 years for measurements of weight and height (length before 2 and standing height after 2 years of age), and blood samples were drawn for measurements of islet autoantibodies with study visits every 3 months until 4 years of age and every 3 or 6 months thereafter, depending on autoantibody positivity. All children who were persistently positive for any autoantibody were followed every 3 months until 15 years of age or onset of T1D. In the analyses, 7,522 children were included after exclusion of 120 children whose HLA eligibility could not be confirmed at a repeated genotyping at 9 months of age, 54 children whose islet autoantibody results were indeterminate, and 980 children with $<4$ growth measurements in the first 4 years of life. The children were followed from birth for a median of 9.0 years (interquartile range [IQR] 5.7–10.6) (Fig. 2*A*).

### Islet Autoantibodies and T1D

Autoantibodies to IAA, GADA, or IA2A were measured in two laboratories by radiobinding assays (16,17). In the U.S., all sera were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado; in Europe, all sera were assayed at the University of Bristol (Bristol, U.K.). Both laboratories demonstrated high sensitivity and specificity as well as concordance (18). All positive and 5% of negative samples were retested in the other reference laboratory and deemed confirmed, if concordant. IA was defined as confirmed positive autoantibodies to IAA, GADA, or IA2A in at least two consecutive samples by both laboratories. T1D was diagnosed using American Diabetes Association criteria (19).

### Statistical Analyses

The children's weight and height trajectories were analyzed using Bayesian two-phase piecewise linear mixed models with a random change point (14). The models were estimated for girls and boys separately. The estimated individual-level random effects (prechange slope, postchange slope, and change point) (Fig. 1*B*) correspond to the individual-specific growth parameters (growth rate in infancy, growth rate in early childhood, and age at the phase transition).

Time-to-event analyses using multiple Cox proportional hazards (PH) models were performed to examine the growth parameters (weight and height separately) related to the risk of IA, IAA, or

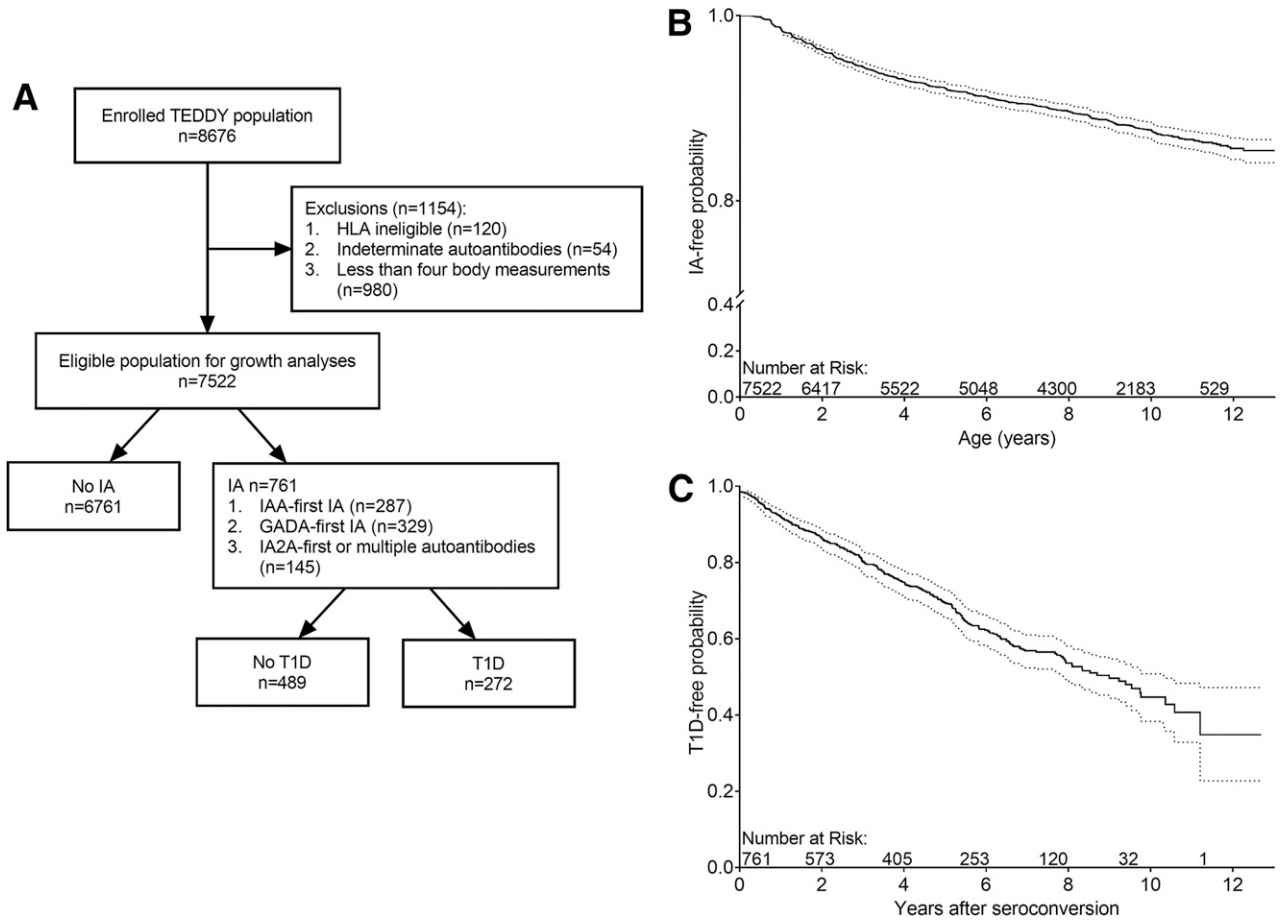


**Figure 2**—Study cohort. *A*: Flow chart of the TEDDY cohort and the study cohort. *B*: Survival curve of the development of IA. *C*: Survival curve of progression to T1D from initial seroconversion.

GADA as the first-appearing autoantibody and progression to T1D. The age at the development of IA was the age at the initial of two or more consecutive positive tests. The analyses of progression to T1D included children who developed persistent IA before the onset of T1D. Duration was calculated from the time at first IA positivity to the diagnosis date of T1D or date of last contact to assess T1D status for those who did not develop T1D. The magnitude of the associations was described by hazard ratios (HRs) with 95% CIs. Gestational age–adjusted birth measurement (birth weight in weight models and birth length in height models), HLA-DR-DQ genotype, family history of T1D, duration of exclusive breastfeeding, sex, and country of residence were adjusted for in the Cox PH models. The gestational age–adjusted birth measurements (birth weight or birth length) were the residuals calculated by linear regression of birth measurements on gestational ages for boys and girls separately. In addition, age at IA and type of first-appearing autoantibody (IAA, GADA, or multiple autoantibodies) were adjusted for in the analysis of progression to T1D, in which a small number of children with only IA2A autoantibody were grouped with children with multiple autoantibodies at initial seroconversion. Subgroup analyses stratified by the type of first-appearing autoantibody were also performed.

Sensitivity analyses with additional adjustments for previously identified dietary and genetic risk factors in the TEDDY study (20–24) were performed. Specifically, two dietary factors (early probiotic use and infant formula type in the first 3 months of life), eight T1D-associated non-HLA single nucleotide polymorphisms (SNPs) (rs1004446 in *INS*, rs10517086, rs2476601 in *PTPN22*, rs2816316 in *RGS1*, rs2292239 in *ERBB3*, rs3184504 in *SH2B3*, rs4948088 in *COBL*, and rs12708716 in *CLEC16A*), and two SNPs in complement genes (rs1143678 and rs4597342 in *ITGAM*) were adjusted for in the analysis of IA, while four SNPs (rs1004446 in *INS*, rs10517086, rs1534422, and rs2327832 in *TNFAIP3*) were adjusted for in the analysis of progression to T1D.

The Bayesian two-phase piecewise linear mixed models with a random change point were estimated using the WinBUGS 1.4.3 software (25). All of the other analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

## RESULTS

As of February 2018, the median (IQR) follow-up time of the last clinic visit for the 7,522 children was 9.0 (5.7–10.6) years. A total of 761 (10.1%) children developed one or more persistent autoantibodies (GADA, IAA, or IA2A) at the median age of 3.0 years (IQR 1.5–6.0), and 3.9% (290/7,522) developed T1D at the median age of 5.5 years (IQR 3.0–8.2) (Fig. 2*B*). Out of the 761 children with IA, 287 (37.7%) children had IAA only (IAA-first), 329 (43%) children had GADA only (GADA-first), 20 (2.6%) children had IA2A only, and 125 (16.4%) children had multiple autoantibodies at initial seroconversion. Of these children, 35.7% (272 out of 761) progressed to T1D (Fig. 2*C*). The characteristics of the children by the status of IA (IA negative, any IA, IAA-first IA, and GADA-first IA) and the children diagnosed with T1D are presented in Supplementary Table 1.

### Growth Parameters and T1D

The details of the children's growth parameters by the status of IA (IA negative, any IA, IAA-first IA, and GADA-first IA) and T1D are presented in Supplementary Table 1, and additional details are provided in Supplementary Figs. 1–4. The fitted growth curves and measures for four randomly selected subjects are plotted in Fig. 1*C*.

A higher rate of weight gain in infancy was associated with an increased IA risk adjusted for gestational age–adjusted birth weight, country of residence, sex, duration of exclusive breastfeeding, family history of T1D, and HLA DR-DQ genotype (HR 1.09 [95% CI 1.02, 1.17] per 1 kg/year increase; $P = 0.015$) (Fig. 3*A* and Supplementary Table 2). The effect of weight growth rate in infancy appeared to be most associated with the risk of GADA-first IA (HR 1.15 [95% CI 1.04, 1.28] per 1 kg/year increase; $P = 0.009$). In addition, gestational age–adjusted birth weight was also positively associated with the risk of IA (HR 1.19 [95% CI 1.02, 1.41] per 1 kg increase; $P = 0.031$) and the risk of GADA-first IA (HR 1.39 [95% CI 1.09, 1.78] per 1 kg increase; $P = 0.008$) (Fig. 3*A* and Supplementary Table 2).

Height, but not weight, growth parameters were strongly associated with the risk of progression from initial IA seroconversion to T1D, adjusted for birth measurement, country, sex, family history of T1D, HLA DR-DQ genotype, age at IA, and type of first-appearing autoantibody (Fig. 4 and Supplementary Table 3). A height growth pattern with a lower rate in infancy (HR 0.79 [95% CI 0.70, 0.90] per 1 cm/year increase; $P < 0.001$), a higher rate in early childhood (HR 1.48 [95% CI 1.22, 1.79] per 1 cm/year increase; $P < 0.001$), and a younger age at the phase transition (HR 0.76 [95% CI 0.58, 0.99] per month increase; $P = 0.044$) were associated with an increased risk of progression from IA to T1D (Fig. 4*B* and Supplementary Table 3).

Subgroup analysis stratified by the type of first-appearing autoantibody showed similar associations between the two height growth rates and the risk of progression to T1D in those who had GADA only or multiple autoantibodies at the time of initial seroconversion (Fig. 4*B* and Supplementary Table 3). In addition, gestational age–adjusted birth weight and the weight growth rate in early childhood were positively associated with the risk of progression from IA to T1D (HR 2.04 [95% CI 1.03, 4.04] per 1 kg increase, $P = 0.040$; HR 2.57 [95% CI 1.34, 4.91] per 1 kg/year increase, $P = 0.004$) in children who had GADA only at the time of initial seroconversion (Fig. 4*A* and Supplementary Table 3).

The results were not affected in the sensitivity analyses with the additional adjustments for previously identified risk factors in the TEDDY study (data not shown), in which two dietary factors (early probiotic use and infant formula type in the first 3 months of life), eight T1D-associated non-HLA SNPs (rs1004446 in *INS*, rs10517086, rs2476601 in *PTPN22*, rs2816316 in *RGS1*, rs2292239 in *ERBB3*, rs3184504 in *SH2B3*, rs4948088 in *COBL*, and rs12708716 in *CLEC16A*), and two SNPs in complement genes (rs1143678 and rs4597342 in *ITGAM*) were adjusted for in the analysis of IA, while four SNPs (rs1004446 in *INS*, rs10517086, rs1534422, and rs2327832 in *TNFAIP3*) were adjusted for in the analysis of progression to T1D. Additional analyses by dichotomizing the growth parameters using country- and sex-specific tertiles showed consistent conclusions on the reported associations (data no shown) with an additional association between weight growth rate in early childhood and the risk of progression to T1D overall.

## CONCLUSIONS

In this large international multicountry cohort of 7,522 children at high genetic risk for T1D, we modeled growth in early

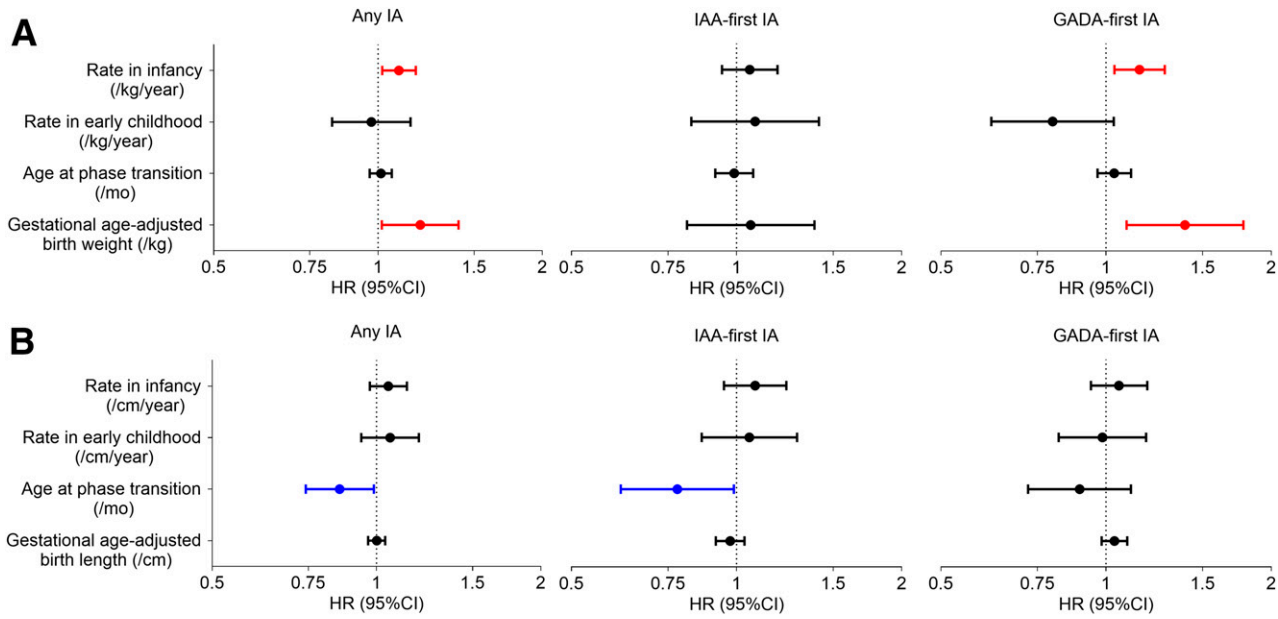


**Figure 3**—Forest plots of HR and 95% CI from multiple Cox PH regression analyses of effect of weight (*A*) and height (*B*) growth parameters, including gestational age–adjusted birth measurement, on the risk of IA, IAA-first IA, and GADA-first IA. Duration of exclusive breastfeeding, HLA-DR-DQ genotype, family history of T1D, sex, and country of residence were included in the Cox models. mo, months.

life using two distinct phases. Growth transited from a fast phase (infancy) to a relatively slow phase (early childhood) at ~7–10 months of age. The weight growth rate in infancy and gestational age–adjusted birth weight were positively associated with the risk of IA and appeared to associate most with the risk of GADA-first IA. Furthermore, the weight growth rate in early childhood and gestational age–adjusted birth weight were associated with the risk of progression from IA to T1D in children with GADA only at initial seroconversion. A lower height growth rate in infancy and a higher height growth rate in early childhood were associated with an increased risk of progression from IA to T1D. The two height growth rates appeared to be more associated with the progression from IA to T1D in children who had GADA only or multiple autoantibodies at initial seroconversion.

Our finding that birth weight and the weight growth rate in infancy, but not in early childhood, were positively associated with the risk of IA is consistent with the findings from our previous study (12) and the Australian Baby Diab Study (9), in which weight at a younger age predicted IA more than weight at an older age. Together with our previous finding of a weak association between weight SDS and the risk of IA (12) in the first 4 years of

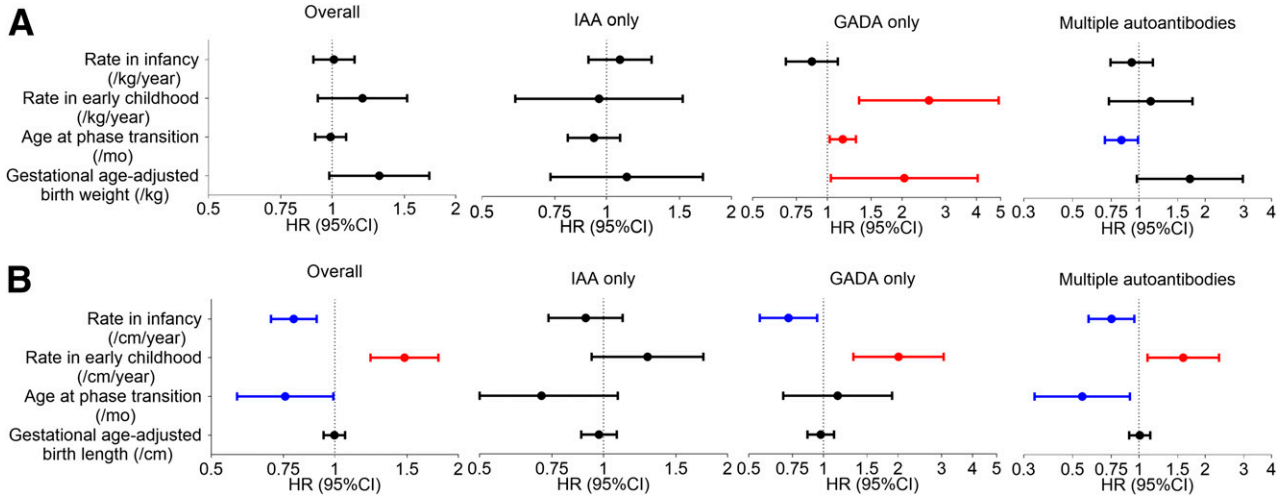


**Figure 4**—Forest plots of HR and 95% CI from multiple Cox PH regression analyses of effect of weight (*A*) and height (*B*) growth parameters, including gestational age–adjusted birth measurement, on the risk of progression to T1D from IA and from subgroup analysis stratified by the type of first-appearing autoantibody (IAA only, GADA only, or multiple autoantibodies). Duration of exclusive breastfeeding, age at the development of IA, type of first-appearing autoantibody (if applicable), HLA-DR-DQ genotype, family history of T1D, sex, and country of residence were included in the Cox models. mo, months.

life, it suggests that birth weight, the weight growth rate in infancy, and the resulting weight over time influence the development of IA. Our finding that the height growth rate in early childhood was associated with the risk of progression to T1D is consistent with the U.S. DAISY study (10), though growth data before 2 years of age were not assessed in the DAISY study. However, we did not confirm the association reported in DAISY that the height growth rate in early childhood increased the risk of IA (10).

Growth in children is directly related to nutrient intake (26) and a marker of metabolic (dys)function. Increased growth is glucose dependent and requires greater insulin secretion. Historically, it has been suggested that an inverse relationship exists between birth weight and diabetes risk, with a period of early rapid postnatal weight gain (27). This has subsequently led to the suggestion that prenatal factors may influence risk of T1D. In this study, we found that both higher birth weight and increased weight gain in infancy were associated with the risk of IA and, in particular, with the risk of IA with GADA as a first-appearing autoantibody. Higher birth weight with increased weight gain in early childhood was also associated with an increased risk of progression to T1D in those who developed GADA first. This provides evidence for the overload hypothesis in which excess growth leads to IA and the progression to T1D (4). Such rapid growth in infancy and early childhood prior to IA or T1D may indicate a marker of metabolic dysregulation by providing an exposure window to help identify potential triggers, such as dietary feeding patterns, related to disease development. Alternatively, it could be an early indication or symptom of disease onset. GADA autoimmunity may cluster with growth dysregulation in those with a greater risk of progressing to clinical T1D. GADA positivity has been linked to reduced insulin secretory capacity, a marker of impaired β-cell function in adults without diabetes (28). However, in the Type 1 Diabetes Prediction and Prevention (DIPP) Study, insulin secretion as measured by first-phase insulin responses was equally compromised in children who had GADA, IAA, or IA2A as the first-appearing autoantibody as compared with those without these autoantibodies (29,30).

TEDDY is a large prospective study covering 4 countries with longitudinal collection of growth data every 3 months from birth to 4 years of age, which provides a great opportunity to examine the role of growth in the development of IA and T1D using the entire growth trajectory in early life. Yet, there are limitations. The accelerator hypothesis suggests that excess weight gain and associated insulin resistance accelerate β-cell apoptosis. However, insulin resistance was not measured in the TEDDY study, and we could not test the accelerator hypothesis to examine whether insulin resistance was in the causal pathway. In the DIPP study, no difference was found in insulin sensitivity (as measured by HOMA index) between children with or without biochemical autoantibodies, even though insulin secretory capacity was lower in autoantibody-positive children (29). Growth hormone, IGF-1, and IGF-binding protein-3 (31,32) have been suggested to associate with T1D and possibly be in the causal pathway; however, these were not measured in TEDDY. Further studies to investigate insulin resistance, insulin secretory capacity, growth hormone, and IGFs at critical time points such as at birth, at 9 months, and at a later age regarding risk of IA and T1D are needed to clarify both the timing and the role that these factors play in the putative causal pathway. Another limitation of the study is that only weight and height were considered, but not BMI in the first 4 years of life because BMI is usually not calculated until 2 years of age. Insulin resistance as an accelerator for progression to T1D may have a greater impact in older children, and the growth pattern during puberty may be different. The children in this study are still young, with a median age of 10.4 years, and will be followed until 15 years of age. It has been reported that the growth trajectory has a childhood BMI rebound (13,14,33); thus, further analyses considering the BMI trajectory at an older age in relation to the clinical onset of T1D would be of great interest and evaluated as the data become available.

In this study, we modeled growth in early life using two distinct growth phases, which is novel and clarified that weight growth in infancy and height growth in early childhood associated with the development of IA and progression to T1D, respectively. Moreover, we assessed whether growth patterns were different depending on the first-appearing autoantibody of IAA or GADA. Our findings showed that overall weight and height are associated with IA and progression to T1D at different phases in early growth, and this effect was more pronounced in those who developed GADA as a first-appearing autoantibody. It is well known that growth is not linear, and during certain time periods in early life, it follows distinct patterns, such as the time from birth to 6 years. The pattern of infancy growth, phase transition, and childhood growth may serve as a surrogate of perinatal programming, similar to catch-up growth. Identifying the distinct growth patterns and age of transition from one growth phase to another may provide a rough time period to assess environmental triggers and other viable biomarkers associated with the T1D prodrome.

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**Author Contributions.** All authors attest to meeting International Committee of Medical Journal Editors uniform requirements for authorship by making substantial contributions to conception and design of this manuscript; acquisition, analysis, and interpretation of the data; drafting or revising the manuscript for intellectual content; and giving final approval of the published version. X.L. proposed and performed the analysis, interpreted the results, and wrote the manuscript. K.V. provided input on the interpretation of the results and reviewed and edited the manuscript. Y.H. performed the analysis and reviewed and edited the manuscript. H.E.L. reviewed and edited the manuscript. J.T., A.G.Z., J.-X.S., M.R., W.A.H., B.A., and J.P.K.

designed the study and reviewed and edited the manuscript. X.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Parts of this study were presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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