Heterogeneity of DKA Incidence and Age-Specific Clinical Characteristics in Children Diagnosed With Type 1 Diabetes in the TEDDY Study

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OBJECTIVE

The Environmental Determinants of Diabetes in the Young (TEDDY) study is uniquely capable of investigating age-specific differences associated with type 1 diabetes. Because age is a primary driver of heterogeneity in type 1 diabetes, we sought to characterize by age metabolic derangements prior to diagnosis and clinical features associated with diabetic ketoacidosis (DKA).

RESEARCH DESIGN AND METHODS

The 379 TEDDY children who developed type 1 diabetes were grouped by age at onset (0–4, 5–9, and 10–14 years; *n* = 142, 151, and 86, respectively) with comparisons of autoantibody profiles, HLAs, family history of diabetes, presence of DKA, symptomatology at onset, and adherence to TEDDY protocol. Time-varying analysis compared those with oral glucose tolerance test data with TEDDY children who did not progress to diabetes.

RESULTS

Increasing fasting glucose (hazard ratio [HR] 1.09 [95% CI 1.04–1.14]; *P* = 0.0003), stimulated glucose (HR 1.50 [1.42–1.59]; *P* < 0.0001), fasting insulin (HR 0.89 [0.83–0.95]; *P* = 0.0009), and glucose-to-insulin ratio (HR 1.29 [1.16–1.43]; *P* < 0.0001) were associated with risk of progression to type 1 diabetes. Younger children had fewer autoantibodies with more symptoms at diagnosis. Twenty-three children (6.1%) had DKA at onset, only 1 (0.97%) of 103 with and 22 (8.0%) of 276 children without a first-degree relative (FDR) with type 1 diabetes (*P* = 0.008). Children with DKA were more likely to be nonadherent to study protocol (*P* = 0.047), with longer duration between their last TEDDY evaluation and diagnosis (median 10.2 vs. 2.0 months without DKA; *P* < 0.001).

CONCLUSIONS

DKA at onset in TEDDY is uncommon, especially for FDRs. For those without familial risk, metabolic monitoring continues to provide a primary benefit of reduced DKA but requires regular follow-up. Clinical and laboratory features vary by age at onset, adding to the heterogeneity of type 1 diabetes.

Worldwide, >1.1 million children and adolescents are estimated to have type 1 diabetes, with >132,000 new cases each year (1). β-cell dysfunction, insulinopenia, and metabolic derangement are known pathophysiologic disturbances of this disease, with the most severe presentation, diabetic ketoacidosis (DKA), occurring in more

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than a third of newly diagnosed pediatric patients (2,3). Following islet autoantibody seroconversion, metabolic changes have been demonstrated to occur in the months and years prior to diabetes onset (4–10). Therefore, early glucose abnormalities (e.g., dysglycemia) are used in differentiation of stages of type 1 diabetes and enrollment in prevention clinical trials (11). However, age is a well-known factor accounting for heterogeneity in the rate of decline in β-cell function and disease progression (12). Therefore, variation in clinical and laboratory characteristics at diabetes onset within age groups may contribute to our understanding of disease progression and identify additional features present in those with a more severe clinical presentation, such as DKA at onset.

We examined age variant categories (0–4, 5–9, and 10–14 years) and family history, HLAs, autoantibody profiles, and widely available metabolic and β-cell function markers (glucose and insulin) along with occurrence of DKA in participants in The Environmental Determinants of Diabetes in the Young (TEDDY) study. TEDDY is a large international cohort of genetically high-risk children followed since birth. Such characterization may allow better understanding of variability of presentation of type 1 diabetes in children and which children might be at risk for developing DKA at onset. This analysis could promote design of immune and omics studies to better understand these differences, while continuing to highlight the benefits of screening and frequency of monitoring for type 1 diabetes risk.

RESEARCH DESIGN AND METHODS

Participants and Monitoring

TEDDY participants were tested at, or shortly after, birth for high-risk HLA genotypes. The study screened newborns from the general population and among first-degree relatives (FDRs) of those with type 1 diabetes (13). This large cohort of children from four countries (Finland, Germany, Sweden, and the U.S.) were followed every 3 months from age 3 months to 4 years and then every 3–6 months based on autoantibody status until the age of 15 years or diabetes onset (14). Oral glucose tolerance tests (OGTTs) were completed every 6 months in participants with two or more autoantibodies starting at age 3 years. The TEDDY OGTT consists of only two time points (0 and 120 min) and collects glucose, insulin, and C-peptide (15). Children with two or more recorded OGTTs during follow-up were included in the analysis. Dysglycemia is defined during an OGTT as fasting plasma glucose of 5.6–6.9 mmol/L (100–125 mg/dL) or 2-h plasma glucose of 7.8–11.0 mmol/L (140–199 mg/dL). Markers of insulin sensitivity were assessed: fasting glucose-to-insulin ratio (glucose in mmol/L and insulin in μIU/mL) and HOMA-IS (22.5/[fasting insulin in μIU/mL * fasting glucose in mmol/L]). BMI thresholds for underweight (<5th percentile) were based on WHO standards (https://www.who.int/childgrowth/en/) and overweight and obese thresholds determined by the International Obesity Task Force (derived from international databases and linked with adult BMI cutoffs for overweight and obese) (16). Children <2 years of age were excluded from BMI measurement (n = 34).

Genetic Risk and Autoantibodies

PCR-based genotyping was performed at birth to categorize HLA class II DR-DQ genetic risk. The highest risk categories were HLA-DR-DQ 3-2/4-8 (DR3/4), HLA-DR-DQ 4-8/4-8 (DR4/4), HLA-DR-DQ 4-8/8-4 (DR4/8), HLA-DR3/3 (DR3/3), and additional HLA categories for FDR eligibility. FDR-specific HLAs include DR4/1, DR4/9, DR4/13, DR3/9, DR4/4-DQB1*20×, and DR4/4-DQB1*304 (13), which were evaluated separately because these children have a familial increase in risk that is not common in the general population of children in TEDDY.

Measurement of insulin autoantibodies (IAAs), GAD autoantibodies (GADAs), and insulinoma-associated antigen 2 autoantibodies was done per previously reported protocols at two separate laboratories (14,17). Zinc transporter 8 autoantibodies was added in January 2012, and results were available for all participants who developed diabetes. Islet autoantibody positivity was based on persistent autoantibodies at two consecutive visits confirmed by both laboratories. The date of first confirmed autoantibody presence was then used for analysis.

Diagnosis Data Collection Including DKA Reporting

The diagnosis of diabetes, using American Diabetes Association criteria (14), was documented in a standardized form by TEDDY clinicians. DKA at diagnosis was captured through report of direct laboratory measurement of pH/bicarbonate levels or free-text response from a physician or medical provider as to the presence of DKA. Demographic information, symptoms at diagnosis, and continuation in monitoring were collected.

Statistical Analysis

Age categories were based on clinically useful categories and historical age groups commonly used in the type 1 diabetes literature (18–20): early childhood (0–4 years), school-age (5–9 years), and early adolescence (10–14 years). Adherence to protocol prior to diagnosis was defined as whether or not a child was lost to follow-up (LTFU) or withdrew (WD) and never rejoined the study prior to diagnosis with diabetes. Fisher exact test or χ^2 test was used to compare proportional/binary differences. For the clinical features, comparisons in median value between age groups were performed using Mann-Whitney U test. Incidence of type 1 diabetes and DKA was described as a rate per 1,000 person-years. Exact 95% CIs for the incidence rates were calculated using the χ^2 relationship assuming a Poisson distribution. Estimated rate differences were assessed using a log-linked Poisson model with an offset to account for different observation periods for different participants. Stratified multivariable Cox proportional hazards models were used to assess risk of diabetes in those with persistent confirmed autoantibodies adjusted for age at time of initial autoantibody seroconversion and country of residence. For metabolic measures, change from first recorded OGTT on risk of progression to type 1 diabetes was assessed longitudinally using time-varying multivariate Cox proportional hazards models in those children eligible for OGTT collection. We also assessed age effects on the change in OGTT measure from baseline to progression to type 1 diabetes using an interaction term in the modeling. Additionally, glucose impairment, defined as the first impaired fasting or stimulated recorded measure, was evaluated from time from first glucose impairment to progression to type 1 diabetes using a stratified Cox proportional hazards model. Multivariate models were adjusted for age at baseline OGTT, baseline recorded OGTT measure, months since two or more positive

autoantibodies, combination of first persistent autoantibodies, sex, HLA DR-DQ genotype, and family history of type 1 diabetes at birth unless otherwise noted. Data were analyzed using Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC) and GraphPad PRISM (version 7.04; GraphPad Software, Inc., San Diego, CA) for figures. Two-tailed *P* values <0.05 were considered significant.

RESULTS

Demographics, HLAs, and Autoantibody Profiles of TEDDY Participants Who Developed Diabetes

The TEDDY study screened 424,788 newborns in the general population and in families with type 1 diabetes from September 2004 to February 2010 and enrolled 8,676 newborns. There were 8,502 enrolled HLA-eligible children with autoantibody data available. As of 31 July 2020, 379 (4.46%) children had developed type 1 diabetes and are the focus of this analysis (Supplementary Fig. 1). A random glucose level (as compared with fasting glucose or 2-h glucose following OGTT) was most commonly used to diagnose diabetes across all ages (49.2%) ($P < 0.0001$). At the time of this analysis, the TEDDY participants had surpassed 10 years of age, with a median age of 12.9 years (interquartile range 11.6–14.1) at the most recent visit. The children who developed diabetes had a significantly different HLA distribution as compared with those who did not in the TEDDY study ($P < 0.0001$). Proportional differences in clinical and laboratory features by age group are presented in Table 1, with clear differences by age at onset. Overall incidence of type 1 diabetes was 4.35 cases per 1,000 person-years (95% CI 3.93–4.81). Type 1 diabetes incidence by age group (cases [95% CI] per 1,000 person--years) was as follows: 3.42 (2.81–4.13) in those age 0–4.99 years, 4.44 (3.77–5.20) in those age 5–9.99 years, and 5.64 (4.66–6.77) in those age 10–14.99 years (Fig. 1). Children 0–4 years of age had a significantly lower incidence of diabetes as compared with children age 5–9 ($P = 0.038$) and 10–14 years ($P = 0.0002$). Incidence of type 1 diabetes for children without an FDR was lower at 3.55 (95% CI 3.14–3.99) compared with 11.13 (9.09–13.50) cases per 1,000 person-years in those with an FDR across all age groups ($P < 0.001$) (Supplementary Fig. 2). The FDR excess risk was highest in children age 0–4 years, with the highest proportion of paternal type 1 diabetes in this age group.

Type 1 diabetes incidence (cases [95% CI] per 1,000 person-years) among those with at least one persistent confirmed autoantibody was 70.29 (58.64–83.57) in those with IAAs first, 42.87 (34.39–52.82) in those with GADAs first, and 156.31 (128.10–188.88) in those with multiple autoantibodies first (Supplementary Fig. 3). Incidence of type 1 diabetes varied by the first appearing autoantibody, with the highest incidence in children with multiple autoantibodies ($P < 0.001$) versus either GADAs or IAAs first, while there was no significant difference if IAAs or GADAs were first ($P = 0.31$) after adjusting for age at seroconversion. There was no significant difference by FDR status (paternal, maternal, or sibling) in whether IAAs or GADAs were present first after adjusting for age at time of seroconversion. Autoantibodies were not identified in 41 (10.8%) of the 379 children who developed diabetes. Thirty-seven of these children had WD from TEDDY or were LTFU (age 0–4 years, $n = 11$; 5–9, $n = 16$; 10–14, $n = 10$). Four children in the 0–4 years age group were enrolled and either were autoantibody negative at diagnosis or did not meet the TEDDY definition of persistent confirmed autoantibody positivity. Of the remaining 338 of 379 children diagnosed, 68.3% had one confirmed autoantibody at initial seroconversion, with only 8.9% having a single autoantibody at diagnosis (7 of the 30 single autoantibody–positive children at diagnosis WD or were LTFU). At diagnosis, 17.9%, 26.4%, and 36.9% of participants had two, three, or four autoantibodies, respectively. Those diagnosed at a younger age had proportionally fewer autoantibodies, and those diagnosed at an older age were more likely to have four autoantibodies, as shown in Table 1.

Characteristics of TEDDY Participants Who Developed DKA

Incidence of DKA, which occurred in 23 children, varied by country (cases [95% CI] per 1,000 person-years), with Sweden (0.11 [0.02–0.31]) having a lower rate as compared with the U.S. (0.40 [0.22–0.67]; $P = 0.038$) and Germany (0.55 [0.11–1.61]; $P = 0.045$). Finland (0.16 [0.03–0.47]; $P = 0.62$) had a similar rate to Sweden; however, there were no significant differences compared with the other countries. Those in the youngest age group (0–4 years) in our study had a higher incidence of DKA (0.38 [0.19–0.66]) compared with those age 5–9 years (0.12 [0.03–0.30]; $P = 0.040$), but not with those age 10–14 years (0.34 [0.14–0.70]; $P = 0.83$) (Fig. 1). Symptoms at diabetes onset were more likely to be present in the youngest group compared with the older groups (64.8% vs. 48.3% and 48.8%, respectively; $P = 0.024$). All children who presented with DKA reported at least one symptom at onset.

Twenty-three episodes of DKA at onset (6.1%) were present, with 16 documented as mild-moderate DKA (pH $\geq$7.1 and $<$7.3), six as severe DKA (pH $<$7.1), and one without laboratory confirmation available. A majority, $\sim$60% of cases, occurred in the U.S. Table 2 details the 23 participants with DKA. HLA DR3/4 was the most prevalent haplotype ($n = 14$ [60.9%] of 23) among those who presented with DKA. Of those with DKA at diagnosis, only one (4.3%) of the 23 children had an FDR with type 1 diabetes (majority were non-FDR), compared with 102 (28.7%) with an FDR of 356 without DKA at diagnosis ($P = 0.008$). Nine (39.1%) of the 23 children with DKA at the time of type 1 diabetes diagnosis were autoantibody negative/unknown; seven of these nine children WD or were LTFU from the study at a median (interquartile range [IQR]) of 6.1 (1.9–7.3) years prior to diagnosis. Additionally, two of the 23 children with DKA did not meet the TEDDY definition of persistent confirmed autoantibody positivity.

Weight loss was reported in $\sim$20% of the 379 children diagnosed with type 1 diabetes (median [IQR] weight loss 1.0 [0.7–2.2] kg). In the children who presented with DKA at onset, 56.5% ($n = 13$ of 23) reported a median (IQR) weight loss of 2.0 (1.4–5.0) kg. None who developed DKA were overweight or obese at the time of diagnosis, and three were underweight (eight were age $<$2 years or missing BMI data). Of those diagnosed with diabetes with BMI information available ($n = 306$ of 379), 14.4% were overweight, 4.9% were obese, and 5.2% were underweight. Thirty-two percent were overweight or obese in the 10–14 years age group. The oldest participant diagnosed with DKA was 13 years of age, with 87% of the children with DKA $\leq$10 years of age.

Table 1—Demographics of the TEDDY cohort diagnosed with type 1 diabetes as of 31 July 2020

	Type 1 diabetes				
	None (*n* = 8,123)	Age 0–4 years (*n* = 142)	Age 5–9 years (*n* = 151)	Age 10–14 years (*n* = 86)	*P**
Female sex	4,017 (49.5)	70 (49.3)	68 (45.0)	36 (41.9)	0.53
FDR	797 (9.81)	48 (33.8)	34 (22.5)	21 (24.4)	0.08
Family member with T1D at screening					0.06
Mother	308 (3.8)	10 (7.0)	6 (4.0)	9 (10.5)	
Father	394 (4.9)	28 (19.1)	16 (10.6)	7 (8.1)	
Sibling	95 (1.2)	10 (7.0)	12 (7.9)	5 (5.8)	
N by site†					0.021
Colorado	1,272 (15.7)	20 (14.1)	28 (18.5)	20 (23.3)	
Georgia/Florida	908 (11.2)	8 (5.6)	16 (10.6)	8 (9.3)	
Washington	1,299 (16.0)	14 (9.9)	15 (9.9)	8 (9.3)	
Finland	1,703 (21.0)	44 (31.0)	35 (23.2)	22 (25.6)	
Germany	535 (6.6)	25 (17.6)	9 (6.0)	5 (5.8)	
Sweden	2,397 (29.5)	31 (21.8)	48 (31.8)	23 (26.7)	
HLA					<0.0001
DR3/4	3,108 (38.3)	78 (54.9)	84 (55.6)	48 (55.8)	
DR4/4	1,592 (19.6)	16 (11.3)	36 (23.8)	17 (19.8)	
DR4/8	1,420 (17.5)	18 (12.7)	18 (11.9)	12 (13.9)	
DR3/3	1,749 (21.5)	17 (12.0)	10 (6.6)	6 (7.0)	
FDR specific‡	254 (3.1)	13 (9.1)	3 (2.0)	3 (3.5)	
N of autoantibodies at diagnosis or last clinical visit					0.0002
0	7,613 (93.7)	15 (10.6)	16 (10.6)	10 (11.6)	
1	289 (3.6)	17 (12.0)	8 (5.3)	5 (5.8)	
2	77 (0.95)	37 (26.1)	16 (10.6)	15 (17.4)	
3	67 (0.82)	42 (29.6)	40 (26.5)	18 (20.9)	
4	77 (0.95)	31 (21.8)	71 (47.0)	38 (44.2)	
DKA at diagnosis		13 (9.2)	4 (2.6)	6 (7.0)	0.06
Symptoms at diagnosis					
Symptomatic (yes)		92(64.8)	73(48.3)	42(48.8)	0.017
Polydipsia (yes)		71(59.2)	57(50.9)	30(53.6)	0.41
Polyphagia (yes)		4(3.3)	10(9.0)	2(3.6)	0.44
Polyuria (yes)		75(62.5)	61(54.5)	37(66.1)	0.020
Hospitalized (yes)		112(78.9)	107(70.9)	50(58.1)	0.005
N reporting weight loss		31	28	18	0.0006
Median (IQR)		0.80 (0.40–1.40)	1.33 (0.89–2.39)	2.00 (0.90–3.00)	
Median (IQR) age at diagnosis, years		2.79 (1.79–4.08)	7.77 (6.43–8.92)	11.51 (10.73–12.56)	<0.0001
Enrollment status at diagnosis					0.048
Regular visits/on study		127 (89.4)	123 (81.5)	65 (75.6)	
LTFU/WD		15 (10.6)	28 (18.5)	21 (24.4)	

T1D, type 1 diabetes. **P* value of comparison for each characteristic among children diagnosed with type 1 diabetes before 5, between 5 and 9, and between 10 and 14 years of age. †Seven children are followed in the U.S. at auxiliary sites located at the Children's Hospital of Pittsburgh and the Naomi Berrie Diabetes Center. ‡FDR-specific HLA DR-DQ genotypes (DR4/1, DR4/9, DR4/13, DR3/9, DR4/4-DQB1*20×, and DR4/4-DQB1*304).

Incidence of DKA among those who did not adhere to the protocol (cases [95% CI] per 1,000 person-years) was higher (0.48 [0.22–0.91]) than among those who did adhere (0.20 [0.11–0.34]; $P = 0.047$). Of the 23 children with DKA, 12 (52.2%) had not had a blood draw within TEDDY in >7 months, and nine children (39.1%) WD or were LTFU. The median time between the last blood draw and diagnosis visit within TEDDY was 10.2 months (IQR 2.3–37.1) compared with 2.0 months (IQR 0.7–3.5) for the 356 participants without DKA at diagnosis ($P < 0.001$). Adherence with regular visits in the children who were diagnosed with type 1 diabetes was achieved by 83.1% of participants (higher in the younger age groups) ($P = 0.05$).

Between 31 January and 31 July 2020, the coronavirus disease 2019 pandemic escalated in severity in all countries involved in TEDDY. During this time, 11 patients presented with type 1 diabetes within TEDDY and none presented with DKA. The median time since the last TEDDY visit in these children diagnosed with diabetes was 2.1 months (IQR 0.7–5.9), and the median (IQR) weight loss was 2.2 (1.3–3.0) kg.

OGTT Metabolic Changes Associated With Progression to Type 1 Diabetes

We assessed if a change in metabolic measure from the first OGTT affected the risk of progression to type 1 diabetes. Specifically, fasting (0-min) and stimulated (120-min) glucose, fasting insulin, glucose-to-insulin ratio, and HOMA-IS were

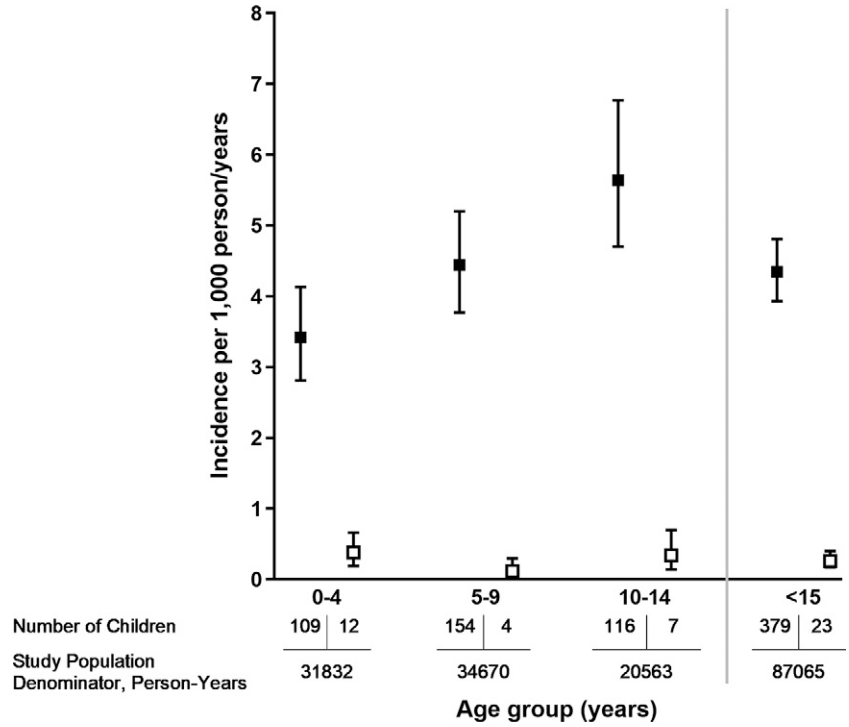

Figure 1—Incidence of type 1 diabetes in TEDDY children (*n* = 379, solid box) and DKA incidence (open box) by age group. Number of children and study population denominator displayed below each group.

evaluated. Given the paucity of OGTT data in children <5 years of age, only those age >4 years were assessed in this analysis of metabolic markers. Two or more OGTTs were collected during follow-up in 65.6% (*n* = 345 of 526) of the eligible children >4 years of age; 48.4% (*n* = 167 of 345) of these children were diagnosed with type 1 diabetes. OGTT eligible children (*n* = 345) who progressed to type 1 diabetes had fewer recorded OGTTs during follow-up [median (IQR) 7 (4–11) vs. 9 (6–13), *P* = 0.001]. The overall median (IQR) age at the first OGTT was 61.1 (44.1–94.7) months, with a median (IQR) of 6.0 (3.4–11.6) months after development of two or more positive autoantibodies.

An increase of one unit from baseline (i.e., first OGTT in TEDDY) in fasting glucose, stimulated glucose, or glucose-to-insulin ratio and a decrease of one unit in fasting insulin were significantly associated with risk of progression to type 1 diabetes in the subset of eligible children with serial OGTT data. Age heterogeneity was observed for change from baseline fasting glucose ($P < 0.0001$ for interaction) and stimulated glucose ($P = 0.008$ for interaction) with regard to risk of progression to type 1 diabetes. As age increased, a change from baseline fasting and stimulated glucose was associated with an increasing risk of progression to type 1 diabetes (Fig. 2). There was no significant difference by age for fasting insulin and glucose-to-insulin ratio with regard to progression.

Overall, an increase of one unit from baseline in fasting glucose (hazard ratio [HR] 1.09 [95% CI 1.04–1.14]; $P = 0.0003$), stimulated glucose (HR 1.50 [1.42–1.59]; $P < 0.0001$), or glucose-to-insulin ratio (HR 1.29 [1.16–1.43]; $P < 0.0001$) was associated with an increased risk of progression to type 1 diabetes. An increase of one unit in fasting insulin from baseline was associated with an 11% lower risk of progression to type 1 diabetes (HR 0.89 [0.83–0.95]; $P = 0.0009$), accounting for age at baseline OGTT, baseline recorded OGTT measure, months since two or more positive autoantibodies, combination of first persistent autoantibodies, sex, HLA DR-DQ genotype, and family history of type 1 diabetes at birth. No significant interactive age effects were noted for baseline fasting ($P = 0.10$) or stimulated glucose ($P = 0.99$) or glucose-to-insulin ratio ($P = 0.33$) on type 1 diabetes risk. However, a higher baseline fasting glucose (HR 1.60 [1.11–2.32]; $P = 0.013$), stimulated glucose (HR 1.96 [1.70–2.27]; $P < 0.0001$), or glucose-to-insulin ratio (HR 1.20 [1.03–1.39]; $P = 0.016$) was associated with an increased risk of progression to type 1 diabetes. Baseline fasting insulin was not shown to be significantly associated with progression ($P = 0.17$). Change from baseline or baseline HOMA-IS was not found to be associated with progression. Longitudinal OGTT measurements demonstrated marked variability over time. Median values for fasting glucose, stimulated glucose, and glucose-to-insulin ratio were higher, while fasting insulin values were lower, for children who progressed to type 1 diabetes (Supplementary Fig. 4).

Furthermore, in these children with reported OGTT metabolic measures, impaired fasting glucose (5.6–6.9 mmol/L) and impaired glucose tolerance (2-h glucose 7.8–11.0 mmol/L) were present in 48.1% (*n* = 166 of 345). Combined, dysglycemia was present in 69.9% (*n* = 241 of 345) of the all children and in 85% (*n* = 142 of 167) of those who progressed to type 1 diabetes, at a median (IQR) time from first presentation of dysglycemia of 1.58 (0.96–3.04) years prior to diagnosis. Glucose impairment (fasting or stimulated) was associated with a >5.5-fold increased risk of progression to type 1 diabetes from first dysglycemic presentation (HR 5.52 [95% CI 3.50–8.81]; $P < 0.0001$).

Children with two or more recorded OGTTs (*n* = 345), as compared with those without (no OGTT, *n* = 133; only one OGTT, *n* = 48), had a longer follow-up (median [IQR] 134.7 (104.6–155.4) vs. 109.9 (54.0–143.1) months; $P < 0.0001$), were more likely to be male ($P = 0.038$), were more likely not have a family history of type 1 diabetes ($P < 0.001$), were less likely to be from Germany ($P < 0.0001$), and were less likely to carry the FDR-specific HLA DR-DQ genotypes ($P < 0.0001$). Overall, this population with OGTT data was less likely to represent those who are FDRs of individuals with type 1 diabetes.

CONCLUSIONS

Type 1 diabetes incidence increased 3–4% annually in the late 20th century, with the greatest increase in the youngest children (5.4% increase in those age 0–4 years) (21). Children who develop autoantibodies and progress to type 1 diabetes early in life have less functional β-cell mass (22)

Table 2—Characteristics of the 23 DKA cases at diabetes diagnosis in TEDDY

	Age at diagnosis of T1D, years	Age at last clinical visit, years	Clinic	HLA	Race and ethnicity	Age at seroconversion, years	First appearing AAb	*N* of AAbs confirmed and persistent at seroconversion (0, 1, 2, 3, 4)	*N* of AAbs confirmed and persistent at diagnosis (0, 1, 2, 3, 4)	Enrolled or WD or LTFU (WD)	DKA severity (mild/moderate, severe, or unknown)	Polydipsia	Polyphagia	Polyuria
1	0.69	0.69	Finland	DR3/4	Non-Hispanic White	0.50	None	0	0*	E	Severe	Unknown	Unknown	Unknown
2	0.87	0.87	WA	DR4/8	Non-Hispanic White	0.81	GADAs, IAAs	2	2	E	Mild/moderate	Yes	No	Yes
3	0.90	0.90	Sweden	DR3/4	Unknown	0.54	IAAs	1	1	E	Severe	Yes	Unknown	Yes
4	0.97	0.97	Sweden	DR3/4	Unknown	0.76	GADAs, IAAs	2	2	E	Mild/moderate	Yes	No	Yes
5	1.22	1.22	CO	DR4/8	Hispanic	1.22	IAAs	1	1	E	Severe	Yes	No	Yes
6	1.43	1.43	CO	DR3/4	Hispanic	1.29	IAAs	1	1	E	Mild/moderate	Yes	No	Yes
7	2.32	2.32	Finland	DR3/4	Non-Hispanic White	1.85	GADAs, IAAs	2	3	E	Mild/moderate	Yes	No	Yes
8	2.47	2.47	Germany	DR3/4	Non-Hispanic White	1.01	GADAs, IAAs	2	2	E	Mild/moderate	Yes	No	Yes
9	2.67	0.28	WA	DR3/4	Unknown	0.28	None	0	0	WD	Mild/moderate	Yes	Unknown	Yes
10	3.07	1.75	WA	DR3/4	Hispanic	1.10	None	0	0	WD	Mild/moderate	Yes	Unknown	Yes
11	3.38	3.38	WA	DR4/4	Non-Hispanic White	2.53	None	0	0	E	Mild/moderate	Yes	Yes	Yes
12	3.92	1.42	WA	DR3/4	African American	1.38	None	0	0	WD	Mild/moderate	Yes	No	Yes
13	4.99	4.99	Germany	DR3/3	Non-Hispanic White	1.54	GADAs	1	4	E	Mild/moderate	Unknown	Unknown	Unknown
14	8.74	8.74	Germany	DR4/4	Non-Hispanic White	8.74	IA-2As, IAAs	2	2	WD	Mild/moderate	Yes	No	Yes
15	8.92	8.92	CO	DR3/4	Hispanic	0.25	None	0	0	WD	Mild/moderate	Yes	Yes	Yes
16	9.20	9.20	CO	DR4/4	Hispanic	0.27	None	0	0	WD	Mild/moderate	Yes	No	Yes
17	9.86	9.86	CO	DR3/4	Hispanic	6.46	GADAs	1	1	E	Severe	Yes	No	Yes
18	10.30	3.11	FL/GA	DR3/4	Non-Hispanic White	2.74	None	0	0	WD	Severe	Yes	Unknown	Yes
19	10.61	10.61	CO	DR3/4	Hispanic	6.24	GADAs, ZnT8As	2	4	E	Mild/moderate	Yes	No	Yes
20	10.87	10.87	Finland	DR3/4	Non-Hispanic White	10.87	GADAs, IA-2As	2	2	E	Mild/moderate	Yes	No	Yes
21	11.31	11.31	WA	DR4/8	Other	11.31	IAAs	1	1	E†	Severe	Yes	No	Yes
22	11.33	11.33	Sweden	DR4/4	Unknown	0.75	IAAs	1	4	WD	Mild/moderate	Yes	Unknown	Yes
23	13.54	5.09	WA	DR4/8	Non-Hispanic White	4.72	None	0	0*	WD	Mild/moderate	Yes	No	Yes

AAb, autoantibody; E, enrolled; T1D, type 1 diabetes; ZnT8A, Zinc transporter 8 autoantibody. *Did not meet the TEDDY definition of persistent confirmed autoantibody positivity. †Participant WD from TEDDY then rejoined (enrolled) prior to T1D diagnosis.

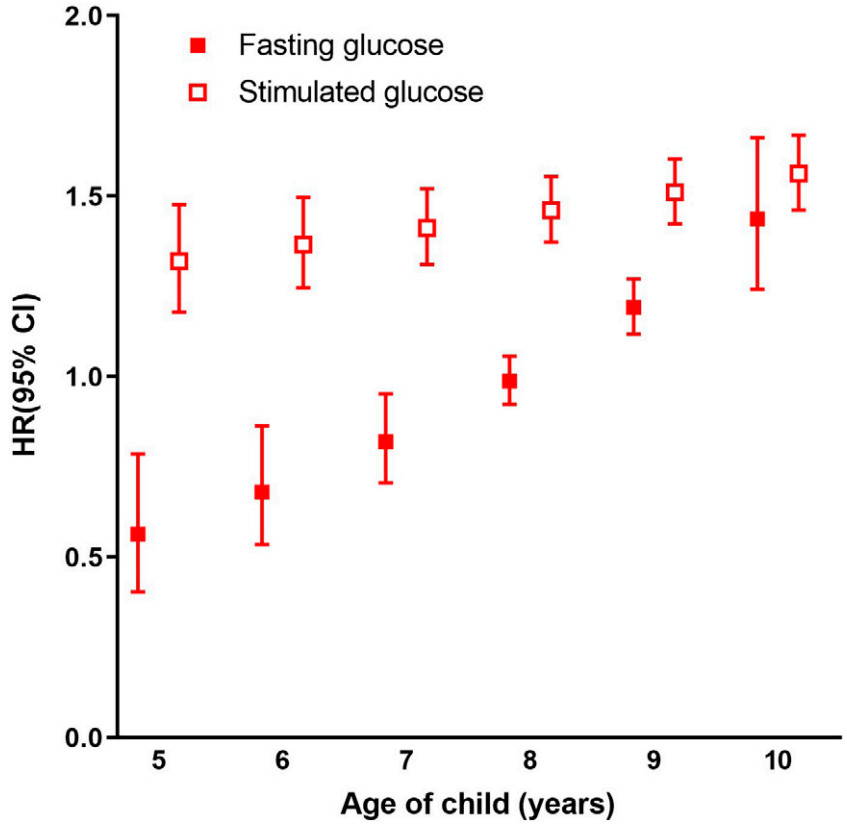

Figure 2—Age-specific HRs (with 95% CIs) associated with a one-unit increase in either fasting glucose (solid box) or 120-min stimulated blood glucose (open box) with regard to progression of type 1 diabetes. The risk of progression to type 1 diabetes was constant over time (age) for baseline levels of fasting and stimulated glucose.

and higher rates of DKA at diagnosis (23). However, children who are closely monitored have significantly lower rates of DKA than the general population (24,25). We analyzed differences in age, genetic, autoantibody, and metabolic profiles among TEDDY children who developed type 1 diabetes and characteristics associated with DKA at diagnosis.

Genetic predisposition accounts for up to 50% of known type 1 diabetes risk, with predominant risk from HLA class II genotype variants (26). The proportion of HLA DR3/4, the highest risk haplotype, was similar across all age groups in our study and different from those in the TEDDY cohort who did not develop diabetes. Overall, however, the genetic profiles varied between age groups among those who developed type 1 diabetes. Genetic heterogeneity may explain some of the phenotypic variation within type 1 diabetes presentation. Additionally, those diagnosed in the youngest age group were more likely to be an FDR. While FDR status (mother, father, or sibling) was not significantly different by age of onset in this study, the Finnish Pediatric Diabetes Register observational study demonstrated a younger age at onset when the FDR was a parent compared with a sibling but did not find a significant difference in age at onset between familial and sporadic cases (27). While paternal type 1 diabetes has an increased risk of proband type 1 diabetes (27–29), we found the highest proportion of paternal FDRs in those diagnosed between age 0 and 4 years. However, the type of FDR did not influence the type of first-appearing autoantibody. The incidence of type 1 diabetes was highest for those presenting with multiple autoantibodies as first appearance of autoantibodies as compared with either IAAs or GADAs first.

Early age of islet autoantibody development and risk of type 1 diabetes have been well assessed in pediatric studies (30–32). The frequency of IAA positivity at initial seroconversion decreased with increasing age category. In our study, a majority of participants initially presented with a single autoantibody but progressed to multiple autoantibodies by the time of diagnosis, with only 7.9% remaining single autoantibody positive at diagnosis. Children diagnosed at younger ages have, by definition, less time to develop autoantibodies, and as such, we observed four autoantibodies at diagnosis more often in older children. Autoantibody seroconversion may not have been captured in all participants because 23% of single autoantibody–positive participants WD or were LTFU. Furthermore, a majority (90%) of autoantibody-negative children WD or were LTFU.

Time leading up to diabetes onset is marked by rising glucose levels, waning insulin production, and reduced β-cell glucose sensitivity (33). Time-varying analysis identified that an increase in glucose (fasting or 120-min), an increase in glucose-to-insulin ratio, or a decrease in fasting insulin in longitudinally collected OGTTs increased the risk of type 1 diabetes progression, irrespective of age (analysis only in those age >4 years). Metabolic values (fasting glucose, stimulated glucose, or glucose-to-insulin ratio) at first OGTT occurrence in TEDDY were also associated with risk of progression.

While metabolic markers can fluctuate up and down from visit to visit, their absolute increase over time was found to increase the risk of progression. This risk increased with each year from age 5 to 10 years as the fasting glucose and stimulated glucose rose one unit from baseline. A metabolic marker in combination with a marker of β-cell function may provide increased specificity of risk across many ages. In our study, a glucose-to-insulin ratio (fasting) at first measurement and increase over time were associated with risk of progression to type 1 diabetes, along with fasting and 120-min glucose measures. Multiple measures that include fasting and stimulated values may be of benefit for monitoring at-risk children, because the DPT-1 study, which recruited patients as young as 3 years of age (median age 11 years), demonstrated impaired β-cell function following stimulus but normal β-cell function in the fasting state (34). However, both a random plasma glucose ≥7.8 mmol/L (140 mg/dL) and dysglycemia as part of an OGTT were found to predict the onset of type 1 diabetes in the DIPP study (35). In addition, a 10% increase in HbA_{1c} was shown to be

associated with an approximate sixfold increased risk of progression to type 1 diabetes in TEDDY children (36). Furthermore, this study supports the need for physiologic studies to better understand the mechanisms contributing to insulin sensitivity and insulin deficiency prior to diabetes onset. While a number of TEDDY-collected variables have been studied as part of efforts to improve type 1 diagnosis prediction models, metabolic data remain somewhat limited and are often not included (37).

The main strength of this analysis is that TEDDY is a large prospective observational study that collects clinical data, including metabolic markers, on children at genetically high risk for type 1 diabetes every 3–6 months in those who develop islet autoimmunity. This granularity provides a clearer picture of the variability of clinical measures leading up to diagnosis with type 1 diabetes. However, the primary limitation of this analysis is the use of the two–time point OGTT (0 and 120 min) in TEDDY. Additional metabolic measures could not be applied, because a six-point OGTT was not collected. C-peptide response (30–0 min C-peptide) or combined glucose and C-peptide markers (e.g., Index60, which combines fasting and 60-min measures from an OGTT) may offer more refined risk of diabetes progression (2,38). A very high metabolic risk marker, such as these, may be a sign of imminent progression. There were fewer participants with OGTT data as a result of the burden of collection (especially in those age $<$3 years who are not eligible for an OGTT per protocol), making direct comparisons difficult. Small numbers of children developed DKA, also inhibiting statistical comparisons. Other limitations of the study include the fact that not all participants have reached the clinical end point of 15 years (or diabetes diagnosis), but all participants have surpassed age 10 years. Also, it is important to remember that the TEDDY population is a genetically preselected group with high-risk HLAs, and findings may not be generalizable to the entire population, because these HLA predispose, in general, to an earlier age at diagnosis. The TEDDY study does, however, include children with and without relatives with type 1 diabetes, similar to the frequency reported by most countries. Newer population-based efforts to screen for autoantibodies (e.g., Global Platform for the Prevention of Autoimmune Diabetes in Europe) include additional type 1 diabetes–related single nucleotide polymorphisms that increase the risk of islet autoimmunity in addition to the presence of class II HLAs (39). While race and ethnicity are not categorized consistently across TEDDY sites, the generalizability of these results across racial and ethnic groups would need further evaluation.

Early detection of diabetes and the prevention of DKA are the hallmarks of prospective monitoring studies, and this continues to be a positive outcome of the TEDDY study, with only 6% of children diagnosed with type 1 diabetes presenting with DKA compared with $>$30% in U.S. youth and adults (3,40). The rate of DKA is known to vary widely by country, at 12–21% in Finland, Sweden, and Germany (41–43). Those countries that have lower rates of DKA within TEDDY also have lower population rates of DKA (24). While all participants in the TEDDY monitoring program are educated on the symptoms of diabetes and the risk of DKA, those with first-hand experience may be more attuned to and suspicious of new symptoms and may be performing spontaneous home glucose monitoring, which may account for the lower rate of DKA in those with an FDR. An alarming increase in DKA has been seen over the years (40). TEDDY and other prospective studies have been able to diagnose children and adults earlier in the disease course (24,25,44). Furthermore, the prevention of DKA can improve long-term outcomes (45,46). Higher DKA rates in the youngest children, who have the highest risk of mortality, were again corroborated.

Children followed in accordance with the TEDDY protocol have a lower frequency of DKA compared with children who WD from the study, were LTFU, or had longer time between visits. Because more than half of children with DKA had not been seen in TEDDY in $>$7 months, semiannual OGTTs could be proposed for monitoring genetically high-risk children. Of note, outside of scheduled OGTTs, maintaining consistent phone contact and promoting community awareness also remain essential in preventing DKA. The benefit of monitoring is significantly lower if adequate follow-up is not maintained. Until a successful prevention therapy becomes standard of care, the main goal of monitoring studies, beyond enhancing our understanding of the natural history of the disease, remains to decrease the morbidity and mortality associated with unexpected new-onset type 1 diabetes. Within TEDDY, the rate of DKA is markedly reduced, with the tradeoff of some parental anxiety around positive autoantibody test results and the risk of type 1 diabetes (47).

Additional anxieties may be at play during major stresses, such as a global pandemic. As with any disease that can become life threatening if unrecognized, the concern among the medical community is that families may delay seeking health care and the rates of DKA could increase further. Since the coronavirus disease 2019 pandemic started, there have been variable data on the rate of type 1 diabetes reported in the literature, with increased cases, no change, and decreased cases of type 1 diabetes all reported (48–50). Unfortunately, during the pandemic, an increased rate of DKA has been reported in children with newly diagnosed type 1 diabetes in the German Diabetes Prospective Follow-up Registry (51). However, in the prospective TEDDY study, there did not appear to be an increase in the number of cases or in DKA between 31 January and 31 July 2020, but larger data collection over longer periods of time is required for conclusive results. Public health initiatives, including the use of telemedicine, must continue to provide education regarding the symptoms of diabetes to avoid delays in treatment and the risk of life-threatening DKA.

In conclusion, this study details heterogeneous and age-related clinical and laboratory features observed at and before the diagnosis of type 1 diabetes in a large cohort of high–genetic risk children. Observational prospective studies continue to clarify the need for multifactorial approaches to understand the natural history of this heterogeneous disease. Following identification of high-risk groups (high-risk HLA DR and presence of islet autoantibodies), we can provide some reassurance that this population of children had changing metabolic measures seen prior to onset. Whether fasting glucose, 120-min glucose, or glucose-to-insulin ratio will be the most ideal for monitoring or if other metabolic measures that use multipoint OGTT data and identify very high-risk populations are the most ideal is yet to be determined. As rates of type 1 diabetes continue to increase, we must

continue to refine the tools for identifying high-risk children in order to prevent DKA and ultimately prevent and reverse type 1 diabetes.

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