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Original Article

Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease

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Objective: The Environmental Determinants of Diabetes in the Young (TEDDY) study is designed to identify environmental exposures triggering islet autoimmunity and type 1 diabetes (T1D) in genetically high-risk children. We describe the first 100 participants diagnosed with T1D, hypothesizing that (i) they are diagnosed at an early stage of disease, (ii) a high proportion are diagnosed by an oral glucose tolerance test (OGTT), and (iii) risk for early T1D is related to country, population, human leukocyte antigen (HLA)-genotypes and immunological markers.
Methods: Autoantibodies to glutamic acid decarboxylase (GADA), insulinoma-associated protein 2 (IA-2) and insulin (IAA) were analyzed from 3 months of age in children with genetic risk. Symptoms and laboratory values at diagnosis were obtained and reviewed for ADA criteria.
Results: The first 100 children to develop T1D, 33 first-degree relatives (FDRs), with a median age 2.3 yr (0.69–6.27), were diagnosed between September 2005 and November 2011. Although young, 36% had no symptoms and ketoacidosis was rare (8%). An OGTT diagnosed 9/30 (30%) children above 3 yr of age but only 4/70 (5.7%) below the age of 3 yr. FDRs had higher cumulative incidence than children from the general population ($p < 0.0001$). Appearance of all three autoantibodies at seroconversion was associated with the most rapid development of T1D (HR = 4.52, $p = 0.014$), followed by the combination of GADA and IAA (HR = 2.82, $p < 0.0001$).
Conclusions: Close follow-up of children with genetic risk enables early detection of T1D. Risk factors for rapid development of diabetes in this young population were FDR status and initial positivity for GADA, IA-2, and IAA or a combination of GADA and IAA.

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Key words: autoantibodies – diagnosis – follow-up studies – TEDDY study – type 1 diabetes

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Type 1 diabetes (T1D) is one of the most common autoimmune diseases in children, with about 70 000 cases diagnosed during childhood world-wide each year (1). However, the environmental triggers associated with islet autoimmunity and the subsequent development of T1D remain poorly understood. To enhance our understanding of the environmental factors associated with T1D, The Environmental Determinants of Diabetes in the Young (TEDDY) study was designed to prospectively follow children identified at birth with human leukocyte antigen (HLA) genotypes indicating increased risk for T1D (2). The TEDDY study was initiated in 2004 and now follows 6481 children with a median age of 58 months. Data analyses of the children in TEDDY who have developed T1D have demonstrated marked reductions in the incidence of diabetic ketoacidosis (DKA) at diagnosis when compared to children diagnosed with T1D in the general population (3). In addition, a large number of TEDDY participants developing T1D have been asymptomatic, with diagnosis being made purely on the basis of an OGTT. Participants diagnosed at an early stage of the disease likely have a greater residual β-cell capacity, which may lead to better initial glycemic control and reduced risk of long-term complications (4, 5). On the basis of these initial observations, the specific aim of this study was to describe the first 100 TEDDY participants diagnosed with T1D according to their genetic background, immunological markers, and clinical presentation at the diagnosis of the disease. We hypothesized that (i) participants followed in TEDDY are diagnosed at an early stage of disease with a low frequency of symptoms and near normal HbA1c; (ii) a high proportion of the participants over 3 yr of age are diagnosed through an OGTT, and (iii) different countries and populations within the TEDDY study as well as immunological markers and HLA-genotypes are important for T1D risk in this young population.

Research design and methods

Participants

TEDDY is a multi-center observational study designed to identify the environmental exposures that may promote or protect from autoimmunity and T1D (2). The clinical sites in the study are located in Sweden, Finland, Germany, Colorado, Washington, and Florida/Georgia. The study is funded by the National Institutes of Health, approved by local Institutional Review Boards, and is monitored by an External Advisory Board formed by the National Institutes of Health. The participants were initially identified at birth via genetic screening for HLA genotypes known to confer an increased risk for T1D (2). Those enrolled are being followed prospectively from birth to 15 yr. Study visits beginning at 3 months of age continue every 3 months until 4 yr and then every 6 months until the age of 15 yr. Children who are positive for islet autoantibodies continue to receive follow-up every 3 months regardless of age. The visits include clinical measurements, the collection of blood and other biological samples, and the collection of data to ascertain environmental exposures (2). A portion of the blood samples are analyzed for autoantibodies to glutamate decarboxylase (GADA), insulinoma-associated protein 2 (IA-2A), and insulin (IAA). In autoantibody positive participants older than 3 yr of age, OGTT are performed every 6 months. Parents are carefully informed about diabetes risk and provided with updated antibody results after each study visit.

Genetic analyses

The participants at all clinical sites were screened at birth for HLA HLA-DQA1, DQB1, and DRB1 genes as previously described (6). Confirmatory testing was performed by the TEDDY HLA Reference Laboratory (7). Nine high-risk haplo-genotypes were identified and participants with these genotypes were eligible for the follow-up phase of the study (7).

Autoantibodies

GADA, IA-2A, and IAA were measured in two laboratories by radio-binding assays (8, 9). For sites in the USA, all serum samples were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver. In Europe, all sera were assayed at the University of Bristol, UK. Both laboratories have previously shown high assay sensitivity and specificity as well as concordance (10). All positive islet autoantibodies results and 5% of

negative samples were re-tested in the other reference laboratory and deemed confirmed if concordant.

Definition of persistent autoimmunity

Persistent islet autoimmunity was defined as confirmed positive GADA, IA-2A, or IAA on at least two consecutive study visits. All positive islet autoantibodies and 5% of negative islet autoantibodies were confirmed in both central autoantibody laboratories, one located in the USA and one in Europe.

Collection of data related to the diagnosis of T1D

At the time of diagnosis of T1D, data were collected using a standardized case report form requiring documentation to fulfill American Diabetes Association criteria for diagnosis (11). Data on symptoms, height and weight at diagnosis, laboratory values such as pH, bicarbonate, and presence of ketones in urine and blood ketones are collected. Since the clinical care of newly diagnosed T1D patients differs between the TEDDY sites, not all participants had samples collected for laboratory evaluation of DKA. Therefore, a free text box for the physician's description of the child's clinical status of the child was added to the diagnosis of diabetes case report form.

Definition of DKA

DKA was defined as an arterial/capillary pH less than 7.30 or a standardized bicarbonate less than 15 mmol/L. Severe DKA was defined as pH less than 7.10 or standardized bicarbonate less than 5 mmol/L. If the pH or standardized bicarbonate were not taken at diagnosis, DKA was excluded on the basis of betahydroxybutyrate less than 1.5 mmol/L, negative urine ketones, lack of symptoms, or physician diagnosis.

Statistical methods

Data were analyzed using the Statistical Analysis System Software (Version 9.2, SAS Institute, Cary, NC, USA). Categorical variables were analyzed using Pearson's chi-squared tests. Continuous variables were tested using the *t* test for differences in means or Wilcoxon rank-sum test for differences in medians. Medians and minimum/maximum values are presented as median (min, max). Autoantibody seroconversion was defined as first confirmed positive sample for a specific autoantibody. Kaplan–Meier life tables were used to determine the time to development of T1D by first confirmed autoantibody combination and compared using the log-rank chi-squared statistic and to determine the cumulative incidence by clinical center. Stratified Cox proportional hazard models (stratified for country of residence) were used to estimate the hazards ratio for risk of T1D development by first confirmed autoantibodies (reference group = IAA only). Multivariable analyses were adjusted for gender, relation to T1D proband and HLA genotype. Efron's method for tied survival times were employed in the Cox analysis.

Results

The screening in TEDDY started on 1 September 2004 and the first TEDDY child was diagnosed with T1D in September 2005. By 30 November 2011, a total of 100 TEDDY participants had been diagnosed, 45 females and 55 males. The median age at diagnosis was 2.3 yr (min 0.69–max 6.27). Thirty-three percentage (33/100) had a first-degree relative (FDR) with T1D [father (n = 20), mother (n = 6), sibling (n = 9)] (Table 1).

Diagnosis per site

Of the first 100 children to develop T1D, Finland had the highest number diagnosed (n = 35) and Florida/Georgia had the lowest (n = 4) (Table 1). The cumulative incidence did not differ significantly between Finland, Sweden, Germany, and the USA when analyzing children recruited from the general population and FDRs separately (Fig. 1, panels A and B). However, FDRs had a significantly higher cumulative incidence compared to children from the general population ($p < 0.0001$) (Fig. 1, panel C).

Clinical symptoms and signs at diagnosis of diabetes

In total, 36 of 100 children were asymptomatic at diagnosis. When symptomatic, the most common symptoms were polydipsia (53%) and polyuria (51%) (Table 2A). The majority of children (87/100) were diagnosed by a random, postprandial, or fasting glucose, while 13 of 100 children were diagnosed by a scheduled OGTT (Table 2B). Among those children diagnosed before 3 yr of age (n = 70), 94% were diagnosed by random (n = 49), postprandial (n = 9), or fasting (n = 8) glucose, while only four (5.7%) were diagnosed on OGTT. In contrast, 9 of 30 (30%) of children above 3 yr of age were diagnosed on OGTT. A total of 8 of 100 children were found to have DKA at diagnosis of disease [5 of 100 mild DKA and 3 of 100 severe DKA (pH < 7.1)] (Table 2B).

Autoantibodies before onset of T1D

All but six of the first 100 children had developed confirmed GADA, IA-2A, and/or IAA before

Table 1. Characteristics of the first 100 the Environmental Determinants of Diabetes in the Young (TEDDY) children diagnosed with T1D

Characteristic	n or median (min–max)
Gender (female)	45
FDR (yes)	33
Family member with T1D	
Mother only	4
Father only	18
Sibling only	9
Mother and father	2
Mothers diabetes status	
Gestational	4
Type 1	6
No diabetes	86
Missing	4
Age at diagnosis (yr)	2.3 (min 0.69, max 6.27)
Number and median age at diagnosis (min–max) by site	
Colorado	n = 14, age 1.76 (1.1–3.7)
Georgia/Florida	n = 4, age 2.45 (1.2–4.3)
Washington	n = 7, age 2.77 (0.87–4.9)
Finland	n = 35, age 2.05 (0.69–5.1)
Germany	n = 13, age 1.96 (1.0–3.2)
Sweden	n = 27, age 2.98 (0.9–6.3)

FDR, first-degree relative.

Table 2. Symptoms and laboratory data at onset of T1D.

(A) Symptoms	N or Median (min–max)
Was child symptomatic (yes)	64
Polydipsia* (yes)	53
Polyphagia* (yes)	4
Polyuria* (yes)	51
Was child hospitalized (yes)	82
Was child treated in emergency room (yes)	6
Weight at diagnosis (kg)	13 (6.5–27)
Height at diagnosis (cm)	90 (70–126)
Weight loss reported at diagnosis (kg)	0.5 (0.03–4.4)
(B) Laboratory values	**n or mean (SD)**
Diagnostic Test	
Fasting glucose	12
OGTT—2 hr	13
Postprandial glucose	14
Random glucose	61
Average pH (n = 80)	7.4 (0.1)
≥7.1 and <7.3	5
<7.1	3
Average Glucose (mmol/l) (n = 98)	19.6 (9.7)
HbA1c (%, mmol/mol) at diagnosis	
All (n = 98)	7.4 (1.9), 57
Colorado	7.1 (1.4), 54
Georgia/FL	7.4 (1.3), 57
Washington	8.7 (2.3), 72
Finland	7.6 (1.7), 60
Germany	8.4 (2.3), 68
Sweden	6.4 (1.7), 46
HbA1c at Diagnosis by Cutpoints (n = 98)	
≥6.5	15
≥5.7 and <6.5	23
<5.7	60
Urine ketones at diagnosis (n = 80)	
Large	9
Moderate	11
Small	9
Trace	5
Negative	46
Blood ketones at diagnosis (mmol/L)	0.98 (2.2)

OGTT, oral glucose tolerance test.
*Missing = 13.

diagnosis of diabetes. The first autoantibody to appear at seroconversion was most often IAA, present as the first autoantibody in 81 of 100 children either alone (49/100), in combination with GADA (28/100), IA-2A (1/100) or both GADA and IA-2A (3/100). In total, 44 of 100 children developed GADA as the first positive autoantibody. Only 13 of 100 had GADA as the single first autoantibody, while 31 of 100 had GADA in combination with IAA (28/100) or both IAA and IA-2 (3/100). None of the children developed IA-2A as the first antibody without positivity for IAA (Fig. 2A). Of the initial 100 children to develop diabetes, 94 of 100 had confirmed positive autoantibodies (Fig. 2B) and 83 of 100 children had persistent confirmed autoantibodies (i.e., more than one confirmed autoantibody positive sample), prior to diagnosis (Fig. 2C).

In six children, no sample with positive islet autoantibodies was obtained before the diagnosis of diabetes. Of those, two children, both FDR's and aged 3.0 and 4.2 yr at diagnosis, dropped out of TEDDY and no islet autoantibody information could be obtained as part of the study before the diagnosis. One of them had islet autoantibodies measured at the hospital (outside of TEDDY protocol) at the time of diagnosis and was found to be positive for GADA, IA-2A, and IAA. The other child did not have any autoantibody measurement performed. Three of the four children followed in TEDDY had tested positive for an autoantibody once but the second laboratory did not confirm this. The mean age at diagnosis was 1.6 yr (range 0.7–3.4). Three of the four children were from the general population and two of the four had high-risk HLA-genotypes (DR4-DQA1*030X-DQB1*0302/DR3-DQA1*0501-DQB1*0201), while the other two had DR4/4 and DR4/9, respectively. The last autoantibody samples were drawn 3 months before diagnosis in two children, and respectively 8 months and 10 months before diagnosis in the remaining two children.

Survival analysis of the first autoantibodies measured and diagnosis of T1D over time was adjusted for sex, relation to proband status, HLA-genotype, and country of origin (Fig. 1, panel D). The analysis demonstrated that the appearance of all three autoantibodies (GADA, IA-2A, and IAA) compared to IAA

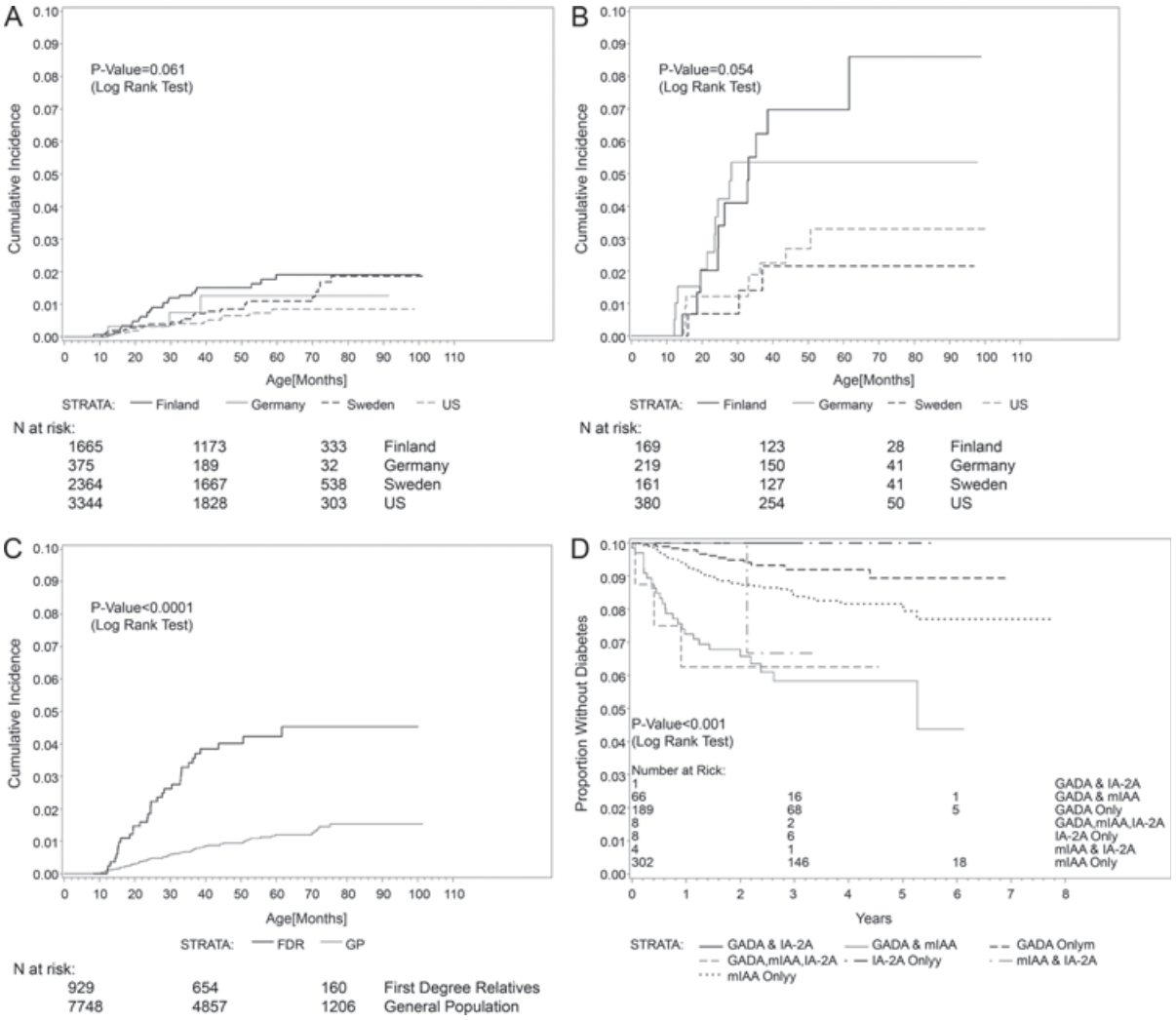

Fig. 1. Panel (A) Cumulative incidence of T1D in the general population by country, Panel (B) Cumulative incidence of T1D in the first degree relatives by country, Panel (C) Cumulative incidence of T1D by first-degree relative (FDR) status, and Panel (D) Survival analysis of first autoantibody measured and proportion of children diagnosed with type 1 diabetes over time.

only as the first confirmed autoantibody was associated with the most rapid development of T1D [HR = 4.52 (95% CI 1.35–15.11; p = 0.014)], closely followed by the combination of GADA and IAA [(HR = 2.82 (1.69–4.71; p < 0.0001)]. In contrast, children with initial positivity for GADA as a single autoantibody had the slowest course to diabetes amongst this very young cohort with T1D [(HR = 0.54 (0.29–1.00; p = 0.05)]. The combination of IA-2 and IAA did not significantly differ from IAA as a single autoantibody (Fig. 1, panel D).

Genetic background

The majority of the children (98%) had a genotype containing the haplotypes DR4-DQA1*030X-DQB1*0302 (DR4), DR3-DQA1*0501-DQB1*0201 (DR3), or both (DR3/4). The high-risk DR3/4 genotype represented 58%.

Discussion

The TEDDY study provides a unique opportunity to longitudinally follow the progression to autoantibody seroconversion and T1D in a large group of children with known HLA risk for the disease. Having reached the unfortunate 'milestone' of 100 diagnosed children we have analyzed this group of predominantly young children who have developed T1D and have questioned if the natural course from seroconversion to diagnosis of T1D may be altered by virtue of participation in a highly intensive longitudinal study.

The observation of multiple autoantibodies at the initial presentation of autoimmunity likely reflects the rapid natural history of T1D in very young children at high genetic risk for developing disease. Since children presenting with all three of GADA, IA-2A, and IAA and the combination of GADA and IAA may be of increased risk of more aggressive autoimmune beta-cell

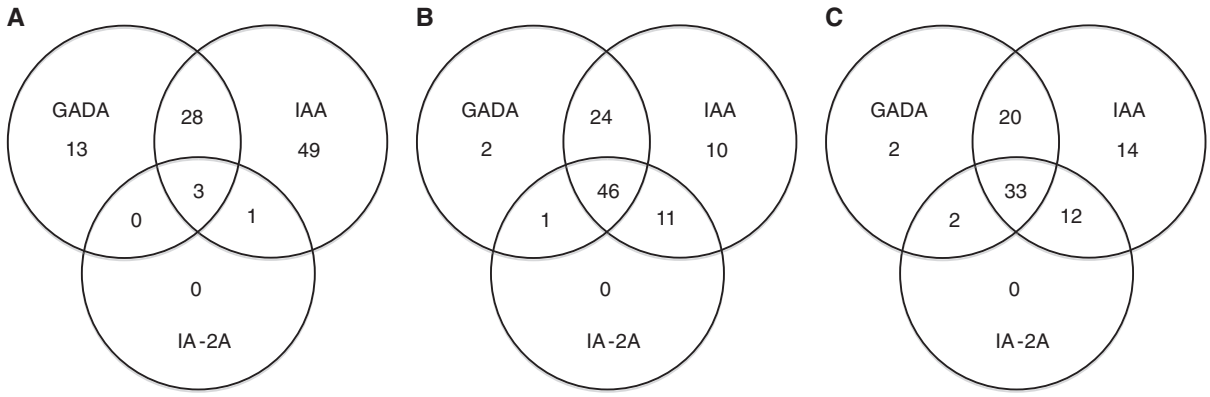

Fig. 2. (A) The first positive autoantibody (n) measured in the Environmental Determinants of Diabetes in the Young (TEDDY) study in the 100 children that later developed type 1 diabetes (T1D), (B) Confirmed autoantibodies at diagnosis of T1D, (C) Persistent confirmed autoantibodies at diagnosis of T1D (17 subjects were not persistent). Subjects (6/100) developing T1D did not have positive autoantibodies before diagnosis.

destruction than children with GADA or IAA as single first autoantibodies, it may be important for future prevention and intervention trials in young children with high-risk HLA-genotypes to stratify treatment groups based on these autoantibody combinations.

In this population of children with genetically increased risk for T1D, we also found that FDRs had a higher cumulative incidence than children from the general population. Children followed in Germany had the highest cumulative incidence at early age of diagnosis when analyzing all children followed together (data not shown). This was explained by the high percentage of FDRs followed at the German site, given that 10 of 13 children diagnosed in Germany were FDRs. The fact that no significant country differences were seen in early incidence when FDRs and children from general population were analyzed separately in our analyses may be explained by the selection of the genetically at risk children within the TEDDY study. In this context, it is interesting to note that the TEDDY protocol allows FDRs with less HLA genetic risk to be followed, while all children followed from the general population have high-risk genotypes (7). However, in this young population we could confirm a high frequency of the high-risk HLA-genotype DR4-DQA1*030X-DQB1*0302/DR3-DQA1*0501-DQB1*0201 also in the FDRs diagnosed (51%), which is consistent with other studies in children diagnosed at a young age (12, 13).

Our data demonstrates that more than one of the three of TEDDY subjects are asymptomatic at diagnosis, despite a median diagnosis age of 2.3 yr. In contrast, 99% of children diagnosed with T1D in the community (i.e., outside of a research study) before age 6 yr have been reported to be symptomatic at diagnosis (14). These observations provide further support for the concept that longitudinal monitoring including HLA screening, autoantibody measurements, and frequent reinforcement of the signs and symptoms of T1D may be highly effective (though not necessarily cost effective) in improving outcomes for young children with T1D. This study also confirmed that DKA rates are very low in TEDDY subjects who developed T1D when compared to rates in the general population (15–19). Other studies with close follow-up of children with risk have shown a similar trend of early diagnosis with a low rate of DKA (20, 21) and symptoms (20, 22, 23), although the latter is in an older population.

The high number of asymptomatic children indicates that dissemination of risk information alone may not be enough to identify young children at an early stage of disease. Frequent follow up with HbA1c, blood or plasma glucose, and OGTTs may be of great importance in early identification of T1D development. That said, only 13 of 100 children were diagnosed based on an OGTT. The vast majority was diagnosed on the basis of random, postprandial, or fasting glucoses. Thus, close follow-up with plasma glucose sampling and HbA1c appear to contribute to the early diagnosis of these children. As the cohort ages, however, it appears that OGTT may become a far more important diagnostic tool in the monitoring of at risk children as 30% of children diagnosed above the age of three met criteria on the basis of an OGTT.

In conclusion, the first 100 children diagnosed within the TEDDY study, where children with increased risk for T1D are closely followed, have a high rate of asymptomatic development of T1D. Combinations of autoantibodies to islet autoantigens may be used to further stratify risk for progression to development of T1D in young children with high risk HLA-genotypes.

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Conflict of interest

The authors declare that there are no conflicts of interest to report regarding this study.

Author contributions

H. E. L. researched data and wrote manuscript, M. J. H researched data and wrote manuscript, P. G. researched data and wrote manuscript, K. V. researched data, reviewed/edited manuscript, B. A., W. H., J. K., Å. L., M. R., O. S., J.-S. X., A. Z. designed study, researched data and reviewed/edited manuscript.

Appendix

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