Predictors of Progression From the Appearance of Islet Autoantibodies to Early Childhood Diabetes: The Environmental Determinants of Diabetes in the Young (TEDDY)

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OBJECTIVE

While it is known that there is progression to diabetes in <10 years in 70% of children with two or more islet autoantibodies, predictors of the progression to diabetes are only partially defined.

RESEARCH DESIGN AND METHODS

The Environmental Determinants of Diabetes in the Young (TEDDY) study has observed 8,503 children who were at increased genetic risk for autoimmune diabetes. Insulin autoantibodies (IAAs), GAD65 autoantibodies (GADAs), and insulinoma-associated protein 2 autoantibodies (IA-2As) were measured every 3 months until 4 years of age and every 6 months thereafter; if results were positive, the autoantibodies were measured every 3 months.

RESULTS

Life table analysis revealed that the cumulative incidence of diabetes by 5 years since the appearance of the first autoantibody differed significantly by the number of positive autoantibodies (47%, 36%, and 11%, respectively, in those with three autoantibodies, two autoantibodies, and one autoantibody, $P < 0.001$). In time-varying survival models adjusted for first-degree relative status, number of autoantibodies, age at first persistent confirmed autoantibodies, and HLA genotypes, higher mean IAA and IA-2A levels were associated with an increased risk of type 1 diabetes in children who were persistently autoantibody positive (IAAs: hazard ratio [HR] 8.1 [95% CI 4.6–14.2]; IA-2A: HR 7.4 [95% CI 4.3–12.6]; $P < 0.0001$]). The mean GADA level did not significantly affect the risk of diabetes.

CONCLUSIONS

In the TEDDY study, children who have progressed to diabetes usually expressed two or more autoantibodies. Higher IAA and IA-2A levels, but not GADA levels, increased the risk of diabetes in those children who were persistently autoantibody positive.

Autoimmune type 1 diabetes is preceded by a preclinical period characterized by the appearance and persistence of islet insulin autoantibodies (IAAs) (1), GAD autoantibodies (GADAs) (2), insulinoma-associated protein 2 autoantibodies (IA-2As) (3), and zinc transporter 8 autoantibodies (4). Guidelines for screening first-degree

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relatives (FDRs) of persons with type 1 diabetes exist (5,6); however, nearly 90% of patients in whom type 1 diabetes has been newly diagnosed have no FDRs with the disease. Previous studies (7–10) have estimated that diabetes will develop within 10 years in 27–40% of the general population children expressing two or more autoantibodies. In Finnish children, double positivity for GADA and IA-2A on a one-time screening identified up to 60% of diabetic cases in the ensuing 27 years (11). A recent study (12) combining three prospective cohorts of multiple autoantibody–positive children from Colorado, Finland, and Germany reported a risk of diabetes of 70% within 10 years and 84% within 15 years after seroconversion.

Once persistent islet autoimmunity develops, progression toward diabetes seems to be locked in, although the time to diabetes diagnosis varies tremendously. The determinants of the progression are only partially understood and include younger age at seroconversion, the number of autoantibodies, and higher levels of IAAs (13).

The Environmental Determinants of Diabetes in the Young (TEDDY) (14) is a multicenter observational study designed to map the events leading to type 1 diabetes from birth to the age of 15 years and to identify the precipitating exposures. In this largest prospective birth cohort of genetically high-risk children, we report predictors of progression from islet autoantibodies to clinical diabetes.

RESEARCH DESIGN AND METHODS

Study Population

Since September 2004, TEDDY has accrued and observed a cohort of 8,503 infants who were at increased genetic risk for type 1 diabetes. The vast majority (89%) have no FDR with type 1 diabetes, while 11% are siblings or offspring of a person with type 1 diabetes. The participants were identified at birth through genetic screening for diabetes susceptibility HLA-DR/DQ genotypes at sites in Sweden, Finland, Germany, Colorado, Washington state, and Florida/Georgia. Those participants enrolled in the study are followed up prospectively from birth to 15 years of age, with study visits beginning at 3 months of age, then every 3 months until 4 years of age and every 6 months thereafter. Children who are positive for islet autoantibodies are followed up every 3 months. The details of screening and follow-up have been previously published (15,16). A total of 577 children in whom persistent confirmed islet autoimmunity developed were included in this study; 164 of those children progressed to diabetes. We did not include children who were not positive for antibodies prior to diagnosis (N = 12). Subjects with positive but not persistent islet autoantibodies (N = 505), subjects who had persistent confirmed autoantibodies but who withdrew from the study (N = 28), or had maternal autoantibodies (N = 198) were excluded from these analyses. The study was approved at all sites by local institutional review boards.

Islet Autoantibodies

GADAs, IA-2As, and IAAs were measured in two laboratories by standard radiobinding assays (17–19). For sites in the U.S., all serum samples were assayed the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver. In Europe, all sera were assayed at the University of Bristol (Bristol, U.K.). Both laboratories have previously shown high assay sensitivity and specificity as well as concordance (20). All results that were positive for islet autoantibodies and 5% of negative samples were retested in the other reference laboratory and deemed confirmed if results were concordant. In addition, the TEDDY study participated in the National Institute of Diabetes and Digestive and Kidney Diseases harmonization project, in collaboration with the Diabetes Research Institute (Munich, Germany), to evaluate the impact of the harmonized assay protocol on the concordance of IA-2A and GADA results (17,21). On the retested TEDDY study samples, discordance decreased from 4% to 1.8% for IA-2As (n = 604 samples) and from 15.4% to 2.7% for GADAs (n = 515 samples). Persistent islet autoantibodies were defined as being confirmed positive GADA, IA-2A, or IAA on at least two consecutive study visits. Transplacental autoantibodies (defined as the transient presence of the same autoantibody in a child younger than 18 months of age and his/her mother) were excluded from analyses as were positive or confirmed but not persistent confirmed autoantibodies. Fluctuating positive autoantibodies were defined as being persistently confirmed positive autoantibodies in subjects whose samples reverted to negativity at one or more time points. Nonfluctuating persistent islet autoantibodies were defined as confirmed autoantibody positivity for a specific autoantibody on two consecutive visits and did not revert to negative after initial detection (i.e., stayed positive throughout follow-up). Diabetes was defined according to American Diabetes Association criteria for diagnosis (22).

Statistical Analysis

Data were analyzed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC). Categorical variables were analyzed using Pearson χ^2 tests. Continuous variables were tested using the t test for differences in means or the Wilcoxon rank sum test for differences in medians. Due to different autoantibody cutoff values in Bristol and Denver and a change in the type of assay over time from the TEDDY assay to the harmonized assay (20% of the enrolled population is missing a harmonized measure prior to January 2010), autoantibody levels were converted to SD units away from threshold ("z scores") for analysis. For IA-2As and GADAs, the harmonized assay was used; if a measure was missing from the harmonized assay, the TEDDY assay was used (the Bristol z score was used and, if missing, then the Denver z score was used). As for IAAs (not harmonized), the Bristol z score was used, and, if missing, the Denver z score was used. The IAA, GADA, and IA-2A levels were log transformed for analyses. Kaplan-Meier life tables were used to determine the time to diabetes onset from the initial seroconversion for each subject and were compared using the log-rank χ^2 statistic.

Multivariate time-varying Cox proportional hazards models were used to estimate the risk of diabetes and to determine significant predictors; country of residence was the stratified variable. Three time-varying covariates were considered (mean autoantibody level for IA-2As, IAAs, and GADAs). Risk periods were taken as the time between serum sample collections at consecutive (3-month) visits where subjects were still deemed to be at risk for diabetes from the time of persistent confirmed autoantibody positivity to the diagnosis of diabetes or last serum sample collection. Time to diabetes was defined as

the time from initial seroconversion. The Efron method for tied survival times was used in the Cox analysis and the Akaike information criterion to assess the best model. The counting process format in SAS version 9.3 was applied to fit the time-dependent Cox proportional hazards models. HLA effect was assessed in the time-varying Cox models as the highest-risk HLA-DR3-DQ2/DR4-DQ8 genotype versus other genotypes as well as by evaluating the following five primary TEDDY eligibility genotypes groups: HLA-DR3/4, DR4/4, DR3/3, DR4/8, and additional eligibility genotypes applied only to FDRs (HLA-DR3/9, DR4/1, DR4/4b, DR4/9, and DR4/13) (16). The non–time-varying variables (age at first persistent confirmed autoimmunity, FDR status, number of autoantibodies when first positive, and HLA genotype) were first evaluated as predictors of progression to type 1 diabetes, then the time-varying variables (mean log micro-IAA [mIAA], mean log GADA, and mean log IA-2A) were added.

In the subpopulation in whom diabetes developed, general linear models were used to evaluate potential predictors of age of diabetes onset; stepwise selection using the Cp statistic was used to assess best fit. A two-tailed *P* value with an α level for significance was set at 0.05.

RESULTS

During a median follow-up time of 5.0 years (interquartile range 2.6–6.6 years), persistent confirmed islet autoimmunity developed in 577 children, 164 of whom have progressed to diabetes. In those with persistent islet autoantibodies, 61% had multiple autoantibodies, including 32% with all three autoantibodies present, 17% with IAAs and GADAs, 7% with IAAs and IA-2As, and 5% with GADAs and IA-2As. Of those with a single confirmed persistent antibody, 22% had GADAs, 16% had IAAs, and 1% had IA-2As. The age of seroconversion was significantly younger in subjects who progressed to diabetes compared with those who did not (1.3 vs. 2.5 years, respectively, $P < 0.0001$) and varied by autoantibody type (Table 1). Among subjects who progressed to diabetes ($N = 164$), the great majority (88%) had multiple autoantibodies, including 54% with all three autoantibodies, 16% with IAAs and GADAs, 15% with IAAs and IA-2As, and 3% with GADAs and IA-2As. Of those who progressed to diabetes, 9% had mIAAs alone, 2% had GADAs alone, and 1% had IA-2As alone.

Progression to diabetes by Kaplan-Meier life table analysis (Fig. 1) revealed that the cumulative incidence of diabetes within 5 years of seroconversion increased with the number of positive autoantibodies, 47%, 36%, and 11%, respectively, in those with three autoantibodies, two autoantibodies, and one autoantibody ($P < 0.001$). There was no significant difference between children expressing two or three autoantibodies ($P = 0.08$). FDRs had an increased 5-year risk of progression to diabetes, compared with children without a close relative with diabetes, in those with one autoantibody (21% vs. 9%, $P = 0.04$) or two autoantibodies (54% vs. 30%; $P = 0.01$), but not in those with three autoantibodies (54% vs. 45%, $P = 0.17$) (Fig. 2). There was no difference in 5-year progression to diabetes by high-risk HLA-DR3-DQ2/DR4-DQ8 genotype in children expressing one autoantibody (16% vs. 7%, $P = 0.08$), two autoantibodies (37% vs. 35%, $P = 0.85$), or three autoantibodies (48% vs. 47%, $P = 0.66$) (Supplementary Fig. 1).

We compared progression to diabetes in children with persistent and fluctuating islet autoantibodies (Supplementary Fig. 2). Subjects with persistent IAAs had an increased risk of progression to diabetes compared with subjects with fluctuating IAA levels (<0.001); the estimated proportion of children progressing to diabetes at 5 years was 57% versus 22%, respectively. In contrast, there was no difference in the progression to diabetes between children with fluctuating versus persistent IA-2As ($P = 0.42$) or GADAs ($P = 0.53$).

In multivariate time-varying Cox proportional hazards models, higher IAA and IA-2A levels were significant predictors of type 1 diabetes in children who

Table 1—Characteristics of TEDDY subjects by antibody and diabetes status

Characteristic	Persistent confirmed Ab+ (*N* = 577)	Ab− (*N* = 7,195)	*P* value (Ab+ vs. Ab−)	Persistent confirmed Ab+ (no diabetes) (*N* = 413)	Type 1 diabetes* (*N* = 164)	*P* value (Ab+ vs. diabetes)†
Male sex, *n* (%)	326 (57)	3,621 (50)	0.0043	236 (57)	90 (55)	0.6206
FDR (%)	124 (21)	586 (8)	<0.0001	73 (18)	51 (31)	0.0004
HLA-DR3/4	293 (51)	2,747 (38)	<0.0001	200 (48)	93 (57)	0.0446
HLA-DR4/4	100 (17)	1,406 (20)		77 (19)	23 (14)	
HLA-DR3/3	72 (12)	1,561 (22)		57 (14)	15 (9)	
HLA-DR4/8	86 (15)	1,294 (18)		65 (16)	21 (13)	
Other HLA genotypes‡	26 (5)	187 (3)		14 (3)	12 (7)	
Follow-up duration (years)	5.73 (4.4–7.2)	4.81 (2.1–6.6)	<0.0001	6.36 (5.1–7.5)	3.35 (2.1–5.2)	<0.0001
Age at first Ab positivity (years)	2.06 (1.2–3.4)			2.52 (1.5–4.0)	1.28 (0.9–2.0)	<0.0001
First mIAA (years)	1.96 (1.1–3.2)			2.46 (1.3–3.6)	1.29 (1.0–2.0)	<0.0001
First GADA (years)	2.48 (1.5–3.8)			3.02 (2.0–4.3)	1.54 (1.1–2.3)	<0.0001
First IA-2A (years)	2.56 (1.8–4.0)			3.58 (2.5–4.9)	2.00 (1.3–2.7)	<0.0001
Age at diabetes diagnosis (years)					3.30 (2.0–5.1)	

Data are reported as *n* (%) or median (quartile 1–quartile 3), unless otherwise indicated. Ab−, antibody negative; Ab+, antibody positive. *Diabetic subjects are included within the persistent confirmed Ab+ (*N* = 577) population. †Comparison between those Ab+ subjects who did not progress to type 1 diabetes and those in whom diabetes developed. ‡FDR-specific HLA genotypes.

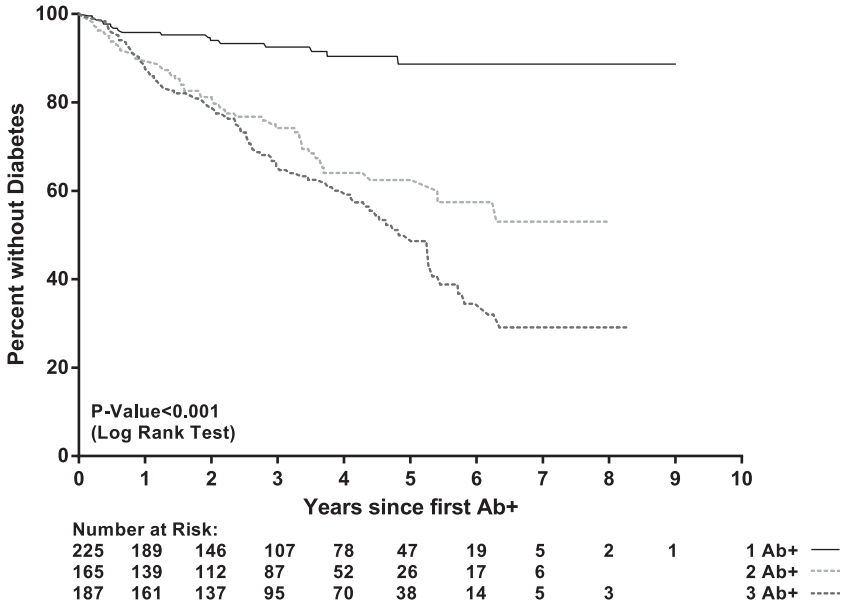

Figure 1—Progression to diabetes in children with confirmed autoantibodies (N = 577). Ab+, antibody positive.

were persistently autoantibody positive for one or more islet autoantibodies. A 1-unit increase in log mean IAA level increased the diabetes risk approximately eightfold (hazard ratio [HR] 8.12 [95% CI 4.6–14.2], $P < 0.0001$), and a 1-unit increase in log mean IA-2A level increased diabetes risk ~7.5-fold (HR 7.4 [95% CI 4.3–12.6], $P < 0.0001$) (Table 2) after adjustment of FDR status (HR 1.6 [95% CI 1.1–2.4], $P = 0.02$), age at first persistent confirmed autoantibodies (HR 0.97 [95% CI 0.92–0.98], $P < 0.0001$), and the number of autoantibodies when first confirmed positive (two antibodies vs. one antibody: HR 1.5 [95% CI 1.0–2.4], $P = 0.046$; three antibodies vs. one antibody: HR 1.7 [95% CI 0.8–3.7], $P = 0.21$). HLA genotype ($P = 0.11$) and log mean GADA level ($P = 0.85$) did not significantly affect the risk of diabetes.

In subjects in whom diabetes developed (N = 164), general linear models were used to explore predictors of the age of diabetes onset. The number of initial autoantibodies, mean IAA and IA-2A levels, initial IA-2A level, country of residence, and age of first seroconversion provided the best predictive model in estimating the age of diabetes onset ($r = 0.56$, $P < 0.0001$).

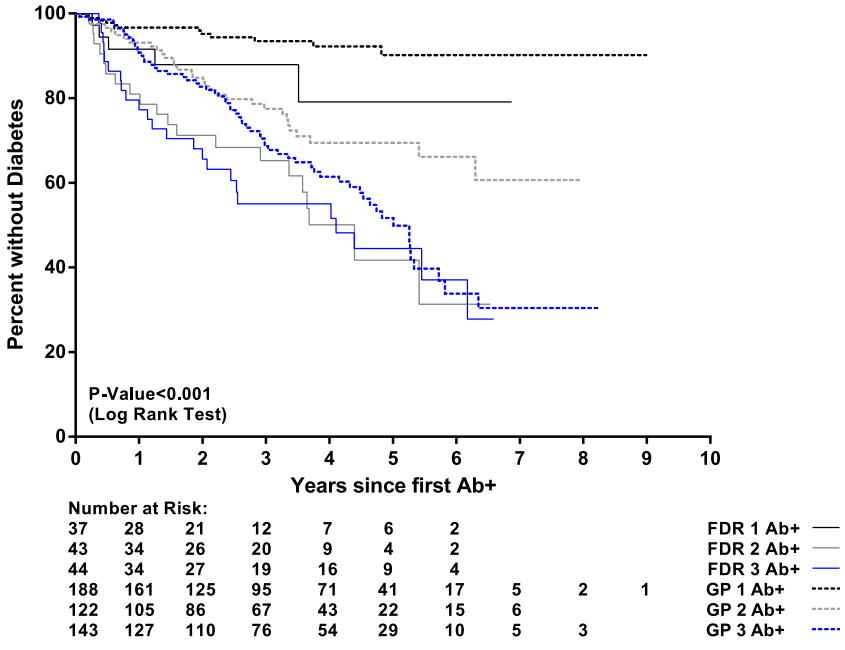

Figure 2—Progression to diabetes in children expressing one, two, or three autoantibodies by family history. Ab+, antibody positive; GP, general population.

CONCLUSIONS

This large prospective cohort study addressed the critical challenge of predicting the absolute risk and the time to progression to clinical diabetes among children in whom persistent islet autoimmunity developed. The majority of children who progressed to diabetes had two or more islet autoantibodies and were very young at seroconversion (median 1.3 years). In children with confirmed positive autoantibodies, progression to diabetes was influenced by family history, but not by the presence of the high-risk HLA-DR3-DQ2/DR4-DQ8 genotype. The high risk of progression to diabetes in children with multiple islet autoantibodies has previously been shown in individual studies (13,23,24) as well as in a recent study (12) combining three prospective cohorts from Colorado, Finland, and Germany. In DAISY, the high-risk HLA-DR3-DQ2/DR4-DQ8 genotype influenced progression to type 1 diabetes in children expressing two or fewer positive islet autoantibodies, but not in those expressing three positive islet autoantibodies (13). On the other hand, family history did not influence progression to diabetes in children with two or more autoantibodies. These discrepancies between previous reports and TEDDY results are most likely due to differences in the duration of follow-up, although differences in autoantibody assays or slight differences in HLA inclusion criteria cannot be excluded.

The TEDDY study is currently the largest prospective study with very detailed genetic and antibody follow-up data from birth of infants with high-risk genes for type 1 diabetes, including both general population children and FDRs. The frequent antibody testing in this young cohort may improve the accuracy of the time-to-event analyses.

Table 2—Multivariate time-varying Cox proportional hazards models

	Adjusted HR	95% CI	*P* value
Mean IAA	8.12	4.64–14.23	<0.0001
Mean IA-2A	7.40	4.34–12.55	<0.0001
Mean GADA	1.06	0.62–1.80	0.845
FDR	1.58	1.07–2.35	0.023
Age at first persistent confirmed Ab+	0.97	0.92–0.98	<0.0001
Number of Abs at first confirmed Ab+			
2 Abs vs. 1 Ab	1.54	1.01–2.35	0.046
3 Abs vs. 1 Ab	1.67	0.75–3.71	0.212
HLA genotype			
DR3/4 vs. DR4/4	1.37	0.82–2.29	0.227
DR3/3 vs. DR4/4	2.71	1.29–5.68	0.008
DR4/8 vs. DR4/4	1.14	0.61–2.13	0.689
FDR-specific† vs. DR4/4	1.36	0.60–3.08	0.457

Ab, antibody. †FDR-specific HLA: HLA DR3/9, DR4/1, DR4/4b, DR4/9, and DR4/13.

Progression toward diabetes seems to be locked in once persistent islet autoimmunity develops; however, the time to diabetes diagnosis varies tremendously, and the factors influencing progression to diabetes are still poorly understood. In this TEDDY cohort of subjects with persistent confirmed islet autoimmunity, higher mean IAA and IA-2A levels were associated with an increased risk of type 1 diabetes in time-varying survival models adjusted for FDR status, number of autoantibodies, age at first persistent confirmed autoantibodies, and HLA genotypes. In addition, in subjects in whom diabetes developed, predictors of the age of diabetes onset included the number of initial autoantibodies, mean IAA and IA-2A levels, initial IA-2A level, country of residence, and age at first seroconversion, confirming that it is possible to estimate the age of diabetes onset, as shown previously in a smaller prospective study (13).

Despite a limited follow-up duration of only 5 years, our results support the notion that diabetes is likely to develop in most children with persistent multiple islet autoantibodies. However, the time of progression to diabetes can be highly variable. Therefore, factors that can predict the age at development of diabetes may have an important prognostic value for parents and providers and may also be of use in interim analyses of prevention trials. In the first 100 children in the TEDDY study in whom diabetes developed, FDRs had a higher cumulative incidence than children from the general population (25), but the FDR status did not affect the progression to diabetes in the present analysis once three or more autoantibodies had developed. While the cumulative risk of diabetes can vary according to age; relationship to the proband; positivity for IAA, IA-2A, and GADA; the number and combination of islet autoantibodies; HLA-DR/DQ genotype; baseline glucose tolerance; and first-phase insulin secretion (26–31), the TEDDY study results narrow down the list of predictors to young age at seroconversion, positivity for multiple autoantibodies, high autoantibody levels, and persistent positivity for IAA. In this regard, our results are consistent with those of prior studies (13,32,33) but include more participants and more frequent antibody testing, which may improve the accuracy of the time-to-event analyses. Only IAA and IA-2A levels (and not GADA levels) were useful in estimating the age at diabetes onset. Both nonfluctuating IAA and IAA levels were significant factors for progression to diabetes, confirming findings from a previous smaller prospective study (13). The mechanism underlying the specific association of levels of IAAs with the rate of progression to diabetes is not defined but may relate to the hypothesized unique biologic importance of insulin autoimmunity β-cell destruction. On the other hand, the IAA is most often the initial antibody to become positive in young children; this TEDDY cohort is still very young, and these antibody findings might be different in an older population.

TrialNet and other studies (34,35) have demonstrated a period of impaired fasting glucose levels or impaired glucose tolerance that precedes type 1 diabetes onset by several months or years among persons positive for islet autoantibodies. The oral glucose tolerance test performed in clinical trials of type 1 diabetes prevention has long been known to have value in predicting progression to diabetes among subjects with islet autoantibodies (34). The DPT-1 (Diabetes Prevention Trial–Type 1) study (36,37) in FDR subjects reported that a risk score based on age, BMI, and oral glucose tolerance test indexes (glucose and C-peptide values), without the use of intravenous glucose tolerance tests or additional autoantibodies, accurately predicted diabetes risk over a short time period in islet cell antibody–positive relatives. The likelihood of progression to diabetes increased with mild fasting or after oral glucose load dysglycemia. However, the interval between dysglycemia and clinical diabetes is often very short, suggesting that the best opportunity to prevent type 1 diabetes is before this "dysglycemic" period and must rely on screening for immunogenetic markers (38) such as HLA and islet autoantibodies, which are extensively measured in the TEDDY study. Further studies will be required to confirm the predictive value of these antibody tests and their combinations for clinical diabetes appearing later in childhood, as well as for children in whom autoantibodies first develop after puberty.

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as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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