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ARTICLE

Characteristics of children diagnosed with type 1 diabetes before vs after 6 years of age in the TEDDY cohort study

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Abstract

Aims/hypothesis Prognostic factors and characteristics of children diagnosed with type 1 diabetes before 6 years of age were compared with those diagnosed at 6–13 years of age in the TEDDY study.

Methods Genetically high-risk children ($n = 8502$) were followed from birth for a median of 9.9 years; 328 (3.9%) were diagnosed with type 1 diabetes. Cox proportional hazard model was used to assess the association of prognostic factors with the risk of type 1 diabetes in the two age groups.

Results Children in the younger group tended to develop autoantibodies earlier than those in the older group did (mean age 1.5 vs 3.5 years), especially insulin autoantibodies (IAA), which developed earlier than GAD autoantibodies (GADA). Children in the younger group also progressed to diabetes more rapidly than the children in the older group did (mean duration 1.9 vs 5.4 years). Children with autoantibodies first appearing against insulinoma antigen-2 (IA-2A) were found only in the older group. The significant diabetes risk associated with the country of origin in the younger group was no longer significant in the older group. Conversely, the diabetes risk associated with HLA genotypes was statistically significant also in the older group. Initial seroconversion after and before 2 years of age was associated with decreased risk for diabetes diagnosis in children positive for multiple autoantibodies, but the diabetes risk did not decrease further with increasing age if initial seroconversion occurred after age 2. Diabetes risk associated with the minor alleles of rs1004446 (*INS*) was decreased in both the younger and older groups compared with other genotypes (HR 0.67). Diabetes risk was significantly increased with the minor alleles of rs2476601 (*PTPN22*) (HR 2.04 and 1.72), rs428595 (*PPIL2*) (HR 2.13 and 2.10), rs113306148 (*PLEKHA1*) (HR 2.34 and 2.21) and rs73043122 (*RNASET2)* (HR 2.31 and 2.54) (HR values represent the younger and older groups, respectively).

Conclusions/interpretations Diabetes at an early age is likely to be preceded by IAA autoantibodies and is a more aggressive form of the disease. Among older children, once multiple autoantibodies have been observed there does not seem to be any association between progression to diabetes and the age of the child or family history.

Trial registration ClinicalTrials.gov identifier: NCT00279318.

Keywords Autoimmunity · Type 1 diabetes

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Research in context

What is already known about this subject?

- Diabetes-related insulin autoantibodies (IAA) appear first in very young children whereas GAD autoantibodies (GADA) usually only appear after the age of 5 years. After the age of 5 years, IAA is rarely the first autoantibody to appear

What is the key question?

- In addition to differences in the way that diabetes-related autoimmunity arises as children grow older, are there also different risk factors and rates of progression for diabetes that are associated with age?

What are the new findings?

- The association of country of origin on diabetes risk found in the younger group declined in the older age group, while the genotypic association significantly increased
- After age 2 years at seroconversion there was no longer a decreasing risk for diabetes in children positive for multiple autoantibodies associated with the age of initial seroconversion
- After multiple autoantibodies were observed, there was not a discernible difference in risk by family history of type 1 diabetes

How might this impact on clinical practice in the foreseeable future?

- This study adds to the growing body of evidence that type 1 diabetes is not a single, homogeneous disease. It differs in its presentation and, perhaps, aetiology. Much of the observed difference in the relationships between genes and exposures is explained by the age at appearance of autoantibodies, establishing that factors associated with diabetes risk need to be conditioned on age to be properly understood

Abbreviations

FDR	First-degree relative
GADA	GAD autoantibodies
IAA	Insulin autoantibodies
IA-2A	Insulinoma antigen-2
PH	Proportional hazard
TEDDY	The Environmental Determinants of Diabetes in the Young

Introduction

The Environmental Determinants of Diabetes in the Young (TEDDY) study has enrolled and followed a cohort of 8676 infants at elevated genetic risk for autoimmune type 1 diabetes from 3 months of age [1–3]. TEDDY is designed to follow children for 15 years. The characteristics of children progressing to type 1 diabetes during the first 6 years of age (the first third of the planned follow-up period) has been published [4], and there is now additional follow-up for the middle third of the planned follow-up period, i.e., through to 12 years of age. This paper describes the characteristics of children developing autoimmunity and type 1 diabetes during their second 6 years of life and seeks to identify differences in the pattern of islet autoantibody development and the changing relationship between previously identified risk factors for autoantibodies and type 1 diabetes endpoints. The aim is to explore whether the younger cohort developing type 1 diabetes differs from the older cohort, suggesting the emergence of a different form of type 1 diabetes in children as they get older.

The age at the first appearance of islet autoantibodies has been shown to be related to which autoantibody appears first, which has, in turn, been linked to specific genotypic subtypes and associated environmental exposures [4]. It was also noted that the incidence of insulin autoantibodies (IAA) as the first-appearing autoantibody during the first 6 years of life, declined with age, almost disappearing, while the incidence of GAD autoantibodies (GADA), as the first-appearing autoantibody, increased and remained stable throughout follow-up [5]. The changing incidence of the first-appearing autoantibody, as children age, signifies a possible difference in both the aetiology and the pathogenesis of type 1 diabetes. Therefore, this study explores differences in characteristics of children who progressed to diabetes among the younger <6 years of age cohort, presumably arising from those who predominantly developed IAA first and compares them with the characteristics of children who progressed to diabetes among the 6–12 years of age cohort, presumably arising from those who predominantly developed GADA first, with particular emphasis on factors that were prognostic for disease initiation (aetiology) and progression (pathogenesis) specific to these age intervals.

Methods

Participants

TEDDY is a prospective cohort study funded by the National Institutes of Health with the primary goal of identifying environmental causes of type 1 diabetes. It includes six clinical research centres – three in the US (Colorado, Georgia/Florida and Washington State) and three in Europe (Finland, Germany and Sweden). Detailed study design and methods have been previously published [1–3]. Written informed consents was obtained for all study participants from a parent or primary caretaker, separately, for genetic screening and participation in the prospective follow-up. The high-risk genotypes 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*05-DQB1*02:01* (DR3/3). Additional genotypes were included for first-degree relatives (FDRs) of an individual with type 1 diabetes: *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). The HLA-DR-DQ genotype abbreviations shown in parentheses will be used throughout this paper. Genotyping was confirmed by reverse blot hybridisation at the central HLA Reference Laboratory at Roche Molecular Systems, Oakland, CA [3], along with the *INS*-23Hph1 (rs689), *CTLA4* T17A (rs231775) and *PTPN22* R620W (rs2476601) SNP primer pairs. The study was approved by local institutional review or ethics boards and is being monitored by an external evaluation committee formed by the National Institutes of Health.

SNP genotyping was performed by the Center for Public Health Genomics at the University of Virginia using the Illumina Immunochip, which is a custom array for genotyping SNPs selected from regions of the human genome firmly associated with autoimmune diseases [6]. The final selection containing approximately 186,000 SNPs in 186 regions for 12 autoimmune diseases was decided by the Immunochip Consortium. TEDDY previously examined whether any of 41 non-HLA SNPs previously shown to be associated with type 1 diabetes conferred risk for islet autoimmunity [7].

Islet autoantibodies

Islet autoantibodies to insulin (IAA), GAD (GADA) or insulinoma antigen-2 (IA-2A) were measured in two laboratories by radiobinding assays. In the USA, all sera 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 demonstrated high sensitivity and specificity as well as concordance [8]. All positive islet autoantibody samples and 5% of the negative samples were re-tested in the other reference laboratory and deemed confirmed if concordant. Persistent islet autoimmunity was defined as confirmed positive IAA, GADA or IA-2A in at least two consecutive samples. Zinc transporter autoantibodies (ZnT8A) were measured in samples positive for one of the other autoantibodies.

Statistical methods

Characteristics of <6 year olds who progressed to diabetes diagnosis were compared with those of children between 6 and 12 years of age who progressed to diabetes diagnosis by non-parametric (Wilcoxon rank sum) tests for continuous variables and Pearson's $\chi 2$ tests for categorical variables. Multiple Cox proportional hazard (PH) models were applied to examine factors related to the risk of diabetes previously published in the TEDDY study [5, 7, 9–12] with and without the adjustment of age at onset of multiple autoantibodies as a time-dependent covariate. The associations between the factors and the risk of type 1 diabetes during the first 6 years of age and in the range of 6–12 years of age were examined, as was the interaction between the factors and the dichotomised time variable (the two age intervals) treated as time-dependent covariates [13]. The magnitudes of the associations were described by HRs with 95% CIs. Comparisons between the younger and older HRs were conducted by testing whether the ratio of the two HRs differed from 1 based on Wald tests. Adjustments for population stratification were made by using the top two principal components from the Immunochip SNP data as covariates in the Cox PH models [14]. Hazard rates of progression to type 1 diabetes since the onset of multiple autoantibodies stratified by the age at initial seroconversion were calculated assuming exponential survival distribution. Data were analysed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC). Two-tailed p values less than 0.05 were considered to be statistically significant. No adjustment for type 1 error was made for multiple comparisons except in the context of the multiple Cox regression model.

Results

From September 2004 until February 2010, TEDDY enrolled 8676 children at birth, of whom 174 were excluded because of HLA ineligibility or indeterminate autoantibody status, leaving 8502 in the analysis. Children were followed quarterly for progression to diagnosis of diabetes. Follow-up of children with one or more islet autoantibodies continued on this

schedule, whereas children who were autoantibody negative were followed semi-annually after 4 years of age. The median (IQR) age at last follow-up was 9.9 (8.1–11.5) years and the age range was 8–14 years.

As of 30 November 2018, 328 children (3.9%) had developed type 1 diabetes; 168 (2.0%) before 6 years of age and 160 (1.9%) at or after 6 years of age (Table 1). The incidence of type 1 diabetes remained fairly stable (Fig. 1), but the cumulative incidence differed by enrolment site ($p = 0.0009$, Fig. 2). However, the excess risk associated with enrolment from Germany may be the consequence of the high proportion of FDRs enrolled (36.1%) compared with all the other TEDDY sites (9.2%). By 10 years of age, children from Germany and Finland had a comparable cumulative diabetes risk, as did children from Sweden and the US, but the risk in Germany and Finland remained higher than in the other two countries. The difference in geographic distribution of new type 1 diabetes patients reflects a drop in the proportion from Finland and Germany and an increase in the US while the proportion remained unchanged in Sweden ($p = 0.001$).

The HLA distribution of diabetes patients was also different with an increase among those who were DR4/4 in the older age group and a corresponding decrease among those who were DR3/3 or had FDR-specific HLA genotypes ($p = 0.005$). Those who were diagnosed with diabetes at 6 years of age or older developed a persistent confirmed autoantibody at an older mean age than those who became autoantibody positive before the age of 6 (3.5 vs 1.5 years, $p < 0.001$). The mean duration of time between the first-appearing autoantibody and the diabetes diagnosis was also much longer (5.4 years vs 1.9 years, $p < 0.001$) in older than in younger children. Similar patterns were observed when considering the appearance of multiple persistent confirmed autoantibodies (3.9 years and 1.8 years) and time until progression to diabetes (4.9 years vs 1.6 years) ($p < 0.001$ for both).

The pattern of first-appearing autoantibody was also significantly different between those who were diagnosed with diabetes before 6 years of age and those who were diagnosed older ($p = 0.001$). As might be expected, the percentage of those with GADA as the first-appearing autoantibody was higher in the older group (26.9% vs 18.5%) and the percentage of those presenting with IAA first was much higher in the younger group (44.6% vs 28.1%). Interestingly, no children in the younger group presented with IA-2A as the first-appearing autoantibody, but 10 (6.3%) among the older children did. In six of these individuals, ZnT8A autoantibodies were also present when IA-2A autoantibodies were detected.

No autoantibodies were detected in 36 (11.0%) of the children diagnosed with diabetes. The median (IQR) interval between the last autoantibody testing and the diabetes diagnosis in the 22 children from the older age group was 8.6 years (7.0–8.9) suggesting that autoantibody positivity at diagnosis, or long before it, was unknown because of lack of testing and poor protocol compliance. Among the 14 who developed type 1 diabetes in the younger age group without detected autoantibodies, the median (IQR) interval was 2.3 years (0.85–2.86). There were six children under 6 years of age whose last autoantibody test was negative within 2 years preceding their diabetes diagnosis. Whole genome sequencing was available for three, one of whom had a variant in the *HNF1A* gene (rs762703502) associated with maturity-onset diabetes of the young, type 3.

Autoantibodies at the time of diabetes diagnosis showed that a higher per cent were IAA negative prior to diagnosis among the older group (28.8%) compared with the younger group (13.1%), $p < 0.001$. A lower per cent were ZnT8A negative in the older group (34.4%) compared with in the younger group (61.9%) ($p < 0.001$).

The incidence of diabetic ketoacidosis (DKA) at diagnosis was marginally lower ($p = 0.046$) in the older age group compared with in the younger group, but the proportion who were symptomatic or not at diagnosis was not different.

The HRs from a multivariate PH model of risk factors published by the TEDDY study also revealed some differences in their association with diabetes comparing the two age groups (Table 2). The risk of type 1 diabetes in families with a mother who had type 1 diabetes significantly increased compared with families without an affected relative, in the older age group (HR 2.64, 95% CI 1.36, 5.12, $p = 0.004$) whereas it was not a significant risk factor in the younger age group (HR 1.51, 95% CI 0.75, 3.05, $p = 0.249$). However, this difference in HRs was not statistically significant, reflecting the wide confidence intervals of the individual HRs. Also, the risk of diabetes associated with DR4/4 vs DR3/3 was significant in the older (HR 4.16, 95% CI 1.99, 8.69, $p < 0.001$), but not in the younger (HR 1.26, 95% CI 0.65, 2.44, $p = 0.496$) age group. This increase in HRs was statistically significant at $p = 0.018$, suggesting that the DR4/4 genotype has a larger role in development of type 1 diabetes in older than in younger individuals. Conversely, in the older age group, the type 1 diabetes risk associated with children from Finland and Germany significantly declined (HR 3.20, 95% CI 1.88, 5.45, $p < 0.001$ to HR 1.26, 95% CI 0.73, 2.18, $p = 0.416$ and HR 2.19, 95% CI 1.27, 3.78, $p = 0.005$ to HR 0.56, 95% CI 0.25, 1.27, $p = 0.167$, respectively) ($p = 0.005$ and $p = 0.007$, respectively) compared with children from the US. Other risk factors were, or were not, statistically significant in both age groups. However, the HRs comparing the two groups were not significantly different.

Once multiple autoantibodies were observed, the rate of progression to type 1 diabetes decreased as the age at initial seroconversion increased ($p = 0.0003$, Fig. 3a). Children under 2 years of age at initial seroconversion progressed much more rapidly to type 1 diabetes once multiple autoantibodies were detected (hazard rate of 0.19) through 6 years of follow-up. If diabetes did not develop during this interval of time, the rate of progression from multiple autoantibodies to type 1 diabetes (hazard rate 0.115) was approximately the same as

Table 1 Characteristics of TEDDY children

Characteristic	No type 1 diabetes (n=8174)	Type 1 diabetes before 6 years of age (n=168)	Type 1 diabetes ≥6 years of age (n=160)	p value[a]
Country				
USA	3515 (43.0)	47 (28.0)	65 (40.6)	0.001
Finland	1711 (20.9)	54 (32.1)	38 (23.8)	
Germany	542 (6.6)	25 (14.9)	7 (4.4)	
Sweden	2406 (29.4)	42 (25.0)	50 (31.3)	
Family history				
FDR: Mother	315 (3.9)	10 (6.0)	13 (8.1)	0.106
FDR: Father	408 (5.0)	30 (17.9)	14 (8.8)	
FDR: Sibling	123 (1.5)	11 (6.5)	12 (7.5)	
General population	7328 (89.7)	117 (69.6)	121 (75.6)	
Sex				
Male	4142 (50.7)	85 (50.6)	84 (52.5)	0.730
Female	4032 (49.3)	83 (49.4)	76 (47.5)	
HLA genotype				
DR3/4	3140 (38.4)	96 (57.1)	82 (51.3)	0.005
DR4/4	1601 (19.6)	20 (11.9)	40 (25.0)	
DR4/8	1423 (17.4)	21 (12.5)	24 (15.0)	
DR3/3	1754 (21.5)	18 (10.7)	10 (6.3)	
FDR-specific[b]	256 (3.1)	13 (7.7)	4 (2.5)	
Probiotics introduction age				
≥28 days	7615 (93.2)	153 (91.1)	151 (94.4)	0.251
<28 days	559 (6.8)	15 (8.9)	9 (5.6)	
Weight z score at 12 months				
n	7460	161	149	
Mean (SD)	−0.1 (1.0)	−0.0 (1.1)	0.0 (1.0)	
Median (IQR)	−0.1 (−0.8–0.6)	0.0 (−0.8–0.7)	−0.0 (−0.6–0.7)	0.582
rs1004446_A (*INS*)				
No	2946 (39.5)	84 (52.5)	73 (49.0)	0.538
Yes	4521 (60.5)	76 (47.5)	76 (51.0)	
rs2476601_A (*PTPN22*)				
No	5979 (80.1)	102 (63.8)	102 (68.5)	0.383
Yes	1488 (19.9)	58 (36.3)	47 (31.5)	
rs10517086_A				
No	3839 (51.4)	62 (38.8)	73 (49.0)	0.070
Yes	3628 (48.6)	98 (61.3)	76 (51.0)	
rs2292239_T (*ERBB3*)				
No	3438 (46.0)	52 (32.5)	67 (45.0)	0.024
Yes	4028 (54.0)	108 (67.5)	82 (55.0)	
rs3184504_T (*SH2B3*)				
No	2314 (31.0)	41 (25.6)	43 (28.9)	0.523
Yes	5153 (69.0)	119 (74.4)	106 (71.1)	
rs12708716_G (*CLEC16A*)				
No	3278 (44.0)	78 (48.8)	82 (55.0)	0.269
Yes	4170 (56.0)	82 (51.3)	67 (45.0)	
rs3825932_T (*CTSH*)				
No	3079 (41.2)	80 (50.0)	75 (50.3)	0.953
Yes	4387 (58.8)	80 (50.0)	74 (49.7)	

Table 1 (continued)

Characteristic	No type 1 diabetes ($n = 8174$)	Type 1 diabetes before 6 years of age ($n = 168$)	Type 1 diabetes ≥6 years of age ($n = 160$)	p value[a]
rs7111341_T (*INS*)				
No	4031 (54.0)	104 (65.0)	91 (61.1)	0.475
Yes	3436 (46.0)	56 (35.0)	58 (38.9)	
rs11711054_G (*CCR5*)				
No	3694 (49.5)	65 (40.6)	69 (46.3)	0.314
Yes	3765 (50.5)	95 (59.4)	80 (53.7)	
rs428595_A (*PPIL2*)				
No	7134 (96.4)	145 (91.8)	133 (92.4)	0.850
Yes	266 (3.6)	13 (8.2)	11 (7.6)	
rs113306148_T (*PLEKHA1*)				
No	7277 (97.5)	149 (93.1)	140 (94.0)	0.766
Yes	190 (2.5)	11 (6.9)	9 (6.0)	
rs73043122_C (*RNASET2*)				
No	7263 (97.3)	151 (95.0)	139 (93.3)	0.530
Yes	202 (2.7)	8 (5.0)	10 (6.7)	
Age at type 1 diabetes diagnosis (years)				
n		168	160	
Mean (SD)		3.3 (1.5)	8.9 (1.8)	
Median (IQR)		3.1 (2.0–4.6)	8.7 (7.5–10.1)	<0.001
Age at persistent confirmed autoantibody (years)				
n	499	154	138	
Mean (SD)	5.1 (3.1)	1.5 (0.8)	3.5 (2.4)	
Median (IQR)	4.6 (2.3–7.7)	1.2 (0.8–1.8)	2.6 (1.9–4.5)	<0.001
Duration of time between first-appearing autoantibody and diagnosis (years)				
n		154	138	
Mean (SD)		1.9 (1.4)	5.4 (2.5)	
Median (IQR)		1.6 (0.6–2.9)	5.4 (3.9–6.8)	<0.001
Age at multiple persistent confirmed autoantibodies (years)				
n	208	133	121	
Mean (SD)	5.7 (3.0)	1.8 (0.9)	3.9 (2.1)	
Median (IQR)	5.5 (3.1–8.4)	1.5 (1.1–2.2)	3.3 (2.3–5.1)	<0.001
Duration of time between multiple appearing autoantibodies and diagnosis (years)				
n		133	121	
Mean (SD)		1.6 (1.3)	4.9 (2.3)	
Median (IQR)		1.3 (0.6–2.7)	5.1 (3.3–6.3)	<0.001
Autoantibody status at seroconversion				
None	7675 (93.9)	14 (8.3)	22 (13.8)	0.001
GADA only	272 (3.3)	31 (18.5)	43 (26.9)	
IA2A only	11 (0.1)	0 (0.0)	10 (6.3)	
IAA only	174 (2.1)	75 (44.6)	45 (28.1)	
GADA, IA2A	5 (0.1)	1 (0.6)	3 (1.9)	
GADA, IAA	29 (0.4)	36 (21.4)	29 (18.1)	
IA2A, IAA	4 (0.0)	1 (0.6)	2 (1.3)	
GADA, IA2A, IAA	4 (0.0)	10 (6.0)	6 (3.8)	
Persistent confirmed GADA before or at type 1 diabetes diagnosis				
No		50 (29.8)	45 (28.1)	0.744
Yes		118 (70.2)	115 (71.9)	

Table 1 (continued)

Characteristic	No type 1 diabetes ($n = 8174$)	Type 1 diabetes before 6 years of age ($n = 168$)	Type 1 diabetes ≥6 years of age ($n = 160$)	p value[a]
Persistent confirmed IAA before or at type 1 diabetes diagnosis				
No		22 (13.1)	46 (28.8)	<0.001
Yes		146 (86.9)	114 (71.3)	
Persistent confirmed IA2A before or at type 1 diabetes diagnosis				
No		64 (38.1)	46 (28.8)	0.073
Yes		104 (61.9)	114 (71.3)	
Persistent confirmed ZnT8A before or at type 1 diabetes diagnosis				
No		104 (61.9)	55 (34.4)	<0.001
Yes		64 (38.1)	105 (65.6)	
DKA at type 1 diabetes diagnosis				
No		151 (89.9)	153 (95.6)	0.046
Yes		17 (10.1)	7 (4.4)	
Symptomatic at type 1 diabetes diagnosis				
No		68 (40.5)	76 (47.5)	0.200
Yes		100 (59.5)	84 (52.5)	

Data are presented as number (percentage) unless otherwise indicated

For each SNP, the minor allele is indicated and data are divided by children with (yes) and without this allele (no)

[a] p value of comparing each characteristic between individuals with type 1 diabetes before 6 years of age and individuals with type 1 diabetes ≥6 years of age. Wilcoxon's rank tests were performed for continuous variables and χ^2 tests were performed for categorical variables

[b] FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9

the rate of progression to type 1 diabetes in the group who initially developed autoantibodies at an older age (hazard rate range from 0.072 to 0.116) irrespective of the age of seroconversion. Additionally, the rate of progression from multiple autoantibodies to type 1 diabetes was statistically associated with a family history of type 1 diabetes in the younger age group, but not in the older age group ($p = 0.25$, Fig. 3b).

Age at the onset of multiple autoantibodies, as a continuous variable, was also included in the analysis to explore whether the age groupings introduced artificial associations when comparing risk factors for early type 1 diabetes onset compared with later type 1 diabetes onset. Age at the onset of multiple autoantibodies was a highly significant factor in each age group (HR 0.56, 95% CI 0.45, 0.70, $p < 0.001$ and HR 0.83, 95% CI 0.75, 0.91, $p < 0.001$) showing decreasing risk with increasing age in both. After adjusting for the age at the development of multiple autoantibodies, the only remaining type 1 diabetes risk factors were family history of type 1 diabetes (father with type 1 diabetes vs those without family history of type 1 diabetes in the younger age group and mother or sibling with type 1 diabetes vs those without this type 1 diabetes family history in the older age group), and rs1004446_A (*INS*) (HR 0.55, $p = 0.001$), rs428595_A (*PPIL2*) (HR 1.88, $p = 0.043$) and rs10517086_A (HR 1.45, $p = 0.033$) in the younger age group and rs3825932_T (*CTSH*) (HR 0.57, $p = 0.002$), rs428595_A (*PPIL2*) (HR 1.97, $p = 0.044$) and rs73043122_C (*RNASET2*) (HR 2.70, $p = 0.008$) in the older age group.

Discussion

The proportion of children who were diagnosed with type 1 diabetes differed by geography between the younger and older age groups, despite the commonality of the high-risk genotypes across the TEDDY sites. Life-table analysis revealed that, over time, diabetes risk among the younger children residing in Finland was greatest, but declined proportionally as the children got older. Diabetes risk in the other sites remained relatively constant; the USA together with Sweden and Finland together with Germany were comparable, but the two country pairs were different. Older children more often presented with GADA as the first-appearing autoantibody and had a different HLA genotype (significantly less HLA DR3/3) than those who developed type 1 diabetes at an earlier age who predominantly presented with IAA as the first-appearing autoantibody. The number of children presenting with IAA as the first-appearing autoantibody declined with increasing age, whereas the incidence of GADA as the first-appearing autoantibody remained relatively constant over the age range. These results confirm earlier findings [e.g., the

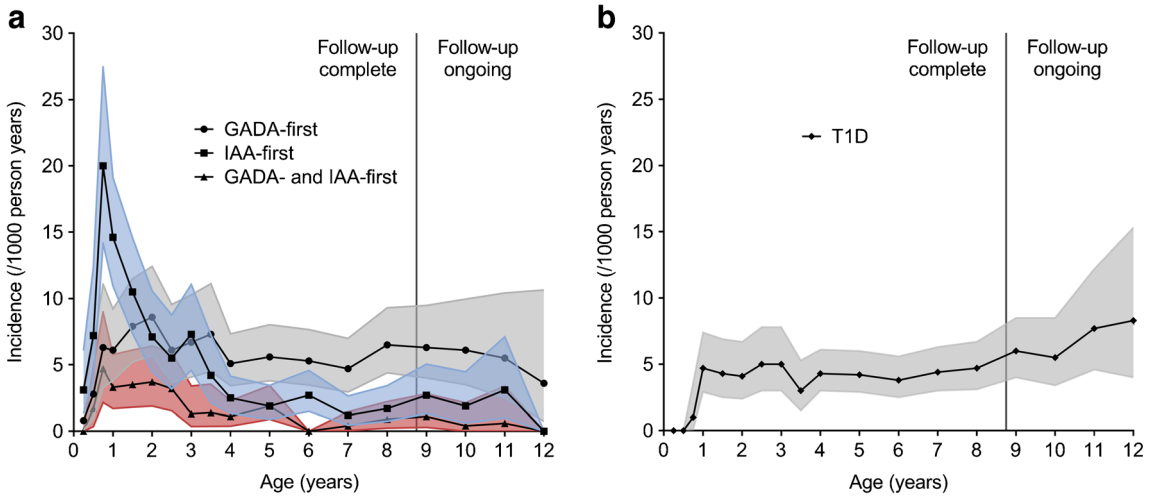

Fig. 1 Type 1 diabetes incidence by age-specific incidence of islet cell autoantibodies (**a**) and type 1 diabetes (**b**). T1D, type 1 diabetes

German BABYDIAB study [15], and the Finnish DIPP study [16, 17]] even in this HLA-defined high-risk population.

A new finding was that diabetes risk after the appearance of multiple autoantibodies did not differ between type 1 diabetes-affected and unaffected families, nor did the relationship of the affected family member to the TEDDY child. Initial seroconversion before 2 years of age was accompanied by higher diabetes risk after the appearance of multiple autoantibodies, but in children whose initial seroconversion to autoantibody positive was after 2 years of age, the risk did not decrease with increasing age of initial seroconversion. To complete the picture, the risk of initial seroconversion and progression to multiple autoantibodies decreased with increasing age, but once multiple autoantibodies were detected, the risk of progression did not decline with increasing age at seroconversion. Coupled with the changing picture of autoantibody presentation, it appears that autoimmunity at an early age is a more aggressive form of the disease.

These results underline the importance of taking into account the age at development of multiple autoantibodies when evaluating risk factors for progression to diabetes diagnosis. The HLA genotype, most SNPs, and family history were not significantly associated with early vs late diabetes diagnosis when taking into account the age at seroconversion to multiple autoantibodies. The implication is that they are risk factors for islet autoimmunity, but not necessarily for progression to diabetes once multiple autoantibodies have been observed.

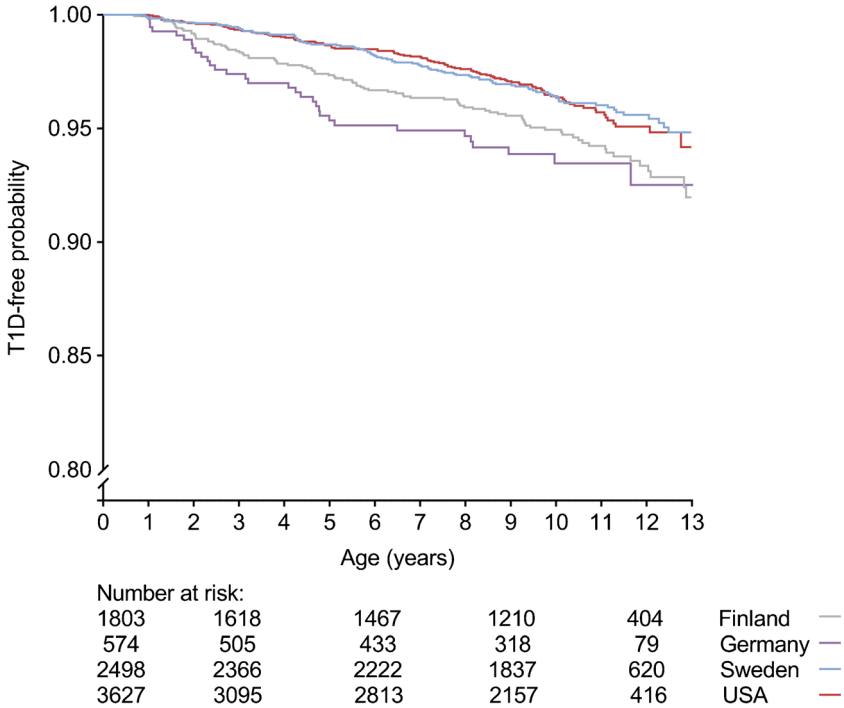

Fig. 2 Kaplan–Meier curve of type 1 diabetes (across all ages) by country of origin ($p = 0.0009$ from logrank test). T1D, type 1 diabetes

Table 2 HR, adjusted for covariates from the multiple PH analysis, of TEDDY published risk factors for type 1 diabetes

		Type 1 diabetes before 6 years of age		Type 1 diabetes ≥6 years of age		
Factor	Comparison	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* value[a]
Sex	Male vs female	1.06 (0.77, 1.46)	0.715	1.12 (0.80, 1.57)	0.507	0.819
Family history of type 1	FDR mother vs GP	1.51 (0.75, 3.05)	0.249	2.64 (1.36, 5.12)	0.004	0.256
Diabetes	FDR father vs GP	3.24 (1.99, 5.26)	<0.001	2.41 (1.31, 4.41)	0.005	0.452
	FDR sibling vs GP	4.55 (2.40, 8.62)	<0.001	5.13 (2.69, 9.80)	<0.001	0.795
HLA genotype	DR4/4 vs DR3/3	1.26 (0.65, 2.44)	0.496	4.16 (1.99, 8.69)	<0.001	0.018
	DR3/4 vs DR3/3	2.79 (1.63, 4.77)	<0.001	4.40 (2.19, 8.82)	<0.001	0.311
	DR4/8 vs DR3/3	1.50 (0.77, 2.93)	0.237	3.36 (1.52, 7.45)	0.003	0.127
	FDR-specific[b] vs DR3/3	1.60 (0.69, 3.70)	0.269	1.29 (0.38, 4.44)	0.683	0.777
Country	Finland vs USA	3.20 (1.88, 5.45)	<0.001	1.26 (0.73, 2.18)	0.416	0.005
	Germany vs USA	2.19 (1.27, 3.78)	0.005	0.56 (0.25, 1.27)	0.167	0.007
	Sweden vs USA	1.20 (0.76, 1.89)	0.436	0.72 (0.47, 1.09)	0.123	0.098
Probiotics introduction age	<28 days vs ≥28 days	0.86 (0.49, 1.51)	0.606	0.94 (0.46, 1.94)	0.871	0.852
Weight at 12 months	z-score	1.10 (0.94, 1.30)	0.223	1.21 (1.03, 1.44)	0.024	0.426
Child conditions before first clinical visit (age 3 months)	Upper resp. (Yes vs No)	1.43 (1.00, 2.04)	0.053	1.00 (0.67, 1.50)	0.999	0.198
	Lower resp. (Yes vs No)	0.85 (0.49, 1.45)	0.545	1.24 (0.75, 2.04)	0.408	0.314
	Diarrhoea	1.01 (0.57, 1.80)	0.973	0.87 (0.45, 1.67)	0.672	0.733
	Rash (Yes vs No)	0.66 (0.42, 1.04)	0.076	0.93 (0.62, 1.41)	0.747	0.275
rs1004446_A (*INS*)	Yes vs No	0.67 (0.48, 0.92)	0.014	0.67 (0.48, 0.95)	0.022	0.964
rs2476601_A (*PTPN22*)	Yes vs No	2.04 (1.46, 2.84)	<0.001	1.72 (1.20, 2.47)	0.003	0.503
rs10517086_A	Yes vs No	1.48 (1.07, 2.05)	0.019	1.04 (0.75, 1.45)	0.808	0.141
rs2292239_T (*ERBB3*)	Yes vs No	1.67 (1.19, 2.34)	0.003	1.06 (0.76, 1.48)	0.740	0.063
rs3184504 _T(*SH2B3*)	Yes vs No	1.23 (0.85, 1.77)	0.275	1.07 (0.74, 1.55)	0.731	0.599
rs12708716_G (*CLEC16A*)	Yes vs No	0.82 (0.60, 1.13)	0.222	0.64 (0.46, 0.89)	0.009	0.287
rs3825932_T (*CTSH*)	Yes vs No	0.76 (0.55, 1.04)	0.087	0.66 (0.47, 0.93)	0.017	0.581
rs7111341_T (*INS*)	Yes vs No	0.68 (0.48, 0.96)	0.026	0.77 (0.54, 1.09)	0.142	0.616
rs11711054_G (*CCR5*)	Yes vs No	1.46 (1.06, 2.02)	0.021	1.15 (0.83, 1.61)	0.404	0.315
rs428595_A (*PPIL2*)	Yes vs No	2.13 (1.20, 3.80)	0.010	2.10 (1.13, 3.92)	0.019	0.972
rs113306148_T (*PLEKHA1*)	Yes vs No	2.34 (1.25, 4.38)	0.008	2.21 (1.07, 4.57)	0.032	0.908
rs73043122_C (*RNASET2*)	Yes vs No	2.31 (1.12, 4.76)	0.023	2.54 (1.27, 5.06)	0.008	0.856

7433 individuals with 296 type 1 diabetes events (155 in the first 6 years and 141 after 6 years of age) were included in the analysis because values of SNPs and/or weight at 12 months of age were missing. For each SNP, the minor allele is indicated and children with this allele (yes) were compared with children without it (no)

The top two principal components from the Immunochip SNP were included as covariates in the Cox PH model

[a] *p* value for comparing the HR in the first 6 years vs the HR after 6 years of age

[b] FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9

Lower resp. lower respiratory tract infection; *Upper resp*. upper respiratory tract infection

Type 1 diabetes risk factors were relatively consistent across the two age groups. Some reached statistical significance in one age group but not in the other, but the difference in HRs between the age groups was not statistically significant. This could be an artifact caused by the age groupings. Nonetheless, it showcases the caution that should be exercised when trying to generalise findings beyond the population actually studied. The other important consideration is that the strength (i.e., the magnitude of the estimate of the HR along with its statistical significance) is derived from a multivariate analysis, which, by definition, adjusts for all the variables considered in the model. Hence, the results reflect the additive or independent contribution of each variable considered after the contribution of all the other variables have been considered. Hence, findings that are nonsignificant, or only marginally significant, might be completely different if all the variables in the model were independent (uncorrelated).

This study is not without limitations. The characteristics of children who develop type 1 diabetes in the TEDDY study

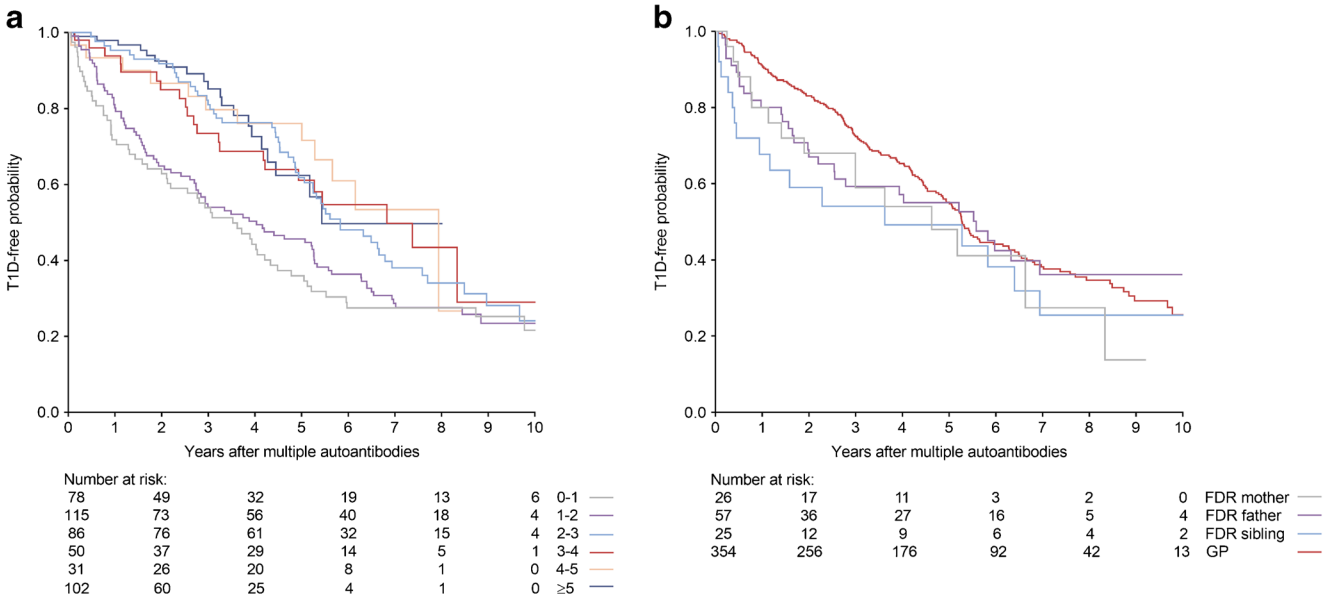

Fig. 3 Type 1 diabetes risk since developing multiple autoantibodies by (**a**) age of initial seroconversion and (**b**) family history of type 1 diabetes. T1D, type 1 diabetes

might not be generalisable to other HLA-defined populations. Despite this study's size of 8502 children, there are still relatively few type 1 diabetes cases. Yet, the before and after age 6 groups consist of nearly exactly the same number of children. This suggest that differences between the two age-defined cohorts were not due to an imbalance in the numbers.

The predominance of IAA first as the single presenting autoantibody in the very young age group compared with the predominance of GADA first as the single presenting autoantibody in the older age groups is entirely consistent with the observed age-related association of exposures and both HLA and non-HLA genotypes. However, caution should be exercised in generalising the results presented here beyond the age range in which they have been discovered and the selected high-risk HLA subgroups that make up the TEDDY population. Yet, the TEDDY children represent, depending on country, about 40–50% of children expected to develop diabetes before 18 years of age [3]. The age at screening for the presence of islet autoantibodies in both the general population or among FDRs and its associated heterogeneity with respect to diabetes risk factors [18, 19] should be taken into account when individuals are randomised in secondary prevention studies of type 1 diabetes.

Finally, the report of study findings in a large epidemiological study, like TEDDY, involves many statistical comparisons, increasing the chance of spurious findings. In our opinion, using multivariate analyses to incorporate adjustments is a practical approach to this issue, whereas adjusting the significance threshold for multiple comparisons is not. There are arguments to be made for and against these approaches [20–22]. We have chosen to not make adjustments for multiple comparisons and advise readers to consider these findings in the context of the published literature on similar populations.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05514-3.

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Data availability The datasets generated and analysed during the current study will be made available in the NIDDK Central Repository at https://www.niddkrepository.org/studies/teddy.

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AZ, and BA designed the study and reviewed/edited the manuscript. JK and XL are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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