An Age-Related Exponential Decline in the Risk of Multiple Islet Autoantibody Seroconversion During Childhood

Ezio Bonifacio,[1,2] Andreas Weiß,[3] Christiane Winkler,[3,4] Markus Hippich,[3] Marian J. Rewers,[5] Jorma Topari,[6] Åke Lernmark,[7] Jin-Xiong She,[8] William A. Hagopian,[9] Jeffrey P. Krischer,[10] Kendra Vehik,[10] Desmond A. Schatz,[11] Beena Akolkar,[12] and Anette-Gabriele Ziegler,[3,4,13,14] for the TEDDY Study Group*

[1]Center for Regenerative Therapies Dresden, Faculty of Medicine, TU Dresden, Dresden, Germany
[2]Paul Langerhans Institute Dresden of the Helmholtz Center Munich at University Hospital Carl Gustav Carus and Faculty of Medicine, TU Dresden, Dresden, Germany
[3]Institute of Diabetes Research, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich-Neuherberg, Germany
[4]Forschergruppe Diabetes e.V. at Helmholtz Zentrum München, German Research Center for Environmental Health, Munich-Neuherberg, Germany
[5]Barbara Davis Center for Childhood Diabetes, University of Colorado, Aurora, CO
[6]Department of Pediatrics, Turku University Hospital, and Research Centre for Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland
[7]Department of Clinical Sciences, Lund University/CRC, Skåne University Hospital (SUS), Malmo, Sweden
[8]Center for Biotechnology and Genomic Medicine, Medical College of Georgia, Augusta University, Augusta, GA
[9]Pacific Northwest Research Institute, Seattle, WA
[10]Health Informatics Institute, Morsani College of Medicine, University of South Florida, Tampa, FL
[11]Department of Pediatrics, University of Florida Diabetes Institute, Gainesville, FL
[12]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD
[13]Forschergruppe Diabetes, Technical University Munich, at Klinikum rechts der Isar, Munich, Germany
[14]German Center for Diabetes Research (DZD e.V.), Munich, Germany

Corresponding authors: Ezio Bonifacio, ezio.bonifacio@tu-dresden.de, and Anette-Gabriele Ziegler, anette-g.ziegler@helmholtz-muenchen.de

OBJECTIVE

Islet autoimmunity develops before clinical type 1 diabetes and includes multiple and single autoantibody phenotypes. The objective was to determine age-related risks of islet autoantibodies that reflect etiology and improve screening for presymptomatic type 1 diabetes.

RESEARCH DESIGN AND METHODS

The Environmental Determinants of Diabetes in the Young study prospectively monitored 8,556 genetically at-risk children at 3- to 6-month intervals from birth for the development of islet autoantibodies and type 1 diabetes. The age-related change in the risk of developing islet autoantibodies was determined using landmark and regression models.

RESULTS

The 5-year risk of developing multiple islet autoantibodies was 4.3% (95% CI 3.8–4.7) at 7.5 months of age and declined to 1.1% (95% CI 0.8–1.3) at a landmark age of 6.25 years ($P < 0.0001$). Risk decline was slight or absent in single insulin and GAD autoantibody phenotypes. The influence of sex, *HLA*, and other susceptibility genes on risk subsided with increasing age and was abrogated by age 6 years. Highest sensitivity and positive predictive value of multiple islet autoantibody phenotypes for type 1 diabetes was achieved by autoantibody screening at 2 years and again at 5–7 years of age.

CONCLUSIONS

The risk of developing islet autoimmunity declines exponentially with age, and the influence of major genetic factors on this risk is limited to the first few years of life.

Age is a modulator of autoimmune diseases (1). Most autoimmune diseases show periods of high and low incidence, and these differences are likely to have an etiological basis. Type 1 diabetes is an autoimmune disease in which the presymptomatic stage is defined by the presence of autoantibodies against multiple islet autoantigens (2). Most children with multiple islet autoantibodies progress to clinical type 1 diabetes (3). The peak incidence of the development of islet autoantibodies occurs in the first years of life (4–6). This early peak also indicates that the risk of developing islet autoantibodies attenuates with age and that age influences the child's risk for developing islet autoantibodies, as demonstrated in relatives of patients with type 1 diabetes (7).

The rate at which the risk of islet autoantibody seroconversion attenuates may also provide insight into the timing of events that cause or protect against autoimmunity. Here, we examined the age-related decline in risk in The Environmental Determinants of Diabetes in the Young (TEDDY) study (8). This prospective study monitored from birth the development of islet autoantibodies in >8,000 children, who were selected based on their genetic predisposition to type 1 diabetes. The TEDDY study includes quarterly measurements of autoantibodies to multiple pancreatic antigens, providing an unprecedented ability to model seroconversion to distinct autoantibody phenotypes throughout childhood. The aim of this study was to determine the rate of change in the risk of type 1 diabetes-associated autoimmunity with increasing age and relative to genetics, demographics, and islet autoantibody phenotypes. The findings were used to identify optimal ages for islet autoantibody screening and to provide etiological models of islet autoimmunity.

RESEARCH DESIGN AND METHODS

Study Design

TEDDY is a prospective cohort study that was designed to identify environmental causes of type 1 diabetes (ClinicalTrials.gov NCT00279318). It includes three clinical research centers in the U.S. (Colorado, Georgia/Florida, Washington State) and three in Europe (Finland, Germany, Sweden). The study design and methods were previously published (8). To identify infants at high genetic risk, newborns were screened for HLA DR-DQ genotypes associated with type 1 diabetes (Supplementary Methods). Participants were enrolled in the prospective follow-up before 4.5 months of age. They were followed up every 3 months until age 4 years and at least semiannually thereafter until 15 years of age. For all participants, written informed consent was obtained from a parent or primary caretaker for genetic screening, and separate consent was obtained for participation in the prospective follow-up. The study was approved by the local Institutional Review or Ethics Boards at each site and is monitored by an External Evaluation Committee formed by the National Institutes of Health.

Participants

Between September 2004 and February 2010, the TEDDY study screened 424,788 newborns. Of those, 21,589 had HLA genotypes of interest associated with increased risk. The parents of 8,676 infants consented to the follow-up study. Of these, 120 children, whose eligibility was not confirmed by high-resolution HLA typing, were excluded from the analyses. Therefore, 8,556 children (4,226 girls [49.4%]) were included in the analyses, of which 955 (11.2%) had a first-degree family history of type 1 diabetes (Supplementary Fig. 1 and Supplementary Table 1).

Assessments of Islet Autoantibodies (Study End Points)

Blood samples were obtained at each study visit to determine islet autoantibodies against insulin (IAA), GAD (GADA), and insulinoma antigen-2 (IA-2A). Islet autoantibody positivity (persistent confirmed) was defined as specific autoantibody presence on two consecutive or more visits 3 months apart and confirmed at two laboratories. The date of positivity was the date on which the first sample of the two consecutive samples confirming islet autoantibody positivity was taken. Multiple islet autoantibody positivity (stage 1 type 1 diabetes) was defined as multiple persistent confirmed islet autoantibodies. The date of positivity for multiple islet autoantibodies was the date on which the first sample of the two consecutive samples of the second appearing autoantibody was taken.

Islet Autoantibody Measurements and Single Nucleotide Polymorphism Typing

The levels of IAA, GADA, and IA-2A were measured in two laboratories by radiobinding assays, as previously described (8). In the U.S., all sera were assayed at the Barbara Davis Center for 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 sensitivity and specificity as well as excellent concordance (9). Single nucleotide polymorphism genotyping was performed at the Center for Public Health Genomics, University of Virginia, using the Illumina Immunochip (10). Genetic risk scores were calculated using 41 single nucleotide polymorphisms, as previously described (11).

Statistical Analyses

We performed analyses of data collected until 30 June 2019. The cumulative risks of islet autoantibodies were examined using the Kaplan-Meier method, and between-group comparisons were done using the log-rank test. To evaluate the risk at different ages, we calculated the cumulative islet autoantibody risks for children who remained islet autoantibody negative from the respective landmark to the outcome status. The autoantibody outcomes were as follows: 1) any islet autoantibody if a child was positive at two laboratories in two consecutive samples and 2) multiple islet autoantibodies (stage 1 type 1 diabetes) if a child was positive for two or more islet autoantibodies in two consecutive samples. The outcomes were subclassified into multiple islet autoantibody phenotypes (IAA first to multiple and GADA first to multiple) based on the islet autoantibody present in the first positive sample and as multiple first if the first autoantibody was unknown because the first positive sample had more than one islet autoantibody. IAA and GADA positivity that did not progress to multiple islet autoantibodies were subclassified as single IAA or single GADA if the child had been monitored and tested for ≥3 years after antibody development or if the child developed diabetes without developing multiple islet autoantibodies.

Landmark models (12) were based on the cumulative incidence curves from the respective landmark ages at 7.5 months, 2.125 years, 4.25 years, 6.25 years, and 8.25 years, which were chosen as the time points between scheduled visits. The follow-up time or horizon was set to 5 years from the landmark age. Because we expected a decline in risk (7), one-phase exponential decay functions were used to describe the 5-year horizon risk with increasing age. The curves describe the residual risk of developing islet autoantibodies in the subsequent 5 years for children who were negative at each landmark age. Curves were generated from the 5-year horizon risk at the landmark ages of 7.5 months and at 6-month intervals until 3.625 years, and at 4.25 years and at 12-month intervals until 8.25 years. For single antibody outcomes, the landmark ages >4.25 years were

excluded because an additional 3 years of follow-up were required to define these outcomes. Parameters used to describe the risks were the baseline risk at the age of 7.5 months; the plateau risk, which refers to the lowest 5-year horizon risk reached by decay before leveling off; the half-life, which is the time required for the risk between baseline and plateau to halve; the decay constant (λ), which is a measure of the decay rapidity (the larger λ, the faster the decline to the plateau is); and the r value, which represents the goodness of fit of the exponential decay curve. Relative risks between groups across time were calculated as a ratio of the 5-year risks using these curve parameters. GraphPad Prism version 8.0.1 (GraphPad Software, San Diego, CA) was used to generate the exponential decay curves, to calculate the curve parameters, and to compare the values between groups by the extra sum of squares F test. To compare relative risks at different ages, the actual 5-year risks and their CIs of the risks were used to calculate a ratio of relative risks (13). All other analyses were performed using R version 3.6.1 using the package *dynpred* (version 0.1.2). For all comparisons (log-rank tests, paired Mann-Whitney U tests, and comparison of relative risks over time), a two-tailed P value of <0.05 was considered significant.

RESULTS

In total, 809 of 8,556 children (9.46%, 95% CI 8.85–10.1) enrolled in the TEDDY study developed islet autoantibodies at a median age of 3.2 years (interquartile range [IQR] 1.5–6.5), including 471 who developed multiple islet autoantibodies within a median time of 0.3 years (IQR 0.0–1.0) after becoming islet autoantibody positive (Supplementary Fig. 1). The first autontibody-positive samples in children who developed multiple islet autoantibodies most frequently contained IAA only (166), GADA only (161), or multiple islet autoantibodies (133). Most of the 338 children with one islet autoantibody had IAA (136) or GADA (190). Most (78.4%) single autoantibody-positive children were monitored for ≥3 years or developed diabetes without testing positive for multiple islet autoantibodies.

The Risk of Islet Autoantibody Seroconversion Declined With Age

The risk of developing islet autoantibodies over a 5-year horizon decreased with

increasing landmark age (Fig. 1 and Supplementary Table 2). At the landmark age of 7.5 months, the risk over a 5-year horizon was 6.3% (95% CI 5.7–6.8) for any islet autoantibodies and 4.3% (95% CI 3.8–4.7) for multiple islet autoantibodies compared with 3.2% (95% CI 2.7–3.6) and 1.1% (95% CI 0.8–1.3), respectively, at a landmark age of 6.25 years (both $P <$ 0.0001). This translates to a fourfold reduction in the risk of developing multiple islet autoantibodies (stage 1 type 1 diabetes) among children who are islet autoantibody negative at age 6 years.

The age-related attenuation of risk could be described by a one-phase exponential decay curve ($r = 0.992$ for any islet autoantibodies and $r = 0.998$ for multiple islet autoantibodies) (Fig. 1C and D). The half-life, plateau risk, and λ were 0.85 years (95% CI 0.7–1.0), 3.1% (95% CI 3.0–3.3), and 0.82 (95% CI 0.67–0.99), respectively, for any islet autoantibodies and 1.25 years (95% CI 1.1–1.4), 1.0% (95% CI 0.8–1.1), and 0.56 (95% CI 0.50–0.62), respectively, for multiple islet autoantibodies. The risk of developing any islet autoantibodies over a 5-year horizon in children who were negative at their last test was described by

$$risk = 3.3 \times \exp^{(-0.82 \times [ageX - 0.625])} + 3.1,$$

where age X is the age at the preceding negative test. The equation for multiple islet autoantibodies was

$$risk = 3.3 \times \exp^{(-0.56 \times [ageX - 0.625])} + 1.0.$$

The Genetic Influence on Multiple Islet Autoantibody Seroconversion Diminished With Age

The baseline cumulative risk of developing multiple islet autoantibodies varied by sex, first-degree family history status, site, *HLA* genotype, and genetic risk score (Supplementary Table 1). A decay in the 5-year risk with increasing age was observed in all subgroups examined (Fig. 1, Table 1, and Supplementary Tables 3–6). The risk decay was similar between children with a first-degree relative with type 1 diabetes (λ, 0.59; 95% CI 0.52–0.68) and children in the general population (λ, 0.53; 95% CI 0.46–0.60; $P =$ 0.44) (Fig. 1E) and between children in European (λ, 0.58; 95% CI 0.50–0.67) and U.S. sites (λ, 0.52; 95% CI 0.40–0.65; $P =$

0.33) (Supplementary Fig. 2A). In contrast, the characteristics of the risk decay varied by sex (Supplementary Fig. 2B) and, in particular, genetics (Fig. 1F–H). There were marked variations in the baseline risk ($P < 0.0001$), plateau risk ($P < 0.0001$), and risk decay ($P < 0.0001$) between the *HLA* genotypes (Fig. 1F). Risks differed by *HLA* genotype at a young age but converged with increasing age so that the remaining risk in autoantibody-negative children at age 6 years was similar between the three *DR4-DQ8*–containing genotypes. The risk also converged with increasing age when children were categorized by their genetic risk score (Fig. 1G) or *INS* genotype (Supplementary Fig. 2C). Convergence was confirmed for genetic risk score categories (Fig. 1H and Supplementary Table 7), *INS* genotype (Supplementary Fig. 2D), and *DR4-DQ8*–containing genotypes, but not the *DR3*-containing genotypes (Supplementary Fig. 2E) when the 5-year risk for multiple islet autoantibodies was expressed as relative risks.

The Risk Decay Was a Feature of Multiple but Not Single Islet Autoantibody Phenotypes

Most (97.2%) of the 809 children who developed islet autoantibodies could be placed in one of five antibody profiles: single IAA, single GADA, IAA first with progression to multiple islet autoantibodies, multiple islet autoantibodies in the first positive sample, and GADA first progressing to multiple islet autoantibodies (Supplementary Fig. 1). The risk decay differed markedly among these profiles ($P < 0.0001$) (Table 1, Fig. 2, and Supplementary Table 8). The risk decay was observed for each of the multiple islet autoantibody phenotypes (Fig. 2A). The IAA-first-to-multiple phenotype showed a steep risk decline (λ, 0.81; 95% CI 0.74–0.89) with a low plateau risk (0.1%). The multiple-antibody-first phenotype also showed a steep risk decline (λ, 0.74; 95% CI 0.54–0.98), but a higher plateau risk (0.4%; $P < 0.0001$) than the IAA-first-to-multiple phenotype. The risk decline was slower in the GADA-first-to-multiple phenotype (λ, 0.28; 95% CI 0.17–0.41; $P < 0.0001$). The previously reported association of IAA with *HLA DR4-DQ8*–containing genotypes (14) was observed for the IAA-first-to-multiple and the multiple-first phenotypes across all
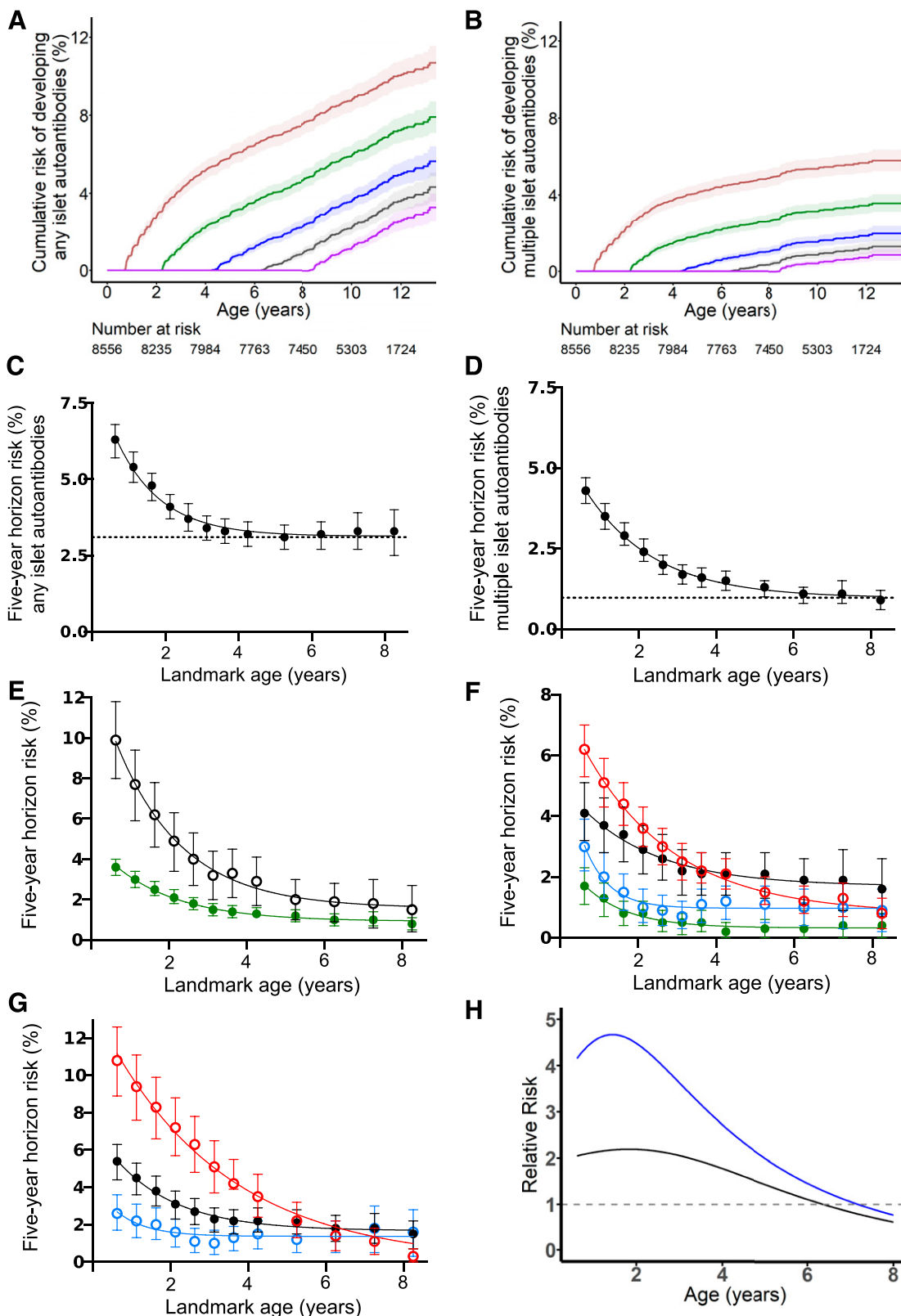
Figure 1—Cumulative risk of developing islet autoantibodies at each landmark age. Cumulative risks (line with shaded 95% CI) of developing any (A) or multiple islet autoantibodies (B) in children who were negative for the respective outcome at the ages of 7.5 months (red), 2.125 years (green), 4.25 years (blue), 6.25 years (dark green), and 8.25 years (purple). Exponential decay curves for the 5-year horizon risks for any islet autoantibodies (C) and multiple islet autoantibodies (D). The curve is represented by the equation: Risk = risk at baseline (0.625 years) × exp$^{(\lambda \times \text{age} - 0.625)}$ − plateau risk. Exponential decay curves are shown for the 5-year horizon risks of developing multiple islet autoantibodies in children with a first-degree relative with type 1 diabetes (black, n = 955) and children in the general population (green, n = 7,601) (E); children with the HLA DR3/4-DQ8 (red, n = 3,339), DR4-DQ8/ DR4-DQ8 (black, n = 1,674), DR4-DQ8/DR8 (blue, n = 1,474), and DR3/3 (green, n = 1,791) genotypes (F); and children in the general population with

Table 1—Characteristics of the one-phase exponential decay curve describing the attenuating risk of developing multiple islet autoantibodies over a 5-year horizon

Outcome and subgroup	Baseline risk at 7.5 months landmark, % (95% CI)	Half-life, years (95% CI)*	Plateau risk, % (95% CI)†	Decay constant, λ (95% CI)‡
Multiple islet autoantibody				
First-degree family history				
Yes	9.9 (9.5–10.3)	1.2 (1.0–1.4)	1.6 (1.0–1.9)	0.59 (0.52–0.67)
No	3.6 (3.5–3.7)	1.3 (1.1–1.5)	0.9 (0.7–1.0)	0.53 (0.46–0.60)
Sex				
Boys	4.6 (4.4–4.9)	1.6 (1.2–2.0)	0.9 (0.5–1.2)	0.45 (0.33–0.57)
Girls	3.9 (3.7–4.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.69 (0.56–0.84)
Site				
European sites	4.9 (4.7–5.1)	1.2 (1.0–1.4)	1.1 (0.9–1.2)	0.58 (0.50–0.67)
U.S. sites	3.6 (3.3–3.8)	1.3 (1.1–1.7)	0.8 (0.6–1.0)	0.52 (0.40–0.65)
HLA genotype				
HLA DR3/4-DQ8	6.2 (6.0–6.4)	1.6 (1.4–1.9)	0.8 (0.5–1.0)	0.43 (0.37–0.50)
HLA DR4-DQ8/DR4-DQ8	4.2 (3.9–4.5)	1.4 (1.0–1.9)	1.7 (1.4–1.9)	0.50 (0.36–0.67)
HLA DR4-DQ8/DR8	3.0 (2.7–3.4)	0.4 (0.3–0.6)	1.0 (0.8–1.1)	1.59 (1.09–2.37)
HLA DR3/3	1.7 (1.5–1.9)	0.8 (0.6–1.1)	0.3 (0.2–0.4)	0.89 (0.64–1.22)
Genetic risk score				
Upper quartile	11.2 (10.6–11.9)	2.2 (1.9–2.4)	0 (0–0.4)	0.32 (0.29–0.37)
25th–75th percentile	5.4 (5.2–5.7)	1.1 (0.9–1.4)	1.7 (1.5–1.9)	0.62 (0.51–0.75)
Lower quartile	2.7 (2.1–3.2)	0.5 (0.2–1.3)	1.4 (1.1–1.6)	1.27 (1.12–1.61)
Autoantibody phenotype				
IAA first to multiple	1.7 (1.6–1.8)	0.85 (0.8–0.9)	0.1 (0.07–0.14)	0.81 (0.74–0.89)
Multiple first	1.2 (1.1–1.3)	0.9 (0.7–1.3)	0.4 (0.4–0.5)	0.74 (0.54–0.98)
GADA first to multiple	1.5 (1.4–1.6)	2.5 (1.7–4.0)	0.2 (0.0–0.4)	0.28 (0.17–0.41)
Single IAA	0.8 (0.7–0.9)	3.4 (1.1–4.4)	0.1 (0.0–0.4)	0.21 (0.16–0.64)
Single GADA	1.0 (0.8–1.2)	No decay observed		

*The half-life describes the time required for the risk between baseline and plateau to halve. †The plateau risk represents the lowest risk reached by decay. ‡The decay constant is a measure of the decay rapidity, whereby a larger value represents a faster decline to the plateau risk.

landmark ages (Supplementary Fig. 3A and B and Supplementary Table 9). The GADA-first-to-multiple phenotypes was associated with HLA DR3-containing genotypes at the youngest landmark ages (Supplementary Fig. 3C).

The similarities in the DR4-DQ8–associated IAA-first-to-multiple and multiple-first phenotypes suggested that these may form one phenotype (IAA/multiple first) that is distinct to the DR3-associated GADA-first phenotype. We, therefore, examined these two outcomes separately and asked how risk declined in relation to susceptibility conferred by genes other than HLA DR-DQ (Fig. 2B and Supplementary Table 7). For both phenotypes, the relative risk in the children with genetic risk scores in the upper quartile compared with the remainder was ~2 at age 7.5 months, and for the GADA-first phenotype, the relative risk peaked at ~3 years. Both subsequently declined to parity (1.0).

Unlike the multiple islet autoantibody phenotypes, we found no risk decay with age for the single GADA phenotype and a slow exponential decay for the single IAA phenotype (λ, 0.21; 95% CI 0.16–0.64) (Fig. 2C). The previously reported association of GADA with DR3-DQ2 (15) was observed for single GADA, which was associated with the HLA DR3/3 genotype and also with HLA DR3/4-DQ8 after age 2 years (Supplementary Fig. 3E).

At the landmark age of 7.5 months, the 5-year horizon risk of developing the multiple islet autoantibody phenotype was twofold greater than the risk of developing the single autoantibody phenotype (4.3% vs. 2.0%; P < 0.0001). In contrast, at the landmark age of 6.25 years, the risk of the multiple autoantibody phenotype was twofold less than the risk of the single autoantibody phenotype (1.1% vs. 2.1%; P < 0.0001).

Optimal Islet Autoantibody Screening Ages

A practical aspect of the age-related islet autoantibody risk decay is how it translates into screening for presymptomatic type 1 diabetes. Important features are the ability to identify future cases of type 1 diabetes (i.e., sensitivity) and the positive predictive value (PPV) for developing type 1 diabetes in those identified as positive. Therefore, we examined the sensitivity by using type 1 diabetes by age 12 years (n = 331 children) as the outcome and the 5-year risk of developing type 1 diabetes as the measure of PPV in children who were found to be positive for multiple islet

the HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8 genotypes stratified by their genetic risk score into the upper score quartile (red, n = 1,104), 25th to 75th quartiles (black, n = 2,206), and lower quartile (blue, n = 1,103) (G). H: Also shown is the 5-year risk for multiple islet autoantibodies in children with genetic risk scores in the highest quartile relative to the children in the lowest quartile (blue) and to the children in the 25th to 75th quartiles (black).
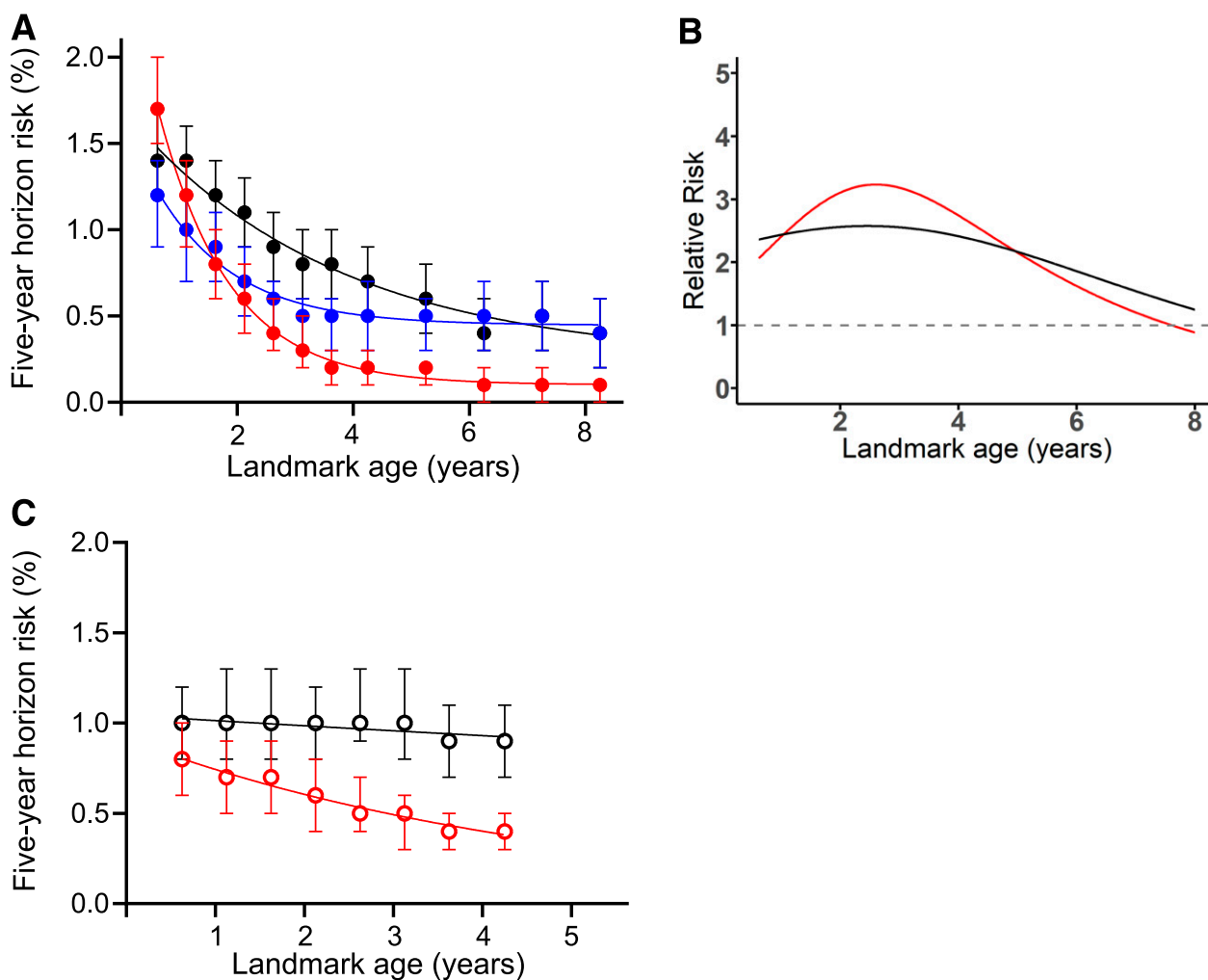
Figure 2—Exponential risk decay curves for islet autoantibody phenotypes. Islet autoantibodies were categorized into the multiple (*A* and *B*) and single (*C*) islet autoantibody phenotypes. *A*: Exponential 5-year horizon risk decay curves for developing the multiple-first (blue), IAA-first-to-multiple (red), and GADA-first-to-multiple (black) phenotypes. *B*: The 5-year risk for developing the IAA-first-to-multiple or multiple-first phenotype (black line) or in the GADA-first-to-multiple phenotype (red line) in children categorized by their genetic risk scores for genes other than the *HLA DR-DQ* genotype. The curves show the relative risks for children with scores in the highest quartile (upper 25th percentile) relative to the children with scores in the lower three quartiles (lower 75th percentile). *C*: Exponential 5-year horizon risk decay curves for developing single IAA (red) and single GADA (black) phenotypes.

autoantibodies if screening was performed at single time points from age 1 year to 8 years (Fig. 3*A*). The sensitivity reached a peak if screening was performed at age 4 years (37.2%; 95% CI 32.0–42.6). At least one-third of the cases of type 1 diabetes (sensitivity >33%) could be identified by a single screening visit between 3 and 5 years of age. The PPV was highest when children were identified as positive for multiple antibodies at the age of 1 year (84%; 95% CI 60.7–93.5) or 2 years (68.1%; 95% CI 57.6–76.0). The PPV remained ∼50% when identified from the age of 3 years.
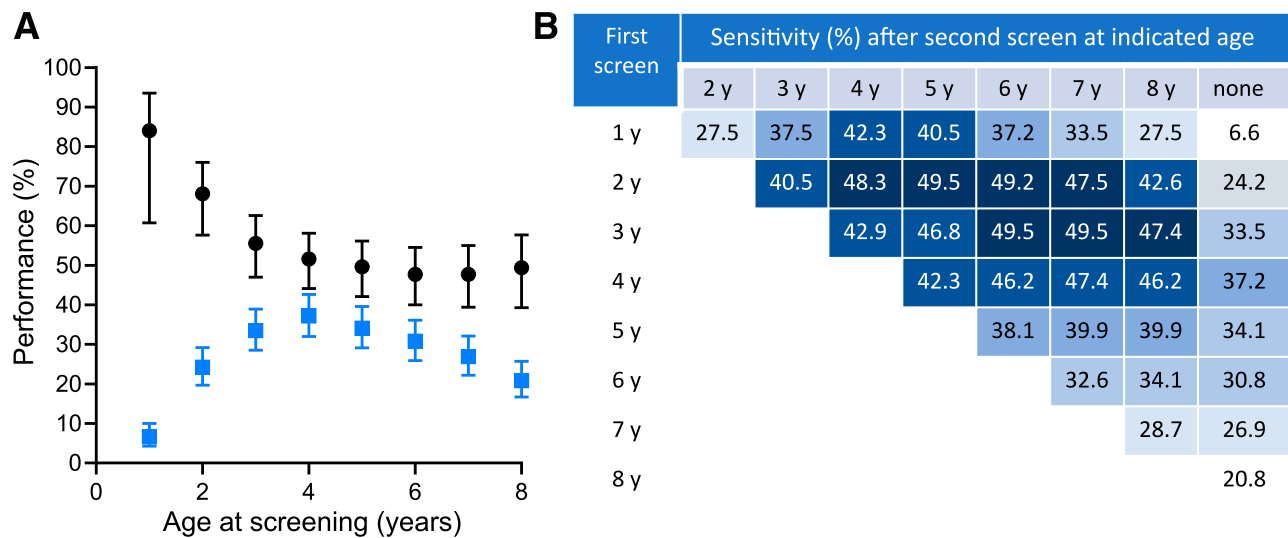
Screening for any islet autoantibodies increased sensitivity, especially at younger ages, but was associated with lower PPV than that of multiple islet autoantibodies at all ages ($P = 0.008$) (Supplementary Table 10). Except for children identified at the age of 1 year, the PPV in children who were identified with a single islet autoantibody was <15%. A two-point screening model for multiple islet autoantibodies was also considered (Fig. 3*B*). The sensitivity increased to almost 50% if screening for multiple islet autoantibodies was performed at the age of 2 years and again at 5 or 6 years, or at the age of 3 years and again at 6 or 7 years. Of the 331 who developed type 1 diabetes by age 12 years, 43 (13.0%) developed diabetes before age 2 years and 16 (4.8%) developed multiple islet autoantibodies after age 7 years.

CONCLUSIONS

We used landmark modeling to assess the influence of age on the risk of developing type 1 diabetes-associated autoantibodies in genetically at-risk children. The risk of developing multiple islet autoantibodies was decreased markedly with age. The influence of *HLA* and other susceptibility genes on risk also declined and was absent or very weak at the landmark age of 6.25 years. In contrast, the risk of developing one, but not multiple islet autoantibodies, remained constant and was minimally influenced by *HLA* genotypes.

The strengths of this study include the large number of children monitored from birth for up to 14 years, the high frequency and rigor of islet autoantibody

A

B

First screen	Sensitivity (%) after second screen at indicated age							
	2 y	3 y	4 y	5 y	6 y	7 y	8 y	none
1 y	27.5	37.5	42.3	40.5	37.2	33.5	27.5	6.6
2 y		40.5	48.3	49.5	49.2	47.5	42.6	24.2
3 y			42.9	46.8	49.5	49.5	47.4	33.5
4 y				42.3	46.2	47.4	46.2	37.2
5 y					38.1	39.9	39.9	34.1
6 y						32.6	34.1	30.8
7 y							28.7	26.9
8 y								20.8

Figure 3—Sensitivity and PPV of multiple islet autoantibodies. Screening for multiple islet autoantibodies was simulated at a single time point (A) and at two time points (B). A: For a single time point, the sensitivity of multiple islet autoantibodies to identify all cases of type 1 diabetes that occurred in TEDDY children by the age of 12 years (blue symbols) and the PPV calculated as the 5-year risk of progressing to type 1 diabetes in children positive for multiple islet autoantibodies (black symbols) are shown for screening at the ages of 1–8 years. Error bars represent the 95% CI. B: For the strategy of screening at two time points, the sensitivity of multiple islet autoantibodies to identify all cases of type 1 diabetes that occurred in TEDDY children by the age of 12 years is given for each combination.

testing, and the relatively large number of outcomes for each of the autoantibody phenotypes analyzed. The attenuated risk observed in our study is consistent with a recent report of children from affected families (7) and in the Diabetes Prevention Trial–Type 1 (DPT-1) study (16). Although the risk did not decrease to zero, both studies showed that the residual risk of developing multiple islet autoantibodies decreased fourfold by 6 years of age, an important finding for families with a family member with type 1 diabetes or a child with genetic features of type 1 diabetes.

A striking feature of the risk decay model was the diminishing influence of factors such as sex, *HLA* genotype, and other type 1 diabetes susceptibility genes with age. This was particularly evident for the *HLA DR3/4-DQ8* genotype, which has the strongest association with the development of islet autoantibodies and type 1 diabetes (14,17). The dominant effect of this genotype over other *HLA DR4-DQ8*–containing genotypes was absent at the landmark age of 6.25 years for all multiple islet autoantibody phenotypes. We also observed a decreasing influence of the *INS* gene and the genetic risk score on multiple islet autoantibody risk. These data suggest that a portion of the genetic contribution to the development of multiple islet autoantibodies and, therefore, type 1 diabetes subsides

before puberty. The relative reduction in the frequency of *HLA DR-DQ* risk genotypes in patients with older-onset type 1 diabetes compared with childhood onset (18), the increased contribution of several susceptibility genes to younger-onset type 1 diabetes (19), and the relatively small impact of type 1 diabetes susceptibility genes with progression to diabetes in children positive for multiple islet autoantibodies (20,21) are consistent with this finding.

It is important to note that our findings are relevant to childhood islet autoimmunity and type 1 diabetes onset. Patients who develop type 1 diabetes as adults have some, but not all, of the features of childhood type 1 diabetes. Adults often have fewer islet autoantibodies with an excess of the single GADA phenotype at diabetes onset (22). No study has monitored sufficient adult cases from early age to know when autoimmunity first appears. It is likely, however, that a portion of the adult cases derives from the children who have the single DR3-associated GADA phenotype. This phenotype appeared relatively frequently in late childhood or adolescence compared with other phenotypes.

The risk decay with age is likely to reflect pathogenetic mechanisms and the etiology of type 1 diabetes-associated islet autoimmunity. We suggest three potential models (Supplementary

Fig. 4). The stimulus decay model proposes that environmental stimuli for developing multiple islet autoantibodies are strongest or most frequent in the 1st year of life and attenuate thereafter. The early stimulus model suggests that the stimuli are restricted to the 1st year of life and that the likelihood of responding with islet autoantibodies is an exponential function of time. In both models, the potential roles of exposures or the host's responses to the exposures are strongest in the 1st year of life. The third model, called the response decay model, suggests that the stimuli are present throughout childhood but that the propensity for autoimmune responses decreases exponentially with age. Observations that support a response decay model include the association between type 1 diabetes and early but not later viral infection (23) and the faster rate of progression to diabetes in children who develop multiple islet autoantibodies in the first years of life (3). Understanding which of the three models correctly reflects the pathogenesis has important implications for primary prevention strategies. Models 1 and 2 will likely require strategies to reduce exposure, whereas model 3 will require modulation of host response.

The findings also have implications for when to test children for islet autoantibodies to diagnose presymptomatic type 1 diabetes and recruit into clinical

trials (24,25). No single time point captured the majority of cases of type 1 diabetes that occurred by the age of 12 years in the study. The highest sensitivity was achieved by screening between 3 and 5 years of age, similar to the screening age in a general population in the Fr1da study (24). Screening genetically at-risk TEDDY children at two time points increased sensitivity. A combination of testing for islet autoantibodies at the age of 2 years and then at 5–7 years may be advantageous by allowing us to identify at the age of 2 years young children positive for multiple islet autoantibodies with a relatively fast progression to clinical type 1 diabetes. Further testing beyond age 7 years was more likely to identify children who developed persistent single islet autoantibodies than children who developed multiple islet autoantibodies. Further refinement of the single islet autoantibody phenotypes using alternative methods may help us to distinguish single islet autoantibody phenotypes relevant to type 1 diabetes (26).

A limitation of this study is the a priori selection of children based on their *HLA* genotype, which limits the generalizability of the findings to lower genetic risk strata that represent ~50% of type 1 diabetes cases throughout life (14). Another limitation is the smaller number of children monitored until teenage years, which prevents us from projecting the residual risk into late adolescence or adulthood and may lead to misclassification of some children positive for a single antibody (27). It is also possible that more frequent sampling would classify some of the multiple-first-islet-autoantibody outcomes as IAA first to multiple or GADA first to multiple. Of note, the multiple-first phenotype shared features with the IAA-first-to-multiple phenotype, and both phenotypes differed from the GADA-first-to-multiple phenotype in the decay constant and *HLA* associations. Therefore, we suggest that the multiple-first- and the IAA-first-to-multiple are similar phenotypes that may represent a distinct endotype to the GADA-first-to-multiple phenotype (17,28). The association of GADA with diseases that manifest throughout life also supports this hypothesis (19,29). We did not include autoantibodies to zinc transporter 8 in the analysis because these were only measured in children who had developed other islet autoantibodies.

In conclusion, we have shown that the first years of life represent a period of heightened risk of developing type 1 diabetes-relevant autoimmunity and that the risk declined exponentially with age in childhood. The risk decline occurred regardless of the genetic and demographic background but varied among the autoantibody response profiles. The findings have practical implications for implementing population-based screening and have led to models for explaining the development of islet autoimmunity. We suggest that our understanding of the etiological causes of type 1 diabetes will be improved by the findings of future studies aimed at confirming or refuting these models.

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An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood

Short running title: Islet autoimmunity risk declines exponentially

Ezio Bonifacio PhD*[1,2], Andreas Weiß MSc[3], Christiane Winkler PhD[3,4], Markus Hippich PhD[3], Marian J. Rewers MD[5], Jorma Toppari MD[6], Åke Lernmark PhD[7], Jin-Xiong She[8], William A. Hagopian[9], Jeffrey P. Krischer[10], Kendra Vehik[10], Desmond A. Schatz[11], Beena Akolkar[12], Anette-Gabriele Ziegler MD*[3,4,13] for the TEDDY Study Group

*Shared corresponding authorship

Online-Only Supplemental Material

The TEDDY Study Group members

HLA eligibility

Supplemental Table 1:
Characteristics of the study population (n = 8,556).

Supplemental Figure 1:
Flow diagram of study participants and islet autoantibody outcomes.

Supplemental Table 2:
Cumulative five-year horizon risk for any and multiple islet autoantibodies from respective landmark age.

Supplemental Table 3:
Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by first degree family history (FDR) status.

Supplemental Table 4:
Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by sex.

The TEDDY Study Group

Colorado Clinical Center: Marian Rewers, M.D., Ph.D., PI[1,4,5,6,9,10], Aaron Barbour, Kimberly Bautista[11], Judith Baxter[8,911], Daniel Felipe-Morales, Kimberly Driscoll, Ph.D.[8], Brigitte I. Frohnert, M.D.[2,13], Marisa Stahl, M.D.[12], Patricia Gesualdo[2,6,11,13], Michelle Hoffman[11,12,13], Rachel Karban[11], Edwin Liu, M.D.[12], Jill Norris, Ph.D.[2,3,11], Stesha Peacock, Hanan Shorrosh, Andrea Steck, M.D.[3,13], Megan Stern, Erica Villegas[2], Kathleen Waugh[6,7,11]. University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes.

Finland Clinical Center: Jorma Toppari, M.D., Ph.D., PI[¥^1,4,10,13], Olli G. Simell, M.D., Ph.D., Annika Adamsson, Ph.D.[^11], Suvi Ahonen[*±§], Mari Åkerlund[*±§], Leena Hakola[*], Anne Hekkala, M.D.[µ¤], Henna Holappa[µ¤], Heikki Hyöty, M.D., Ph.D.[*6], Anni Ikonen[µ¤], Jorma Ilonen, M.D., Ph.D.[¥¶3], Sinikka Jäminki[*±], Sanna Jokipuu[^], Leena Karlsson[^], Jukka Kero M.D., Ph.D.[¥^], Miia Kähönen[µ¤11,13], Mikael Knip, M.D., Ph.D.[*5], Minna-Liisa Koivikko[µ¤], Merja Koskinen[*±], Mirva Koreasalo[*±§2], Kalle Kurppa, M.D., Ph.D.[*12], Jarita Kytölä[*±], Jutta Laiho, Ph.D.[*6], Tiina Latva-aho[µ¤], Katri Lindfors, Ph.D.[*12], Maria Lönnrot, M.D., Ph.D.[*6], Elina Mäntymäki[^], Markus Mattila[*], Maija Miettinen[§2], Katja Multasuo[µ¤], Teija Mykkänen[µ¤], Tiina Niininen[±*11], Sari Niinistö[±§2], Mia Nyblom[*±], Sami Oikarinen, Ph.D.[*6], Paula Ollikainen[µ¤], Zhian Othmani[^], Sirpa Pohjola[µ¤], Petra Rajala[^], Jenna Rautanen[±§], Anne Riikonen[*±§2], Eija Riski[^], Miia Pekkola[*±], Minna Romo[^], Satu Ruohonen[^], Satu Simell, M.D., Ph.D.[¥12], Maija Sjöberg[^], Aino Stenius[µ¤11], Päivi Tossavainen, M.D.[µ¤], Mari Vähä-Mäkilä[¥], Sini Vainionpää[^], Eeva Varjonen[^11], Riitta Veijola, M.D., Ph.D.[µ¤13], Irene Viinikangas[µ¤], Suvi M. Virtanen, M.D., Ph.D.[*±§2]. ¥University of Turku, *Tampere University, µUniversity of Oulu, ^Turku University Hospital, Hospital District of Southwest Finland, ±Tampere University Hospital, ¤Oulu University Hospital, §National Institute for Health and Welfare, Finland, ¶University of Kuopio.

Georgia/Florida Clinical Center: Jin-Xiong She, Ph.D., PI[1,3,4,10], Desmond Schatz, M.D.[*4,5,7,8], Diane Hopkins[11], Leigh Steed[11,12,13], Jennifer Bryant[11], Katherine Silvis[2], Michael Haller, M.D.[*13], Melissa Gardiner[11], Richard McIndoe, Ph.D., Ashok Sharma, Stephen W. Anderson, M.D.[^], Laura Jacobsen, M.D.[*13], John Marks, DHSc.[*11,13], P.D. Towe[*]. Center for Biotechnology and Genomic Medicine, Augusta University. *University of Florida, ^Pediatric Endocrine Associates, Atlanta.

Germany Clinical Center: Anette G. Ziegler, M.D., PI[1,3,4,10], Ezio Bonifacio Ph.D.[*5], Cigdem Gezginci, Anja Heublein, Eva Hohoff[¥2], Sandra Hummel, Ph.D.[2], Annette Knopff[7], Charlotte Koch, Sibylle Koletzko, M.D.[¶12], Claudia Ramminger[11], Roswith Roth, Ph.D.[8], Jennifer Schmidt, Marlon Scholz, Joanna Stock[8,11,13], Katharina Warncke, M.D.[13], Lorena Wendel, Christiane Winkler, Ph.D.[2,11]. Forschergruppe Diabetes e.V. and Institute of Diabetes Research, Helmholtz Zentrum München, Forschergruppe Diabetes, and Klinikum rechts der Isar, Technische Universität München. *Center for Regenerative Therapies, TU Dresden, ¶Dr. von Hauner

Children's Hospital, Department of Gastroenterology, Ludwig Maximillians University Munich, ¥University of Bonn, Department of Nutritional Epidemiology.

Sweden Clinical Center: Åke Lernmark, Ph.D., PI[1,3,4,5,6,8,9,10], Daniel Agardh, M.D., Ph.D.[6,12], Carin Andrén Aronsson, Ph.D.[2,11,12], Maria Ask, Rasmus Bennet, Corrado Cilio, Ph.D., M.D.[5,6], Susanne Dahlberg, Helene Engqvist, Emelie Ericson-Hallström, Annika Björne Fors, Lina Fransson, Thomas Gard, Monika Hansen, Hanna Jisser, Fredrik Johansen, Berglind Jonsdottir, M.D., Ph.D.[11], Helena Elding Larsson, M.D., Ph.D.[6,13], Marielle Lindström, Markus Lundgren, M.D., Ph.D.[13], Marlena Maziarz, Ph.D., Maria Månsson-Martinez, Jessica Melin[11], Zeliha Mestan, Caroline Nilsson, Karin Ottosson, Kobra Rahmati, Anita Ramelius, Falastin Salami, Anette Sjöberg, Birgitta Sjöberg, Carina Törn, Ph.D.[3], Åsa Wimar[13]. Lund University.

Washington Clinical Center: William A. Hagopian, M.D., Ph.D., PI[1,3,4,5,6,7,10,12,13], Michael Killian[6,7,11,12], Claire Cowen Crouch[11,13], Jennifer Skidmore[2], Masumeh Chavoshi, Arlene Meyer, Jocelyn Meyer, Denise Mulenga[11], Nole Powell, Jared Radtke, Matei Romancik, Shreya Roy, Davey Schmitt, Sarah Zink. Pacific Northwest Research Institute.

Pennsylvania Satellite Center: Dorothy Becker, M.D., Margaret Franciscus, MaryEllen Dalmagro-Elias Smith[2], Ashi Daftary, M.D., Mary Beth Klein, Chrystal Yates. Children's Hospital of Pittsburgh of UPMC.

Data Coordinating Center: Jeffrey P. Krischer, Ph.D.,PI[1,4,5,9,10], Sarah Austin-Gonzalez, Maryouri Avendano, Sandra Baethke, Brant Burkhardt, Ph.D.[5,6], Martha Butterworth[2], Joanna Clasen, David Cuthbertson, Christopher Eberhard, Steven Fiske[8], Jennifer Garmeson, Veena Gowda, Kathleen Heyman, Belinda Hsiao, Christina Karges, Francisco Perez Laras, Qian Li, Ph.D.[2,3], Shu Liu, Xiang Liu, Ph.D.[2,3,8,13], Kristian Lynch, Ph.D. [5,6,8], Jamie Malloy, Cristina McCarthy[11], Hemang Parikh, Ph.D.[3], Cassandra Remedios, Chris Shaffer, Laura Smith, Ph.D.[8,11], Susan Smith[11], Noah Sulman, Ph.D., Roy Tamura, Ph.D.[1,2,11,12,13], Dena Tewey, Michael Toth, Ulla Uusitalo, Ph.D.[2], Kendra Vehik, Ph.D.[4,5,6,8,13], Ponni Vijayakandipan, Jimin Yang, Ph.D., R.D.[2]. *Past staff: Michael Abbondondolo, Lori Ballard, Rasheedah Brown, Stephen Dankyi, David Hadley, Ph.D., Hye-Seung Lee, Ph.D., Colleen Maguire, Wendy McLeod, Aubrie Merrell, Steven Meulemans, Ryan Quigley.* University of South Florida.

Project scientist: Beena Akolkar, Ph.D.[1,3,4,5,6,7,9,10]. National Institutes of Diabetes and Digestive and Kidney Diseases.

Autoantibody Reference Laboratories: Liping Yu, M.D.[^5], Dongmei Miao, M.D.[^], Polly Bingley, M.D., FRCP*[5], Alistair Williams*, Kyla Chandler*, Ilana Kelland*, Yassin Ben Khoud*, Huma Zahid*, Matthew Randell *. [^]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, *Bristol Medical School, University of Bristol, UK.

HLA Reference Laboratory: William Hagopian[3], MD, PhD, Masumeh Chavoshi, Jared Radtke, Sarah Zink. Pacific Northwest Research Institute, Seattle WA. (Previously Henry Erlich, Ph.D.[3], Steven J. Mack, Ph.D., Anna Lisa Fear. Center for Genetics, Children's Hospital Oakland Research Institute.)

SNP Laboratory: Stephen S. Rich, Ph.D.[3], Wei-Min Chen, Ph.D.[3], Suna Onengut-Gumuscu, Ph.D.[3], Emily Farber, Rebecca Roche Pickin, Ph.D., Jonathan Davis, Jordan Davis, Dan Gallo, Jessica Bonnie, Paul Campolieto. Center for Public Health Genomics, University of Virginia.

Repository: Sandra Ke, Niveen Mulholland, Ph.D. NIDDK Biosample Repository at Fisher BioServices.

Other contributors: Thomas Briese, Ph.D.[6], Columbia University. Suzanne Bennett Johnson, Ph.D.[8,11], Florida State University. Eric Triplett, Ph.D.[6], University of Florida.

Committees:

[1]Ancillary Studies, [2]Diet, [3]Genetics, [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Psychosocial, [9]Quality Assurance, [10]Steering, [11]Study Coordinators, [12]Celiac Disease, [13]Clinical Implementation.

HLA eligibility

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 a subject with T1D: 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).

Supplemental Table 1: Characteristics of the study population (n = 8,556)

Variable (n)	Category	Number (%)	Risk of multiple islet autoantibodies by age 12 years [95% CI]
Sex	Girls	4,226 (49.4)	5.2% [4.5 – 5.9]
	Boys	4,330 (50.6)	6.4% [5.6 – 7.2]
First-degree relative with type 1 diabetes	Yes	955 (11.2)	12.4% [10.2 – 14.6]
	No	7,601 (88.8)	5.0% [4.5 – 5.5]
Site	Europe	4,895 (57.2)	6.7 % [5.9 – 7.4]
	U.S.A.	3,661 (42.8)	4.7 % [3.9 – 5.5]
HLA genotype	*DR3/DR4-DQ8*	3,339 (39.0)	8.0% [7.0 – 8.9]
	DR4-DQ8/DR4-DQ8	1,674 (19.6)	6.2% [5.0 – 7.4]
	DR4-DQ8/DR8	1,474 (17.2)	4.5% [3.4 – 5.7]
	DR3/DR3	1,791 (20.9)	2.2% [1.4 – 3.0]
	Other*	278 (3.3)	7.3% [4.2 – 10.4]
Genetic risk score† (n=4,413)	Highest quartile	1,104 (25)	12.8% [10.8 – 14.8]
	2nd and 3rd quartiles	2,206 (50)	7.8% [6.6 – 8.9]
	Lowest quartile	1,103 (25)	4.1% [2.9 – 5.4]

*All of the other *HLA DR4-DQ8*-containing genotypes were in children with a first-degree relative with type 1 diabetes

†Only calculated in general population children with complete SNP data and the *HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8* genotypes

Supplemental Figure 1: Flow diagram of study participants and islet autoantibody outcomes.
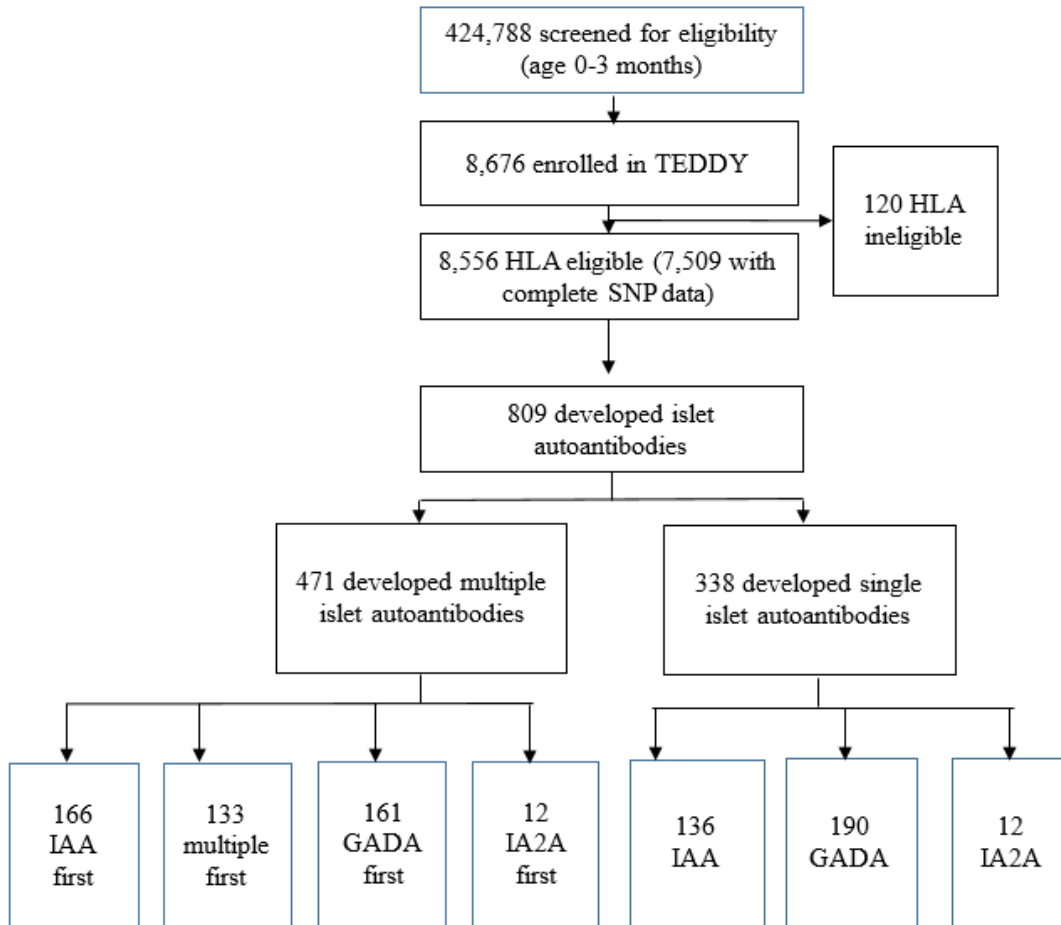
Supplemental Table 2: Cumulative five-year horizon risk for any and multiple islet autoantibodies from respective landmark age

Landmark age	Any islet autoantibodies	Multiple islet autoantibodies
From 7.5 months	6.3% [5.7-6.8]	4.2% [3.8-4.7]
From 1.125 years	5.4% [4.9-5.9]	4.3% [3.9-4.7]
From 1.625 years	4.8% [4.3-5.2]	3.5% [3.1-3.9]
From 2.125 years	4.1% [3.7-4.5]	2.9% [2.6-3.3]
From 2.625 years	3.7% [3.3-4.2]	2.4% [2.1-2.8]
From 3.125 years	3.4% [3.0-3.8]	2.0% [1.7-2.3]
From 3.625 years	3.3% [2.9-3.7]	1.7% [1.4-2.0]
From 4.25 years	3.2% [2.8-3.6]	1.6% [1.3-1.9]
From 5.25 years	3.1% [2.7-3.5]	1.5% [1.2-1.8]
From 6.25 years	3.2% [2.7-3.6]	1.3% [1.0-1.5]
From 7.25 years	3.3% [2.7-3.9]	1.1% [0.8-1.3]
From 8.25 years	3.3% [2.5-4.0]	1.1% [0.8-1.5]

Supplemental Table 3: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by first degree family history (FDR) status

Landmark age	Risk after 5 years of follow-up FDR	Risk after 5 years of follow-up No FDR
From 7.5 months	9.9% [8.0-11.8]	3.6% [3.2-4.0]
From 1.125 years	7.7% [5.9-9.4]	3.0% [2.6-3.4]
From 1.625 years	6.2% [4.6-7.8]	2.5% [2.2-2.9]
From 2.125 years	4.9% [3.4-6.3]	2.1% [1.8-2.5]
From 2.625 years	4.0% [2.7-5.3]	1.8% [1.5-2.1]
From 3.125 years	3.2% [2.0-4.4]	1.5% [1.2-1.8]
From 3.625 years	3.3% [2.1-4.5]	1.4% [1.1-1.7]
From 4.25 years	2.9% [1.7-4.1]	1.3% [1.1-1.6]
From 5.25 years	2.0% [1.0-3.0]	1.2% [0.9-1.5]
From 6.25 years	1.9% [0.9-2.8]	1.0% [0.7-1.3]
From 7.25 years	1.8% [0.6-3.0]	1.0% [0.7-1.4]
From 8.25 years	1.5% [0.4-2.7]	0.8% [0.5-1.1]

Supplemental Table 4: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by sex

Landmark age	Risk after 5 years of follow-up	Risk after 5 years of follow-up
	Male	Female
From 7.5 months	4.8% [4.1-5.4]	3.8% [3.2-4.4]
From 1.125 years	3.7% [3.2-4.3]	3.3% [2.7-3.8]
From 1.625 years	3.2% [2.7-3.8]	2.6% [2.1-3.1]
From 2.125 years	2.9% [2.4-3-4]	2.0% [1.5-2.4]
From 2.625 years	2.4% [1.9-2.8]	1.7% [1.3-2.1]
From 3.125 years	2.0% [1.5-2.4]	1.4% [1.0-1.7]
From 3.625 years	1.9% [1.4-2.3]	1.4% [1.0-1.7]
From 4.25 years	1.7% [1.3-2.1]	1.3% [0.9-1.7]
From 5.25 years	1.6% [1.2-2.1]	1.2% [0.8-1.5]
From 6.25 years	1.2% [0.8-1.7]	1.1% [0.7-1.7]
From 7.25 years	1.1% [0.6-1.5]	1.2% [0.7-1.7]
From 8.25 years	0.8% [0.4-1.1]	1.0% [0.5-1.5]

Supplemental Table 5: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by *HLA* genotype

| Landmark age	DR3/4-DQ8	DR4-DQ8/DR4-DQ8	DR4-DQ8/DR8	DR3/3
From 7.5	6.2% [5.3-7.0]	4.1% [3.2-5.1]	3.0% [2.2-3.9]	1.7% [1.1-2.3]
From 1.125	5.1% [4.3-5.9]	3.7% [2.8-4.6]	2.0% [1.3-2.8]	1.3% [0.7-1.8]
From 1.625	4.4% [3.7-5.1]	3.4% [2.5-4.3]	1.5% [0.9-2.1]	0.8% [0.4-1.2]
From 2.125	3.6% [3.0-4.3]	2.9% [2.1-3.7]	1.0% [0.5-1.6]	0.8% [0.4-1.2]
From 2.625	3.0% [2.4-3.6]	2.6% [1.9-3.4]	0.9% [0.4-1.4]	0.5% [0.2-0.9]
From 3.125	2.5% [1.9-3.1]	2.2% [1.4-2.9]	0.7% [0.3-1.2]	0.5% [0.1-0.8]
From 3.625	2.2% [1.7-2.8]	2.1% [1.4-2.8]	1.1% [0.5-1.6]	0.5% [0.2-0.9]
From 4.25 years	2.1% [1.6-2.6]	2.1% [1.4-2.8]	1.2% [0.6-1.7]	0.2% [0.0-0.5]
From 5.25 years	1.5% [1.1-2.0]	2.1% [1.3-2.8]	1.1% [0.5-1.7]	0.3% [0.0-0.6]
From 6.25 years	1.2% [0.8-1.7]	1.9% [1.1-2.6]	1.0% [0.4-1.6]	0.3% [0.0-0.9]
From 7.25 years	1.3% [0.7-1.8]	1.9% [0.9-2.9]	1.0% [0.3-1.8]	0.4% [0.0-0.9]
From 8.25 years	0.8% [0.3-1.3]	1.6% [0.7-2.6]	0.9% [0.2-1.6]	0.4% [0.0-0.8]

Supplemental Table 6: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by genetic risk score in general population children with the HLA DR3/4-DQ8 or DR4-DQ8/DR4-DQ8 genotypes

Landmark age	≤ 1st quartile of genetic risk score	> 1st and < 3rd quartile of genetic risk score	≥ 3rd quartile of genetic risk score
From 7.5 months	2.3% [1.4-3.3]	4.5% [3.6-5.4]	9.8% [7.9-11.7]
From 1.125 years	1.9% [1.0-2.7]	3.9% [3.0-4.7]	8.9% [7.0-10.7]
From 1.625 years	1.7% [0.9-2.5]	3.2% [2.4-4.0]	7.8% [6.1-9.5]
From 2.125 years	1.2% [0.5-1.9]	2.8% [2.1-3.6]	6.8% [5.2-8.4]
From 2.625 years	0.9% [0.3-1.5]	2.4% [1.7-3.1]	5.9% [4.4-7.5]
From 3.125 years	0.8% [0.3-1.4]	2.0% [1.4-2.6]	5.0% [3.6-6.5]
From 3.625 years	1.0% [0.4-1.7]	1.8% [1.2-2.4]	4.0% [2.6-5.2]
From 4.25 years	1.3% [0.6-2.0]	1.9% [1.3-2.5]	3.3% [2.1-4.5]
From 5.25 years	1.2% [0.5-1.9]	1.9% [1.3-2.6]	2.0% [1.1-3.0]
From 6.25 years	1.4% [0.6-2.3]	1.6% [0.9-2.2]	1.1% [0.4-1.8]
From 7.25 years	1.9% [0.5-3.2]	1.7% [0.8-2.5]	0.9% [0.2-1.5]
From 8.25 years	1.6% [0.3-2.9]	1.4% [0.6-2.2]	0.1% [0.0-0.4]

Supplemental Figure 2: Exponential risk decay curves for multiple islet autoantibodies stratified by (A) children in European and U.S. sites, (B) sex, and (C) *INS* genotype. The relative 5-year risks for multiple islet autoantibodies is also shown for (D) children with the *INS* AA genotype as compared to other *INS* genotypes, and (E) for children with the *HLA DR3/DR4-DQ8* genotype compared to children with the *HLA DR4-DQ8/DR4-DQ8* or *DR4-DQ8/DR8* genotypes (black line) and compared to children with the *DR3/3* genotypes (blue line).
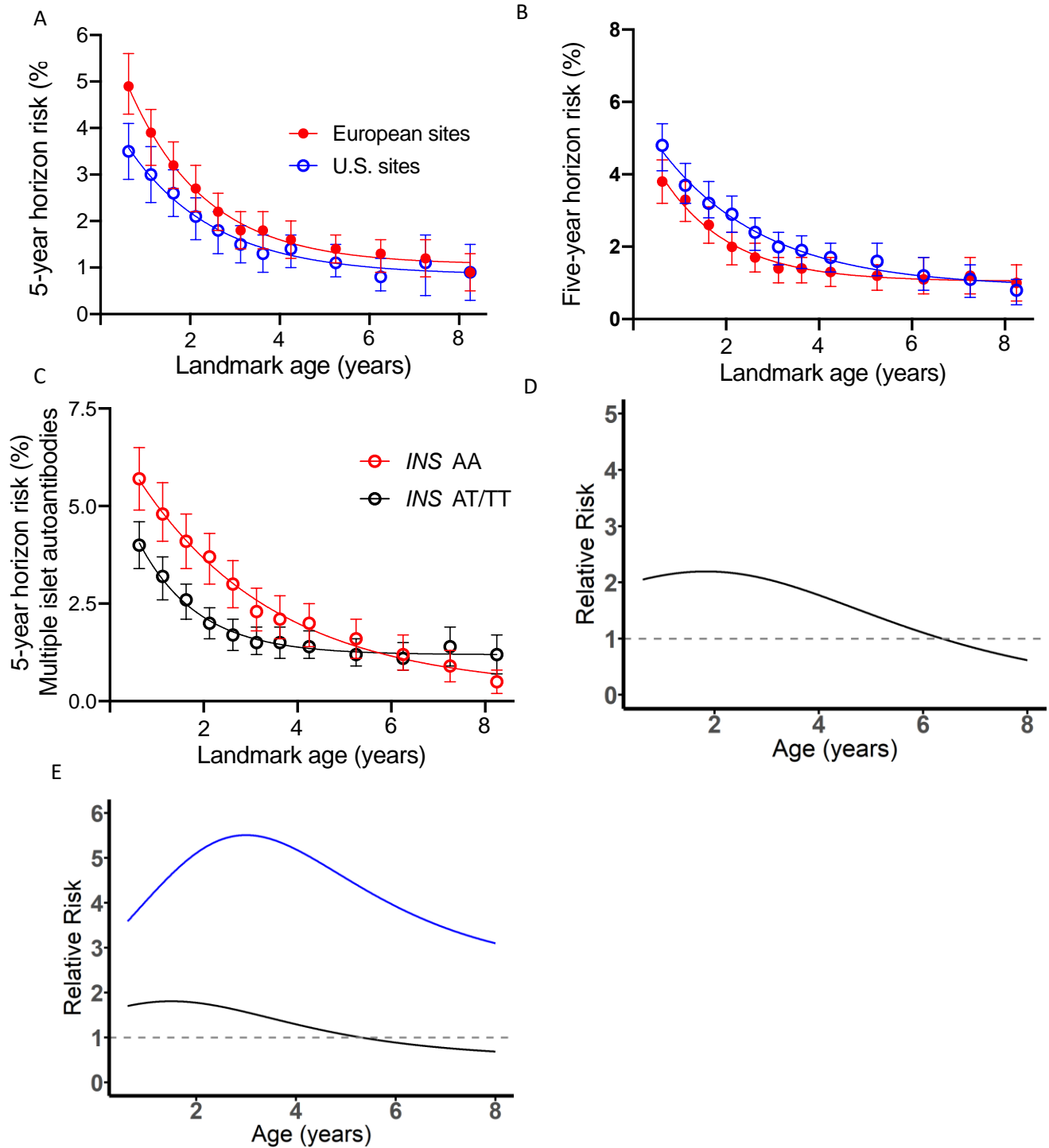
Supplemental Table 7: Relative cumulative five-year horizon risks for multiple islet autoantibodies and respective 95% confidence intervals at different timepoints

| Age	GRS highest quartile vs. lowest quartile	GRS highest quartile vs. middle quartiles	DR3/4-DQ8 vs. DR3/3	DR3/4-DQ8 vs. DR4-DQ8/DR4-DQ8 or DR4-DQ8/DR8
0.625 years	4.2 [2.7-6.5]	2.2 [1.6-2.9]	3.6 [2.5-5.3]	1.7 [1.4-2.1]
2.125 years	5.7 [3.1-10.5]	2.4 [1.7-3.5]	4.5 [2.6-7.8]	1.8 [1.3-2.5]
5.25 years	1.8 [0.8-3.8]	1.1 [0.6-2.0]**	5.0 [2.0-12.5]	1.0 [0.6-1.5]***
6.25 years	1.0 [0.4-2.3]*	0.8 [0.4-1.8]***	3.5 [1.4-9.0]	0.8 [0.5-1.4]***

*P=0.003 vs 0.625 years; ** P=0.001 vs 0.625 years; *** p<0.0001 vs 0.625 years

Supplemental Table 8: Cumulative five-year horizon risk for islet autoantibody phenotypes from respective landmark age

Landmark age	IAA first to multiple	Multiple first	GADA first to multiple	Single IAA	Single GADA
From 7.5 months	1.7% [1.5-2.0]	1.2% [0.9-1.4]	1.4% [1.2-1.7]	0.8% [0.6-1.0]	1.0% [0.8-1.2]
From 13.5 months	1.2% [0.9-1.4]	1.0% [0.7-1.2]	1.4% [1.1-1.6]	0.7% [0.5-0.9]	1.0% [0.8-1.3]
From 19.5 months	0.8% [0.6-1.0]	0.9% [0.7-1.1]	1.2% [0.9-1.4]	0.7% [0.5-0.9]	1.0% [0.8-1.3]
From 25.5 months	0.6% [0.4-0.8]	0.7% [0.5-0.9]	1.1% [0.9-1.3]	0.6% [0.4-0.8]	1.0% [0.8-1.2]
From 31.5 months	0.4% [0.3-0.6]	0.6% [0.4-0.7]	0.9% [0.7-1.1]	0.5% [0.4-0.7]	1.0% [0.8-1.3]
From 37.5 months	0.3% [0.2-0.5]	0.5% [0.3-0.6]	0.8% [0.6-1.0]	0.5% [0.3-0.6]	1.0% [0.8-1.3]
From 43.5 months	0.2% [0.1-0.3]	0.5% [0.3-0.6]	0.8% [0.6-1.0]	0.4% [0.3-0.5]	0.9% [0.7-1.1]
From 51 months	0.2% [0.1-0.3]	0.5% [0.3-0.7]	0.7% [0.5-0.9]	0.4% [0.3-0.5]	0.9% [0.7-1.1]
From 63 months	0.2% [0.1-0.2]	0.5% [0.3-0.6]	0.6% [0.4-0.8]		
From 75 months	0.1% [0.0-0.2]	0.5% [0.3-0.7]	0.4% [0.3-0.6]		
From 87 months	0.1% [0.0-0.2]	0.5% [0.3-0.7]	0.5% [0.3-0.7]		
From 99 months	0.1% [0.0-0.1]	0.4% [0.2-0.6]	0.4% [0.2-0.6]		

Supplemental Figure 3: Exponential risk decay curves for islet autoantibody phenotypes stratified by HLA genotype.
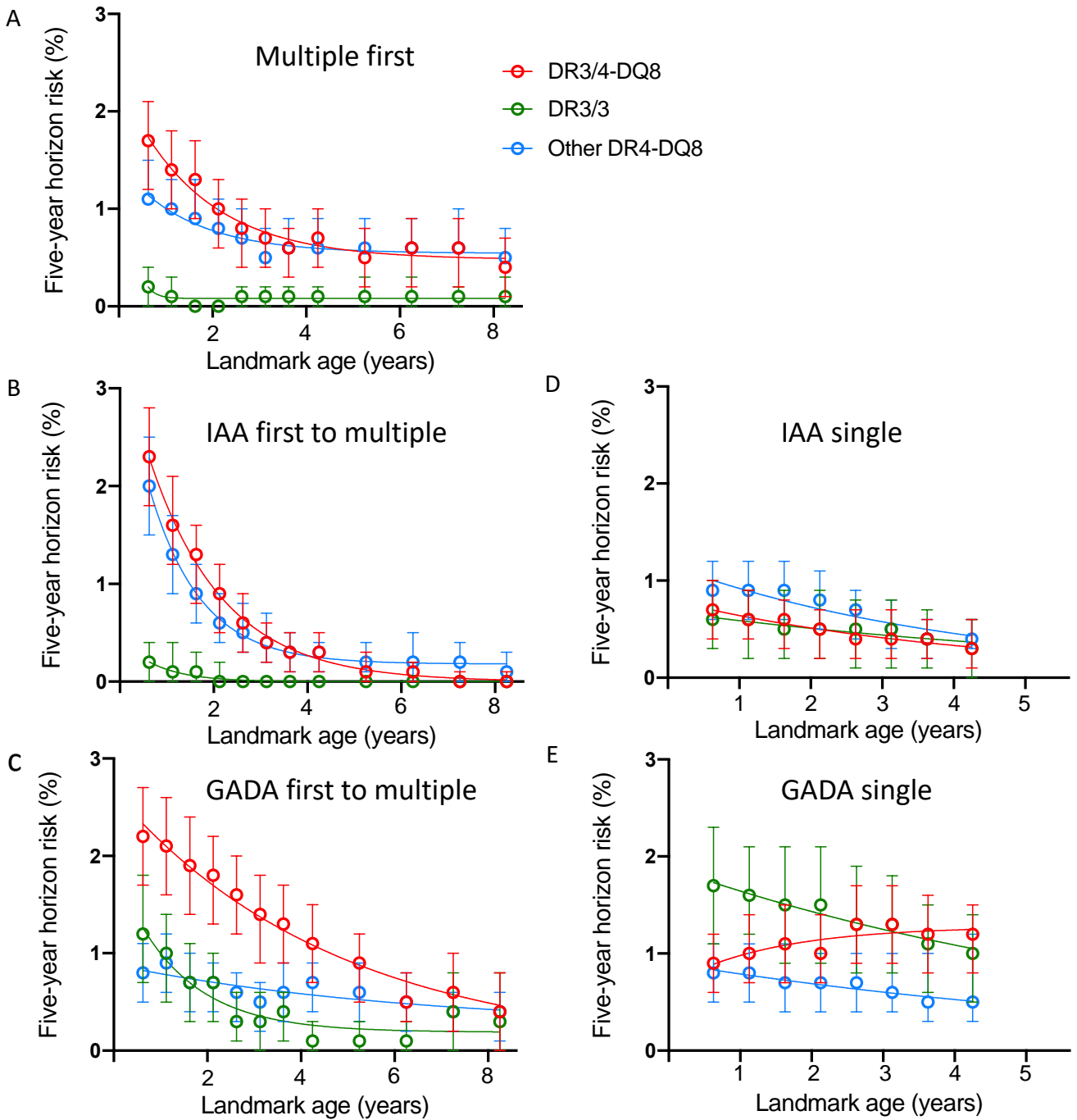
Supplemental Table 9: Cumulative 5-year risk for islet autoantibody phenotypes from respective landmark age by *HLA* genotype

Landmark age	Risk after 5 years of follow-up	Risk after 5 years of follow-up	Risk after 5 years of follow-up
	DR3/DR4-DQ8	DR3/DR3	Other HLA genotype
IAA first to multiple			
From 0.625 years	2.3% [1.8-2.8]	0.2% [0.0-0.4]	2.0% [1.5-2.5]
From 1.125 years	1.6% [1.2-2.1]	0.1% [0.0-0.3]	1.3% [0.9-1.7]
From 1.625 years	1.2% [0.8-1.6]	0.1% [0.0-0.2]	0.9% [0.6-1.2]
From 2.125 years	0.9% [0.5-1.2]	0% [0-0]	0.6% [0.4-0.9]
From 2.625 years	0.6% [0.3-0.9]	0% [0-0]	0.5% [0.3-0.8]
From 3.125 years	0.4% [0.2-0.6]	0% [0-0]	0.4% [0.2-0.7]
From 3.625 years	0.3% [0.1-0.5]	0% [0-0]	0.3% [0.1-0.5]
From 4.25 years	0.3% [0.1-0.5]	0% [0-0]	0.3% [0.1-0.4]
From 5.25 years	0.1% [0.0-0.3]	0% [0-0]	0.2% [0.1-0.4]
From 6.25 years	0.1% [0.0-0.2]	0% [0-0]	0.2% [0.0-0.5]
From 7.25 years	0.0% [0.0-0.1]	0% [0-0]	0.2% [0.0-0.4]
From 8.25 years	0.0% [0.0-0.1]	0% [0-0]	0.1% [0.0-0.3]
Multiple first			
From 0.625 years	1.7% [1.2-2.1]	0.2% [0.0-0.4]	1.1% [0.8-1.5]
From 1.125 years	1.4% [1.0-1.8]	0.1% [0.0-0.3]	1.0% [0.6-1.3]
From 1.625 years	1.3% [0.9-1.7]	0% [0-0]	0.9% [0.6-1.3]
From 2.125 years	1.0% [0.6-1.3]	0% [0-0]	0.8% [0.5-1.1]
From 2.625 years	0.8% [0.4-1.1]	0.1% [0.0-0.2]	0.7% [0.4-1.0]
From 3.125 years	0.7% [0.4-1.0]	0.1% [0.0-0.2]	0.5% [0.3-0.8]
From 3.625 years	0.6% [0.3-0.8]	0.1% [0.0-0.2]	0.6% [0.3-0.9]
From 4.25 years	0.7% [0.4-1.0]	0.1% [0.0-0.2]	0.6% [0.3-0.9]
From 5.25 years	0.5% [0.2-0.8]	0.1% [0.0-0.3]	0.6% [0.3-0.9]
From 6.25 years	0.6% [0.2-0.9]	0.1% [0.0-0.3]	0.6% [0.3-0.9]
From 7.25 years	0.6% [0.2-0.9]	0.1% [0.0-0.2]	0.6% [0.2-1.0]
From 8.25 years	0.4% [0.1-0.7]	0.1% [0.0-0.2]	0.5% [0.2-0.8]
GADA first to multiple			
From 0.625 years	2.2% [1.7-2.7]	1.2% [0.7-1.8]	0.8% [0.5-1.1]
From 1.125 years	2.1% [1.6-2.6]	1.0.% [0.5-1.4]	0.9% [0.6-1.2]
From 1.625 years	1.9% [1.4-2.4]	0.7% [0.3-1.1]	0.7% [0.4-1.0]
From 2.125 years	1.8% [1.3-2.2]	0.7% [0.3-1.1]	0.6% [0.4-0.9]
From 2.625 years	1.6% [1.2-2.0]	0.3% [0.1-0.6]	0.6% [0.3-0.8]
From 3.125 years	1.4% [0.9-1.8]	0.3% [0.0-0.6]	0.5% [0.2-0.7]
From 3.625 years	1.3% [0.9-1.7]	0.4% [0.1-0.6]	0.6% [0.3-0.9]
From 4.25 years	1.1% [0.7-1.5]	0.1% [0.0-0.3]	0.7% [0.4-0.9]
From 5.25 years	0.9% [0.5-1.2]	0.1% [0.0-0.3]	0.6% [0.3-0.9]

From 6.25 years	0.5% [0.3-0.8]	0.1% [0.0-0.3]	0.5% [0.2-0.8]
From 7.25 years	0.6% [0.2-1.0]	0.4% [0.0-0.8]	0.4% [0.2-0.6]
From 8.25 years	0.4% [0.0-0.8]	0.3% [0.0-0.8]	0.4% [0.1-0.6]
Single IAA			
From 0.625 years	0.7% [0.4-1.1]	0.6% [0.3-1.0]	0.9% [0.6-1.2]
From 1.125 years	0.6% [0.4-0.9]	0.6% [0.2-0.9]	0.9% [0.6-1.2]
From 1.625 years	0.6% [0.3-0.8]	0.5% [0.2-0.9]	0.9% [0.6-1.2]
From 2.125 years	0.5% [0.2-0.7]	0.5% [0.2-0.9]	0.8% [0.5-1.1]
From 2.625 years	0.4% [0.2-0.7]	0.5% [0.1-0.8]	0.7% [0.4-0.9]
From 3.125 years	0.4% [0.2-0.7]	0.5% [0.1-0.8]	0.5% [0.3-0.8]
From 3.625 years	0.4% [0.2-0.6]	0.4% [0.1-0.7]	0.4% [0.2-0.6]
From 4.25 years	0.3% [0.1-0.6]	0.3% [0.1-0.7]	0.4% [0.2-0.6]
Single GADA			
From 0.625 years	0.9% [0.6-1.2]	1.7% [1.1-2.3]	0.8% [0.5-1.1]
From 1.125 years	1.0% [0.7-1.4]	1.6% [1.0-2.1]	0.8% [0.5-1.1]
From 1.625 years	1.1% [0.7-1.5]	1.5% [0.9-2.1]	0.8% [0.5-1.1]
From 2.125 years	1.0% [0.7-1.4]	1.5% [0.9-2.1]	0.7% [0.4-1.0]
From 2.625 years	1.3% [0.9-1.7]	1.3% [0.8-1.8]	0.7% [0.4-0.9]
From 3.125 years	1.3% [1.0-1.8]	1.3% [0.8-1.8]	0.7% [0.4-0.9]
From 3.625 years	1.2% [0.8-1.6]	1.1% [0.6-1.5]	0.6% [0.4-0.9]
From 4.25 years	1.2% [0.8-1.5]	1.0% [0.5-1.4]	0.5% [0.3-0.8]

Supplemental Table 10: Sensitivity and positive predictive value of screening for islet autoantibodies

Screening Age	Positive predictive value* [95 % CI]	Sensitivity † [95% CI]
Multiple autoantibodies as positive		
1 year	84.0% [60.7-93.5]	6.6% [4.3-10.0]
2 years	68.1% [57.6-76.0]	24.2% [19.7-29.2]
3 years	55.5% [47.0-62.6]	33.5% [29.5-38.9]
4 years	51.6% [44.1-58.1]	37.2% [32.0-42.6]
5 years	49.6% [42.1-56.1]	34.1% [29.1-39.6]
6 years	47.7% [40.0-54.4]	30.8% [25.9-36.1]
7 years	47.7% [39.4-55.0]	26.9% [22.3-32.1]
8 years	49.4% [39.3-57.7]	20.8% [16.7-25.7]
Any autoantibodies as positive		
1 year	49.5% [39.1-58.2]	19.3% [15.3-24.1]
2 years	41.8% [35.0-47.9]	37.2% [32.0-42.6]
3 years	33.9% [28.4-39.0]	45.3% [39.9-50.9]
4 years	32.8% [27.9-37.4]	46.2% [40.8-51.8]
5 years	29.1% [24.4-33.6]	41.1% [35.8-46.6]
6 years	27.9% [23.1-32.4]	35.3% [30.2-40.8]
7 years	28.5% [23.3-33.4]	30.8% [25.9-36.1]
8 years	29.7% [23.4-35.5]	23.9% [19.5-28.9]
Single autoantibodies as positive		
1 year	24.5% [20.5-28.2]	12.4% [9.1-16.5]
2 years	14.9% [11.3-18.3]	13.0% [17.2-26.3]
3 years	12.2% [8.7-15.6]	11.8% [8.6-15.9]
4 years	11.5% [7.9-14.9]	9.1% [6.3-12.8]
5 years	9.2% [5.8-12.5]	6.9% [4.6- 10.4]
6 years	10.3% [6.4-14.1]	4.5% [2.7-7.5]
7 years	11.6% [6.8-16.1]	3.9% [2.2-6.8]
8 years	11.8% [5.8-17.4]	3.0% [1.5-5.7]

* Positive predictive value refers to the five-year horizon risk to develop type 1 diabetes from the screening age.
† Sensitivity was calculated as the proportion of the total number of children in the TEDDY study who developed type 1 diabetes by age 12 years.

Supplemental Figure 4: Models of multiple islet autoantibody pathogenesis based on the landmark analysis of the TEDDY study.