

Screening Children for Early-Stage Type 1 Diabetes

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IMPORTANCE Detecting type 1 diabetes in presymptomatic stages is essential for therapies aimed at delaying clinical onset.

OBJECTIVE To estimate early-stage (stage 1 or 2) type 1 diabetes prevalence and disease progression to clinical (stage 3) type 1 diabetes in children in a population-based screening study.

DESIGN, SETTING, AND PARTICIPANTS From February 2015 to July 2025, children living in Bavaria, Germany, were screened for early-stage type 1 diabetes. Screening was conducted by 716 primary care pediatricians. Screening was performed once in children aged 1.75 to 5.99 years until March 2019 and was subsequently expanded to include up to 2 screenings in children aged 1.75 to 10.99 years. Families of children with early-stage disease were offered diabetes education, metabolic staging, and longitudinal monitoring in 18 specialized diabetes centers.

EXPOSURES Measurement of islet autoantibodies.

MAIN OUTCOMES AND MEASURES The primary outcome was early-stage type 1 diabetes, defined as 2 or more autoantibodies against insulin, glutamic acid decarboxylase, islet antigen-2, or zinc transporter 8 confirmed in consecutive blood samples, with categorization into stages 1 (normoglycemia) and 2 (dysglycemia) and progression to clinical (stage 3) diabetes.

RESULTS Among 220 476 enrolled children (median [IQR] age, 3.1 [2.2-5.0] years; 106 952 [48.7%] females), 590 had presymptomatic early-stage type 1 diabetes at first screening (adjusted population frequency, 0.3% [95% CI, 0.28%-0.32%]) with prevalences of 0.23% for stage 1 and 0.06% for stage 2 type 1 diabetes. Repeat screening in 11 726 children after a median of 3.3 years identified 29 additional cases. During a median follow-up of 5.7 years, 212 children with an early-stage diagnosis at first screening, 5 with a diagnosis at rescreening, and 43 without an early-stage diagnosis developed clinical (stage 3) diabetes. Five-year progression from early-stage to clinical diabetes was 36.2% (95% CI, 31.2%-40.8%; annualized rate, 9.6%), and not significantly different between children with and without a first-degree family history ($P = .54$).

CONCLUSIONS AND RELEVANCE General population screening of children identified early-stage type 1 diabetes and similar progression rates to clinical diabetes between children with and without a first-degree family history. These findings inform disease-modifying therapy trials and suggest that screening can be considered beyond genetically selected populations.

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 Editorial

 Supplemental content

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The management and treatment of type 1 diabetes have entered an era in which disease-modifying therapies have become a realistic component of clinical care.¹ Pharmacologic intervention can delay the onset of clinical, symptomatic type 1 diabetes, thereby altering the underlying disease course.^{1,2} A prerequisite for implementing these therapies is the identification of presymptomatic type 1 diabetes, which depends on testing for islet autoantibodies.^{1,3} The presymptomatic phase of type 1 diabetes is now included in the *International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* and is subclassified based on the presence of islet autoantibodies and the level of glycemic dysregulation. Stage 1 (E10.A1) is defined by the presence of 2 or more islet autoantibodies with normoglycemia, and stage 2 (E10.A2) by the presence of 2 or more islet autoantibodies and dysglycemia. Stage 3 is defined by hyperglycemia, meeting American Diabetes Association (ADA) glycemic and clinical diagnostic criteria,^{4,5} with or without symptoms, marking the clinical diagnosis of type 1 diabetes.

Previous screening programs have shown that public health screening in primary care and community settings is feasible, acceptable to families, and capable of identifying early-stage type 1 diabetes, with overall prevalence typically ranging from 0.3% to 0.5%.⁶⁻⁸

Critical gaps remain regarding stage-specific prevalence, progression rates, and the natural history of type 1 diabetes in children without increased genetic risk, information that is required for optimizing screening strategies, counseling families, and guiding therapeutic deployment.

Initiated in 2015, the F11da study has conducted 10 years of screening to detect and monitor early-stage type 1 diabetes. The objectives of the current analysis are to provide the frequency and disease prognosis of an early-stage type 1 diabetes diagnosis in a general pediatric population.

Methods

Study Design

F11da is a public health research study designed to detect and monitor early-stage type 1 diabetes in children in Bavaria, Germany (NCT04039945). Between February 2015 and July 2025, primary care pediatricians who had registered to be part of the study invited children without a clinical diabetes diagnosis to participate in screening for islet autoantibodies as part of routine well-child visits.^{6,9,10} Participation by pediatricians was voluntary, as was their decision on whom to enroll into the study. Participation required written informed consent from parents or legal guardians. The study was approved by the institutional review board of the Technical University of Munich. Data on 90 632 study participants have been previously reported.⁶ For screening, capillary blood samples were obtained and sent to a central laboratory (Helmholtz Munich). Age, sex, weight, height, and first-degree family history of type 1 diabetes of participants were collected by a questionnaire.

If the screening sample result was positive for 2 or more islet autoantibodies, the pediatrician was notified and a con-

Key Points

Question What is the frequency and prognosis of presymptomatic type 1 diabetes in children?

Findings In a German population-based screening study of islet autoantibody testing in 220 476 children, 590 were diagnosed with early (stage 1 or 2) type 1 diabetes (adjusted population prevalence, 0.3%). Screening identified 81% (212 of 260) of the children who developed clinical (stage 3) type 1 diabetes during follow-up; progression to clinical type 1 diabetes occurred at an annualized rate of 9.6%.

Meaning These findings inform screening programs to diagnose early-stage type 1 diabetes in children and the design of trials aimed at delaying clinical type 1 diabetes.

firmatory venous blood sample was requested. A diagnosis of early-stage type 1 diabetes was made in children with a positive screening sample result if 2 or more islet autoantibodies were confirmed in the venous blood sample. Families were informed of the diagnosis by the pediatrician and were invited to transition to specialized care at 1 of 18 pediatric diabetes centers established across Bavaria for monitoring and prospective follow-up. This transition was centrally coordinated (Helmholtz Munich) and required a separate written informed consent.

At the diabetes center, families completed an educational program and metabolic staging using an oral glucose tolerance test (OGTT) and hemoglobin A_{1c} (HbA_{1c}) measurement. The schedule for future monitoring was tailored to the results of the metabolic staging—typically every 6 months for stage 1 and every 3 months for stage 2 type 1 diabetes. The final follow-up included in the current analysis occurred on December 8, 2025. Families who declined staging were offered follow-up with their primary care pediatrician, including periodic glucose and HbA_{1c} testing to detect clinical (stage 3) type 1 diabetes. Families who discontinued monitoring were contacted by telephone to assess symptoms of hyperglycemia, elevated home glucose levels, or a diabetes diagnosis. For participants without an early-stage type 1 diabetes diagnosis, clinical (stage 3) type 1 diabetes was ascertained through family pediatricians, who were contacted annually by the central study center to report new cases, and through participating diabetes centers. For the current analysis, the final follow-up with family pediatricians to ascertain diabetes onset among screened participants was in 2025.

From February 2015 to March 2019, children aged 1.75 to 5.99 years were eligible for a single screening; from April 2019 to July 2025, eligibility expanded to ages 1.75 to 10.99 years with up to 2 screenings recommended approximately 3 years apart. Participating pediatricians were informed of the protocol change. The decision to offer a second screen was voluntary.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

Outcome Definitions

Early-stage type 1 diabetes was defined as the presence of 2 or more islet autoantibodies against insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A), and zinc transporter 8 (ZnT8A) in both the screening and confirmation samples. The date of the first sample with 2 or more islet autoantibodies was defined as the early-stage diagnosis date.

Stage 1, stage 2, and clinical (stage 3) type 1 diabetes were classified according to 2025 ADA criteria⁴ (eMethods in Supplement 1).

Laboratory Assessments

First-line testing of islet autoantibodies was performed on serum from capillary blood using the 3 Screen Islet Cell Autoantibody ELISA kit (RSR Ltd), which detects GADA, IA-2A, and ZnT8A, therefore enabling the detection of all those with 2 or more islet autoantibodies in second-line testing.^{10,11} Samples with an ELISA value greater than 35 U were tested separately for GADA, IA-2A, ZnT8A, and IAA by radiobinding assays (RBAs).¹²⁻¹⁴ If 2 or more islet autoantibodies were detected in the RBAs, a confirmatory blood sample was obtained and measured for GADA, IA-2A, ZnT8A, and IAA using RBAs. OGTTs were performed using a glucose load of 1.75 g/kg of body weight (maximum, 75 g) of anhydrous glucose dissolved in water. Glucose and HbA_{1c} concentrations were measured by the local laboratory used by the diabetes centers or pediatricians.

Statistical Analysis

Estimates of the eligible population screened were based on yearly birth rates in Bavaria from 2013 to 2023. Screening yields were calculated separately for the first screening and rescreening. Yields were calculated at each screening as a frequency out of the total enrolled participants after exclusion of those with presumed stage 3 type 1 diabetes at screening and as population frequencies adjusted for loss of screening due to insufficient sample and for those who did not provide a confirmation sample. The population frequency of stage 1 and stage 2 type 1 diabetes were further adjusted for the proportion of participants with diagnosed early-stage type 1 diabetes who did not have a staging visit (eMethods in Supplement 1).

The cumulative risk of progression from screening to clinical (stage 3) type 1 diabetes was calculated using Kaplan-Meier analyses. The time to event was calculated from the date of screening to the date at clinical (stage 3) diagnosis or the date of last contact. The hazard rate of annualized progression was estimated assuming an exponential survival model. Variables examined for their effect on progression from screening were sex, age (older vs younger than median age at screening), first-degree family history of type 1 diabetes, positivity for each islet autoantibody, number of positive islet autoantibodies (2 vs >2), and obesity. Comparisons between groups were performed using the log-rank test. Hazards ratios (HRs) were estimated using the Cox model. Kaplan-Meier analyses were used to examine progression from stage 1 to clinical diabetes (stage 3), from stage 1 to stage 2 or clinical diabetes (stage 3), and from stage 2 to clinical diabetes (stage 3), where the time to event was calculated from the date of staging to the date at diagnosis of stage 2 or stage 3 diabetes or the date at last con-

Table. Demographics of Children Screened for Islet Autoantibodies

Category	No. (%)
Total	219 951
Sex	n = 219 685
Male	112 733 (51.3)
Female	106 952 (48.7)
First-degree relative with type 1 diabetes	8719 (4.0)
BMI ^a	n = 219 615
Normal	168 559 (76.8)
Overweight	39 100 (17.8)
Obese	11 956 (5.4)
Age at first screening, y	n = 219 733
<3	88 165 (40.1)
3-3.99	44 459 (20.2)
4-4.99	29 962 (13.6)
5-5.99	33 305 (15.2)
≥6	23 832 (10.8)
Age at rescreening, y	n = 11 721
<3	289 (2.5)
3-3.99	931 (7.9)
4-4.99	1346 (11.5)
5-5.99	2593 (22.1)
≥6	6562 (56.0)

^a Standardized body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was calculated using the World Health Organization Child Growth Standards based on height and weight and age.¹⁵ Normal BMI is defined as a standardized value <1, overweight as standardized value of 1 to 2, and obese as standardized value >2.¹⁵ There were 23 528 missing BMI values before imputation and for 324 of these children, imputation of standardized BMI values was not possible due to missing sex or age.

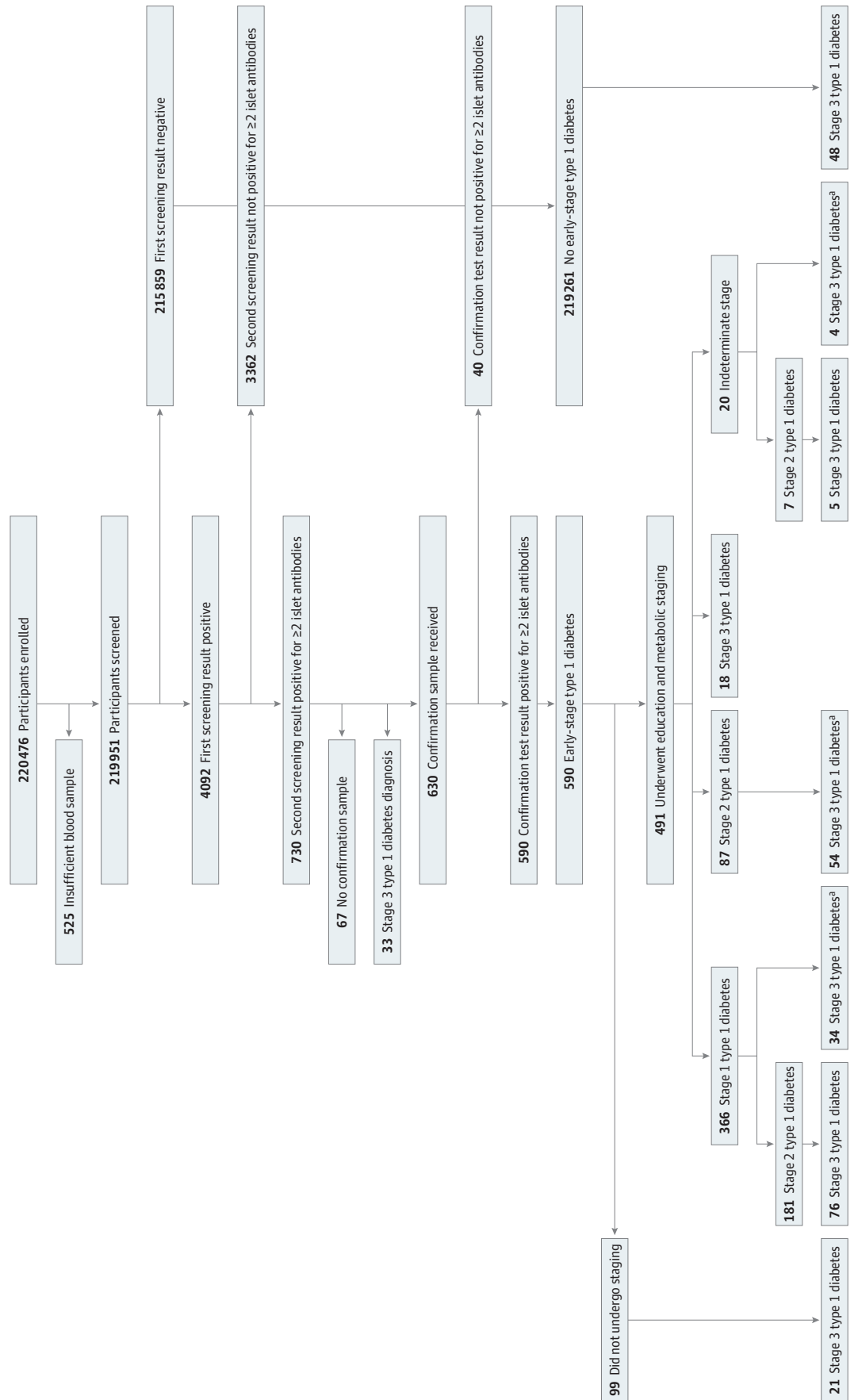
tact. Frequencies were calculated and are presented with 95% CIs. Data were analyzed using SAS version 9.4 (SAS Institute) and R version 3.5.3 (R Foundation) using the survival and survminer packages. Two-sided *P* values less than .05 were considered statistically significant.

Results

Yield of Screening for Islet Autoantibodies

Between February 2015 and July 2025, a total of 220 476 children (48.7% girls) were enrolled in the islet autoantibody screening program by 716 of 969 practicing primary care pediatricians (73.9%) in Bavaria at a median (IQR) age of 3.1 (2.2-5.0) years (Table). This represents 17% of the 1.3 million estimated eligible children in the region during this period. Insufficient sample for screening was obtained for 525 children (0.24%). Of the remaining 219 951 participants, 4092 (1.86%) had a positive ELISA result, which triggered testing for each of the 4 major islet autoantibodies using RBAs in the same sample (Figure 1). Of these participants, 730 (17.8% [0.33% of the total screened]) had 2 or more islet autoantibodies and 3362 did not have 2 or more islet autoantibodies. Of the 730 participants with 2 or more islet autoantibodies in the screening sample, 33 (4.5%) were diagnosed with stage 3 type 1 diabetes before providing a confirmatory sample and

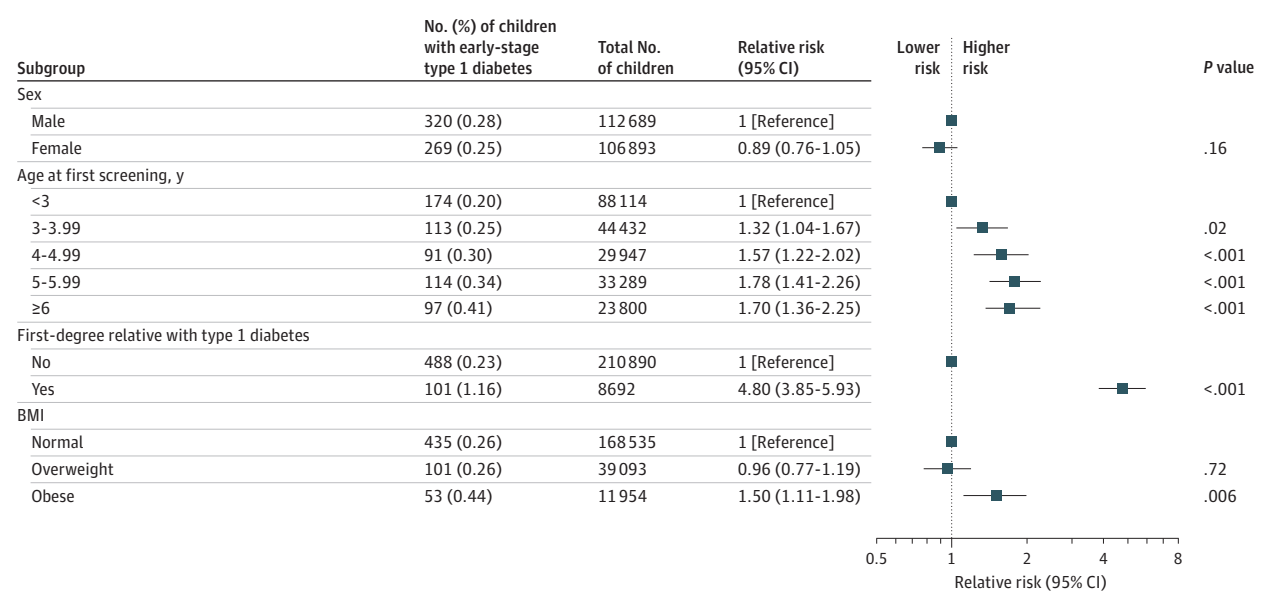
Figure 1. Flow of Children in the Frida Study



First screening was 3-Screen ELISA and second screening was radiobinding assays.

^aPremature termination of follow-up of 25 participants with stage 1, 3 participants with stage 2, and 1 participant with indeterminate-stage type 1 diabetes.

Figure 2. Dot-and-Whisker Plot of Subgroup Multivariable Analyses of Relative Risks for Early-Stage Type 1 Diabetes in Participants at First Screening



Prevalences are unadjusted. P values were calculated from a multivariable logistic regression model with the outcome of early-stage type 1 diabetes at first screening. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared).

were excluded from the analysis. An additional 67 (9.2%) did not provide a confirmation sample and were also excluded. Of the 630 participants with a confirmation sample, 40 (6.3%) had 1 or zero islet autoantibodies and were reported as not having early-stage type 1 diabetes and 590 (93.7%) again had results positive for 2 or more islet autoantibodies. The process identified 590 children (0.27% [95% CI, 0.25%-0.29%]) with early-stage type 1 diabetes of 220 476 enrolled participants, with an adjusted population frequency of 0.30% (95% CI, 0.28%-0.32%) after considering those lost at screening and confirmation.

In a multivariable logistic regression model, the relative risk for early-stage type 1 diabetes increased with age and was higher in children who had a first-degree relative with type 1 diabetes and in children with obesity, but was not associated with sex (Figure 2). The frequency of IAA, GADA, IA-2A, and ZnT8A and of 2, 3, and 4 islet autoantibodies was similar in those with and without a first-degree relative with type 1 diabetes (eTable 1 in Supplement 1).

Metabolic Staging

A total of 491 of 590 children (83.2%) with early-stage type 1 diabetes at the first screen participated in metabolic staging using OGTT and HbA_{1c}. An additional 16 children were awaiting a staging visit and 83 (14.1%) did not participate in staging. No differences in the sex, age at screening, or first-degree family history of type 1 diabetes status were observed between participants who completed and did not complete staging (eTable 2 in Supplement 1).

Staging classified 366 children (74.5% [0.17% of all screened]) as having stage 1, 87 (17.7% [0.04% of all screened]) as having stage 2, and 18 (3.7% [0.008% of all screened]) as having stage 3 type 1 diabetes, while 20 (4.1%) could not be clas-

sified because of missing values in either OGTT or HbA_{1c} measures (Figure 1). The adjusted population frequency of stage 1 type 1 diabetes was 0.23% (95% CI, 0.21%-0.24%) and of stage 2 type 1 diabetes was 0.06% (95% CI, 0.05%-0.07%) among enrolled children.

Sensitivity and Specificity of Early-Stage Type 1 Diabetes

Of the screened children, 260 developed clinical diabetes over a median (IQR) follow-up of 5.7 (3.2-8.9) years (1 291 961 total person-years), yielding a rate of 20.1 (95% CI, 17.8-22.7) per 100 000 years. A diagnosis of clinical (stage 3) type 1 diabetes occurred in 212 of the 590 children diagnosed with early-stage type 1 diabetes at first screening. Clinical diabetes was also reported in 48 children without an early-stage diagnosis. Of these children, 23 had 1 positive islet autoantibody and 25 had zero autoantibodies at first screening. Of the 24 children with autoantibody data at clinical diagnosis, 13 had 2 or more islet autoantibodies, 8 had 1 autoantibody, and 3 had no autoantibodies. The sensitivity of an early-stage diagnosis for identifying clinical diabetes was 81.5% (212 of 260) and the specificity was 99.8% (219 213 of 219 591).

Yield of Rescreening for Islet Autoantibodies

Of 219 261 children who remained without an early-stage diagnosis in the first screening, 11 726 (5.3%) participated in a second screening at a median (IQR) age of 7.2 (5.1-9.1) years and a median (IQR) time between the first and second screening of 3.3 (2.0-5.5) years (eFigure 1 in Supplement 1). Rescreening participation within 5 years was 5.7% in children younger than 4 years at first screening (eFigure 2 in Supplement 1). Rescreened children were slightly younger at first screening and were enriched for a first-degree family history of type 1 diabetes and the absence of obesity (eTable 3 in Supplement 1).

Among rescreened children, 35 (0.30%) had a positive 3-Screen ELISA result and 2 or more islet autoantibodies by RBA. Three did not provide a confirmation sample, 3 had 1 or no autoantibody, and 29 had results that remained positive for 2 or more islet autoantibodies. The rescreening procedure identified 29 children (0.25% [95% CI, 0.17%-0.36%]) with early-stage type 1 diabetes of 11 726 enrolled children, with an adjusted population prevalence of 0.27% (95% CI, 0.19%-0.38%).

Progression From Early-Stage to Clinical Type 1 Diabetes

In total, 619 participants were diagnosed with early-stage (stage 1 or 2) type 1 diabetes in the first and second screens (Figure 1; eFigure 1 in Supplement 1). The cumulative progression to clinical diabetes (stage 3) was 36.2% (95% CI, 31.2%-40.8%; 156 cases) at 5 years of follow-up, with an annualized rate of 9.6% (Figure 3A, eTable 4 in Supplement 1). The risk did not differ significantly between children with and without a first-degree relative with type 1 diabetes (5-year risk, 41.4% [95% CI, 27.9%-52.4%]; 28 cases, vs 35.3% [95% CI, 29.9%-40.2%]; 128 cases; $P = .54$; Figure 3B, eTable 4 in Supplement 1). Factors associated with the rate of progression to clinical diabetes (stage 3) in a multivariable analysis were IA-2A (HR, 2.32 [95% CI, 1.39-3.61]; $P < .001$) and GADA (HR, 0.51 [95% CI, 0.33-0.80]; $P = .001$) (Figure 3C). Combinations of IA-2A and GADA positivity stratified the 5-year risk of progression to stage 3 from 16.9% (95% CI, 10.6%-22.8%) in 218 children who were GADA positive/IA-2A negative to 58.6% (95% CI, 40.6%-71.1%) in the 67 children who were GADA negative/IA-2A positive ($P < .001$; Figure 3D). Progression rates also varied by combinations of all 4 antibodies, with the lowest risk observed in 119 participants who were GADA and IAA positive only (15.0% [95% CI, 6.9%-22.4%]) and the highest risk observed in 31 participants who were IA-2A, IAA, and ZnT8A positive without GADA (73.9% [95% CI, 47.4%-87.0%]; eTable 5 in Supplement 1).

Ten of 619 children (1.6%) with early-stage type 1 diabetes became islet autoantibody negative during follow-up at a median (IQR) of 5.1 (4.2-7.5) years from screening. This included 2 children who had all 4 islet autoantibodies, 1 with 3 autoantibodies, and 7 with 2 islet autoantibodies. Four of these 10 children developed clinical (stage 3) type 1 diabetes after becoming islet autoantibody negative.

Stage Progression in Metabolically Staged Participants

From the time of staging, 493 children were followed up until clinical (stage 3) type 1 diabetes or last contact for a median (IQR) of 3.4 (1.3-6.0) years (1938 total person-years). Of these children, 29 prematurely discontinued monitoring during follow-up. Progression to stage 3 occurred in 113 of 382 children (29.6%) with stage 1 type 1 diabetes, in 54 of 89 (60.7%) with stage 2 type 1 diabetes, and 10 of 22 (45.5%) with missing staging values. In addition to the 89 children with stage 2 diabetes at initial staging, an additional 187 progressed from stage 1 to stage 2 during follow-up (Figure 1 and eFigure 1 in Supplement 1).

Stage progression occurred at a similar rate for stage 1 and 2. The 5-year cumulative risk of developing stage 2 or 3 type 1 diabetes for the 382 children with stage 1 was 69.0% (95% CI, 62.7%-74.3%; 205 cases), with an annualized rate of 21.4%

(Figure 4A and eTable 4 in Supplement 1). The risk of progression to stage 3 by 5 years in children who had stage 2 at initial staging was 60.4% (95% CI, 47.0%-70.5%; 46 cases; $P = .94$), with an annualized risk of 21.1% (Figure 4A and eTable 4 in Supplement 1).

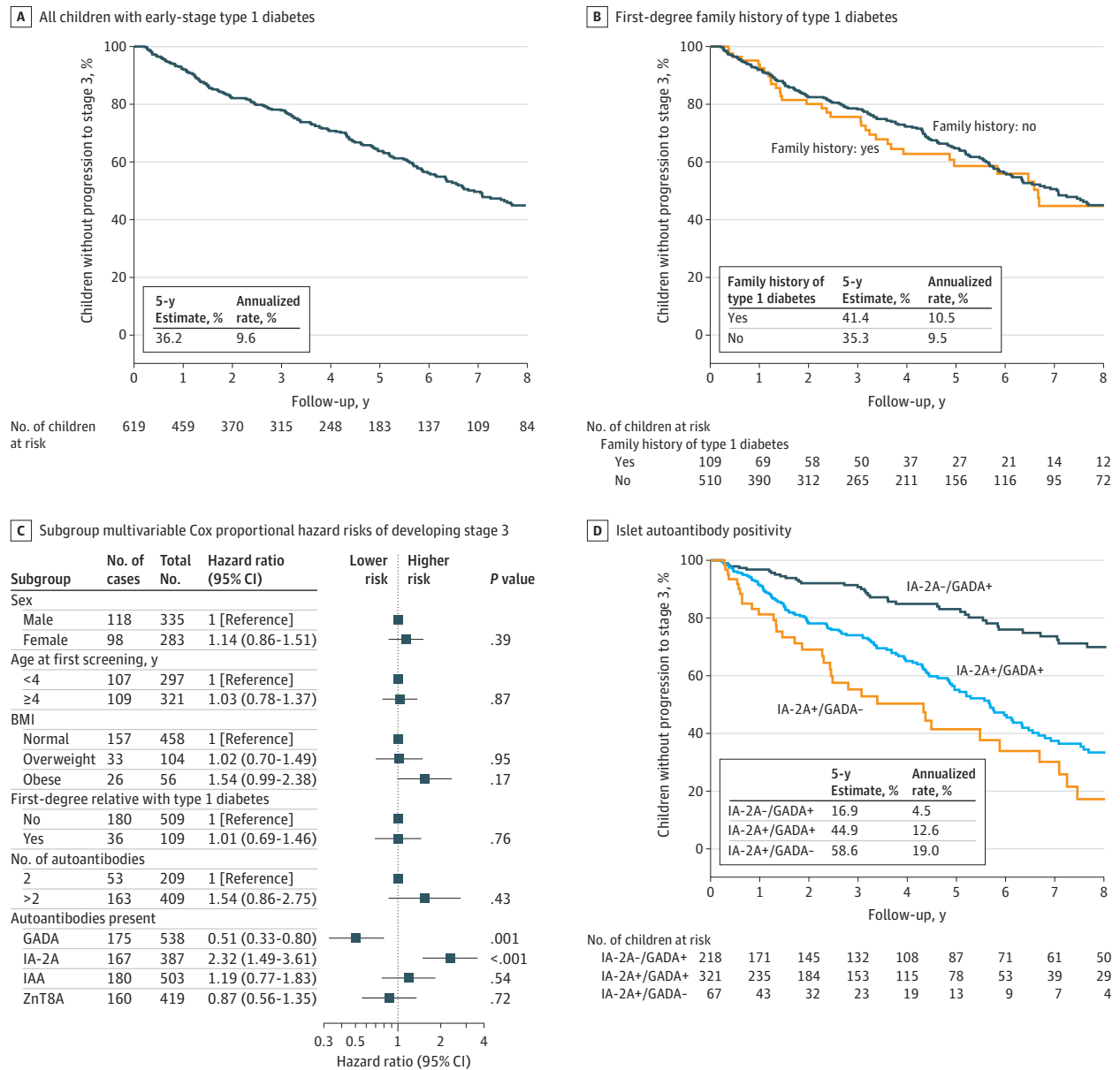
The five-year progression from stage 2 to stage 3 in the 194 children who developed stage 2 type 1 diabetes during follow-up was 47.6% (95% CI, 38.2%-55.6%; 71 cases; annualized rate, 13.8%) and was slower than children who had stage 2 type 1 diabetes at first screening ($P = .03$; eTable 4 in Supplement 1 and Figure 4B). The 5-year cumulative risk of progression from stage 1 to stage 3 type 1 diabetes was 29.5% (95% CI, 23.5%-34.9%; 78 cases; Figure 4C and eTable 4 in Supplement 1).

Discussion

To the authors' knowledge, this is the first long-term, population-level estimate of presymptomatic type 1 diabetes prevalence and progression, providing key data to inform screening policies and therapeutic indications. Integrating screening and follow-up into routine primary care demonstrates the sustainability of such programs, even during disruptions like the COVID-19 pandemic during which the program was combined with the measurement of SARS-CoV-2 antibodies.¹⁶ Screening the general population for early-stage type 1 diabetes using islet autoantibodies was efficient and sensitive. First-line screening ruled out the need for second-line testing in 98% of screened samples. Among the 2% requiring second-line testing, 18% had 2 or more islet autoantibodies and were notified for confirmatory sampling. Of those who responded, 94% had confirmed early-stage type 1 diabetes and another 4.5% were diagnosed with stage 3 disease prior to sending a confirmation sample. Rescreening in more than 11 000 children who initially tested negative identified new early-stage cases almost as frequently as at first screening. This finding empirically supports prior projections derived from studies in genetically at-risk children, which modeled that repeat screening would substantially increase the sensitivity of early detection of type 1 diabetes.^{17,18} It underscores the importance of performing at least one rescreen in children who test negative.

The majority (81%) of those who developed clinical (stage 3) type 1 diabetes during the study period had an early-stage (stage 1 or 2) type 1 diabetes diagnosis at first screening. The overall incidence of reported diabetes was 20.1 per 100 000 person years, similar to rates reported in German registries in the same period.^{19,20} The ADA and the International Society for Pediatric and Adolescent Diabetes recommend screening for people with a family history of type 1 diabetes.^{4,21} Restricting screening to children with a first-degree family history would have identified only 101 of the 590 children (17%) with early-stage type 1 diabetes at first screening and 34 of the 212 (16%) who subsequently developed clinical (stage 3) type 1 diabetes. Importantly, no difference in risk of progression was observed between children with and without a first-degree family history of type 1 diabetes in this study. The rate of progression to clinical diabetes in the current study was slightly

Figure 3. Kaplan-Meier Curves of Progression to Clinical (Stage 3) Type 1 Diabetes From Screening in Children Diagnosed With Early-Stage (Stage 1 and Stage 2) Type 1 Diabetes



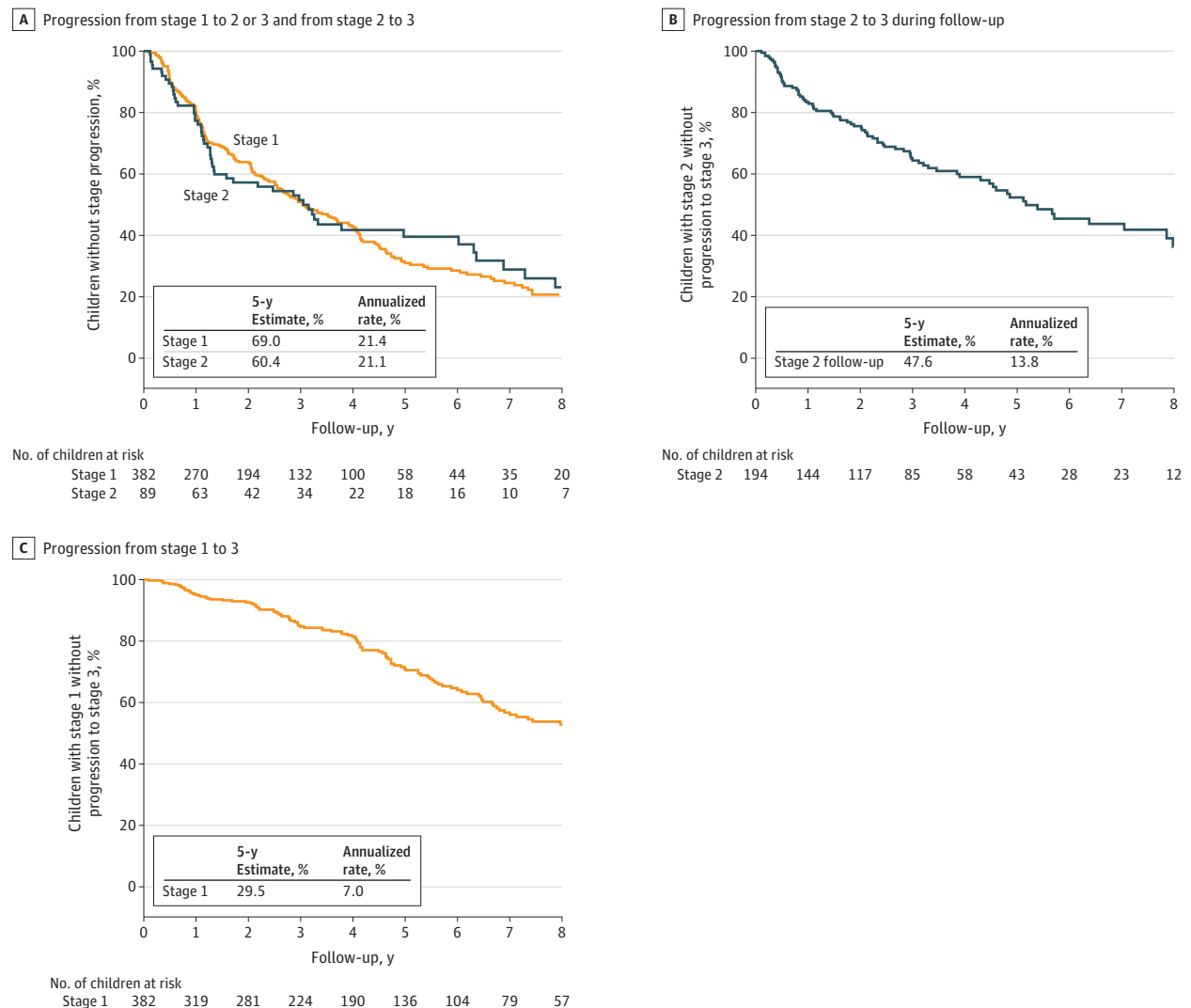
Kaplan-Meier survival analyses with time to event calculated from the date of screening to the date at diagnosis of stage 3 or the date of last contact. A, Median [IQR] observation time of 3.1 (0.9-5.6) years for all 619 children with early-stage (stage 1 or stage 2) type 1 diabetes diagnosed at first and second screening. B, Median (IQR) observation time of 2.2 (0.4-5.0) years for children with first-degree family history of type 1 diabetes and 3.2 (1.1-5.7) years for children without first-degree family history with type 1 diabetes. C, Subgroup multivariable analysis using Cox proportional hazards model. P values were

calculated from a multivariable Cox proportional hazards model with the outcome of stage 3 type 1 diabetes. D, Median (IQR) observation time of 3.9 (1.3-7.7) years for IA-2A-negative/GADA-positive participants, 2.7 (0.8-5.0) years for IA-2A-positive/GADA-positive participants, and 1.7 (0.7-4.3) years for IA-2A-positive/GADA-negative participants. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); GADA, glutamic acid decarboxylase autoantibody; IA-2A, islet antigen 2 autoantibody; IAA, islet autoantibodies against insulin; ZnT8A, zinc transporter 8.

lower than that seen in historical birth cohorts of children with increased genetic risk.²² The 5-year risk of progression to clinical diabetes (stage 3) was 44% in those cohorts compared with 36.2% in the current study. The rates reported in earlier studies may be modestly inflated because they include a percentage of children who have new-onset clinical diabetes (stage 3)

at the time they were identified as being multiple islet autoantibody positive. With the shift in nomenclature to early-stage type 1 diabetes, these cases of occult diabetes were excluded in the current analysis. Similar to the TEDDY study,²³ only a small percentage of participants (<2%) diagnosed with early-stage type 1 diabetes became islet autoantibody negative

Figure 4. Kaplan-Meier Curves of Disease Progression From Metabolic Staging in Children With Stage 1 and Stage 2 Type 1 Diabetes



Kaplan-Meier survival analyses showing progression from initial staging in A, children with stage 1 (progression to stage 2 or clinical diabetes [stage 3]; median [IQR] observation time, 2.0 [0.8-4.1] years) and stage 2 (progression to stage 3; median [IQR] observation time, 1.6 [1.0-3.9] years); B, progression from

stage 2 to stage 3 in children who developed stage 2 in follow-up (median [IQR] observation time, 2.6 [0.9-4.6] years); and C, progression from stage 1 to stage 3 (median [IQR] observation time, 4.0 [1.7-6.4] years). Numbers include children who underwent staging from first and second screening.

and almost half of these children developed clinical diabetes after losing their antibodies. These findings suggest that, when robust criteria such as confirmed and persistent islet autoantibodies are used to define early-stage type 1 diabetes, screening can be applied to the childhood population regardless of the a priori genetic risk for type 1 diabetes.

Although early-stage type 1 diabetes is defined by 2 or more islet autoantibodies, prognosis varies by autoantibody specificity.²⁴ IA-2A is a marker of faster progression, whereas GADA is associated with slower progression to stage 3.^{6,24-27} Results of the current study showed that GADA was associated with slower progression even in children with IA-2A, allowing stratification of early-stage disease into 3 risk groups with 5-year risk ranging from 17% to 59% based on combined IA-2A and GADA status. Specific antibody combinations including IAA and ZnT8A

may further stratify risk.²⁴ The lowest risks were observed in the 3 combinations that included GADA without IA-2A, which represented more than one-third of participants with early-stage type 1 diabetes. Although treatment assignment is based on metabolic assessment, a percentage of participants in the current study did not undergo or are awaiting staging. In these cases, islet autoantibody combinations can provide interim prognostic information.

A notable and unexpected finding was the consistency in progression rates between stages. While progression to clinical diabetes (stage 3) was faster for those with stage 2 type 1 diabetes than for those with stage 1, the progression rate from stage 1 to a later stage (2 or 3) was comparable to the rate from stage 2 to stage 3 type 1 diabetes, with median times of approximately 3 years. Although factors such as infection have

been associated with initiation or an acceleration of disease,²⁸⁻³⁰ these data suggest that mechanisms driving the disease after its initiation may be operating relatively constantly throughout early-stage disease, rather than accelerating solely near the time of clinical diagnosis. This finding carries implications for therapeutic development, particularly in individuals with stage 1 type 1 diabetes, who comprise most early-stage diagnoses.

Pharmacologic intervention in people with stage 2 type 1 diabetes can delay the onset of clinical type 1 diabetes. Teplizumab, a monoclonal anti-CD3 antibody, is approved as a treatment from 8 years of age in multiple countries, and several other potential disease-modifying therapies are in clinical development.¹ There are currently no pharmacological treatment options for stage 1 diabetes. The current data may facilitate and accelerate prevention trials in stage 1 type 1 diabetes because they indicate that stage progression may be a feasible and clinically meaningful trial end point. Also relevant to therapeutic development, trial design and randomization is the observation that time to stage 3 was longer among individuals newly developing stage 2 than among those identified by cross-sectional staging. Beyond available therapies, early detection offers substantial clinical benefits, including a reduction in the incidence of diabetic ketoacidosis and clinical symptoms, reduction in hospitalization days, and improvement in metabolic control and more residual beta cell function at clinical diagnosis.³¹⁻³³

Limitations

This study has several limitations. First, participation was voluntary and, although it was reported that screened children were broadly representative of the population,^{6,34} potential socioeconomic bias could not be assessed and ethnicity data were unavailable. Second, the study did not assess the number of children who were asked to participate, and therefore could

not determine participation rates or reasons for nonparticipation in screening or rescreening. Third, because screening was limited to preschool- and primary school-aged children, findings may not be generalizable to older age groups. In particular, previous studies have demonstrated lower rates of progression to stage 3 type 1 diabetes in adolescents and adults compared with children^{24,35}; this could not be assessed in the current study.

Fourth, ascertainment of stage 3 disease for participants who left the study or were not systematically followed up was reliant on reporting by family pediatricians, diabetes centers, and phone contact and is, therefore, likely to be underestimated. As a consequence, the screening sensitivity may be overestimated. Fifth, a sizeable percentage of those with early-stage type 1 diabetes did not undergo staging. Understanding the reasons for not performing staging may help improve the clinical impact of screening. Sixth, rescreening was only performed in a subset of participants. Seventh, the findings may not be generalizable to populations with low incidences of type 1 diabetes. Eighth, evaluation for potential harms of screening and cost analyses were not performed in this study.

Conclusions

In this 10-year public health screening program, population-based screening for early-stage type 1 diabetes was sustainable and identified most children who progressed to clinical (stage 3) type 1 diabetes, with repeat screening detecting additional cases. Progression rates were similar between children with and without a type 1 diabetes family history, and transitions to higher metabolic stages occurred at comparable rates. These findings inform disease-modifying therapy trials and suggest that screening can be considered beyond genetically selected populations.

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