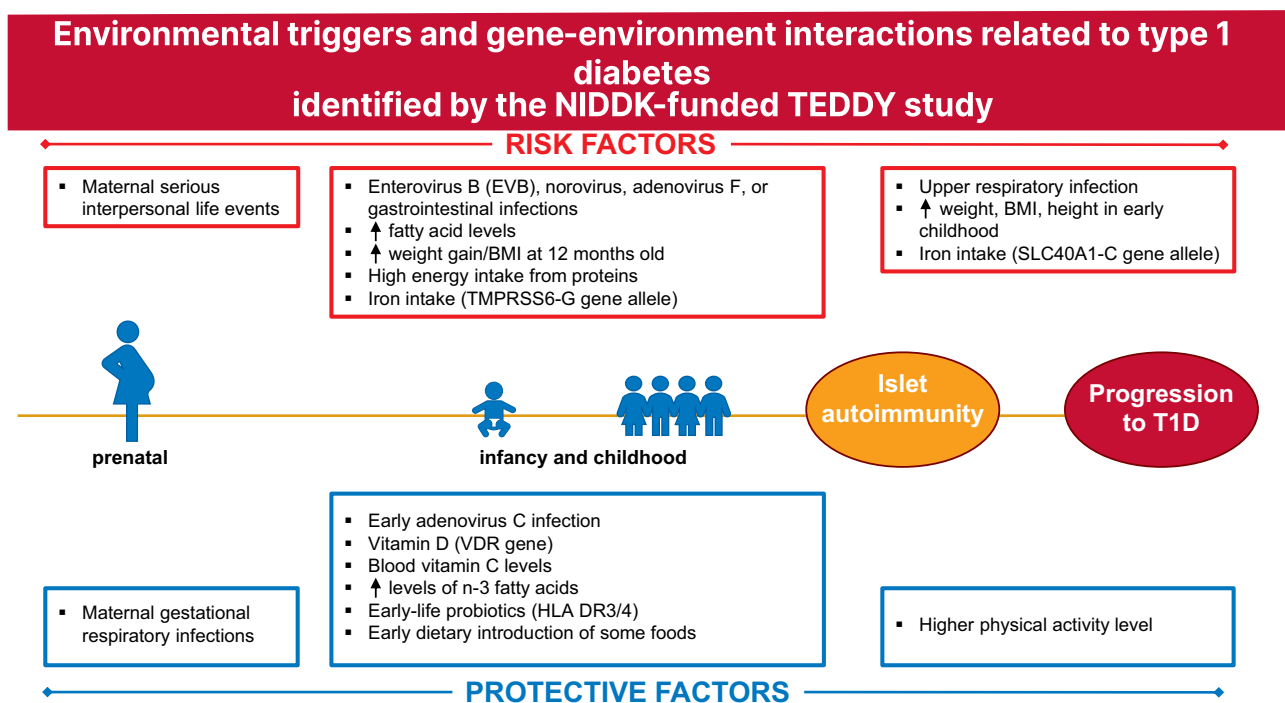


## Unfolding the Mystery of Autoimmunity: The Environmental Determinants of Diabetes in the Young (TEDDY) Study

Marian Rewers, Daniel Agardh, Suzanne Bennett Johnson, Ezio Bonifacio, Helena Elding Larsson, Patricia Gesualdo, William Hagopian, Michael J. Haller, Heikki Hyöty, Randi Johnson, Richard McIndoe, Eoin McKinney, Jessica Melin, Åke Lernmark, Richard E. Lloyd, Kristian F. Lynch, Jill M. Norris, Stephen S. Rich, Roswith Roth, Desmond Schatz, Jorma Toppari, Eric Triplett, Kendra Vehik, Suvi M. Virtanen, Anette-G. Ziegler, Beena Akolkar, and Jeffrey P. Krischer, on behalf of the TEDDY Study Group

Diabetes Care 2025;48(7):1125–1135 | <https://doi.org/10.2337/dc24-2886>



### ARTICLE HIGHLIGHTS

#### • Why did we undertake this study?

The aim of TEDDY is to advance understanding of the causes and the natural history of type 1 diabetes and other autoimmune diseases.

#### • What is the specific question(s) we wanted to answer?

TEDDY has evaluated multiple environmental factors operating prenatally and in childhood as candidate triggers, drivers or modifiers of autoimmunity.

#### • What did we find?

Viral infections, including enteroviruses B, appear to trigger islet autoimmunity, when persistent. Vitamin D, vitamin C, n-3 fatty acids, probiotics, or iron may play modifying roles in genetically susceptible children. Excessive weight gain and protein-rich diet may accelerate progression to clinical diabetes, while physical activity may delay it.

#### • What are the implications of our findings?

These findings have narrowed the field of potential interventions to be tested in clinical trials.



# Unfolding the Mystery of Autoimmunity: The Environmental Determinants of Diabetes in the Young (TEDDY) Study

*Diabetes Care* 2025;48:1125–1135 | <https://doi.org/10.2337/dc24-2886>

In 2025, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health celebrates 75 years of leadership in diabetes research. The NIDDK serves people of the U.S. affected by or at risk for many chronic diseases, including diabetes and other endocrine, metabolic, and digestive disorders, by funding innovative research to develop better treatment and prevention and a cure for these conditions. Autoimmunity that leads to type 1 diabetes or celiac disease or thyroid autoimmunity affects 1 in 20 children and adolescents in the U.S. While treatments are available, prevention of these common autoimmune diseases has been elusive due to poor understanding of the environmental causes and their interactions with common predisposing or protective genetic variants. In 2002, the NIDDK established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium to advance understanding of the causes and the natural history of type 1 diabetes and other autoimmune diseases. The overarching goal of TEDDY is to inform novel approaches to primary prevention of autoimmunity. In this large international prospective birth cohort study, standardized information has been collected concerning candidate environmental exposures along with serial blood, stool, nasal swab, and other biosamples, with creation of a central repository of data and biologic samples for hypothesis-based research. This review summarizes TEDDY's major contributions to our understanding of environmental triggers, drivers, and modifiers of autoimmunity, and gene-environment interactions, leading to type 1 diabetes.

For the past 75 years, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has served people of the U.S. affected by or at risk for many chronic diseases, including type 1 diabetes and celiac and thyroid disease, by funding innovative research to develop better treatment and prevention and a cure for these conditions. Type 1 diabetes affects 1.7 million people in the U.S. (1) and 8.4 million worldwide; its incidence in childhood continues to rise by ~3% annually (2,3). In October 2001, experts gathered by the NIDDK, the Centers for Disease Control and Prevention (CDC), JDRF, and the American Diabetes Association reviewed the ontogeny of autoimmunity, plausible environmental causes of type 1 diabetes, and novel methods for pathogen discovery. The workshop participants concluded that a coordinated approach to identify environmental triggers of type 1 diabetes was a challenging undertaking but feasible and timely. A large prospective cohort study was proposed

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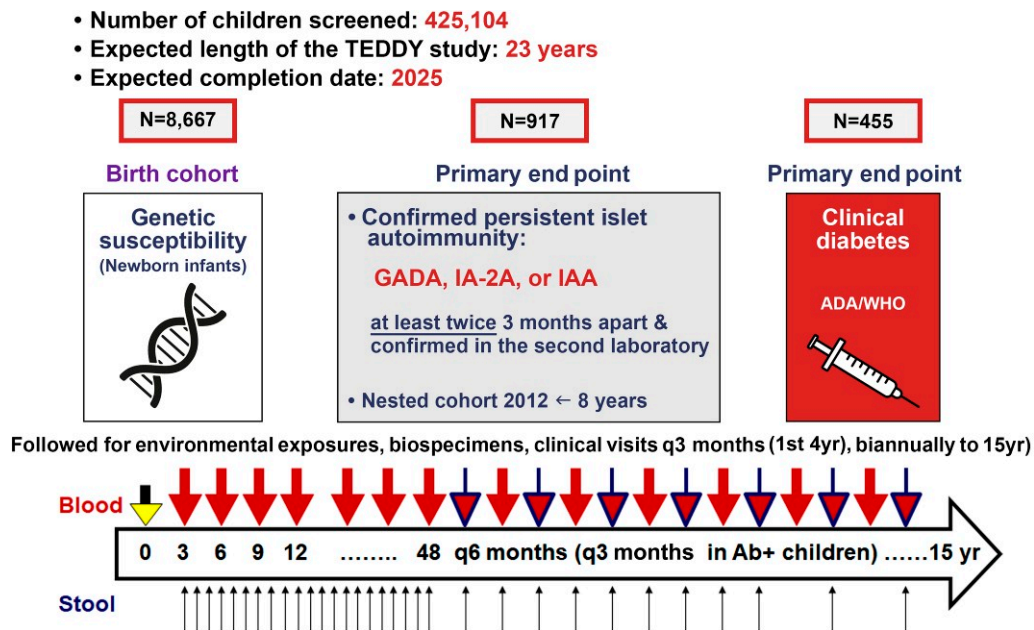
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Received 28 December 2024 and accepted 19 February 2025

This article contains supplementary material online at <https://doi.org/10.2337/figshare.28489196>.

\*A list of members of the TEDDY Study Group can be found in the supplementary material online.



**Figure 1**—TEDDY study design. Ab, autoantibody; ADA, American Diabetes Association; q, every; WHO, World Health Organization; yr, years.

to collect exposure information and samples in a standardized manner and create a central repository of data and biologic samples for subsequent hypothesis-based research. Funding for this, known as The Environmental Determinants of Diabetes in the Young (TEDDY) consortium (4,5), was possible thanks to the Special Diabetes Program, a federally funded program for research on the prevention and cure of type 1 diabetes that began in 1998 and provided \$3.39 billion over 26 years. NIDDK administers the Special Diabetes Program in collaboration with multiple National Institutes of Health (NIH) institutes and the CDC. This review summarizes TEDDY's major contributions to our understanding of environmental triggers, drivers, and modifiers of autoimmunity, and gene-environment interactions, leading to type 1 diabetes, reported in more than 170 peer-reviewed publications.

### THE GOALS OF TEDDY

1. Identify modifiable environmental factors responsible for the development of islet autoimmunity (IA).
2. Identify predictors of progression from IA to clinical diabetes.

3. Disentangle the heterogeneity of type 1 diabetes phenotypes to characterize possible endotypes.
4. Explore triggers and drivers of celiac disease and autoimmune thyroid disease.
5. Collect and bank specimens for studies of the etiology and pathogenesis of type 1 diabetes and other autoimmune diseases of childhood.

### TEDDY STUDY DESIGN AND POPULATION

The TEDDY consortium includes six Clinical Centers (three in the U.S. and three in Europe) and the Data Coordinating Center. This large, intensively followed cohort (Fig. 1) offers a unique opportunity to disentangle the role of genetic and environmental factors in the complex etiology of type 1 diabetes. In 2004–2010, TEDDY screened 425,104 newborns for HLA DR-DQ genotypes conferring increased type 1 diabetes risk. In the general population (GP) newborns, the eligible haplotypes were HLA DR3-DQ2.5/DR4-DQ8, DR4-DQ8/DR4-DQ8, DR4-DQ8/DR8-DQ4, and DR3-DQ2.5/DR3-DQ2.5. In newborns with a first-degree relative (the FDRs group) affected by type 1 diabetes, an additional five haplotypes were

also eligible (4,6). HLA DRB1\*04:03 was an exclusion allele (7,8). Of the 21,589 eligible infants, 8,667 (40%) enrolled. Enrollment rates were higher among FDRs than among GP children (9). FDRs accounted for 10.6% of the TEDDY cohort at enrollment. By 2024, an additional 105 TEDDY participants became FDRs, as a sibling or parent was diagnosed with type 1 diabetes. Among the U.S. TEDDY-eligible infants, underrepresented ethnic groups were less likely to participate due to lack of response to TEDDY staff phone calls and letters. However, if they were successfully contacted, they enrolled at rates similar to those of non-Hispanic White individuals (10).

### Follow-up Schedule

Participating children completed their initial study visit by 4 months of age. Clinic visits occurred quarterly until age 4 years and then every 6 months through age 15 years (Fig. 1). Children with one or more persistent islet autoantibodies (IAb) were followed quarterly; an oral glucose tolerance test was performed in these children every 6 months. Parents filled out questionnaires at regular intervals and recorded information on diet, allergies, vaccinations, illnesses, medication,

supplements, daycare, pets, school, social groups, and significant life events. Anthropometric measurements were taken at each visit. Blood, stool, nasal swab, saliva, urine, toenail clippings, and drinking water were collected. Physical activity was measured by accelerometer from age 5 years. Detailed procedures were used to standardize data collection, harmonization, and management (11). Retention of study participants was prioritized with the goals of minimizing withdrawal and assessing possible bias. Of the original cohort, 5,633 (65%) participants were actively engaged in the protocol 19 years after enrollment began. Most withdrawals occurred within the first 2 years of life, and withdrawals steadily declined thereafter to rates of <2% for age 9–15 years (12).

Dropout rate was higher among GP than FDR families, among U.S. than European families, and among parents with inaccurate perceptions of their child's diabetes risk as well as those who were highly anxious and accurate about their child's risk (13). In the U.S., Hispanic ethnicity was associated with increased early dropout (10). However, later withdrawal was not associated with race/ethnicity. Reasons for withdrawing included younger maternal age, maternal lifestyle behaviors, accuracy of the mother's risk perception, and concerns related to blood draws (14,15). "Having someone watching my child for the development of diabetes" was the primary reason for staying in TEDDY (16).

A successful intervention was developed targeting those at greatest risk for study dropout (17). Withdrawn participants were contacted annually to update contact information, assess disease

status, and offer reenrollment; among 2,634 withdrawn participants, 660 (25%) later returned to the study (12). From this surveillance an additional 43 participants diagnosed with diabetes and 50 with celiac disease were found. A long-distance protocol allowed for remote data and sample collection and was used at some point by 17.6% of the cohort. Local and national diabetes registries were engaged in surveillance for type 1 diabetes among withdrawn participants and those lost to follow-up.

### Study Outcomes

Tables 1 and 2 summarize TEDDY outcomes regarding IA ( $n = 917$ ) and type 1 diabetes ( $n = 455$ ) (Table 1) and celiac disease and autoimmune thyroid disease (Table 2). The primary outcome was persistent confirmed IA defined according to the presence of an IAb to insulin (IAA), GAD (GADA), or insulinoma antigen-2 (IA-2A) in at least two consecutive samples. IAb were measured in two laboratories with radiobinding assays (4,5). Both laboratories showed high sensitivity and specificity as well as concordance (18). All positive IAb and 5% of negative samples were reevaluated in the other laboratory, and results were considered confirmed if concordant. The first of the two consecutive samples was used to designate the age of seroconversion. Positive results that were due to maternal IgG transmission were excluded in determining the child's autoantibody status.

Additional study outcomes included multiple persistent autoantibodies with normoglycemia (stage 1) or dysglycemia (stage 2), and clinical diabetes (stage 3) diagnosed according to the American

Diabetes Association criteria (19). Despite their young age, TEDDY participants who developed type 1 diabetes were often asymptomatic (20) and rarely had diabetic ketoacidosis, in comparison with the community cases (21). At diagnosis, mean HbA<sub>1c</sub> was lower in TEDDY (6.8%, 51 mmol/mol) than in community (10.5%, 91 mmol/mol;  $P < 0.0001$ ) children. TEDDY children had significantly greater area under the oral glucose tolerance test curve and higher peak C-peptide values in comparison with the community control children throughout the first year postdiagnosis (22).

### Nested Case-Control Study

A multidimensional "omic" analysis of serial samples collected from children who reached the study outcomes started in 2012 (23). The first phase (NCC1) of the nested case-control study (NCC) included 418 children who developed persistent confirmed IAb, at median age 1.8 years (interquartile range 1.0–2.8), and 1,253 control children matched on clinical center, sex, and family history of type 1 diabetes. A substudy included 114 children diagnosed with clinical diabetes at median age 2.4 years (1.6–3.4) and 342 matched IA-negative control participants. As of 24 October 2024, an additional 499 TEDDY participants had developed IAb, an additional 341 were diagnosed with diabetes, and matched control participants were selected, forming the foundation of the second NCC study. Metagenomic, genomic, transcriptomic, proteomic, and metabolomic analyses of both NCC studies are being harmonized.

**Table 1—TEDDY islet autoantibody (IAb) and diabetes end points by study group, as of 24 October 2024**

Center	FDRs				GP			
	Enrolled	Single IAb	Multiple IAb	Type 1 diabetes	Enrolled	Single IAb	Multiple IAb	Type 1 diabetes
COL	155	7	20	26	1,215	45	60	55
FIN	201	11	32	32	1,632	73	107	80
GEO	110	7	12	10	854	24	31	30
GER	221	11	25	31	373	13	19	15
SWE	199	19	28	22	2,329	132	132	100
WAS	141	9	14	13	1,237	43	43	41
All	1,027	64	131	134	7,640	330	392	321

Data are  $n$ .



**Table 2—TEDDY CDA and thyroid autoimmunity end points, as of 24 October 2024**

Center	Tested	CDA	Celiac disease	Tested	Thyroid autoimmunity	Autoimmune thyroid disease
U.S.	2,841	500	197	2,249	314	46
FIN	1,593	284	96	1,294	143	16
GER	447	78	24	357	25	6
SWE	2,132	502	257	1,795	192	16
All	7,013	1,364	574	5,695	674	84

Data are *n*.

### INCIDENCE OF IA AND RISK OF PROGRESSION TO TYPE 1 DIABETES

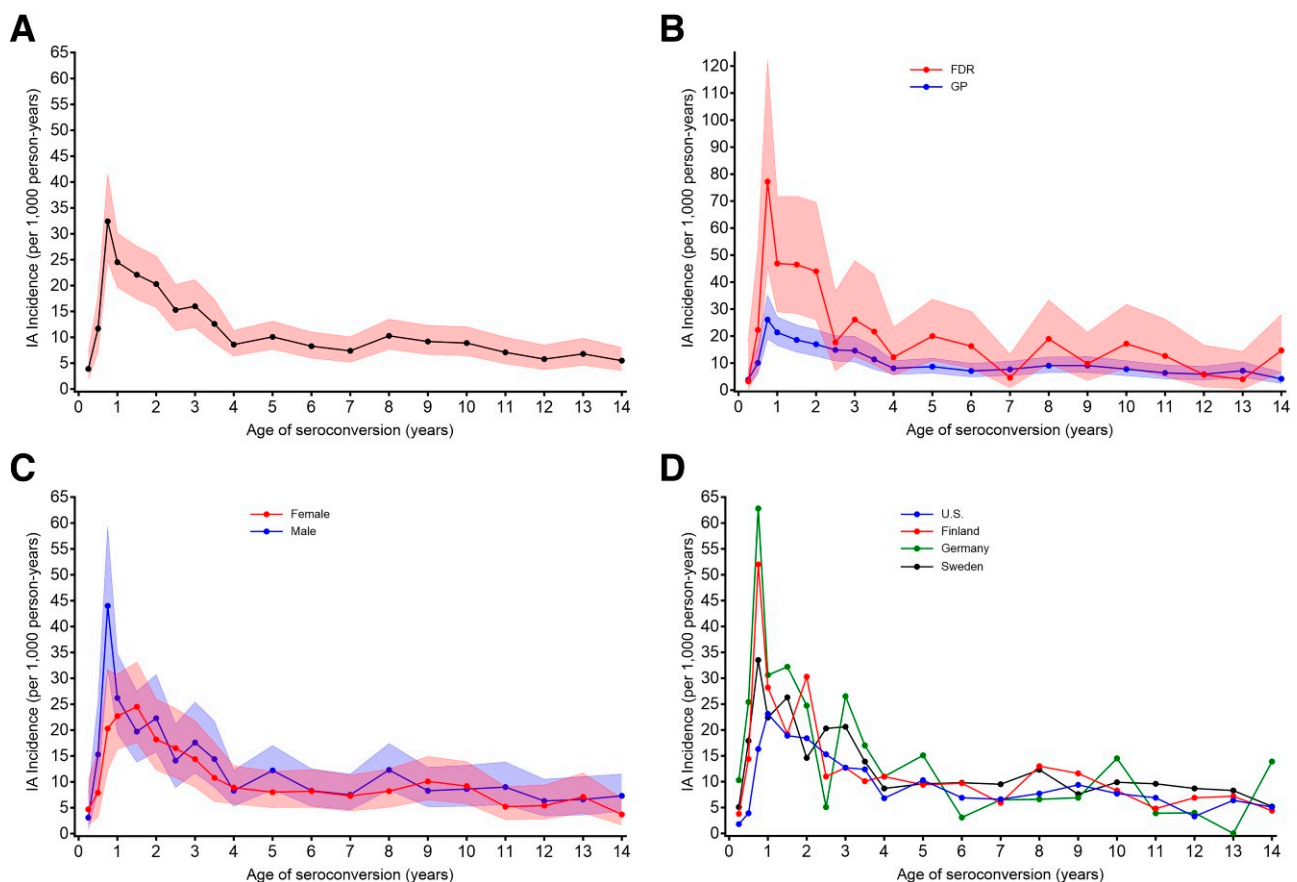
The incidence of IA peaked at 9 months of age at 32.0/1,000 person-years (95% CI 24.8, 41.5), declined to 10.1/1,000 person-years by age 5 years, and has remained relatively constant since (Fig. 2A). The peak at 9 months was prominent among FDRs, 77.2/1,000 person-years (45.8, 122.1) vs. 26.1/1,000 person-years (19.0, 35.1) in GP children (Fig. 2B); male participants, 44.0/1,000 person-years (31.8, 59.2) vs. 20.3/1,000 person-years

(12.2, 31.6) in female participants (Fig. 2C); and children from Finland, 52.0/1,000 person-years (32.6, 78.7), or Sweden, 33.5/1,000 person-years (20.2, 52.3). The incidence peak was delayed to the second year of life in the lower-risk U.S. population: 23.1/1,000 person-years (16.1, 32.2) (Fig. 2D). Higher incidence rates among German TEDDY participants reflect the high proportion (37%) of FDRs in this cohort. Incidence rates after the peak were indistinguishable among countries. There was a noticeable lack of the early peak among children with the HLA DR3/3 genotype.

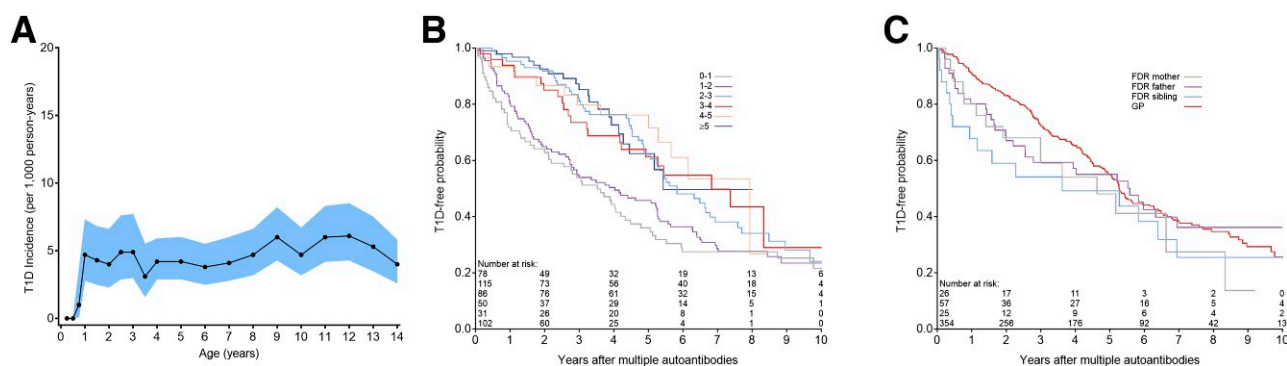
The incidence of type 1 diabetes remained constant (Fig. 3A) over the follow-up period and was higher in Finland than in Sweden or the U.S. ( $P < 0.0001$ ). The risk differed according to the age of IA onset (24) (Fig. 3B). The highest rate of progressing to diabetes was among children age  $<2$  years. The rate for progression to diabetes was slightly higher for FDRs than for GP children (Fig. 3C). HLA DR3/4 genotype carried a higher risk of progressing to diabetes regardless of age, while DR4/4 and 4/8 genotypes carried higher risk than DR3/3 for children aged  $\geq 6$  years (24).

### REFINING THE CONCEPT OF GENETIC SUSCEPTIBILITY

TEDDY's design enables well-powered evaluation of the role of genetic variation, in interaction with environmental exposures, regarding initiation and progression of IA to clinical type 1 diabetes. The genetic basis of type 1 diabetes has been established in a variety of case-control studies of European and non-European or mixed ancestry, ultimately identifying



**Figure 2—**Persistent confirmed IAb incidence (with 95% CIs) per 1,000 person-years by age at IAb seroconversion (A), family history of type 1 diabetes (B), sex (C), and country (D).



**Figure 3**—Incidence of stage 3 type 1 diabetes (T1D), per 1,000 person-years by age at diagnosis (A), age of initial IAb seroconversion (25) (B), and family history of type 1 diabetes and relation to the proband (25) (C).

>100 loci contributing to type 1 diabetes risk. Variation in HLA alone accounts for up to 40% of the overall genetic risk. TEDDY's HLA DR-DQ inclusion criteria include the most common diabetogenic haplotypes in most ethnicities. This limited selection elevated cohort-wide risk and, through the resulting improved power, enabled the study of preclinical IA end points and HLA-environment interactions. Finally, it allows isolation of the effects of the two major haplotypes (abbreviated DR4 and DR3), which undoubtedly present distinct islet and/or environmental antigens to the immune system (6).

TEDDY has extended genetic discovery in type 1 diabetes beyond the well-studied HLA region, first to known autoimmune regions mapped to type 1 diabetes, autoimmune thyroid disease, celiac disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, Crohn disease, and psoriasis, covered by the Immunochip. Later applied customized HumanCore-Exome Bead array included ~90,000 additional variants from putative causal genes and pathways and provided genome-wide coverage. Whole-genome sequencing centered on the TEDDY NCC series enabled discovery of low-frequency and rare variation in initiation and progression of disease. This intense characterization of genome-wide genetic variation differentiated genes implicated in initiation of IA (25,26) versus those acting during progression to clinical diabetes (26–28). It further allowed identification of unique genetic variants identifiable only in the context of type 1 diabetes-related environmental exposures, such as nutrients and infections.

With use of fine mapping data from the Type 1 Diabetes Genetics Consortium (29), a genetic risk score (GRS) was developed and widely used to identify individuals at genetic risk (30,31). Using this GRS, TEDDY investigators confirmed that a population-based risk score could be used to find those most at risk for developing IA and progressing to diabetes in a population of HLA-defined high-risk children. This suggested that early (2–6 years of age) population screening might accurately predict type 1 diabetes onset up to 5 years in the future (32). Further, unlike with individual susceptibility loci, the accumulation of risk genotypes created a single type 1 diabetes GRS associated with both initiation and progression to clinical disease (33). As only 5% of individuals who develop type 1 diabetes have a positive family history, the GRS might serve as an important tool to identify individuals who might benefit from IAb screening (34).

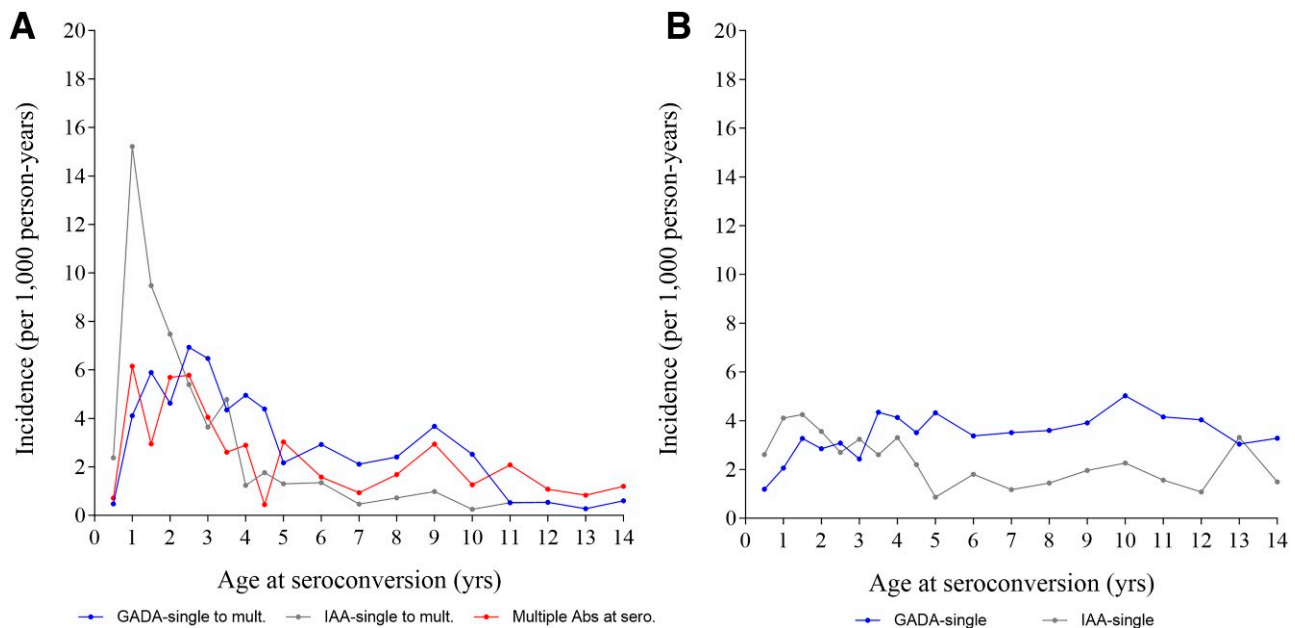
TEDDY has also generated extensive nongenetic data on participants over multiple examination periods, including transcriptomic (array and RNA sequencing), epigenomic (DNA methylation with the EPIC array), proteomic, and metabolomic data. While these data hold promise for understanding the underlying biology of the disease process and the mechanisms of its modulation by environmental exposures, to date their integration with clinical and non-omic markers has not significantly improved the prediction of IA or progression to type 1 diabetes (35–37).

#### EVIDENCE FOR HETEROGENEITY OF IA AND TYPE 1 DIABETES

In analyzing the appearance of a persistent confirmed IAb, three autoantibodies (IAA, GADA, and IA-2A) were considered.

It was unclear at the outset how the timing of each IAb appearance should be interpreted relative to appearance of other IAb. Already at the 6-year follow-up, 549 of 8,503 (6.5%) children had developed one or more autoantibodies. However, in the first seropositive sample 43.7% had IAA only, 37.7% GADA only, 13.8% both GADA and IAA, 1.6% IA-2A only, and 3.1% other combinations (38). The proportion of children initially with IAA only was higher among those <6 years old (44.6%), compared with 28.1% among those >6 years old. The opposite was found for GADA as the first-appearing autoantibody (18.0% vs. 26.9%, respectively) (24) (Fig. 4 [39]).

TEDDY findings suggested haplotype-specific phenotypes of disease initiation, including an HLA DR4-related phenotype characterized by the appearance of IAA first (IAA-first) during the initial years of life and an HLA DR3-related phenotype characterized by the appearance of GADA first (GADA-first) later in childhood (28). This unique finding has intriguing implications for distinct environmental triggers as well as possible endotypes. Phenotypic differences between children developing either IAA only or GADA only as the first appearing IAb included factors such as early introduction of solid foods and gluten and gastrointestinal or enterovirus infections, as well as maternal life events, as recently reviewed (39). Other genetic variants indicating heterogeneity in the risk for IA included insulin gene (*INS*) association with IAA-first as well as *CLEC16A* and *IL2RA* with GADA-first (28). GADA-first was also related to the Cocksackie adenovirus receptor (*CAR*) that modifies the association between enterovirus B (EVB) and IA (40) as well as to *GSTM1* expression (41).



**Figure 4**—A: Incidence rate of GADA-only (A) as the first appearing autoantibody later developing into multiple autoantibodies (blue) in comparison with IAA-only later developing into multiple autoantibodies (gray). Red: Multiple autoantibodies at seroconversion, shown for comparison. B: Incidence rate of GADA-only (blue) and IAA-only (gray) as the first-appearing autoantibody but in individuals remaining positive for a single autoantibody. yrs, years.

Further analyses of transcriptional networks (41,42) as well as of integrating the multiomics approach in TEDDY (35,43) should prove useful to further dissect the possible heterogeneity of IA.

### IS IA TRIGGERED BY AN INFECTION?

TEDDY conducted the largest longitudinal capture of infectious exposures, including stool bacteriome, virome, phageome, and mycobiome in high-risk children up to 6 years of age. This prospective analysis informed the type, timing, and order of infections associated with risk of IA. Numerous viruses were detected in stools with mass sequencing. Both acute and prolonged infections with EVB, particularly group B Coxsackieviruses, predicted development of IA (40). Independently, the single nucleotide polymorphism rs6517774 in the loci coding the Coxsackie adenovirus receptor (CAR) used by group B Coxsackieviruses was correlated with fewer EVB infections but a higher risk of IA. Furthermore, an adenovirus C infection detected before 6 months of age predicted lower risk of IA, while an increasing number of adenovirus F infections predicted increased risk of IA (40). No association of exposure to severe acute respiratory syndrome coronavirus 2 during

adolescence with IA or type 1 diabetes was found in TEDDY (44).

TEDDY showed that reported respiratory and gastrointestinal infections during specific exposure windows modified risk of IA and the age-related first-appearing IAA versus GADA phenotypes (45–47). Respiratory infections, particularly when occurring with fever within a year prior to IA, increased the risk, while gastroenteritis either increased or decreased the risk depending on the age of infection. Moreover, gestational respiratory infections had a genetic-dependent effect with *CTLA4* G allele and HLA DR4/8 genotype modifying risk of developing IAb early in life (47). Cesarean section did not affect the risk for IA (48). Detection of norovirus in stools during the first year of life was associated with a greater than five-fold risk of IA-first after 2 years of age, and detection of EVB before age 2 years increased risk of IAA-first by ninefold after 2 years of age (45), suggesting that these viruses could contribute to the associations seen in symptomatic infections. Blood transcriptomics showed that innate immune response to EVB infections was more heterogeneous and weaker in children who developed IA than in control participants, which may reflect susceptibility to EVB infections and their persistence.

The TEDDY analysis of 16S rRNA from 12,003 serial stool samples from 903 at-

risk children documented rapid changes in the microbiome communities in the first year of life (49). Metagenomics analysis of 10,913 samples from 783 children showed that while the bacterial taxa varied over time and between participants, bacterial functions remain constant but with perhaps some protection from IA by butyrate producers (50). Phageome analysis of 12,262 stool samples from 887 children showed that phage mirrored their bacterial hosts in abundance and diversity across time but were more transitory than their host bacteria with little association with future type 1 diabetes (51). Gut fungi were also investigated temporally among 888 TEDDY children from 3 to 48 months of age. Geography, age, diet, and probiotic use all affected fungal diversity and composition, but only minor associations were found with IA (52). Overall, few associations were found between the microbiome and IA, which was consistent with no effect of early childhood antibiotic use on IA risk (53).

### IS IA TRIGGERED BY A DIETARY FACTOR?

#### Macronutrients

Macronutrients include proteins, carbohydrates, and fats. Carbohydrates consist of starch, dietary fiber, and sugars. TEDDY found that intake of soluble fiber in early

childhood was not associated with development of IA (54). Increased erythrocyte n-3 fatty acid status in infancy and conjugated linoleic acid status after infancy were associated with lower risk of IA (55), while some saturated and monounsaturated fatty acids were associated with higher risk of IA. Inverse association between n-3 fatty acid status/intake with IA has been shown in other cohorts and may suggest an important role of this anti-inflammatory component of the diet. TEDDY found increased infant growth to be associated with the development of IA (56,57). Higher energy intake was associated with a higher BMI, which led to an increased risk of IA (58). In addition, a larger contribution of energy from protein in the diet increased the risk of GADA-first, but not through increased BMI, suggesting a possible role of protein intake in the etiology of type 1 diabetes.

### Micronutrients

Micronutrients are vitamins and minerals that are essential for healthy development, growth, and well-being. TEDDY found that higher intake of pyridoxine and vitamin B<sub>12</sub> was associated with decreased risk of IAA-first, whereas higher intake of riboflavin was associated with increased risk of GADA-first (59). Moreover, higher plasma ascorbic acid was associated with reduced risk of IAA-first (60) and IAA-first was earlier among infants with reduced plasma ascorbic acid (61).

### Gene-Nutrient Interactions

The large population size allowed investigation in TEDDY of gene-nutrient interactions, to determine whether dietary exposures impact disease risk in specific risk groups. Probiotics supplementation in infancy reduced the risk of IA only in children with the high-risk HLA DR3/4 genotype (62). Moreover, early introduction of solid food (before age 6 months) was associated with increased risk of IA in children with the HLA DR3/4 genotype in the case of no probiotic exposure—not in those exposed to probiotics in the first year of life (63).

25-hydroxyvitamin D concentration was associated with IA more strongly among those with effect alleles in the vitamin D receptor gene (64). Higher intake of iron

was associated with increased risk of IAA-first only in those with iron metabolism genetic variants that increase intestinal iron absorption and impair cellular iron release (65). This may suggest that the underlying susceptibility may be related to the ability to adequately use 25-hydroxyvitamin D or dietary iron rather than the nutrient intake itself.

TEDDY has generated important information for potential precision nutrition approaches. The dietary findings in TEDDY, based on dietary data harmonized between the participating countries (66,67) and standardized nutrition biomarker measurements, suggest that micro- and macronutrients may act more as moderators, rather than triggers, of IA and that this action may work differently in individuals with different genetic predispositions.

### THE ROLE OF GROWTH AND PHYSICAL ACTIVITY IN DEVELOPMENT OF IA AND PROGRESSION TO CLINICAL DIABETES

Growth during the first years of life is of special interest, since IA often begins early in life. Excessive growth may increase demand of insulin, stressing the  $\beta$ -cells and thereby increasing the susceptibility to other triggers of autoimmunity, such as viruses. Increased insulin resistance could potentially speed up the progression from IA to clinical diabetes, through increased demand of insulin. In TEDDY, higher weight z scores at 12 months of age predicted development of multiple IAb at 12 and 24 months of age (56). Weight gain during infancy was related to development of IA, while high weight gain during early childhood increased the rate of progression from IA to diabetes (57). Increased BMI z scores during puberty, but not pubertal stage itself, were associated with development of IA, primarily in girls (68). Importantly, for children spending more time in moderate-to-vigorous physical activity per day there was lower risk of progression from multiple IAb to type 1 diabetes, while no effect on initiation of IA was seen (69).

### COULD IA BE TRIGGERED BY OTHER ENVIRONMENTAL FACTORS?

A link between psychological stress and type 1 diabetes has been documented in both epidemiological and animal studies,

although few studies have included examination of the link between stress and the development of IA. In TEDDY, psychological stress was measured through parent reports of major life events experienced by the parent and child until age 10 years, after which the child's own reports were also collected. In addition, saliva samples were successfully obtained from the child at ages 3, 4, and 5 years, providing biospecimens for possible cortisol assay (70). A link was observed between maternal reports of life events experienced during pregnancy and subsequent early development of IAA and later development of GADA (71). The mechanism(s) by which stressful life events could influence the development of autoimmunity in children is yet to be determined. Stress could have a direct effect on immune functioning or could be associated with an increased risk for infections. In TEDDY, children with more life events in their first 4 years of life had more respiratory infections (72), which may be linked to the development of IA (45,46).

Streptozotocin and alloxan have been used in experimental animal research to induce  $\beta$ -cell destruction and thereby type 1 diabetes. Environmental toxicants, e.g., bisphenol A, can target  $\beta$ -cells directly or indirectly by affecting the immune system. In collaboration with the Children's Health Exposure Analysis Resource program, urine samples of the 1,025 TEDDY children in the NCC were analyzed for phthalates, urinary creatinine, phenols, parabens, polycyclic aromatic hydrocarbons, trace metals, organophosphate flame retardants, and pesticides. Overall, no consistent associations were found.

### DRIVERS OF IA

Asymptomatic IA is detectable from weeks to years before diagnosis. While the number, type, and level of IAb are associated with long-term disease risk and this information can be useful in stratification of progression risk (73), they do not cause disease. TEDDY has generated evidence for increased risk of IA after persistent enteroviral infection (40). However, understanding the pathological mechanisms—immune changes resulting from this exposure and other IA-associated exposures and how they result in broken tolerance and disease—remains arguably



the major challenge in understanding type 1 diabetes.

TEDDY combined prospective, longitudinal sampling in at-risk individuals from birth for weighted case-control cohort analyses (74). These studies have helped exploration of immune mechanisms of type 1 diabetes onset and progression using high-throughput omic analysis to characterize progression in detail from the earliest stages.

TEDDY metabolomic and proteomic analyses identified altered features prior to seroconversion, with changes differing between groups based on first-appearing autoantibody and showing distinct longitudinal trajectories in comparison with matched control participants (43,75). Integration of early (43) and longitudinal (36,76) metabolite and protein markers with demographic and genetic traits has identified early differences from matched control participants that could be used to predict the onset of IA. Enrichment of specific metabolites (especially lipid metabolism [36,75,76]) or proteomic pathways (complement, antigen presentation [43]) was incorporated into predictive models but have as yet stopped short of clarifying a clear mechanism of triggering autoimmunity or progression to clinical diabetes.

Altered longitudinal patterns of whole blood transcription prior to seroconversion also tracked with progression to both IA and type 1 diabetes (41,42) reflecting altered proportions of circulating natural killer cells, monocytes, and B cells (41) on a background of complex and dynamic age-related changes. Observed changes also differed between individuals stratified by first-appearing islet antibody, although similarities between the two were also apparent before IA (41,42). These distinct but overlapping trajectories may reflect different responses resulting from the same environmental stimulus breaking tolerance, or different etiologies altogether. Further clarifying this key question relies on stratification for differing ages and HLA backgrounds such as is possible in TEDDY. With integration of RNA-seq and viomic data, a signature of innate immune activation was characteristic for control participants after enteroviral infection but was absent from those progressing to IA (41).

The analyses undertaken to date suggest that progression to type 1 diabetes requires both exposure to an environmental

trigger and an aberrant response, with risk declining exponentially with increasing age (77). Ongoing efforts to characterize mechanisms of progression to IA or type 1 diabetes through nested case-control studies include using integration of the broad range of genomic data generated in TEDDY. Validation of findings already seen in TEDDY in other cohorts (36,42) supports that they may be generalized features of disease.

## CELIAC AND THYROID AUTOIMMUNITY IN CHILDHOOD

Screening for celiac disease autoimmunity (CDA), defined according to persistent tissue transglutaminase autoantibody positivity, was performed from age 2 years. Highest incidence of CDA was observed before age 4 years (78) (Fig. 5A). The HLA DR3-DQ2/DR3-DQ2 haplogenotype was the strongest predictor of CDA. Additional predictors included variants of genes *TAGAP*, *IL18R1*, *RGS21*, *PLEK*, and *CCR9*; family history of celiac disease; female sex; and country (53,79). Swedish children had the highest risk, independent of HLA DR-DQ genotype (78). Higher gluten intake during the first 5 years of life predicted CDA (78,80). In contrast, breastfeeding and timing of gluten introduction did not affect CDA risk (81). Parent-reported gastrointestinal infections increased, while rotavirus vaccination decreased, CDA risk (82). Children developing CDA had a higher frequency of enterovirus infection prior to seroconversion than matched control participants (78), and there was an interaction between enterovirus infection at age 1–2 years and cumulative gluten intake for risk of CDA. In TEDDY nested case-control analyses both low and high vitamin D serum concentrations were found to be associated with increased risk of CDA (83).

Cesarean section delivery (84) and gluten consumption and dietary supplementation of vitamin D, n-3 fatty acids, or iron during pregnancy were not associated with CDA in the offspring (85,86). No association was found between cumulative antibiotic use or early probiotic use in the first year of life and CDA risk (53,87).

TEDDY participants identified with CDA are referred to pediatric gastroenterologists. So far, 574 children have been diagnosed with celiac disease and

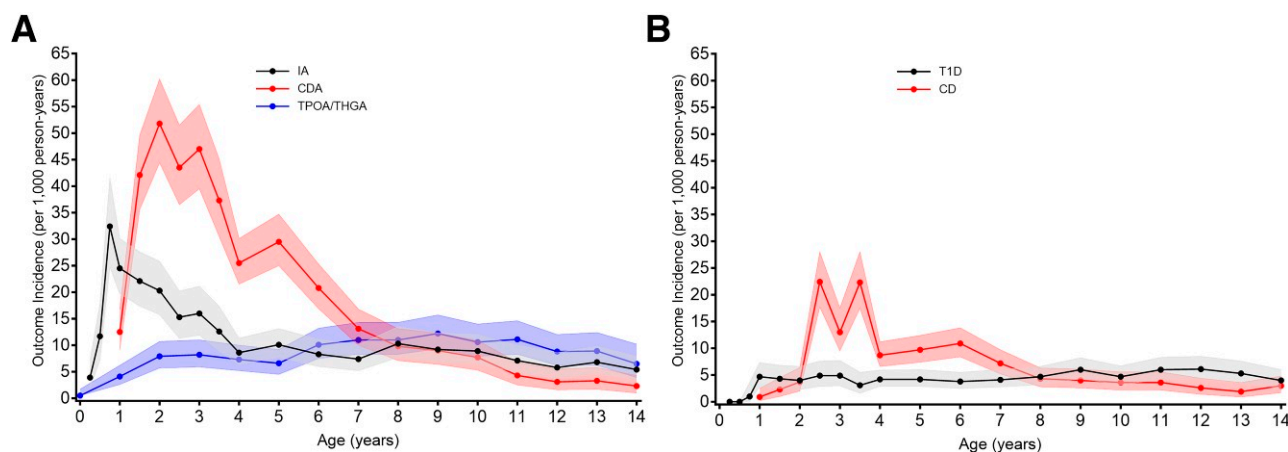
placed on a gluten-free diet (Table 2), usually before the age of 7 years (Fig. 5B).

TEDDY explored the natural history of thyroid autoimmunity in children genetically predisposed to type 1 diabetes. Thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies were measured in 5,695 TEDDY participants (Table 2). The earliest appearance of TPOAb and thyroglobulin autoantibodies was at 10 and 15 months, respectively. Incidence rates of both autoantibodies were higher among girls. Risk of developing TPOAb (hazard ratio [HR] 1.90) and TgAb (HR 2.55) was significantly increased with family history of autoimmune thyroid disease. Risk of progressing to clinical thyroid disease was higher for children with both autoantibodies present simultaneously (HR 6.34) than for those with only one autoantibody. The findings suggest that thyroid autoantibodies can appear during the first years of life, particularly in girls, and that simultaneous appearance of both autoantibodies increases risk for hypothyroidism or hyperthyroidism. This underscores the need for vigilant screening of thyroid autoimmunity and potential early intervention in populations genetically at risk for type 1 diabetes (88).

## LIMITATIONS

The TEDDY study population was representative of major ethnic groups in the U.S. and Europe as well as FDRs and GP children. However, for efficiency, the population included only children with the highest-risk HLA genotypes. Only 31% of FDRs were eligible, representing 69% of future T1D cases among FDRs. Similarly, 5.7% of GP infants were eligible, representing 50% of future T1D cases among GP children (6). It is possible that the environmental factors examined could play a bigger or smaller role in the etiology of type 1 diabetes among children with lower-risk HLA genotypes not included in TEDDY. Current and future GP screening programs may shed more light on the natural history and determinants of IA among groups not included in TEDDY.

With the TEDDY observation period extending from 2004 to 2024, it is possible that triggers and drivers of IA evolved during this period and will continue to evolve. The incidence of childhood type 1 diabetes should remain under surveillance



**Figure 5**—A: Incidence (95% CI) of IA, CDA, and thyroid autoimmunity (thyroid peroxidase autoantibodies [TPOA] or thyroglobulin autoantibodies [THGA]). B: Incidence of clinically confirmed type 1 diabetes (T1D) and celiac disease (CD) (B).

for detection of significant changes attributable to evolving environment.

### TEDDY AS A RESOURCE FOR FUTURE STUDIES OF THE ETIOLOGY OF TYPE 1 DIABETES

TEDDY has collected an extraordinary amount of prospective data and biological samples from high-risk children followed through the initial 15 years of life—the critical period for triggering islet, celiac, and thyroid autoimmunity. The TEDDY cohort's size and population diversity, intensive follow-up, and application of unbiased omics technologies position the study well for discovery of the environmental cause(s) of type 1 diabetes and the mechanisms by which they act. TEDDY can evaluate both highly prevalent and rare environmental triggers and drivers that occur from an early age and evolve during childhood and adolescence. Extended follow-up to the age of 15 years was critical, as the effects of the exposures may have a long lag time.

One of the main goals of TEDDY moving forward is detailed interrogation of top identified candidate triggers and drivers of IA, such as viral infections. TEDDY is currently analyzing epigenetic, transcriptomic, proteomic, and metabolomic profiles of hundreds of case and control participants to integrate these multiomics data into predictive models.

The TEDDY population covered a wide spectrum of genetic variation and environmental exposures with inclusion of diverse populations: Finnish, Swedish, German, southeast U.S. with representation of African Americans, southwest U.S.

with Hispanic individuals, and northwest U.S. including Asian Americans. The large-scale banking of study specimens, including serum, plasma, and peripheral blood mononuclear cells, in the NIDDK Central Repository (<https://repository.niddk.nih.gov/>) will facilitate access to the samples by the research community for years to come. Ancillary applications are encouraged.

As outlined above, TEDDY has contributed greatly to our understanding of disease development for type 1 diabetes and related autoimmune disorders. Given that the last study participant has now completed the clinical protocol, the new few years of sophisticated analysis on millions of data points will be key in understanding the specific environmental factors that contribute to the development and progression of type 1 diabetes. None of the TEDDY contributions to science, or the potential to understand factors that contribute to type 1 diabetes development, would be possible without sustained, long-term, and outstanding support from the NIDDK during the most recent 22 years of its 75 yearslong legacy.

**Acknowledgments.** The authors thank the participants of TEDDY for their generous contributions and the dedicated study personnel at the study sites. A full list of TEDDY Study Group members and their affiliations can be found in the Supplementary Material.

M.J.H. and S.S.R. are editors of *Diabetes Care* but were not involved in any of the decisions regarding review of the manuscript or its acceptance.

**Funding.** The TEDDY study is funded by the NIDDK, National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver

National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, CDC, and Breakthrough T1D (formerly JDRF) (grants U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836, UC4 DK95300, UC4 DK100238, UC4 DK106955, UC4 DK112243, UC4 DK117483, U01 DK124166, and U01 DK128847 and contract no. HHSN-267200700014C). This work is supported in part by the NIH/National Center for Advancing Translational Sciences Clinical and Translational Science Awards to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR002535).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Duality of Interest.** H.H. is a stakeholder in and member of the board of a Finnish biotech company, Vactech Oy, which develops vaccines against picornaviruses. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** M.R. conceptualized, drafted, and revised the manuscript. All other authors wrote sections of the manuscript and contributed to the discussion and/or revision of the final draft of the manuscript. M.R., W.H., R.M., Å.L., J.T., and A.-G.Z. as principal investigators of the Clinical Centers, as well as J.P.K. as principal investigator of the Data Coordinating Center, verified the underlying data.

**Handling Editors.** The journal editor responsible for overseeing the review of the manuscript was M. Sue Kirkman.

### References

1. National Diabetes Statistics Report. Centers for Disease Control and Prevention, 2024. Accessed 30 October 2024. Available from <https://www.cdc.gov/diabetes/php/data-research/index.html>
2. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. *Diabetes* 1990;39:858–864

3. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 2009;373:2027-2033
4. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. *Pediatr Diabetes* 2007;8:286-298
5. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Ann N Y Acad Sci* 2008;1150:1-13
6. Hagopian WA, Erlich H, Lernmark A, et al.; TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. *Pediatr Diabetes* 2011;12:733-743
7. Cucca F, Lampis R, Frau F, et al. The distribution of DR4 haplotypes in Sardinia suggests a primary association of type 1 diabetes with DRB1 and DQB1 loci. *Hum Immunol* 1995;43:301-308
8. Erlich HA, Valdes AM, Noble JA. Prediction of type 1 diabetes. *Diabetes* 2013;62:1020-1021
9. Lernmark B, Johnson SB, Vehik K, et al. Enrollment experiences in a pediatric longitudinal observational study: The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Contemp Clin Trials* 2011;32:517-523
10. Baxter J, Vehik K, Johnson SB, Lernmark B, Roth R, Simell T; TEDDY Study Group. Differences in recruitment and early retention among ethnic minority participants in a large pediatric cohort: the TEDDY Study. *Contemp Clin Trials* 2012;33:633-640
11. Vehik K, Fiske SW, Logan CA, et al.; TEDDY Study Group. Methods, quality control and specimen management in an international multicentre investigation of type 1 diabetes: TEDDY. *Diabetes Metab Res Rev* 2013;29:557-567
12. Gesualdo P, Melin J, Karban R, et al.; TEDDY Study Group. Structures and strategies for retaining an international pediatric cohort from birth: lessons from The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Contemp Clin Trials Commun* 2025;44:101405
13. Johnson SB, Lee H-S, Baxter J, Lernmark B, Roth R, Simell T; TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: predictors of early study withdrawal among participants with no family history of type 1 diabetes. *Pediatr Diabetes* 2011;12:165-171
14. Lernmark B, Lynch K, Baxter J, et al.; TEDDY Study Group. Participant experiences in The Environmental Determinants of Diabetes in the Young study: common reasons for withdrawing. *J Diabetes Res* 2016;2016:2720650
15. Johnson SB, Lynch KF, Baxter J, et al.; TEDDY Study Group. Predicting later study withdrawal in participants active in a longitudinal birth cohort study for 1 year: the TEDDY study. *J Pediatr Psychol* 2016;41:373-383
16. Lernmark B, Lynch K, Ballard L, et al. Reasons for staying as a participant in The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study. *J Clin Trials* 2012;2:1000114
17. Johnson SB, Lynch KF, Lee H-S, et al.; TEDDY Study Group. At high risk for early withdrawal: using a cumulative risk model to increase retention in the first year of the TEDDY study. *J Clin Epidemiol* 2014;67:609-611
18. Bonifacio E, Yu L, Williams AK, et al. Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for national institute of diabetes and digestive and kidney diseases consortia. *J Clin Endocrinol Metab* 2010;95:3360-3367
19. American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care* 2017;40(Suppl. 1):S11-S24
20. Elding Larsson H, Vehik K, Gesualdo P, et al.; TEDDY Study Group. Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease. *Pediatr Diabetes* 2014;15:118-126
21. Elding Larsson H, Vehik K, Bell R, et al.; TEDDY Study Group; SEARCH Study Group; Swediabkids Study Group; DPV Study Group; Finnish Diabetes Registry Study Group. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. *Diabetes Care* 2011;34:2347-2352
22. Steck AK, Larsson HE, Liu X, et al.; TEDDY Study Group. Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls. *Pediatr Diabetes* 2017;18:794-802
23. Lee H-S, Briese T, Winkler C, et al.; TEDDY study group. Next-generation sequencing for viruses in children with rapid-onset type 1 diabetes. *Diabetologia* 2013;56:1705-1711
24. Krischer JP, Liu X, Lernmark Å, et al.; TEDDY Study Group. Characteristics of children diagnosed with type 1 diabetes before vs after 6 years of age in the TEDDY cohort study. *Diabetologia* 2021;64:2247-2257
25. Törn C, Hadley D, Lee H-S, et al.; TEDDY Study Group. Role of type 1 diabetes-associated SNPs on risk of autoantibody positivity in the TEDDY study. *Diabetes* 2015;64:1818-1829
26. Sharma A, Liu X, Hadley D, et al.; TEDDY Study Group. Identification of non-HLA genes associated with development of islet autoimmunity and type 1 diabetes in the prospective TEDDY cohort. *J Autoimmun* 2018;89:90-100
27. Krischer JP, Liu X, Lernmark Å, et al.; TEDDY Study Group. The influence of type 1 diabetes genetic susceptibility regions, age, sex, and family history on the progression from multiple autoantibodies to type 1 diabetes: a TEDDY study report. *Diabetes* 2017;66:3122-3129
28. Krischer JP, Liu X, Lernmark Å, et al.; TEDDY Study Group. Predictors of the initiation of islet autoimmunity and progression to multiple autoantibodies and clinical diabetes: the TEDDY study. *Diabetes Care* 2022;45:2271-2281
29. Onengut-Gumuscu S, Chen W-M, Burren O, et al.; Type 1 Diabetes Genetics Consortium. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. *Nat Genet* 2015;47:381-386
30. Oram RA, Patel K, Hill A, et al. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care* 2016;39:337-344
31. Sharp SA, Rich SS, Wood AR, et al. Development and standardization of an improved type 1 diabetes genetic risk score for use in newborn screening and incident diagnosis. *Diabetes Care* 2019;42:200-207
32. Ferrat LA, Vehik K, Sharp SA, et al.; TEDDY Study Group. A combined risk score enhances prediction of type 1 diabetes among susceptible children. *Nat Med* 2020;26:1247-1255
33. Beyerlein A, Bonifacio E, Vehik K, et al.; TEDDY Study Group. Progression from islet autoimmunity to clinical type 1 diabetes is influenced by genetic factors: results from the prospective TEDDY study. *J Med Genet* 2019;56:602-605
34. Hippich M, Beyerlein A, Hagopian WA, et al.; TEDDY Study Group. Genetic contribution to the divergence in type 1 diabetes risk between children from the general population and children from affected families. *Diabetes* 2019;68:847-857
35. Webb-Robertson B-JM, Nakayasu ES, Frohnert BI, et al. Integration of infant metabolite, genetic, and islet autoimmunity signatures to predict type 1 diabetes by age 6 years. *J Clin Endocrinol Metab* 2022;107:2329-2338
36. Webb-Robertson B-JM, Bramer LM, Stanfill BA, et al. Prediction of the development of islet autoantibodies through integration of environmental, genetic, and metabolic markers. *J Diabetes* 2021;13:143-153
37. Krischer JP, Liu X, Vehik K, et al.; TEDDY Study Group. Predicting islet cell autoimmunity and type 1 diabetes: an 8-year TEDDY study progress report. *Diabetes Care* 2019;42:1051-1060
38. Krischer JP, Lynch KF, Schatz DA, et al.; TEDDY Study Group. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. *Diabetologia* 2015;58:980-987
39. Lernmark Å, Agardh D, Akolkar B, et al. Looking back at the TEDDY study: lessons and future directions. *Nat Rev Endocrinol* 2025;21:154-165
40. Vehik K, Lynch KF, Wong MC, et al.; TEDDY Study Group. Prospective virome analyses in young children at increased genetic risk for type 1 diabetes. *Nat Med* 2019;25:1865-1872
41. Lin J, Moradi E, Salenius K, et al.; TEDDY Study Group. Distinct transcriptomic profiles in children prior to the appearance of type 1 diabetes-linked islet autoantibodies and following enterovirus infection. *Nat Commun* 2023;14:7630
42. Xhonneux L-P, Knight O, Lernmark Å, et al. Transcriptional networks in at-risk individuals identify signatures of type 1 diabetes progression. *Sci Transl Med* 2021;13:eabd5666
43. Nakayasu ES, Bramer LM, Ansong C, et al.; TEDDY Study Group. Plasma protein biomarkers predict the development of persistent autoantibodies and type 1 diabetes 6 months prior to the onset of autoimmunity. *Cell Rep Med* 2023;4:101093
44. Krischer JP, Lernmark Å, Hagopian WA, et al.; TEDDY Study Group. SARS-CoV-2 - no increased islet autoimmunity or type 1 diabetes in teens. *N Engl J Med* 2023;389:474-475
45. Lönnrot M, Lynch KF, Rewers M, et al.; TEDDY Study Group. Gastrointestinal infections modulate the risk for insulin autoantibodies as the first-appearing autoantibody in the TEDDY study. *Diabetes Care* 2023;46:1908-1915
46. Lönnrot M, Lynch KF, Elding Larsson H, et al.; TEDDY Study Group. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. *Diabetologia* 2017;60:1931-1940
47. Lynch KF, Lee H-S, Törn C, et al.; TEDDY Study Group. Gestational respiratory infections interacting with offspring HLA and CTLA-4 modifies incident

- $\beta$ -cell autoantibodies. *J Autoimmun* 2018;86:93–103
48. Singh T, Weiss A, Vehik K, et al.; TEDDY Study Group. Cesarean section and risk of type 1 diabetes. *Diabetologia* 2024;67:1582–1587
  49. Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature* 2018;562:583–588
  50. Vatanen T, Franzosa EA, Schwager R, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. *Nature* 2018;562:589–594
  51. Tisza M, Lloyd R, Hoffman K, et al. TEDDY Study Group. Phage-bacteria dynamics during the first years of life revealed by trans-kingdom marker gene analysis. *Nat Microbiol* 2024;10:420–430
  52. Auchtung TA, Stewart CJ, Smith DP, et al. Temporal changes in gastrointestinal fungi and the risk of autoimmunity during early childhood: the TEDDY study. *Nat Commun* 2022;13:3151
  53. Kempainen KM, Vehik K, Lynch KF, et al.; Environmental Determinants of Diabetes in the Young (TEDDY) Study Group. Association between early-life antibiotic use and the risk of islet or celiac disease autoimmunity. *JAMA Pediatr* 2017;171:1217–1225
  54. Beyerlein A, Liu X, Uusitalo UM, et al.; TEDDY Study Group. Dietary intake of soluble fiber and risk of islet autoimmunity by 5 y of age: results from the TEDDY study. *Am J Clin Nutr* 2015;102:345–352
  55. Niinistö S, Erlund I, Lee H-S, et al.; TEDDY Study Group. Children's erythrocyte fatty acids are associated with the risk of islet autoimmunity. *Sci Rep* 2021;11:3627
  56. Elding Larsson H, Vehik K, Haller MJ, et al.; TEDDY Study Group. Growth and risk for islet autoimmunity and progression to type 1 diabetes in early childhood: The Environmental Determinants of Diabetes in the Young study. *Diabetes* 2016;65:1988–1995
  57. Liu X, Vehik K, Huang Y, et al.; TEDDY Study Group. Distinct growth phases in early life associated with the risk of type 1 diabetes: the TEDDY study. *Diabetes Care* 2020;43:556–562
  58. Aronsson CA, Tamura R, Vehik K, et al. Dietary intake and body mass index influence the risk of islet autoimmunity in genetically at-risk children: a mediation analysis using the TEDDY cohort. *Pediatr Diabetes* 2023;2023:3945064
  59. Hakola L, Mramba LK, Uusitalo U, et al.; TEDDY Study Group. Intake of B vitamins and the risk of developing islet autoimmunity and type 1 diabetes in the TEDDY study. *Eur J Nutr* 2024;63:1329–1338
  60. Mattila M, Erlund I, Lee H-S, et al.; TEDDY Study Group. Plasma ascorbic acid and the risk of islet autoimmunity and type 1 diabetes: the TEDDY study. *Diabetologia* 2020;63:278–286
  61. Li Q, Liu X, Yang J, et al.; TEDDY Study Group. Plasma metabolome and circulating vitamins stratified onset age of an initial islet autoantibody and progression to type 1 diabetes: the TEDDY study. *Diabetes* 2021;70:282–292
  62. Uusitalo U, Liu X, Yang J, et al.; TEDDY Study Group. Association of early exposure of probiotics and islet autoimmunity in the TEDDY study. *JAMA Pediatr* 2016;170:20–28
  63. Uusitalo U, Mramba LK, Aronsson CA, et al.; TEDDY Study Group. HLA genotype and probiotics modify the association between timing of solid food introduction and islet autoimmunity in the TEDDY study. *Diabetes Care* 2023;46:1839–1847
  64. Norris JM, Lee H-S, Frederiksen B, et al.; TEDDY Study Group. Plasma 25-hydroxyvitamin D concentration and risk of islet autoimmunity. *Diabetes* 2018;67:146–154
  65. Thorsen SU, Liu X, Kataria Y, et al.; TEDDY Study Group. Interaction between dietary iron intake and genetically determined iron overload: risk of islet autoimmunity and progression to type 1 diabetes in the TEDDY study. *Diabetes Care* 2023;46:1014–1018
  66. Uusitalo U, Kronberg-Kippila C, Aronsson CA, et al.; The TEDDY Study Group. Food composition database harmonization for between-country comparisons of nutrient data in the TEDDY Study. *J Food Compos Anal* 2011;24:494–505
  67. Joslowski G, Yang J, Aronsson CA, et al.; TEDDY Study Group. Development of a harmonized food grouping system for between-country comparisons in the TEDDY Study. *J Food Compos Anal* 2017;63:79–88
  68. Warncke K, Tamura R, Schatz DA, et al. The influence of pubertal development on autoantibody appearance and progression to type 1 diabetes in the TEDDY study. *J Endocr Soc* 2024;8:bvae103
  69. Liu X, Johnson SB, Lynch KF, et al.; TEDDY Study Group. Physical activity and the development of islet autoimmunity and type 1 diabetes in 5- to 15-year-old children followed in the TEDDY study. *Diabetes Care* 2023;46:1409–1416
  70. Roth R, Baxter J, Vehik K, et al.; TEDDY Study Group. The feasibility of salivary sample collection in an international pediatric cohort: the TEDDY study. *Dev Psychobiol* 2017;59:658–667
  71. Johnson SB, Lynch KF, Roth R, et al.; TEDDY Study Group. First-appearing islet autoantibodies for type 1 diabetes in young children: maternal life events during pregnancy and the child's genetic risk. *Diabetologia* 2021;64:591–602
  72. Roth R, Lynch K, Hyöty H, Lönnrot M, Driscoll KA, Bennett Johnson S; TEDDY Study Group. The association between stressful life events and respiratory infections during the first 4 years of life: The Environmental Determinants of Diabetes in the Young study. *Stress Health* 2019;35:289–303
  73. Vehik K, Bonifacio E, Lernmark Å, et al.; The TEDDY Study Group. Hierarchical order of distinct autoantibody spreading and progression to type 1 diabetes in the TEDDY study. *Diabetes Care* 2020;43:2066–2073
  74. Lee H-S, Lynch KF, Krischer JP; TEDDY Study Group. Nested case-control data analysis using weighted conditional logistic regression in The Environmental Determinants of Diabetes in the Young (TEDDY) study: a novel approach. *Diabetes Metab Res Rev* 2020;36:e3204
  75. Li Q, Parikh H, Butterworth MD, et al.; TEDDY Study Group. Longitudinal metabolome-wide signals prior to the appearance of a first islet autoantibody in children participating in the TEDDY study. *Diabetes* 2020;69:465–476
  76. Balzano-Nogueira L, Ramirez R, Zamkovaya T, et al. Integrative analyses of TEDDY omics data reveal lipid metabolism abnormalities, increased intracellular ROS and heightened inflammation prior to autoimmunity for type 1 diabetes. *Genome Biol* 2021;22:39
  77. Bonifacio E, Weiß A, Winkler C, et al.; TEDDY Study Group. An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood. *Diabetes Care* 2021;44:2260–2268
  78. Stahl M, Koletzko S, Andrén Aronsson C, Lindfors K, Liu E, Agardh D; TEDDY Study Group. Coeliac disease: what can we learn from prospective studies about disease risk? *Lancet Child Adolesc Health* 2024;8:63–74
  79. Sharma A, Liu X, Hadley D, et al.; TEDDY Study Group. Identification of non-HLA genes associated with celiac disease and country-specific differences in a large, international pediatric cohort. *PLoS One* 2016;11:e0152476
  80. Andrén Aronsson C, Lee H-S, Koletzko S, et al.; TEDDY Study Group. Effects of gluten intake on risk of celiac disease: a case-control study on a Swedish birth cohort. *Clin Gastroenterol Hepatol* 2016;14:403–409.e3
  81. Aronsson CA, Lee H-S, Liu E, et al.; TEDDY Study Group. Age at gluten introduction and risk of celiac disease. *Pediatrics* 2015;135:239–245
  82. Kempainen KM, Lynch KF, Liu E, et al.; TEDDY Study Group. Factors that increase risk of celiac disease autoimmunity after a gastrointestinal infection in early life. *Clin Gastroenterol Hepatol* 2017;15:694–702.e5
  83. Andrén Aronsson C, Liu X, Norris JM, et al. 25(OH)D levels in infancy is associated with celiac disease autoimmunity in at-risk children: a case-control study. *Front Nutr* 2021;8:720041
  84. Koletzko S, Lee H-S, Beyerlein A, et al.; TEDDY Study Group. Cesarean section on the risk of celiac disease in the offspring: the Teddy study. *J Pediatr Gastroenterol Nutr* 2018;66:417–424
  85. Yang J, Tamura RN, Aronsson CA, et al.; Environmental Determinants of Diabetes in The Young Study Group. Maternal use of dietary supplements during pregnancy is not associated with coeliac disease in the offspring: The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Br J Nutr* 2017;117:466–472
  86. Uusitalo U, Lee H-S, Aronsson CA, et al.; TEDDY Study Group. Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort. *Am J Clin Nutr* 2015;102:1216–1221
  87. Uusitalo U, Aronsson C, Liu X, et al.; TEDDY Study Group. Early probiotic supplementation and the risk of celiac disease in children at genetic risk. *Nutrients* 2019;11:1790
  88. Jonsdottir B, Clasen JL, Vehik K, et al.; TEDDY Study Group. Early appearance of thyroid autoimmunity in children followed from birth for type 1 diabetes risk. *J Clin Endocrinol Metab* 2025;110:498–510