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

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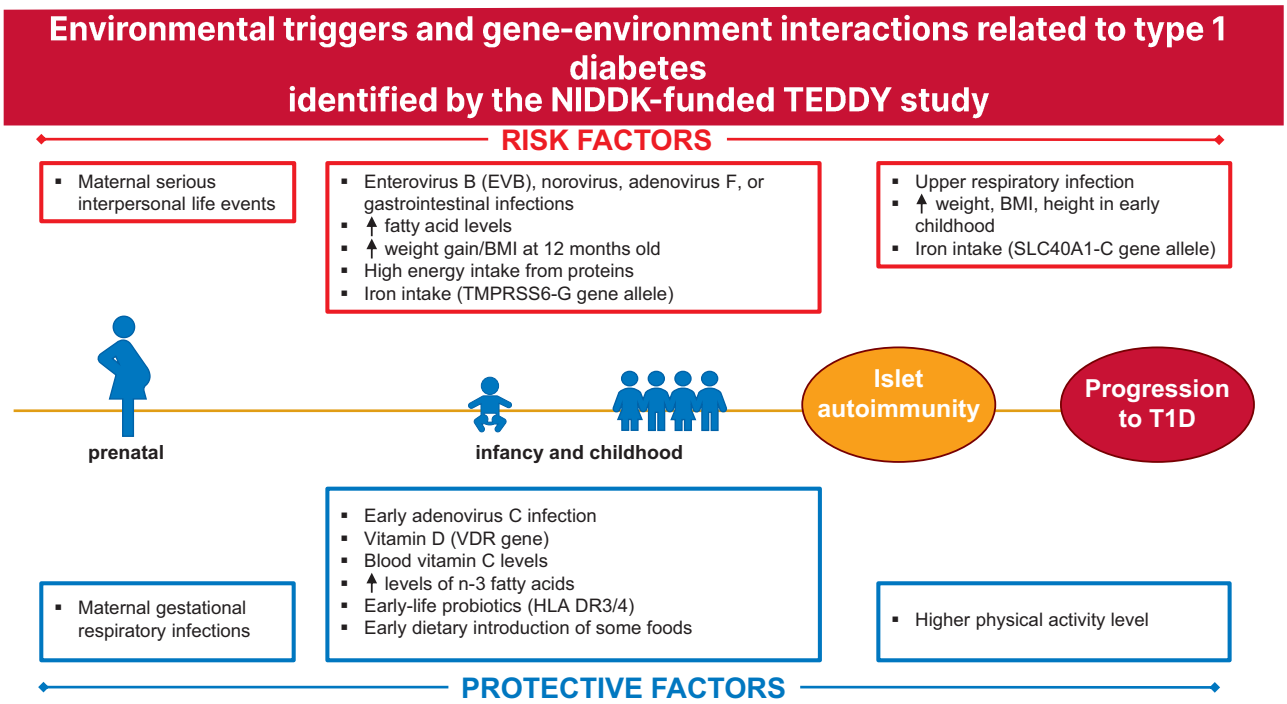

ARTICLE HIGHLIGHTS

- **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

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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

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

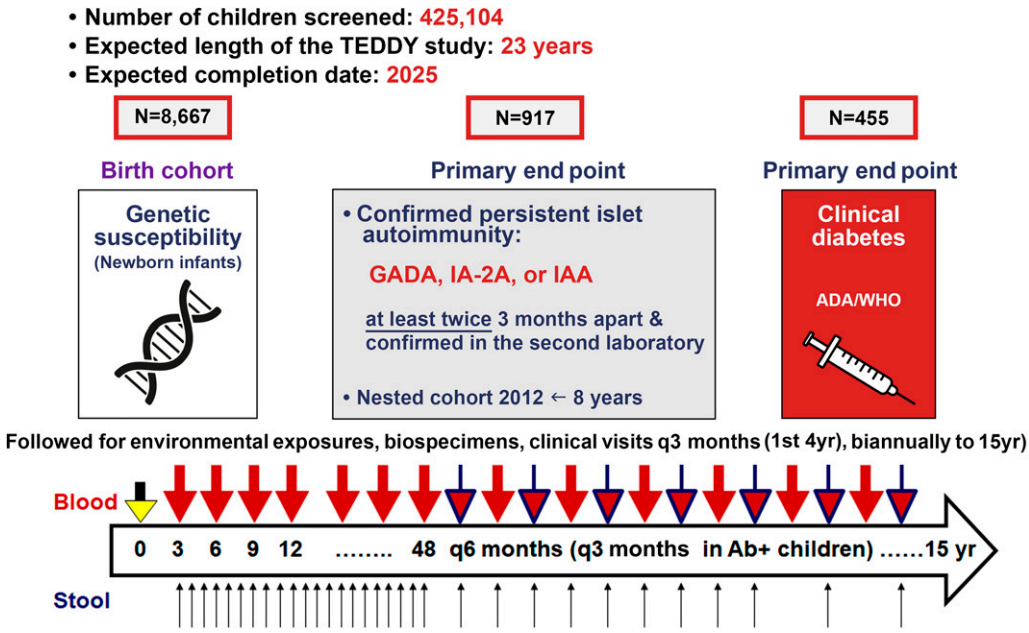

Figure 1—TEDDY study design. Ab, autoantibody; ADA, American Diabetes Association; q, every; WHO, World Health Organization; yr, years.

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 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 haplogenotypes 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 haplogenotypes 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 Whites (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 fil-led out qu-

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estionnaires 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 subjects 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_{1c} 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

	FDRs				GP			
Center	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. 2*A*). 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. 2*B*); 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. 2*C*); 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. 2*D*). 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. 3*A*) 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. 3*B*). 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. 3*C*). 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 ≥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

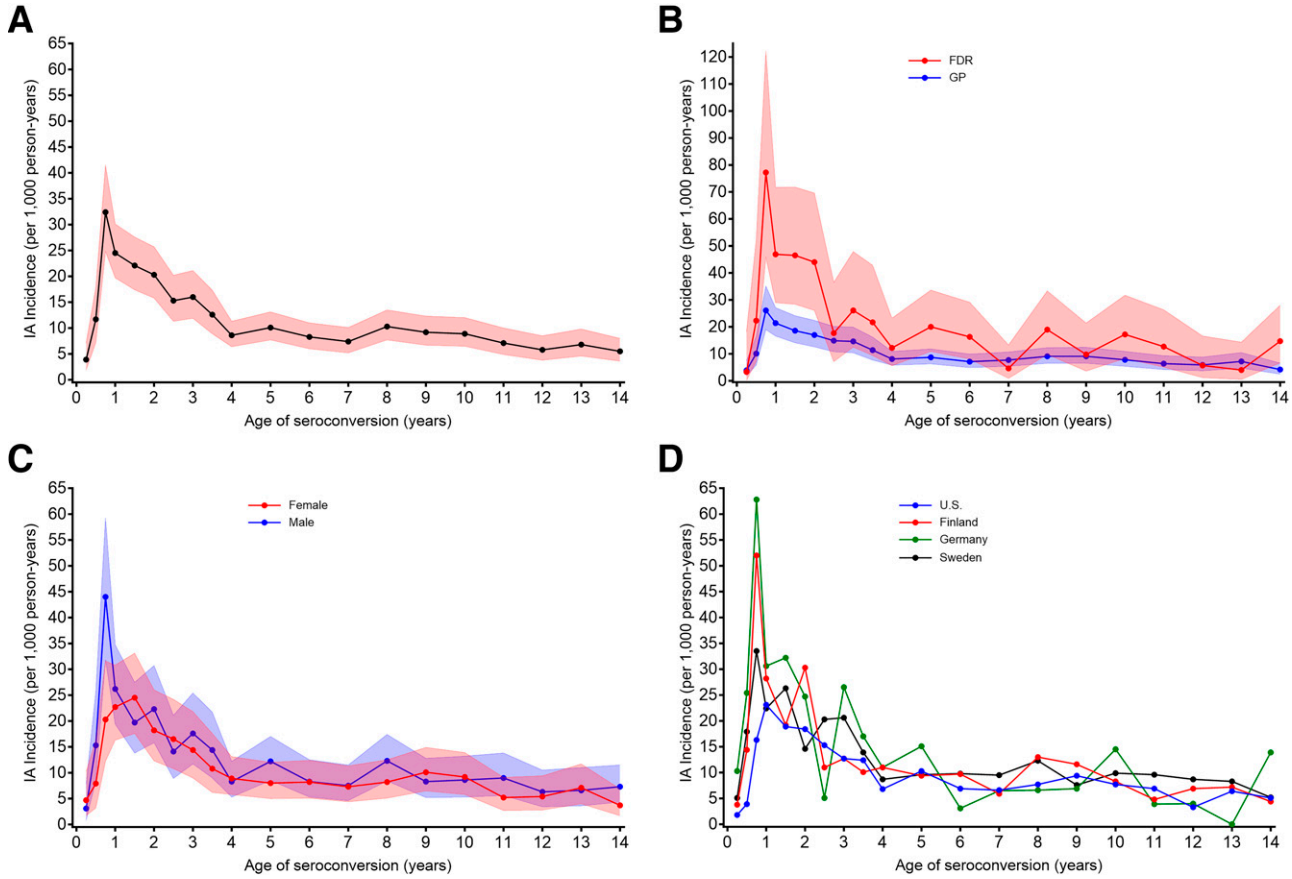

Figure 2—Persistent confirmed IAb incidence (with 95% CIs) per 1,000 person-years by age at IAb seroconversion (*A*), family history of type 1 diabetes (*B*), sex (*C*), and country (*D*).

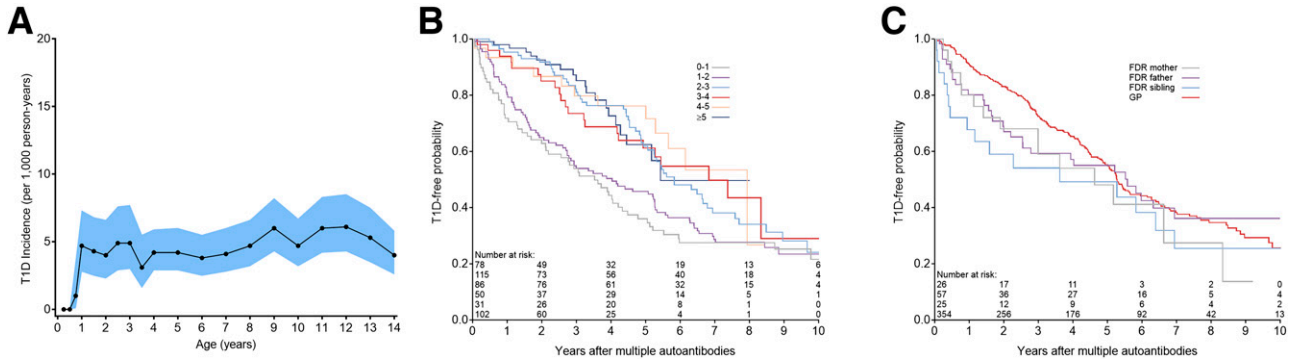

Figure 3—Incidence of stage 3 type 1 diabetes (T1D), per 1,000 person-years by age at diagnosis (*A*), age of initial IAb seroconversion (25) (*B*), and family history of type 1 diabetes and relation to the proband (25) (*C*).

>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 haplogenotypes 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 HumanCoreExome 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 Coxsackie adenovirus receptor (*CAR*) that modifies the association between enterovirus B (EVB) and IA (40) as well as to *GSTM1* expression (41).

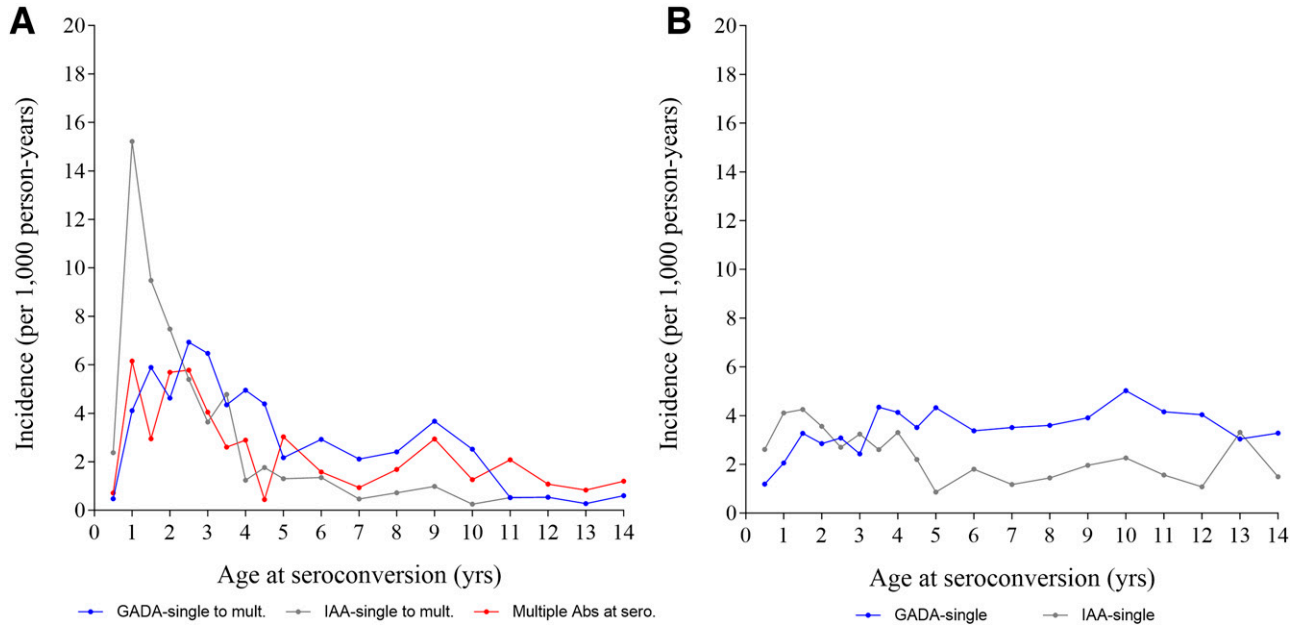

Figure 4—*A*: Incidence rate of GADA-only (*A*) as the first appearing autoantibody later developing into multiple autoantibodies (blue) in comparison with IAA-only later developing into multiple autoantibodies (gray). Red: Multiple autoantibodies at seroconversion, shown for comparison. *B*: Incidence 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 fivefold 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 heterogenous 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 subjects, 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_{12} 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 β-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 β-cell destruction and thereby type 1 diabetes. Environmental toxicants, e.g., bisphenol A, can target β-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 viromic 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. 5*A*). 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).

Caesarean 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. 5*B*).

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

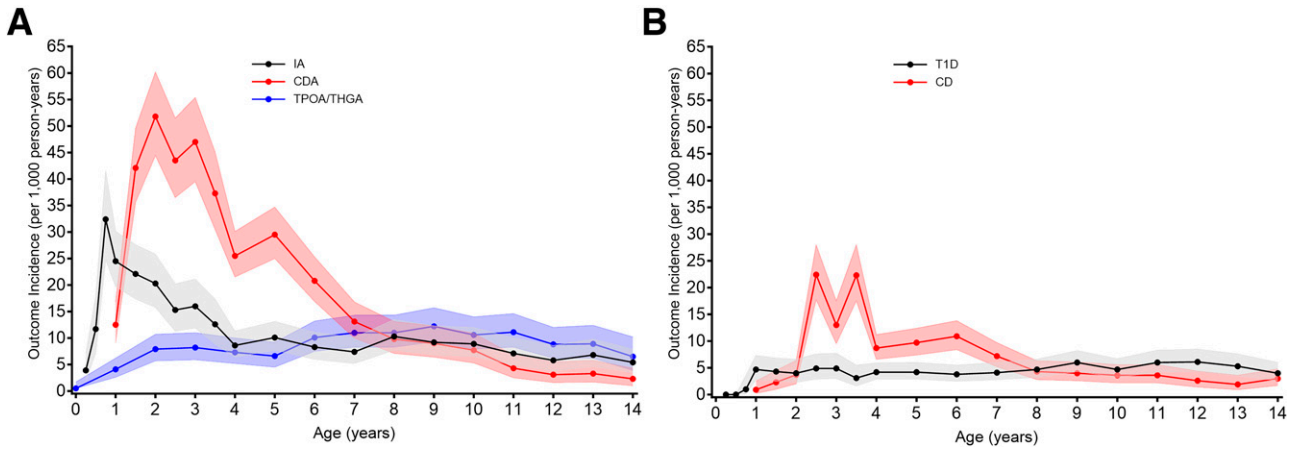

Figure 5—*A*: Incidence (95% CI) of IA, CDA, and thyroid autoimmunity (thyroid peroxidase autoantibodies [TPOA] or thyroglobulin autoantibodies [THGA]). *B*: Incidence of clinically confirmed type 1 diabetes (T1D) and celiac disease (CD) (*B*).

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 Hispanics, 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.

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