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# Thyroid autoimmunity and the subsequent development of islet and celiac autoimmunity in the TEDDY study

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## Abstract

We aimed to determine if thyroid autoimmunity is associated with a child's risk for subsequent development of islet or celiac autoantibodies.

Children at high genetic risk of type 1 diabetes were followed for thyroid autoimmunity (thyroid peroxidase antibodies [TPOAb] and thyroglobulin antibodies [TGAb]), islet autoimmunity (IA), and celiac disease autoimmunity [CDA] in The Environmental Determinants of Diabetes in the Young (TEDDY) study.

Out of 5482 children tested for thyroid autoimmunity, IA, and CDA, 39% developed at least one autoantibody. At age 14 years, thyroid autoimmunity co-occurred with IA in 59 children (15 more cases than expected by chance alone, p = 0.02), and with CDA in 125 children (26 cases above expected, p = 0.01). The risk of developing IA or CDA after thyroid autoimmunity varied by which thyroid autoantibody appeared first: TPOAb-first was associated with both IA (HR 1.92, 95% CI 1.09, 3.40) and CDA (1.69, 95% CI 1.03, 2.76), whereas TGAb-first was not associated with the risk of either.

IA and CDA are frequently found in connection to thyroid autoimmunity in children and young adolescents. The relationships of thyroid autoimmunity with IA and CDA depend on which thyroid autoantibody appears first.

### Keywords

thyroid autoantibodies; islet autoantibodies; tissue transglutaminase autoantibodies; comorbidity; longitudinal data

## Introduction

Autoimmune thyroid disease co-occurs frequently with type 1 diabetes and celiac disease, and these autoimmune diseases share genetic and environmental risk factors[1–3]. Thyroid autoimmunity might contribute to the risk of developing type 1 diabetes and celiac disease. However, the nature of this relationship is obscured because the three conditions are preceded by periods of latent, subclinical autoimmunity: Thyroid autoimmunity defined by the presence of thyroid peroxidase autoantibodies (TPOAb) or thyroglobulin autoantibodies (TGAb), islet autoimmunity (IA), and celiac disease autoimmunity (CDA). There is wide variability in the length of time from the initial appearance of autoantibodies to the onset of clinical disease[4], and not everyone with autoantibodies progresses to a diagnosis. Therefore, in order to understand the etiology of these diseases, it is critical to examine the co-occurrence of the autoantibodies.

Previous studies investigating the co-occurrence of autoantibodies have mainly reported their prevalence, and not their order of appearance. Limited evidence on the timing of autoantibody appearance in smaller cohorts of children genetically at high risk for type 1 diabetes has shown that thyroid autoimmunity can appear before, after, or at the

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approximate same time as IA[5,6], and likewise with CDA[6]. The co-occurrence of IA and CDA has previously been reported in The Environmental Determinants of Diabetes in the Young (TEDDY) cohort: IA was shown to be associated with risk of subsequent development of CDA (HR 1.48, 95% CI 1.15, 1.91) whereas CDA was not associated with IA seroconversion (HR 1.12, 95% CI 0.75, 1.67)[7]. Thyroid autoimmunity appeared at a young age in some children in TEDDY[8], but it is unclear if these children are at an increased risk for developing additional autoantibodies following the appearance of thyroid autoimmunity.

A better understanding of the order of autoantibody appearance is critical to identifying biological mechanisms or shared causes that contribute to the clustering of autoimmune diseases and will prove useful in advancing the early detection of autoimmune disease and the design of efficient screening programs. Therefore, our aim was to assess how thyroid autoimmunity associates with the later development of IA or CDA in a population of genetically susceptible children.

## Methods

### Study design

TEDDY is an international cohort study designed to identify environmental causes of islet autoimmunity and type 1 diabetes[9,10]. CDA and thyroid autoimmunity were assessed in the TEDDY population as well. Across 6 centers in the US, Finland, Germany, and Sweden, 424,788 newborns were screened for HLA-conferred risk of type 1 diabetes from 2004 to 2010 (Table S1). Children with high-type 1 diabetes-risk HLA genotypes were eligible (n = 21,589), and 8676 children were enrolled prior to age 4.5 months and followed until age 15 years, type 1 diabetes diagnosis, or loss to follow-up. Characteristics predicting enrollment and continued compliance in the TEDDY study have been previously described, with the highest enrollment and compliance rates in Sweden and among families with an older mother[11,12]. Local institutional review board or ethics committee approval and parental informed consent for both genetic screening and follow-up of all children were obtained. The study is monitored by an External Evaluation Committee of the US National Institutes of Health.

### Participants

Children included in this analysis were tested at least once for the presence of islet, celiac, and thyroid autoantibodies. Those with missing information on family history of type 1 diabetes, celiac disease, and autoimmune thyroid disease were excluded as well as those missing genetic risk scores (GRS). Among 8676 children enrolled in the TEDDY cohort, 5482 were tested for all autoantibodies under study and met eligibility criteria for the present analysis (25% of those eligible for HLA screening and 63% of those enrolled; Figure 1).

### Procedures

Serum samples were collected every 3 months from ages 3 to 48 months, then every 6 months to age 15 years. A standardized protocol was implemented for autoantibody measurements across the four countries. Three islet autoantibodies were measured

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prospectively at every study visit (Figure 2). Glutamate decarboxylase autoantibodies (GADA), insulinoma antigen-2 autoantibodies (IA-2A), and insulin autoantibodies (IAA) were analyzed in two harmonized laboratories with radiobinding assays, incorporating extensive quality control[13]. All islet autoantibody measurements were conducted at the laboratory in Denver, Colorado for US participants, and in Bristol, United Kingdom for European participants, with positive samples and a subset of negative samples being confirmed in the other laboratory. Tissue transglutaminase (tTGA; the biomarker of CDA) was screened by radiobinding assay in two laboratories with final status determined by the central reference laboratory in Bristol as previously described[14]. tTGA testing started at age 24 months because it was considered rare to develop celiac disease before 24 months of age at the time when TEDDY was planned. Screening continued annually as a practical approach to capture the incidence of celiac disease over time. If the result of any sample was positive, all previous samples from that child were analyzed to identify the most recent negative tTGA and determine when tTGA first appeared. Starting in 2016, TPOAb and TGAb were measured by radioimmunoassay twice, at approximately ages 9 and 14 years[8]. These time points were chosen because previous literature suggested the incidence rate would be highest during puberty[6]. Additionally, both thyroid autoantibodies were measured in samples from all children diagnosed with type 1 diabetes, from the nearest visit at or before diagnosis. For all children positive for either TPOAb or TGAb, a subset of previously collected samples was analyzed to identify the age when the first-appearing thyroid autoantibody appeared[8], with the same level of precision as for age at first appearing IA and CDA. All TPOAb and TGAb measurements were conducted in Gainesville, Florida. Serum samples were used for all autoantibody measurements.

The high-risk HLA genotypes selected for inclusion for participants screened from the general population have been reported previously[16]. In addition to HLA-DR-DQ haplogenotypes, the cohort was genotyped using the ImmunoChip and the T1DExomeChip, a custom genotyping array with more than 90,000 custom content single nucleotide polymorphisms (SNPs) added to the Infinium® CoreExome-24 v.1.1 BeadChip (Illumina, CA), at the Center for Public Health Genomics at the University of Virginia, VA, U.S.A. Quality control measures involved excluding individuals with a low call rate (<95%) or discordance with reported sex, and SNPs with a low call rate (<95%), deviating from Hardy-Weinberg equilibrium in controls with the European ancestry, or with concordance <99% in duplicates[17]. GWAS imputation analysis was conducted using the Trans-Omics for Precision Medicine (TOPMed) Version R3, which includes 133,597 reference samples and more than 445 million genetic variants as reference panels. Genotyped and imputed SNPs were used to calculate the type 1 diabetes genetic risk score (T1D GRS2) from 67 SNPs[18], and the celiac disease GRS from 42 SNPs[19] using the PRSedm package[20].

A family history of type 1 diabetes was reported at the time of screening, and a family history of any autoimmune disease, including type 1 diabetes, celiac disease, and autoimmune thyroid disease was reported by parents at multiple visits during follow-up. TEDDY questionnaires and data collection forms used in the present study are available on the following website: https://repository.niddk.nih.gov/study/24.

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## Outcomes

Persistent IA was defined as a positive result in both laboratories for the same autoantibody (IAA, GADA, or IA-2A) in two consecutive samples. Persistent CDA (tTGA) and thyroid autoimmunity (TPOAb or TGAb) required a positive result for samples obtained at two consecutive visits. Throughout the current analysis, only persistent IA, CDA, and thyroid autoimmunity were considered. Thyroid autoimmunity was divided into TPOAb-first, TGAb-first, and both-first subtypes, depending on which autoantibody appeared first. Children were followed to age 14 or type 1 diabetes diagnosis. Participants left the TEDDY study after a type 1 diabetes diagnosis, whereas a diagnosis of celiac disease or autoimmune thyroid disease did not affect their enrollment status.

Because children were not followed prospectively for thyroid autoimmunity, we expect that there were missed individuals who were transiently positive before the first screening. In contrast, transient individuals were not missed for the prospectively followed endpoints of IA (starting from age three months) and CDA (starting from age two years), and it has been previously reported that reversion occurred in 24% of children positive for a single islet autoantibody in TEDDY[21]. Therefore, we also assessed the secondary outcomes of non-transient IA, CDA, and thyroid autoimmunity. Non-transient individuals were defined as those who remained positive for the respective autoantibody at the time of the child's last thyroid autoimmunity screening, or who developed type 1 diabetes (for IA cases) or celiac disease (for CDA cases) before that time.

## Statistical analysis

Inverse probability of selection weighting was used to account for the oversampling of thyroid autoantibodies among children with type 1 diabetes (the eligibility criteria for thyroid autoantibody testing was more lenient for children with type 1 diabetes). Chi-squared tests were used to compare the demographic characteristics of children excluded versus those included in analyses. Temporal trends of autoimmunity (first appearing of IA, CDA, or thyroid autoimmunity) were visualized in an age-specific incidence plot.

Weighted Cox proportional hazards models were used to investigate the associations between thyroid autoimmunity status (overall, TPOAb-first, and TGAb-first) and the risk of subsequent development of IA. Follow-up was from birth to IA seroconversion, and thyroid autoimmunity status was a time-varying covariate. Models were adjusted for sex, family history of type 1 diabetes, and HLA haplogenotypes, and the baseline hazard was stratified by country. We then further adjusted for the T1D GRS2. The associations between thyroid autoimmunity status and risk of subsequent CDA (with and without adjustment for the celiac disease GRS) were assessed similarly, with the follow-up for CDA starting from birth, and thyroid autoimmunity status as a time-varying covariate. As a complementary analysis, we also assessed the association between CDA status and risk of subsequent thyroid autoimmunity following an analogous approach, with follow-up from birth to thyroid autoimmunity, with CDA status as a time-varying covariate. Assessment of Schoenfeld residuals indicated that the assumption of proportional hazards was met for all Cox models.

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Children in TEDDY have not been followed past type 1 diabetes diagnosis, and this non-random censoring may bias the estimates of associations between CDA and thyroid autoimmunity if children with type 1 diabetes are more (or less) likely to develop thyroid autoimmunity. Therefore, in a sensitivity analysis, multiple imputation was utilized to obtain estimates of complete follow-up past the age of type 1 diabetes diagnosis[22]. This method allows specification of the assumed incidence rate of thyroid autoimmunity after type 1 diabetes diagnosis (Supplementary Methods).

We do not know how many transient thyroid autoimmunity cases occurred prior to the first screening visit in those who tested negative at the first screening. To approximate the rate of thyroid autoantibody reversion from persistent positive to negative, the results from the second screening were examined among children who were persistent positive for TPOAb or TGAb at the first screening. Then, to account for the influence of reversion to autoantibody negativity for IA, CDA, or thyroid autoimmunity, a secondary analysis was conducted to assess the associations between thyroid autoimmunity status and subsequent risk of IA or CDA using non-transient case definitions.

SAS 9.4 Software (SAS Institute, Cary, NC) was used for data preparation. Analyses were conducted in R version 4.4.3[23] with the survival package version 3.8–3[24].

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Because all children with type 1 diabetes were eligible for thyroid autoantibody testing, those with a higher risk of type 1 diabetes (from Finland or Sweden, or with a first-degree relative with an autoimmune disease) were more likely to be included. The results are therefore weighted to account for the child's type 1 diabetes status (unweighted counts of children by first appearing autoantibody are shown in Table S2). The first or only type of autoimmunity to develop was thyroid autoimmunity for 8%, IA for 10%, and CDA for 21%, while 61% remained autoantibody negative (Table 1; median follow-up age 13.7 years). When examining subgroups, thyroid autoimmunity was the first or only type of autoantibody among 10% of females, 10% of children in the US, and 15% of children who had a first-degree relative with autoimmune thyroid disease.

In this HLA-selected population, IA was the most common type of autoimmunity to develop first during early infancy, followed by a peak in CDA-first, then thyroid autoimmunity-first had the highest incidence from age 11 years (Figure 3).

The co-occurrence of thyroid autoimmunity with IA at age 14 years exceeded the expected rate, with 59 children having both types of autoantibodies while 44 children would be expected to have both if they were independent events (Table 2). Similarly, 125 children had both thyroid autoimmunity and CDA at age 14 years – significantly more than the 99 that would be expected under independence. Co-occurrence exceeded the expected rate for

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thyroid autoimmunity with GADA as the first appearing islet autoantibody (26 expected and 42 observed), but not with IAA appearing first (13 expected and 12 observed), however, the limited number of cases prevented further examination of first appearing islet autoantibodies in the present analysis.

TPOAb-first thyroid autoimmunity was associated with an increased risk of subsequent development of IA (HR 1.92, 95% CI 1.09, 3.40; Figure 4), as well as CDA (HR 1.69, 95% CI 1.03, 2.76). TGAb-first thyroid autoimmunity was not associated with the development of either IA or CDA. Both thyroid autoantibodies appearing at the same time was associated with an increased risk of CDA (HR 2.55, 95% CI 1.04, 6.26), while the estimate for IA had a wide confidence interval and did not reach statistical significance (HR 2.03, 95% CI 0.76, 5.43). The associations between TPOAb-first and IA, and between both-first and CDA remained significant after adjusting for the T1D GRS2 or celiac disease GRS, while the association between TPOAb-first and CDA was attenuated (Figure S1).

CDA status was associated with the risk of subsequent development of TGAb-first thyroid autoimmunity (HR 1.45, 95% CI 1.12, 1.86), but not TPOAb-first thyroid autoimmunity (HR 0.96, 95% CI 0.62, 1.48). The association between CDA and thyroid autoimmunity was unlikely to be impacted by the lack of follow-up after type 1 diabetes diagnosis: The multiple imputation sensitivity analysis indicated that even a substantial (50%) increase in the incidence of thyroid autoimmunity after type 1 diabetes diagnosis would not notably change the findings (Table S3).

Among children persistent positive for TPOAb at the first screening, 3% had an indeterminate result at the second screening, and 3% had a negative result. Likewise, among children persistently positive for TGAb, 3% and 6% had indeterminate and negative results at the second screening, respectively. Because autoantibody reversion does occur for the three included autoimmune conditions, but could not be fully characterized for thyroid autoimmunity, non-transient case definitions were employed in a secondary analysis. Using the non-transient case definitions, IA was the first or only type of autoimmunity in 8% of children, CDA was first in 12%, and thyroid autoimmunity was first in 8% while 72% remained negative for non-transient autoimmunity. With non-transient definitions, the association between TPOAb-first and subsequent IA was stronger (HR 2.95, 95% CI 1.65, 5.26), whereas the association between TPOAb-first and subsequent CDA was attenuated (HR 1.28 95% CI 0.62, 2.65) as compared to the analyses including transient autoantibodies (Table S4). The non-transient compared to transient CDA individuals had an older average seroconversion age, were more likely to have the HLA DR3/3 haplogenotype, and were more likely to have a first-degree relative with celiac disease.

## Discussion

In this population of children at increased genetic risk of type 1 diabetes and thereby also for celiac disease and thyroiditis, the children with TPOAb-first, but not TGAb-first thyroid autoimmunity, were at increased risk of IA and CDA. In contrast, CDA as the first appearing autoimmunity was associated with the subsequent development of TGAb-first, but not TPOAb-first thyroid autoimmunity. We previously reported that, among 99 children with

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clinical autoimmune thyroid disease in the TEDDY cohort, 19 have also been diagnosed with celiac disease, while 10 children have developed autoimmune thyroid disease prior to diagnosis of type 1 diabetes[25]. The current analysis of autoantibodies allows for a more in-depth assessment of comorbidity through the examination of this earlier stage of the pathogenesis process when the timing of incident cases can be identified with precision.

Mirroring previous findings from TEDDY on the timing of IA and CDA[7], we show here that the association between CDA and thyroid autoimmunity is not bidirectional, but rather, the nature of the association between autoantibodies depends on which appeared first. This suggests that confounding from a common cause may not be the sole explanation for autoantibody overlap. In agreement with our finding of an association between TPOAb-first thyroid autoimmunity and subsequent IA, the BABYDIAB and DiPiS studies both have reported positive associations between TPOAb and IA status, and the latter found no association between TGAb and IA[5,6].

We found that the risk of CDA was highest among children who developed both TPOAb and TGAb at the same time (within the same six-month window between study visits), whereas IA risk for these children was similar to that for children developing TPOAb only first (but with a higher level of uncertainty). It has previously been shown in the TEDDY Study that children with both thyroid autoantibodies appearing at the same age had an increased risk for progressing to clinical onset of autoimmune thyroid disease compared to those developing a single thyroid autoantibody first[8]. Further investigation is needed to determine why children developing both autoantibodies together have an increased risk for both CDA and clinical autoimmune thyroid disease, with a possible next step being the identification of genetic or metabolic features distinguishing children who present with both thyroid autoantibodies at the same age.

IA, CDA, and thyroid autoimmunity share several common genetic determinants. Many genes contributing to autoimmune disease susceptibility have a systemic immune-modulating function, rather than an organ-specific role, in particular, the HLA region of the genome is responsible for much of the shared genetic risk[26–28]. However, non-HLA genes are involved as well, for example, SNPs in *CTLA-4* (encoding cytotoxic T-lymphocyte-associated antigen, a regulator of T-cell activation) have been shown to be associated with risk of several autoimmune diseases including type 1 diabetes, celiac disease, Hashimoto's thyroiditis, and Graves' disease[2,29]. Associations between thyroid autoimmunity and subsequent IA or CDA were only slightly attenuated by the adjustment for the T1D GRS2 and the celiac disease GRS. No doubt, this summarized assessment of genetic risk did not capture the full extent of the role of genetic predisposition in autoimmune overlap; a more exhaustive study will be needed to identify novel SNPs, assess gene-gene and gene-environment interactions, and examine different models of inheritance.

While genetic risk plays a key role in the overlap of autoimmune diseases, it is possible that thyroid autoimmunity itself could causally contribute to the development of other autoimmune conditions, but the mechanisms underlying this potential link are unclear. There is a reciprocal relationship between autoimmunity and oxidative stress[30], with thyroid autoimmunity resulting in increased oxidative stress, which in turn could plausibly

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contribute to the development of IA or CDA. Changes in metabolism could further contribute to the association between thyroid autoimmunity and subsequent IA, as patients with subclinical and clinical thyroid disease may have an altered insulin demand which could give rise to an amplified beta-cell stress and increased risk of IA[31]. Both TPOAb and TGAb target organ-specific antigens, and both can precede either hypothyroidism or, more seldom and often transient, hyperthyroidism so the divergent findings for the two thyroid autoantibodies are unexplained and warrant further investigation. Exploration of cytokine profiles associated with each autoantibody may provide further insights.

The association we found between CDA and subsequent thyroid autoimmunity may reflect a causal link, as suggested by a phenome-wide Mendelian randomization study reporting that celiac disease was causally linked with both Graves' disease and hypothyroidism[32]. One possibility is that malabsorption due to intestinal damage in CDA individuals who have progressed to clinical celiac disease leads to nutritional deficiencies contributing to thyroid autoimmunity[33]. We have previously shown that children with TGAb-first versus with TPOAb-first thyroid autoimmunity have similar risk of progressing to clinical autoimmune thyroid disease[8]. Given that CDA is associated with both TPOAb-first (appearing before CDA) and TGAb-first (appearing after CDA), it may be beneficial to screen children with celiac disease for both thyroid autoantibodies.

A key limitation of this analysis was the inability to identify transient thyroid autoimmunity prior to the first screening. Therefore, we aimed to further explore how our findings may have been impacted by transience. We found evidence that thyroid autoimmunity is associated with an increased risk of overall CDA but not of non-transient CDA. Children with non-transient CDA (compared to transient CDA) were more likely to have a family history of celiac disease and to have the highest risk HLA haplogenotype (DR3/3), suggesting that CDA appearance is driven by genetic predisposition in these children. In contrast, the co-occurrence of thyroid autoimmunity with overall CDA may reflect a distinct pathology suggestive of systemic immune dysfunction.

There are additional limitations that must be considered in the context of our findings. Our analysis was focused on children and young adolescents, as we followed children through age 14 years (up to 15 years for those diagnosed with type 1 diabetes). Our findings therefore may not generalize to older adolescents or adults – populations with a higher incidence of autoimmune thyroid disease. Likewise, TEDDY includes an HLA-restricted population with eligibility limited to HLA haplogenotypes that confer a greatly increased risk of type 1 diabetes within all six study site populations[16], and it cannot be excluded that a significant number of type 1 diabetes children with thyroid autoimmunity or celiac disease have been missed as these comorbidities may be more common in HLA haplogenotypes not included in TEDDY. Children in TEDDY have not been followed past type 1 diabetes diagnosis, so we were unable to assess CDA and thyroid autoantibody status post-diagnosis. Therefore, because censoring after IA seroconversion was not at random, but dependent on the rate of progression to type 1 diabetes diagnosis, we did not examine IA in relation to the risk of subsequent thyroid autoimmunity. The cohort has so far not been screened for thyroid-stimulating hormone receptor antibodies or autoantibodies marking Addison's

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disease or atrophic gastritis, both conditions present at an increased frequency among type 1 diabetes patients[34].

The longitudinal collection of three different types of autoantibodies across a large, international population is a major strength of our study. Samples were collected every three or six months, allowing for a more precise estimate of autoantibody timing than has been possible in past studies. The availability of extensive genotyping data and the standardized reporting of the child's family history of autoimmune disease also make TEDDY a uniquely comprehensive resource.

Discussions on widespread screening for autoantibodies have gained traction in recent years, especially in regions with high disease incidence rates, including the TEDDY site locations in the US and northern Europe[35,36]. Our results support the notion that such programs should account for patterns of autoantibody co-occurrence. Together with previous research, our findings indicate that the relationships between the autoantibodies characterizing different autoimmune diseases cannot be fully described without considering variability across disease phenotypes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability Statement:

Data from The Environmental Determinants of Diabetes in the Young (https://doi.org/10.58020/y3jk-x087) reported here will be made available for request at the NIDDK Central Repository (NIDDK-CR) website, Resources for Research (R4R), https://repository.niddk.nih.gov/.

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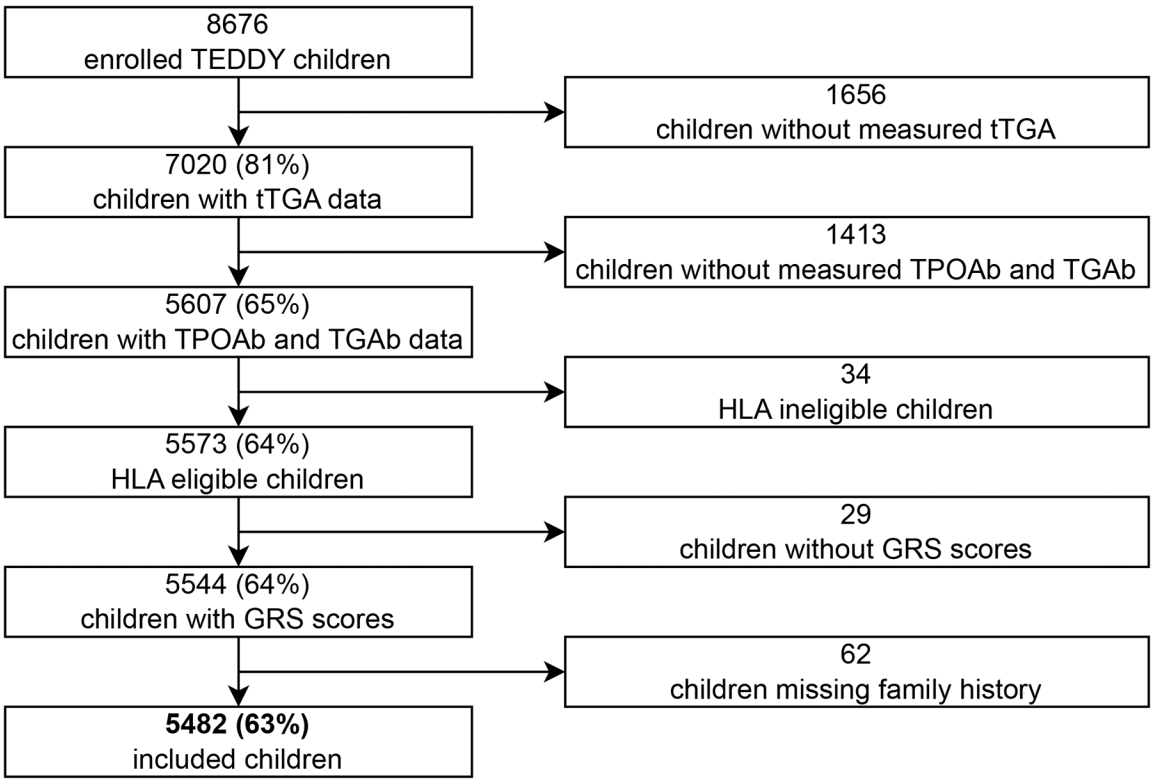


**Figure 1: Flow chart of children from the TEDDY study included in the analysis of islet, celiac disease (tTGA), and thyroid (TPOAb and TGAb) autoantibodies.**

The percentage out of the total enrolled is shown in parentheses. Abbreviations: GRS, genetic risk score; HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; tTGA, tissue transglutaminase antibody.

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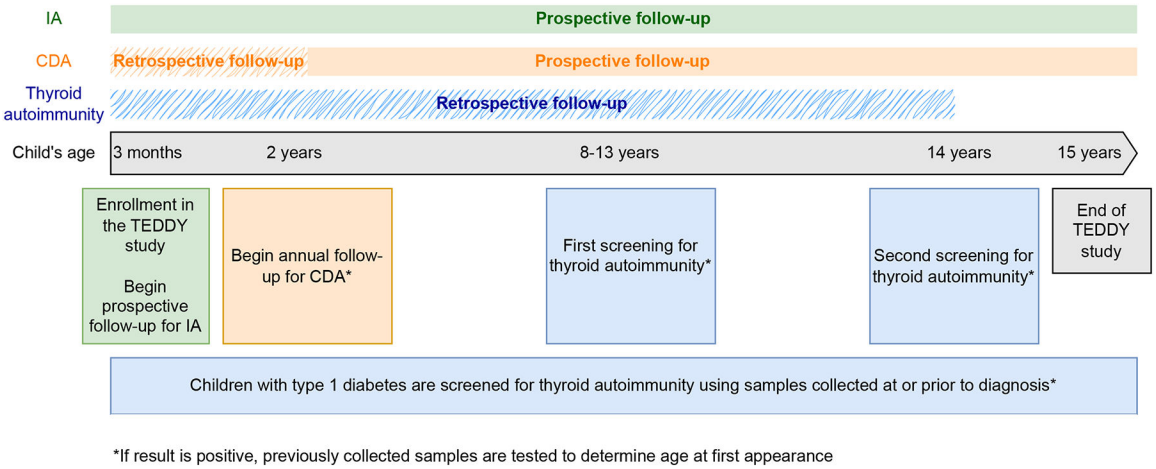


**Figure 2: TEDDY Study timeline for the follow-up of IA, CDA, and thyroid autoimmunity.**
Abbreviations: CDA, celiac disease autoimmunity; IA, islet autoimmunity; TEDDY, The Environmental Determinants of Diabetes in the Young.

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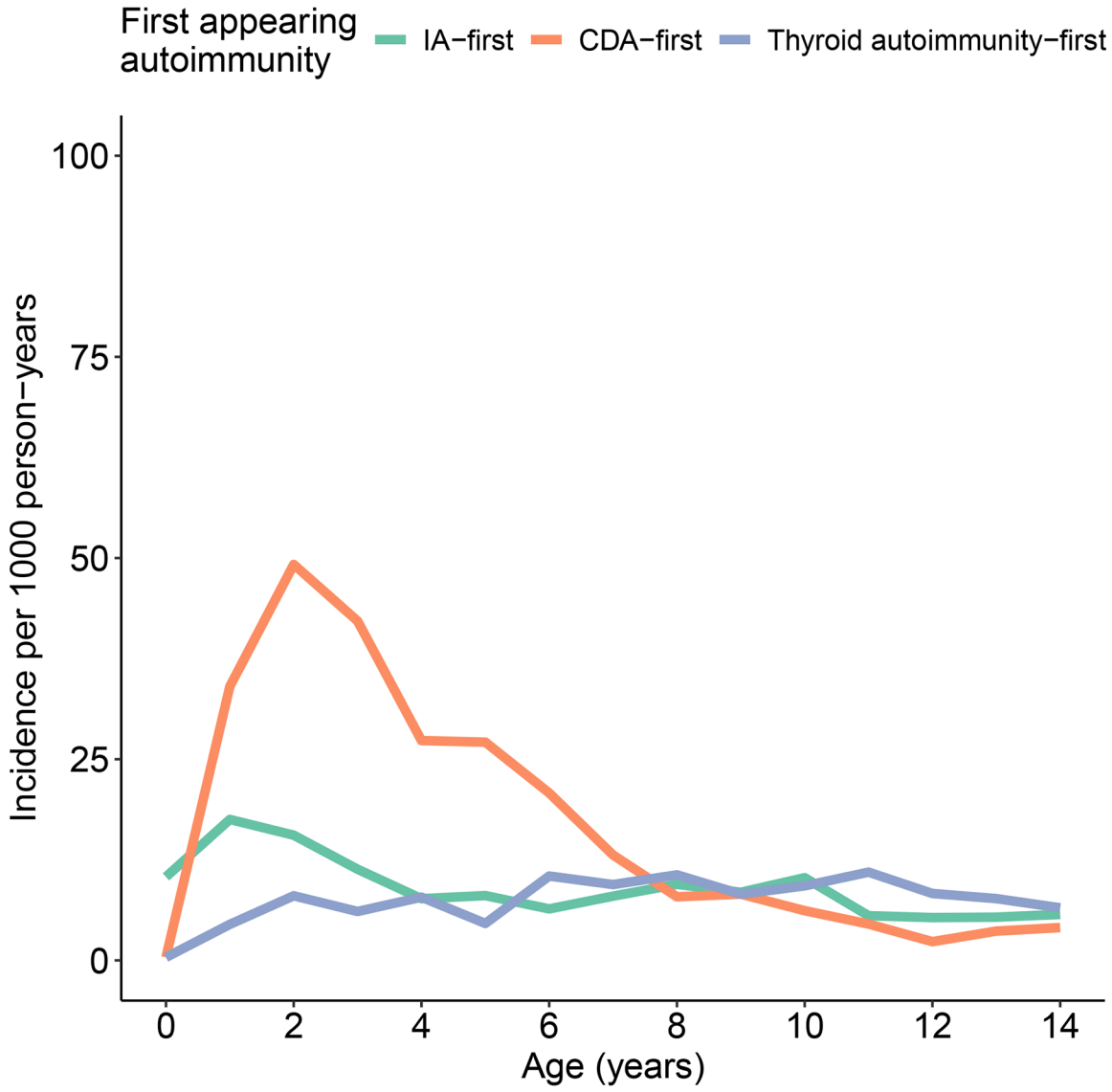


**Figure 3: Age-specific incidence of IA, CDA, or thyroid autoimmunity as the first appearing type of autoimmunity among 5482 children in the TEDDY study, 2004 – 2024.**

Weighted to account for the oversampling of children diagnosed with type 1 diabetes.

Abbreviations: CDA, celiac disease autoimmunity; IA, islet autoimmunity; TEDDY, The Environmental Determinants of Diabetes in the Young.

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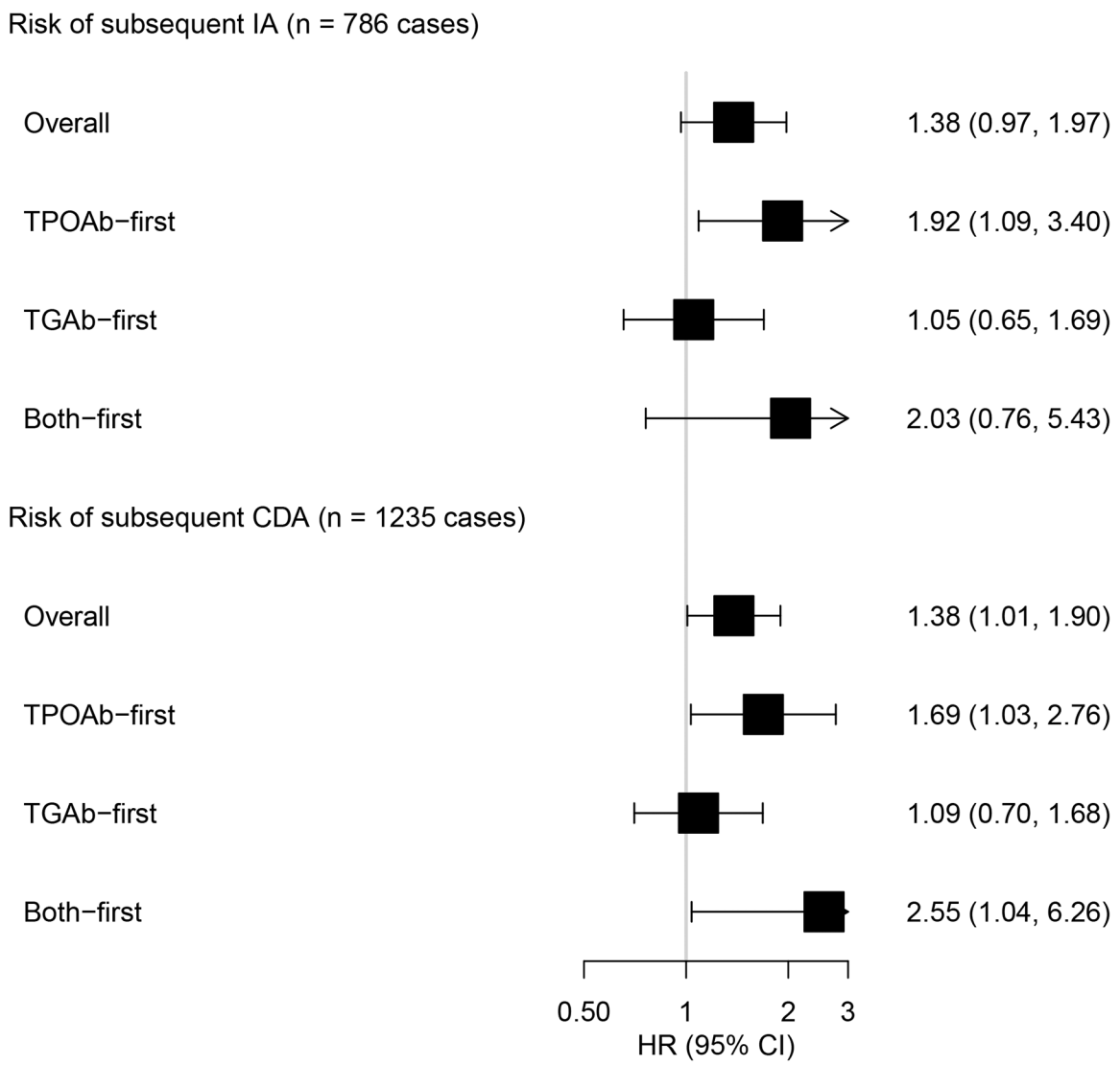


**Figure 4: Associations between thyroid autoimmunity status and risk of subsequent development of IA or CDA among 5482 children in the TEDDY Study, 2004 – 2024.**

HRs and 95% CIs are shown for overall thyroid autoimmunity, TPOAb as the first appearing thyroid autoantibody (TPOAb-first), TGAb as the first appearing thyroid autoantibody (TGAb-first), and both TPOAb and TGAb appearing at the same age (both-first). Models are adjusted for sex, family history, HLA, and country, and weighted to account for the oversampling of children with a type 1 diabetes diagnosis. 36 children developed thyroid autoimmunity followed by IA, while 490 children developed thyroid autoimmunity and remained IA negative. 44 children developed thyroid autoimmunity followed by CDA, while 427 children developed thyroid autoimmunity and remained CDA negative. Abbreviations: CDA, celiac disease autoimmunity; CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; IA, islet autoimmunity; TEDDY, The Environmental Determinants of Diabetes in the Young; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

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**Table 1:**

Baseline characteristics of 5482 children with thyroid, islet, and celiac disease autoantibodies measured in the TEDDY Study, 2004 – 2024.

| | | First appearing type of autoantibody (%[a]) | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Category** | **Thyroid autoimmunity** | **IA** | **CDA** | **Multiple** | **Not autoantibody positive** |
| Total | | 7.6 | 10.3 | 20.5 | 0.4 | 61.2 |
| Sex | Female | 10.4 | 9.0 | 23.4 | 0.5 | 56.7 |
| | Male | 4.9 | 11.5 | 17.7 | 0.3 | 65.6 |
| Country | USA | 9.7 | 8.9 | 18.8 | 0.5 | 62.1 |
| | Finland | 7.0 | 11.2 | 19.3 | 0.3 | 62.2 |
| | Germany | 3.5 | 10.6 | 17.3 | 0.3 | 68.3 |
| | Sweden | 6.3 | 11.3 | 23.9 | 0.3 | 58.2 |
| HLA | DR3/4 | 8.2 | 12.5 | 20.0 | 0.3 | 58.9 |
| | DR4/4 | 8.7 | 10.4 | 14.8 | 0.8 | 65.4 |
| | DR4/8 | 7.5 | 10.6 | 5.3 | 0.4 | 76.2 |
| | FDR specific | 9.0 | 10.4 | 7.0 | 0.0 | 73.6 |
| | DR3/3 | 5.4 | 5.8 | 41.2 | 0.1 | 47.5 |
| FDR - T1D, celiac, or AITD | No | 6.8 | 9.7 | 18.7 | 0.3 | 64.5 |
| | Yes | 9.9 | 11.7 | 25.3 | 0.6 | 52.5 |
| FDR - T1D | No | 7.4 | 9.7 | 20.8 | 0.3 | 61.8 |
| | Yes | 9.1 | 14.2 | 18.5 | 0.7 | 57.6 |
| FDR - celiac | No | 7.7 | 10.6 | 18.5 | 0.4 | 62.7 |
| | Yes | 6.2 | 5.8 | 47.0 | 0.3 | 40.7 |
| FDR - AITD | No | 6.5 | 10.1 | 20.2 | 0.3 | 62.8 |
| | Yes | 15.4 | 11.7 | 22.4 | 0.7 | 49.8 |

Abbreviations: AITD, autoimmune thyroid disease; CDA, celiac disease autoimmunity; FDR, first degree relative; HLA, human leukocyte antigen; IA, islet autoimmunity; T1D, type 1 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young.

[a]Weighted to account for the oversampling of type 1 diabetes children for thyroid autoantibody testing.

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**Table 2:**

Excess risk of cooccurrence of thyroid autoimmunity with IA or with CDA at age 14 years among 5482 children in the TEDDY Study.

| | | Overlap with IA (IA prevalence: 11%) | | | Overlap with CDA (CDA prevalence: 24%) | | |
|---|---|---|---|---|---|---|---|
| **Thyroid autoimmunity** | **Thyroid autoantibody prevalence (%)** | **Expected (n)** | **Observed (n)** | **p-value** | **Expected (n)** | **Observed (n)** | **p-value** |
| Overall | 15.4 | 44 | 59 | 0.02 | 99 | 125 | 0.01 |
| TPOAb-first | 4.1 | 12 | 19 | 0.03 | 26 | 32 | 0.27 |
| TGAb-first | 10.0 | 28 | 34 | 0.29 | 65 | 79 | 0.08 |

Abbreviations: CDA, celiac disease autoimmunity; IA, islet autoimmunity; TEDDY, The Environmental Determinants of Diabetes in the Young; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.