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Review article

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Looking back at the TEDDY study: lessons and future directions

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Abstract

The goal of the TEDDY (The Environmental Determinants of Diabetes in the Young) study is to elucidate factors leading to the initiation of islet autoimmunity (first primary outcome) and those related to progression to type 1 diabetes mellitus (T1DM; second primary outcome). This Review outlines the key findings so far, particularly related to the first primary outcome. The background, history and organization of the study are discussed. Recruitment and follow-up (from age 4 months to 15 years) of 8,667 children showed high retention and compliance. End points of the presence of autoantibodies against insulin, GAD65, IA-2 and ZnT8 revealed the HLA-associated early appearance of insulin autoantibodies (1–3 years of age) and the later appearance of GAD65 autoantibodies. Competing autoantibodies against tissue transglutaminase (marking coeliac disease autoimmunity) also appeared early (2–4 years). Genetic and environmental factors, including enterovirus infection and gastroenteritis, support mechanistic differences underlying one phenotype of autoimmunity against insulin and another against GAD65. Infant growth and both probiotics and high protein intake affect the two phenotypes differently, as do serious life events during pregnancy. As the end of the TEDDY sampling phase is approaching, major omics approaches are in progress to further dissect the mechanisms that might explain the two possible endotypes of T1DM.

Sections

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Introduction

Type 1 diabetes mellitus (T1DM) is a serious and burdensome chronic disease that can affect children and young adults. However, the disease can manifest itself at any age, and a high proportion of patients are adults at disease onset (~50%)[1]. T1DM is characterized by chronic hyperglycaemia preceded by the appearance of islet autoantibodies against insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A) or the ZnT8 transporter (ZnT8A). The autoimmunity phase is often prolonged and leads to β cell destruction that requires insulin replacement therapy. T1DM is strongly associated with specific HLA class II genotypes, but genetics alone does not seem to explain the cause of the disease as temporal changes in the frequencies of HLA genotypes have been reported from Finland[2], UK[3], Sweden[4] and Australia[5], supporting an increasing role of the environment. Environmental exposures (including toxicants, pathogens, diet and psychosocial factors) have all been correlated with the initiation of autoimmunity, but the trigger(s) remain largely unknown.

Thus the goal of the TEDDY (The Environmental Determinants of Diabetes in the Young) study is to elucidate factors leading to the initiation of islet autoimmunity (first primary outcome) and to progression to T1DM (second primary outcome)[6,7].

The first child to be included in TEDDY was born in September 2004 and recruited at 3 months of age. Recruitment continued until March 2010 when 8,676 children had been recruited out of 440,000 screened. The last recruited child will turn 15 years of age in March 2025. So far, >160 peer-reviewed investigations have been published using TEDDY data. Reviews of the TEDDY study have included methodology and progress reports[8–12]. TEDDY data on T1DM[13] and coeliac disease[14] have been reviewed by authors not affiliated with the study.

This current Review was born out of the need (prior to the completion of sampling and the beginning of the next phase) to harvest the data to better identify hypotheses for the mechanisms of the first primary outcome (and perhaps of the second primary outcome). The present Review highlights the most important findings to date as selected by various committee chair persons. In this Review, we provide a brief background to the history of the TEDDY study and then focus on screening, enrolment and recruitment challenges, and approaches taken to maintain retention and compliance. The key findings related to the first primary end point are reviewed with an emphasis on heterogeneity of islet autoimmunity, genetic factors, infectious agents, vaccination, coeliac disease autoimmunity (CDA), growth and dietary findings, as well as psychosocial findings. Key research gaps and future directions of study are also highlighted.

Background to the TEDDY study

The TEDDY study was made possible through a consortium agreement between the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and collaborators. With oversight from an external evaluation committee, funded investigators together with the director and staff from the data coordinating centre (DCC) prepared a common protocol to be used in four different countries.

The TEDDY study established its large, prospective cohort at six clinical centres in Finland, Germany, Sweden and the USA structured around a DCC (Fig. 1). TEDDY began in 2002, started screening in 2004 and enrolled 8,503 eligible children (926 from families with a relative affected by T1DM and 7,577 from families without a first-degree relative with T1DM (FDR)) with a high genetic risk of T1DM (selected HLA-DR-DQ genotypes). The children were followed from approximately 3 months of age (quarterly until age 4 years and then semi-annually unless islet autoantibody-positive) until a diagnosis of T1DM or 15 years of age, whichever came first[7,15].

IAA, GADA and IA-2A were measured in two laboratories by radio binding assays. ZnT8A was added later. In the USA, all serum samples were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado, Denver, CO; in Europe, all serum samples were assayed at the University of Bristol, UK. Both laboratories demonstrated high sensitivity and specificity as well as concordance[16]. All positive islet autoantibody samples and 5% of the negative samples were re-tested in the other reference laboratory and deemed confirmed if concordant. Persistent islet autoimmunity was defined as confirmed positive IAA, GADA or IA-2A in at least two consecutive samples. Genotyping was confirmed by reverse blot hybridization at the central HLA Reference Laboratory at Roche Molecular Systems, Oakland, CA, along with the *INS*-23Hph1 (rs689), *CTLA4* T17A (rs231775) and *PTPN22* R620W (rs2476601) single nucleotide polymorphism (SNP) primer pairs. SNP genotyping was performed by the Center for Public Health Genomics at the University of Virginia, using the Illumina Immunochip, which is a custom array for genotyping of SNPs selected from regions of the human genome firmly associated with autoimmune diseases. The final selection of SNPs containing approximately 186,000 SNPs in 186 regions for 12 autoimmune diseases was decided by the Immunochip Consortium[17].

The structure of the sampling, biosample management and dissemination of data are illustrated in Fig. 1. Samples and data are maintained at the DCC at the Health Informatics Institute, University of South Florida, Tampa, FL. The seven principal investigators along with the TEDDY Steering Committee direct 14 study committees and 25 TEDDY-affiliated laboratories (Box 1).

Microbiome, virome, proteome, metabolome, genomics (whole-genome sequencing (WGS) and whole-exome sequencing), toxicants measured in urine, inflammatory biomarkers (cytokines) and virome analyses are conducted in four nested case–control (NCC) populations identified in 2012 and 2021, respectively, to explore biomarker associations with the first primary outcome. The cases and controls are matched by study site, genetic sex and FDR status. The first two matched NCC studies captured all cases of islet autoimmunity (NCC1-IA, 418 cases) and cases of T1DM (NCC1-T1DM, 114 cases) identified as of 31 May 2012; the more recent NCC studies (NCC2-IA, 420 cases; NCC2-T1DM, 254 cases) captured all remaining cases as of 31 July 2021. The cases among the NCC1 and NCC2 are independent based on end point. However, an NCC1-IA case may be an NCC2-T1DM case or a control for an islet autoimmunity or T1DM case at an earlier time point. Islet autoimmunity positivity was defined as the presence of a specific autoantibody on two or more consecutive visits 3 months apart and confirmed in two TEDDY laboratories. Symptomatic T1DM (stage 3) was defined according to American Diabetes Association criteria for diagnosis. The power for the NCC1 study has been published in detail[18]. The power for the NCC2-IA study is similar to the power of the NCC1-IA study. The additional number of T1DM cases in the NCC2-T1DM study results in detectable odds ratios of ≥2.1 for a 1:1 match or ≥1.9 for a 1:3 match.

Screening and enrolment

Study recruitment

The details of enrolment and follow-up have been published elsewhere[19]. Only 40% of eligible infants joined TEDDY[20]. Many eligible families (~17%) failed to respond to calls and messages about the study. More than a third (~36%) refused to join the study, primarily because of blood draw concerns or being too busy for the demanding protocol[21]. Families

with an FDR were more likely to join the TEDDY study than those without; families from Europe were more likely to join than those from the USA[22]. Within the USA, ethnic-minority families failed to respond to contacts about the study at higher rates than non-Hispanic white families. However, if ethnic-minority families were successfully contacted, they joined the study at the same rates as their non-Hispanic white counterparts[20]. The distribution of enrolled participants between the four countries was 43% USA, 29% Sweden, 21% Finland and 7% Germany.

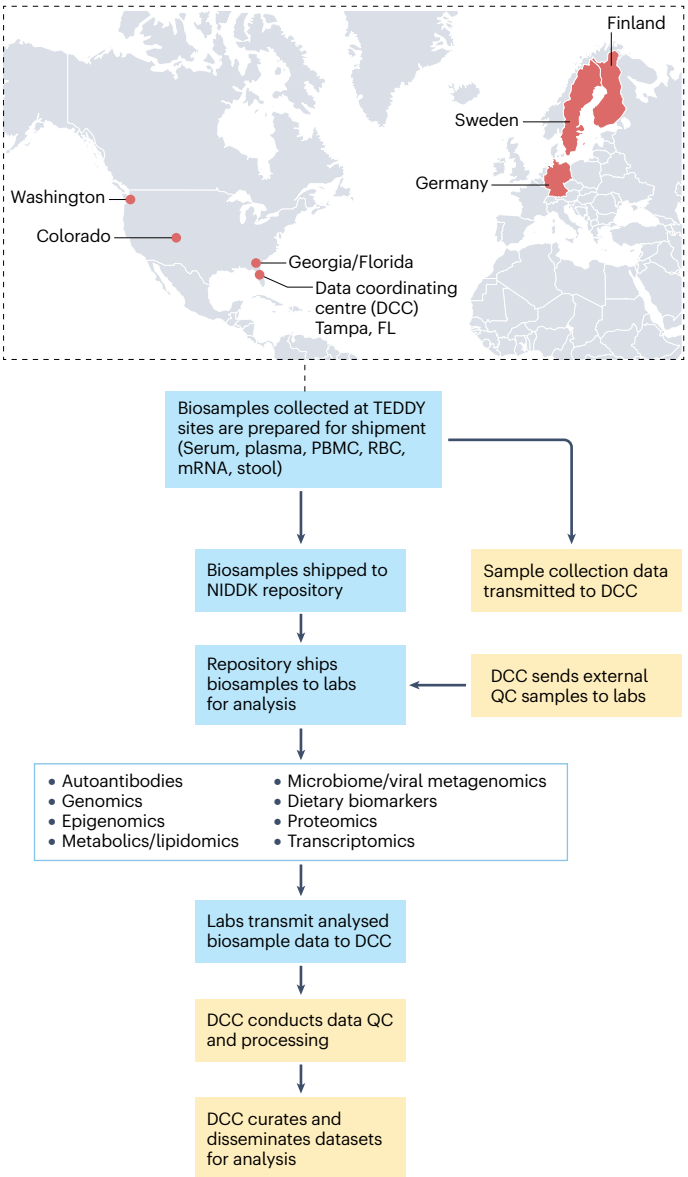


Fig. 1 | Organizational chart of the TEDDY study data coordinating centre, clinical sites and flow of samples and data. The illustration is based on the TEDDY study design[15] and the subsequent design of methods and quality control (QC)[130]. Key steps are the contributions by the TEDDY sites in four different countries to first ship all biosamples directly to the NIDDK repository in the USA and to upload all information and questionnaire data directly to the data coordinating centre (DCC) database. The DCC coordinates and adds QC samples to the shipment of re-coded samples from the NIDDK repository to different TEDDY assay laboratories in the USA, Finland and the UK. The respective laboratories transmit analysed biosamples to the DCC, which curates and disseminates datasets for analysis. PBMC, peripheral blood mononuclear cells; QC, quality control; RBC, red blood cells.

Study retention

The study Coordinators committee represents the nurses, managers and staff conducting the research visits. Having a voice at the table and a focus on retention and compliance, the study Coordinators committee identified and presented challenges and solutions to the Steering Committee. Data-informed approaches have been utilized to develop harmonized cross-centre retention and compliance strategies. Age-appropriate approaches for keeping child participants engaged and informed about the study were developed.

Drop-out rates were highest in the first year of the protocol, although few FDR families dropped out. Study retention was higher in Finland and Sweden than in the USA. Within the USA, Hispanic families were more likely to leave TEDDY in the first year[21,22]. TEDDY studies have repeatedly documented the importance of behavioural and psychological factors (for example, parent perception and anxiety about their child's T1DM risk and parent study satisfaction) as statistically significant predictors of study drop-out over and above demographic factors[20]. Importantly, identification of factors associated with study drop-out were used to develop a successful intervention directed at those at high risk of dropping out[23]. The primary reasons parents gave for leaving TEDDY were the same reasons given for refusing to enrol[24]. The primary reasons for staying in TEDDY included having someone watch the child for the development of T1DM, helping science to discover the causes of T1DM and getting the child's islet autoantibody results[25].

Study compliance

TEDDY studies have identified various factors associated with compliance with study visits[26], food records[27], salivary sample collection[28] and the oral glucose tolerance test[29]. Although some demographic variables (such as country, FDR and ethnic-minority status) were associated with protocol compliance, behavioural and psychological factors (for example, parent perception of their child's T1DM risk, post-partum depression and study satisfaction) offer important guidance for developing interventions to improve study compliance.

Heterogeneity in initial islet autoimmunity

The islet autoimmunity preceding the clinical manifestation of T1DM includes IAA, GADA, IA-2A and ZnT8A, added later in the study[30]. IAA or GADA are typically the first to appear and, therefore, are considered the major primary targets of islet autoantibodies in childhood. The presence of two or more islet autoantibodies in stage 1 T1DM is associated with a high probability of developing clinical, symptomatic stage 3 T1DM over time[31].

The incidence rate of islet autoantibody seroconversion in TEDDY participants was highest in the age range 6 months to 3 years, peaking at age 9 months[32]. This peak is notably evident for autoantibody phenotypes that target insulin at seroconversion (IAA-first) and specifically in an IAA-first phenotype that progresses to multiple islet autoantibodies (IAA-first to multiple) (Fig. 2). Although much less pronounced, seroconversion to phenotypes that target GAD65 first with progression to other islet autoantibodies (GADA-first to multiple) or that first target multiple islet autoantigens (multiple-first) also peaks within the first 3 years of life (Fig. 2). By contrast, the incidence rates of IAA or GADA that persist as single autoantibody phenotypes (IAA-single or GADA-single) are relatively stable throughout childhood[33] (Fig. 2).

One critical issue addressed by the TEDDY study is the presence of phenotypes (mistakenly referred to as 'endotypes'[34]) associated with distinct environmental factors and mechanisms underlying autoimmunity. In addition to age-related differences, notable genetic heterogeneity is observed between the persistent single and multiple islet autoantibody phenotypes and the IAA-first and GADA-first phenotypes. This heterogeneity might indeed suggest that true endotypes exist (that is, with differences in molecular mechanisms) but these are yet to be defined. An IAA-first to multiple phenotype is strongly associated with HLA DR4-DQ8-containing genotypes, whereas a GADA-first to multiple phenotype is associated with DR3-DQ2-containing genotypes[32,33]. Similar observations were reported in the Finnish Prediction and Prevention Project (DIPP) study[35]. Moreover, some environmental factors have a more pronounced association with an IAA-first or GADA-first phenotype. This genetic and environmental heterogeneity is highly relevant to identifying both aetiological differences and pathogenetic mechanisms that might be targeted based on personalized risk. These themes are discussed in subsequent sections. Nevertheless, TEDDY data convincingly show that insulin is the primary first autoantibody target in the first 3 years of life, with GAD65 becoming the predominant first target after this period.

Genetic factors

The genetic basis of initiation and progression of islet autoimmunity in TEDDY has been examined by completing a comprehensive determination of genomic variation. The Illumina Immunochip (a custom fine-mapping array of ~186,000 SNPs)[36] and the TEDDY array (genome-wide association with protein-coding content using a base of the Illumina HumanCoreExome BeadChip, and custom content, of ~700,000 SNPs) were applied to nearly all ~7,000 TEDDY participants and a large number of FDRs. These data were expanded by imputing ~9 million additional variants using the National Heart, Lung, and Blood Institute (NHLBI) TOPMed reference panel, a resource of ~200,000 whole-genome sequences from individuals of diverse genetic ancestry. These genetic data have been applied to the NCC1 and NCC2 studies referred to above. In addition, WGS was performed in 1,119 children in NCC1 (ref. 37).

Genetic factors account for ~50% of the risk of T1DM[38], including both the aetiological initiation of islet autoimmunity and the pathogenic progression to clinical hyperglycaemia[9,39,40]. *HLA-DR* and *HLA-DQ* genetic variants contribute ~40% of the genetic risk[41–43], presumably by affecting immunological presentation of foreign-derived or self-derived peptide antigens underlying the autoimmune disease process[44,45]. Other loci with modest effects include the insulin (*INS*) promoter[46], *CTLA4* (ref. 47), *PTPN22* (ref. 48) and *Il2RA* (also known as *CD25*)[49]. Genome-wide association studies and fine-mapping efforts have now identified >100 loci with statistically significant replicated evidence of association with T1DM. This discovery of the majority of genetic risk has enabled development of genetic risk scores[50–52] to identify individuals who might benefit from islet autoantibody screening. Most non-HLA T1DM risk loci seem to act through effects on gene expression or splicing, with most credible SNPs overlapping with enhancer regions in immune-relevant T cells, B cells and $CD34^+$ stem cells, and little evidence of effect on pancreatic islet gene expression[17]. Other cell types might have additional impact on T1DM pathogenesis (for example, plasmacytoid dendritic cells, classic monocytes, acinar cells and ductal cells).

TEDDY recruitment was based upon HLA susceptibility, but not protection; thus, the distribution of HLA DR-DQ haplogenotypes is restricted in the cohort[19]. As a result, associations between HLA alleles and specific triggers are indirect, as infections associated with 'autoantibody-first' endotypes[53] are themselves associated with HLA alleles[10]. These endotypes are also associated with other genetic variants; for example, IAA-first is associated with the *INS* promoter (rs689), and GADA-first is associated with SNPs in *CLEC16A* and *IL2RA*[54]. TEDDY identified an association in the Coxsackievirus and adenovirus receptor (*CAR*) viral receptor that modifies the association between enterovirus B shedding and islet autoimmunity[53]. Similarly, genetic variation in the vitamin D receptor (*VDR*) modulated the association between vitamin D levels and risk of islet autoimmunity[55]. Levels of HLA class II heterodimer expression are affected by a regulatory polymorphism in the *HLA-DRA* first intron[56,57] with opposing effects on the risk of IAA-first and tissue transglutaminase autoantibodies (tTGA; the biomarker for CDA)[58]. Similarly, gene dose-driven expression of *GSTM1* is associated with GADA[59].

Longitudinal blood transcriptomic profiles were used to generate gene co-expression networks for progression from islet autoimmunity to clinical onset[60]. Similarly, longitudinal blood transcriptomes before islet autoimmunity identified age-associated gene expression changes tracking progression to islet autoimmunity beginning before other evidence of islet autoimmunity was present[61]. DNA methylation has been analysed in prospective samples from both NCC1 and NCC2 to study exposures leading to islet autoimmunity and modulation of activity levels of T1DM genes and their changes with age. Further studies will allow co-localization of genetic variants with epigenetic status and gene expression in relation to environmental exposures and the appearance of either IAA-first or GADA-first.

Box 1 | TEDDY-affiliated laboratories and study committees

Laboratories

Autoantibody reference laboratory, PBMC certification and quality control laboratory, dietary biomarkers laboratory, RNA laboratory, enterovirus/rotavirus quality control laboratory, thyroid laboratory, Covid-19 antibody laboratory, neutralizing virus antibodies laboratory, HbA_{1c} laboratory, HLA reference and screening laboratory, gene expression laboratory, RNA-seq laboratory, microbiome/viral metagenomics laboratory, cortisol laboratory, inflammatory biomarkers laboratory, single-cell ATAC-seq laboratory, repository laboratory, whole-genome sequencing and SNP laboratory, OGTT laboratory, proteomics laboratory, metabolomics laboratory, epigenetics laboratory, multiplex viral and allergen antibody profiling laboratory, single-cell transcriptomics laboratory.

Committees

Steering, Coeliac disease, Genetics, Psychosocial, Ancillary studies, Clinical implementation, Immune markers, Coordinators, Laboratory implementation, Diet, Infectious agents, Maternal studies, Quality assurance, Human subjects/publications, Executive.

Further details are available in refs. 15,130. ATAC, assay for transposase-accessible chromatin using sequencing; OGTT, oral glucose tolerance test; PBMC, peripheral blood mononuclear cell; RNA-seq, RNA sequencing; SNP, single-nucleotide polymorphism.

Infectious agents

A metagenomic virome analysis of >12,000 stool samples collected monthly during follow-up was carried out to obtain comprehensive information regarding possible viral associations with first-appearing IAA or GADA[53]. The microbiome was also analysed but did not reveal any associations between specific taxa and islet autoimmunity or progression to T1DM[62,63] However, metagenomics analysis indicated a statistically significant reduction in bacteria with genes for fibre fermentation and biosynthesis of short-chain fatty acids in children who developed islet autoimmunity, T1DM, or both[62]. Whether this observation is relevant to a triggering mechanism related to aetiology or is more important to the pathogenesis once autoimmunity has been initiated remains to be determined.

Among the >600 detected viral taxa, only human enteroviruses and adenoviruses showed an association with islet autoimmunity. Enteroviruses, particularly species B enteroviruses (EVB) including Coxsackie B viruses, were associated with an increased risk of islet autoimmunity with preference for IAA-first[53], supporting the findings from other prospective studies[64,65]. In addition, islet autoimmunity-associated infections were characterized by delayed clearance of the virus after the acute phase[53]. Prolonged enterovirus infection could be due to a high virulence of the virus strain or a weakness in immune responsiveness in some susceptible individuals. The results from peripheral blood RNA-sequencing analyses showed that children who developed islet autoimmunity had a weak response to enterovirus infection[59]. Prolonged infection might also be a marker of viral persistence. Persistent enterovirus infection in β cells has been proposed as one possible mechanism mediating enterovirus-induced β cell damage[66].

The association between adenovirus infections and islet autoimmunity is more complex. Adenovirus infections, when occurring early in life (<6 months of age), showed a negative association with islet autoimmunity[53]. This phenomenon was linked to adenovirus-C species, which usually cause respiratory symptoms. The mechanisms of this inverse association are not understood, but they might be mediated by viral immunomodulatory effects or by viral interference. Adenovirus infection might protect the child from concomitant infection by EVB or other potentially diabetogenic viruses by activating antiviral defence mechanisms of the innate immune system. Adenoviruses might also compete with Coxsackie B viruses for receptor binding, as both use the Coxsackievirus and adenovirus receptor (CAR). Given that adenovirus-C infections are common at this age (<6 months), these mechanisms could have a considerable influence on the dynamics of virus infections. In contrast to adenovirus-C, adenovirus-F infections were associated with an increased risk of islet autoimmunity. However, this association was less robust and was not statistically significant after correction for multiple comparisons[53].

Parentally reported respiratory infections were associated with an increased risk of islet autoimmunity[67], supporting findings in previous prospective studies[68]. Gastroenteritis either increased or decreased the risk of islet autoimmunity depending on the age of infection. This association was seen in children who developed IAA as the first-appearing autoantibodies and was associated with the presence of norovirus in stools[69]. Early-life antibiotic use was not associated with future islet autoimmunity or CDA[70]. This finding agrees with the results of the largest meta-analysis to date in which T1DM and coeliac disease outcomes in 22,103,129 children were not associated with prior antibiotic exposure[71].

Vaccinations

The possibility that childhood vaccinations affect or modulate the risk of islet autoimmunity cannot be excluded. Immunization practices in the USA, Finland, Germany and Sweden differ, along with the standard of recording and documenting vaccinations. The TEDDY study has yet to overcome several administrative hurdles to analyse the development of islet and CDA in relation to immunizations.

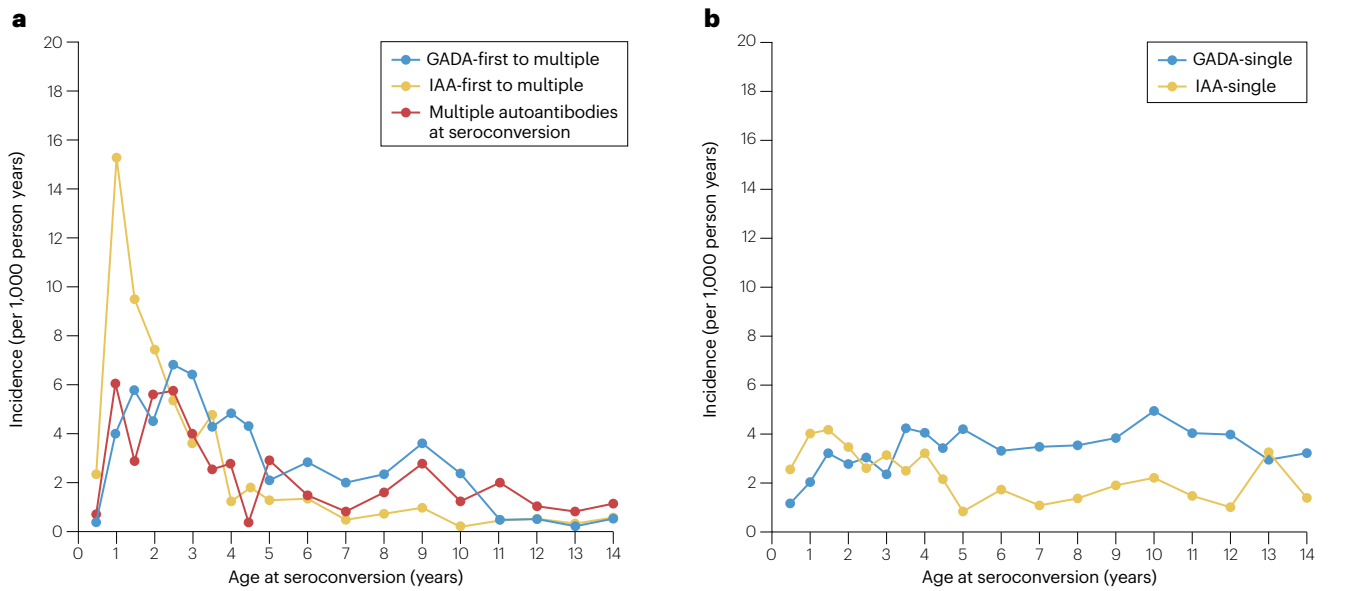


Fig. 2 | Incidence rates of IAA, GADA and multiple islet autoantibodies at seroconversion. a, IAA-first to multiple (yellow), GADA-first to multiple (blue) and multiple-first (red). The incidence of IAA-first to multiple is significantly higher in the first year of life than GADA-first to multiple (Wald $\chi^2 = 23.28$, $P < 0.0001$). **b**, Incidence of IAA (yellow) or GADA (blue) persisting as single autoantibodies. Data obtained from ref. 10. GADA, GAD65 autoantibodies; IAA, insulin autoantibodies.

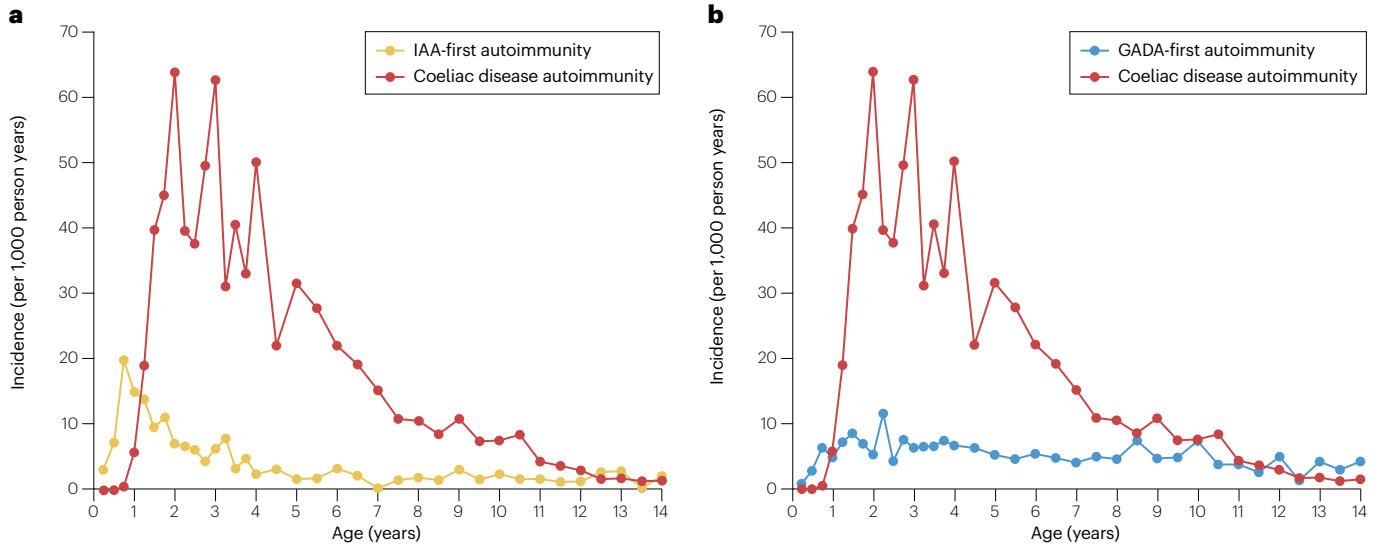


Fig. 3 | Incidence rates comparing IAA-first and GADA-first with coeliac disease autoimmunity (CDA). a, IAA-first compared with CDA. **b**, GADA-first compared with CDA. The cumulative incidence rates at 14 years of age in the TEDDY study reached 5.1% for IAA-first, 7.1% for GADA-first and 18.9% for CDA. Data obtained from ref.12. GADA, GAD65 autoantibodies; IAA, insulin autoantibodies.

After the H1N1 pandemic in 2009, it was found that Pandemrix, the vaccine given in Sweden and Finland, increased the risk of narcolepsy. The effect of Pandemrix on the development of islet autoimmunity in TEDDY children from Finland and Sweden was analysed. The data did not reveal an increased risk of islet autoimmunity after the vaccination[72]. On the contrary, the risk of developing islet autoimmunity, multiple islet autoantibodies and T1DM decreased in Finland (but not in Sweden)[72].

The competing risk of coeliac disease autoimmunity

TEDDY children are screened annually for tTGA, and when results are persistently positive, patients are referred to as having CDA. According to TEDDY data, the highest incidence of CDA diagnosis occurs between the ages of 1 and 4 years[73]. The incidence rate of CDA was about three to four times that of IAA-first and two to three times that of GADA-first[12]. Co-occurrence of both CDA and islet autoimmunity exceeded the expected rate according to HLA risk alone[74]. HLA-DR3-DQ2 homozygosity is the single strongest risk factor for CDA; children with HLA-DR3-DQ2 homozygosity were more than five times as likely to develop CDA than children who were HLA-DQ8 heterozygous or homozygous. HLA-DQ2 heterozygous children had an intermediate risk of coeliac disease[70]. Other important contributing factors to CDA risk were preceding IAA-first, GADA-first or a family history of T1DM after adjusting for HLA, coeliac-associated SNPs, family history of coeliac disease, female sex and geographical region[75,76] (Fig. 3).

The early high incidence rate of CDA might have competing effects on GADA as the first-appearing islet autoantibodies in the DR3-DQ2/DR3-DQ2 haplogenotype. Possible mechanisms include competing effects between enteroviruses. The infection with one enterovirus might not allow another enterovirus to infect the child at the same time. Notably, mastadenovirus C was associated with a decreased risk of islet autoimmunity[53], which could be interpreted similarly. On the same DR3-DQ2 heterodimer, one type of virus might have a preference for CDA and another virus might have a preference for GADA. The hypothesis is that only one virus infection can occur at one time.

Using the Immunochip, 54 SNPs in five genes (*TAGAP*, *Il18R1*, *RGS21*, *PLEK* and *CCR9*) were associated with the appearance of tTGA over time[76]. A NCC study found that the presence of HLA-DPB1*04:01 protected genetically susceptible children, especially those with HLA-DQ2.5, from developing CDA[77].

Among perinatal risk factors, neither caesarean section delivery[78] nor gluten consumption and maternal dietary supplementation of vitamin D, ω-3 fatty acids and iron during pregnancy was associated with CDA in the offspring[79,80]. However, a NCC analysis revealed that both low and high vitamin D serum concentrations were associated with an increased risk of CDA[81]. Studies on early infant feeding found neither breastfeeding nor timing of gluten introduction to affect CDA risk[82]. By contrast, high gluten intake was consistently associated with subsequent CDA[73,83]. No association was found between cumulative antibiotic use and CDA risk. Similarly, early probiotic use in the first year of life was not associated with a decreased risk of CDA[84].

An association was found between parent-reported gastrointestinal infections and subsequent risk of CDA, and rotavirus vaccination decreased the incidence of CDA[85]. An association between enterovirus infection and subsequent CDA was demonstrated through stool samples collected before 3 years of age and serum samples collected 24 months before seroconversion[86]. This study also found an interaction between enterovirus infection between 1 and 2 years of age, early-life cumulative gluten intake and subsequent CDA development.

Growth and macronutrient intake

Rapid growth has been speculated to be a trigger or a moderator of islet autoimmunity and progression to clinical onset of T1DM. The possible mechanisms are thought to include increased insulin resistance, stress to β cells, or both. Molecular stress response pathways in β cells have been reviewed elsewhere[87]. Interestingly, virus-induced β cell stress needs to be taken into account as an SNP in *CXADR* (which enables coxsackievirus

Box 2 | Key research gaps and future investigations

Although we are closer today to understanding the role of environmental and genetic factors in the aetiology of T1DM, many questions remain.

Is there an omics signature prior to the first-appearing autoantibody?
Results from the TEDDY study point to activation of the humoral[138] and natural killer cellular innate immune response[61] in the months preceding the appearance of a first islet autoantibody. TEDDY will continue to deconvolute multiple time point transcriptomic, proteomic, immune and metabolomic profiles preceding islet autoimmunity to better characterize potential triggers and pathways leading to autoimmunity.

Is the relationship between viral infection and the subsequent islet autoimmunity observed in TEDDY causal?
More work is needed to reconcile the innate immune response, suggestive of a viral trigger, with an apparently weaker immune response to enterovirus infection in children who develop islet autoimmunity[59]. Although the evidence is currently strongest for a causal role of enteroviral infections, other viruses need to be ruled out using multiplex serology and sequencing.

Is islet autoimmunity triggered postnatally or in utero?
TEDDY participants were enrolled at 4 months of age. Potential prenatal and perinatal exposures were assessed, and cord blood samples are available for many of the study participants. TEDDY will explore a role for maternal virus antibodies in cord blood as a protective factor. However, additional studies are needed (ENDIA[139], PROMISE) to explore prenatal and perinatal exposures to definitively rule out the possibility that key exposure(s) occur before 4 months of age.

What is the meaning of persistent single islet autoantibody positivity?
Does it provide clues that some children can develop immune tolerance and remission of islet autoimmunity? Are the β cells partially damaged, increasing the risk of latent autoimmune diabetes in adults let alone type 2 diabetes mellitus later in life? The progression from multiple islet autoantibodies (stage 1 T1DM) to clinical diabetes takes on average 5 years; in some patients it takes 15–20 years. What have we learned from these 'slow progressors' and how do we translate this knowledge into prevention?

What is the role of other environmental factors (for example, diet)?
The associations between micronutrient and macronutrient intake and islet autoimmunity observed in TEDDY might suggest their role as modifiers rather than triggers of autoimmunity. Does vitamin D or polyunsaturated fatty acid intake make β cells less vulnerable to a virus attack? Is the evidence sufficient to justify randomized clinical trials?

The incidence of T1DM has increased 3–5% a year in the past four decades. Does TEDDY provide actionable evidence to stem this rise?
This and other questions are high priority for the TEDDY study group and the world of scientists at large; all TEDDY data as well as biospecimens are available from the NIDDK.

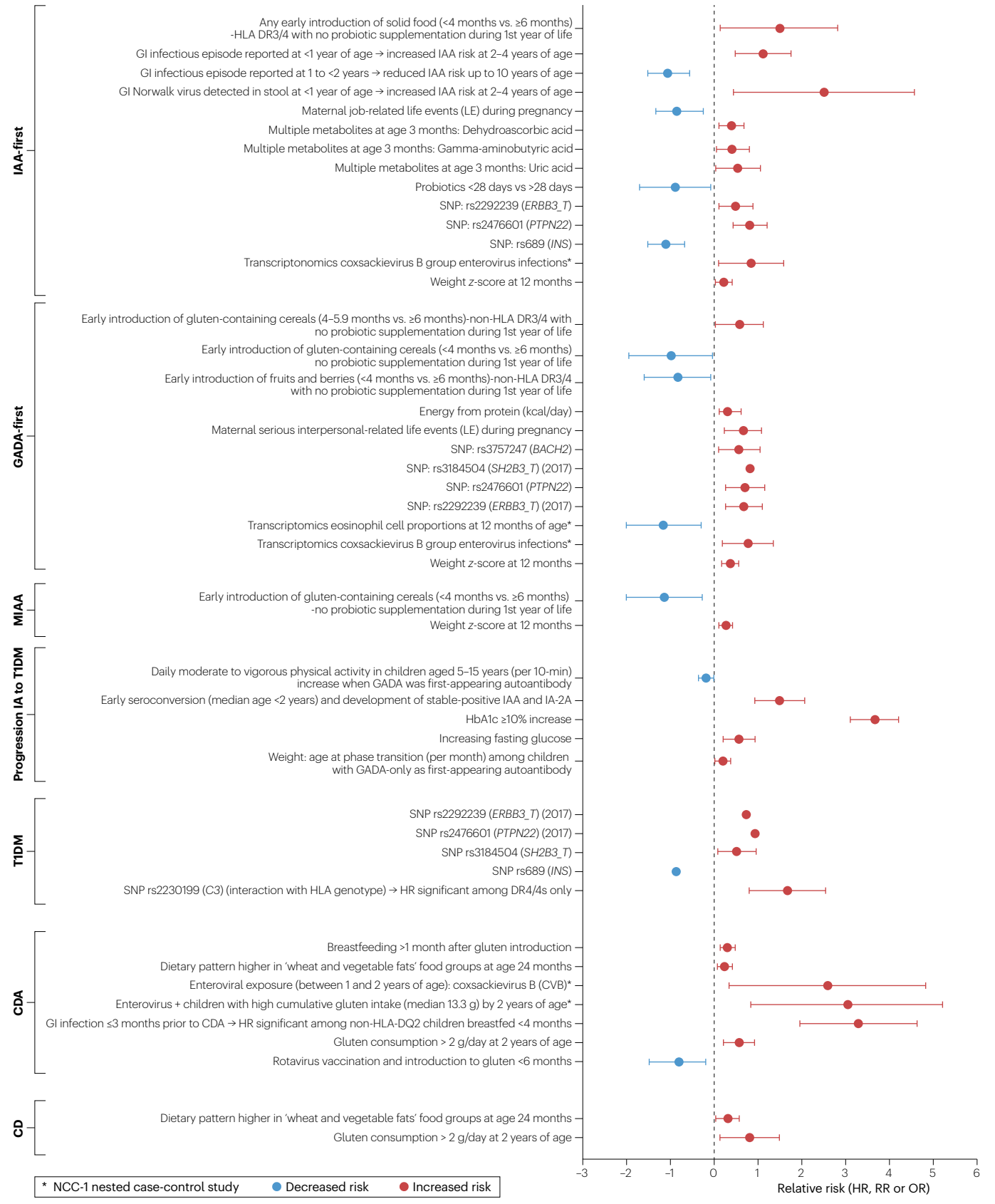
and adenovirus to infect β cells) independently correlates with the development of islet autoimmunity[53]. Furthermore, the possible contribution of oxidative stress cannot be excluded as a gene dosage-driven expression of GSTM1 (glutathione *S*-transferase) was associated with GADA[59], as previously demonstrated in patients with newly diagnosed T1DM[88]. Similar monogenic polymorphisms need to be considered when children from the TEDDY study are catalogued based on their genetic aetiology.

On the other hand, excessive growth could, according to the accelerator hypothesis[89], cause an increased demand for insulin due to insulin resistance, which in turn stresses the β cells. In addition, insulin resistance might lead to an increase in plasma glucose, which through glucotoxicity could possibly damage β cells, expose intracellular β cell immunogens to the immune system and initiate a β cell autoimmune reaction[89–91].

Islet autoimmunity is often initiated during early life, and early infant growth is therefore of specific interest. Weight and height development in relation to islet autoimmunity were analysed during the first 4 years of life[91]. The height and weight *z*-scores at 12 months of age were related to a higher risk of islet autoimmunity. Similarly, weight *z*-scores were associated with the development of multiple islet autoantibodies at both 12 and 24 months of age. However, no relationship with the development of T1DM was found[91]. Growth in early life was modelled in two distinct growth patterns[90]: weight gain during the infancy phase was associated with an increased risk of islet autoimmunity, especially GADA-first; and rapid height gain increased the risk of progression from GADA-first to clinical onset of T1DM[90].

These findings were further investigated by analysing the effect of energy-yielding macronutrient intake on islet autoimmunity, using BMI *z*-scores as a mediator. Children who were islet autoantibody-negative at 2 years of age were followed with growth data and biannual 3-day food records, which allowed macronutrient intake to be calculated.

Fig. 4 | TEDDY observations suggesting that the phenomena associated with either risk or protection from IAA-first are different from those associated with GADA-first. Microinsulin autoantibody analysis[131] was used throughout the TEDDY study. Progression from islet autoimmunity (IA) (stage 1 and stage 2 type 1 diabetes mellitus (T1DM)) to stage 3 T1DM is also indicated[31]. Coeliac disease (CD) autoimmunity (CDA) risk factors are summarized along with risk factors for CD once CDA has developed. Relative risks (HR, RR or OR) are shown with 95% confidence intervals. The data are categorized by the TEDDY outcomes: insulin autoantibodies (IAA)-only as the first-appearing autoantibodies (IAA-first)[48,58,85,93,101,132], glutamic acid decarboxylase autoantibodies (GADA)-only as the first-appearing autoantibodies (GADA-first)[48,78,85,101,132], multiple islet autoantibodies (MIAA)[70,85], and progression from IA to T1DM[17,77,133–136], CDA[61,72,73,76,85] and CD[61,137]. The definition of the MIAA end point varies across TEDDY publications as either the appearance of a second autoantibody or two or more autoantibodies at first appearance. GI, gastrointestinal; IA-2A, islet antigen 2 autoantibodies; SNP, single-nucleotide polymorphism.


IAA-first
Any early introduction of solid food (<4 months vs. ≥6 months) -HLA DR3/4 with no probiotic supplementation during 1st year of life
GI infectious episode reported at <1 year of age → increased IAA risk at 2–4 years of age
GI infectious episode reported at 1 to <2 years → reduced IAA risk up to 10 years of age
GI Norwalk virus detected in stool at <1 year of age → increased IAA risk at 2–4 years of age
Maternal job-related life events (LE) during pregnancy
Multiple metabolites at age 3 months: Dehydroascorbic acid
Multiple metabolites at age 3 months: Gamma-aminobutyric acid
Multiple metabolites at age 3 months: Uric acid
Probiotics <28 days vs >28 days
SNP: rs2292239 (ERBB3_T)
SNP: rs2476601 (PTPN22)
SNP: rs689 (INS)
Transcriptonomics coxsackievirus B group enterovirus infections*
Weight z-score at 12 months
GADA-first
Early introduction of gluten-containing cereals (4–5.9 months vs. ≥6 months)-non-HLA DR3/4 with no probiotic supplementation during 1st year of life
Early introduction of gluten-containing cereals (<4 months vs. ≥6 months) no probiotic supplementation during 1st year of life
Early introduction of fruits and berries (<4 months vs. ≥6 months)-non-HLA DR3/4 with no probiotic supplementation during 1st year of life
Energy from protein (kcal/day)
Maternal serious interpersonal-related life events (LE) during pregnancy
SNP: rs3757247 (BACH2)
SNP: rs3184504 (SH2B3_T) (2017)
SNP: rs2476601 (PTPN22)
SNP: rs2292239 (ERBB3_T) (2017)
Transcriptomics eosinophil cell proportions at 12 months of age*
Transcriptomics coxsackievirus B group enterovirus infections*
Weight z-score at 12 months
MIAA
Early introduction of gluten-containing cereals (<4 months vs. ≥6 months) -no probiotic supplementation during 1st year of life
Weight z-score at 12 months
Progression IA to T1DM
Daily moderate to vigorous physical activity in children aged 5–15 years (per 10-min) increase when GADA was first-appearing autoantibody
Early seroconversion (median age <2 years) and development of stable-positive IAA and IA-2A
HbA1c ≥10% increase
Increasing fasting glucose
Weight: age at phase transition (per month) among children with GADA-only as first-appearing autoantibody
T1DM
SNP rs2292239 (ERBB3_T) (2017)
SNP rs2476601 (PTPN22) (2017)
SNP rs3184504 (SH2B3_T)
SNP rs689 (INS)
SNP rs2230199 (C3) (interaction with HLA genotype) → HR significant among DR4/4s only
CDA
Breastfeeding >1 month after gluten introduction
Dietary pattern higher in 'wheat and vegetable fats' food groups at age 24 months
Enteroviral exposure (between 1 and 2 years of age): coxsackievirus B (CVB)*
Enterovirus + children with high cumulative gluten intake (median 13.3 g) by 2 years of age*
GI infection ≤3 months prior to CDA → HR significant among non-HLA-DQ2 children breastfed <4 months
Gluten consumption > 2 g/day at 2 years of age
Rotavirus vaccination and introduction to gluten <6 months
CD
Dietary pattern higher in 'wheat and vegetable fats' food groups at age 24 months
Gluten consumption > 2 g/day at 2 years of age
* NCC-1 nested case-control study
Decreased risk
Increased risk
−3
−2
−1
0
1
2
3
4
5
6
Relative risk (HR, RR or OR)

A direct association was noted between GADA-first islet autoimmunity and energy intake from protein, but not fat or carbohydrates[92] (in which a larger contribution of energy from protein intake increased the risk of GADA). These analyses confirm the finding that growth and BMI are associated with islet autoimmunity, and indicate that excessive energy intake has an indirect effect. Whether energy intake from protein is an important trigger of islet autoimmunity remains to be determined[92]. An interaction with insulin and IGF1 cannot be excluded.

Further evidence for the role of excessive growth has been found when studying the role of puberty in relation to islet autoimmunity. Increased BMI *z*-scores during puberty are associated with development of islet autoimmunity, primarily IAA-first and particularly in girls, unrelated to pubertal stage[93].

Key dietary findings

The TEDDY study retrospectively assessed maternal diet during pregnancy and is one of the few studies in the world with prospective longitudinal information on nutritional biomarkers and children's total diet collected by repeated food records. All the dietary data collection and biomarker sampling has been standardized across the six study centres. The food consumption and nutrient intake data processing is harmonized for between-country comparisons[94,95]. The observation that islet autoimmunity was not reduced but rather might be increased by hydrolysed compared with non-hydrolysed cow's milk-based infant formula[96], is in partial agreement with the results of the TRIGR trial[97,98].

The data showing that exposure to dietary gluten in offspring of mothers and fathers with T1DM before 4 months of age is associated with an increased risk of developing islet antibodies[99] is consistent with the notion that more studies on infant gluten-free diet are needed[100]. However, this finding is complicated by a TEDDY observation that the risk of IAA-first increased each month when gluten introduction was delayed up to 9 months of age[101]. It cannot be excluded that gluten might be a driver in an autoimmune reaction initiated by enterovirus, similar to its role in the development of coeliac disease.

The finding that probiotic supplementation in infancy reduces the risk of islet autoimmunity, particularly in children at the highest genetic risk of T1DM, is novel[84,102], and suggests either that probiotics reduce enterovirus infections and thereby reduce IAA-first or that a role for the microbiome in the aetiology of islet autoimmunity needs to be further investigated. In addition, early introduction of solid food (<6 months) was associated with an increased risk of IAA-first and multiple autoantibodies in children with the highest-risk genotype and no probiotic exposure, but not in those exposed to probiotics in the first year (also with the highest-risk genotype)[103], which might explain the previous inconsistent results regarding infant diet.

Furthermore, high intake of pyridoxine and vitamin B_{12} was associated with a decreased risk of IAA-first, whereas high intake of riboflavin was associated with an increased risk of GADA-first[104]. Iron intake was associated with risk of GADA-first in a U-shaped relationship, and higher iron intake 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[105].

Among nutritional biomarkers, increased levels of some saturated and mono-unsaturated fatty acids might precede islet autoimmunity, and decreased levels of ω-3 fatty acid might be protective[106], which is in line with previous studies[107–109]. Similarly, high levels of circulating ascorbic acid were associated with a reduced risk of IAA-first[110]. TEDDY's longitudinal untargeted metabolomics study underscored that the appearance of GADA-first or IAA-first was preceded by distinct plasma metabolic precursors[111], supporting the hypothesis that the causes of each type of initial autoimmunity might differ (also fulfilling the criteria for true endotypes).

Psychosocial factors

Literature reviews and prospective studies provide evidence of psychological stress as a possible trigger for both islet autoimmunity and the subsequent progression to clinical onset of T1DM[112–115]. However, the mechanisms by which this might occur are unknown. Stress might have a direct effect on the development of islet autoimmunity through the effects of the hypothalamic–pituitary–adrenal axis on immune or neuroendocrine function[113]. Alternatively, stress might have an indirect effect by increasing the likelihood of other exposures. In TEDDY, a positive association was documented between the number of major life events experienced by the child between 12 and 48 months of age and the number of childhood respiratory infections[116], offering some support for an indirect pathway through infections.

Two prior prospective studies have shown a link between serious life events during pregnancy and the development of T1DM in the child[115,117] but no prior study has examined the association between life events during pregnancy and the development of islet autoimmunity, let alone the two endotypes, IAA-first or GADA-first. Both maternal respiratory infections and job-related life events during pregnancy were associated with a reduced risk of IAA-first in the child before 7 years of age, primarily among children with the HLA-DR4-DQ8 haplogenotype[118,119]. However, the reduced risk of IAA associated with respiratory infections during pregnancy was additionally dependent on the child having an SNP (rs231775) in the *CTLA-4* gene (G allele)[119]. A very different pattern emerged for GADA as the first-appearing autoantibodies, as serious interpersonal life events during pregnancy increased the risk of GADA in children with the HLA-DR3-DQ2 haplogenotype and the SNP-rs3757247 (T allele) in *BACH2* (ref. 119). These findings highlight the importance of gene–environmental interactions in the development of islet autoimmunity and suggest that different components act synergistically to create different pathways by which a child might develop either IAA-first or GADA-first.

Findings from other longitudinal studies

The TEDDY longitudinal study was preceded by local smaller studies including BABY DIAB[120,121], DIPP[122], Diabetes Autoimmunity Study in the Young (DAISY)[123], Prospective Assessment of Newborn for Diabetes Autoimmunity (PANDA)[124], Diabetes Prediction in Skåne (DiPiS)[125], Diabetes Evaluation in Washington (DEW-IT)[126], Environmental Causes of Type 1 Diabetes (MIDIA)[127], and All Babies in South-east Sweden (ABIS)[128]. The TEDDY study has confirmed the early appearance of IAA during the first year of life in a population of children at increased genetic risk of T1DM[32,35,120,127] as well as the relationship between IAA appearance and prior enterovirus infection[53,64]. Psychological stress in pregnant mothers as a risk factor for islet autoimmunity was reported[112,114,129], and confirmed and detailed in TEDDY[119]. Key research gaps and future directions are outlined in Box 2.

Conclusions

The first primary outcome of the TEDDY study — to elucidate factors leading to the initiation of islet autoimmunity (detected as either IAA-first or GADA-first, or both) — reveals a distinct pattern of associated factors (Fig. 4). The background factors important to the second

primary outcome (that is, progression to clinical onset) also show some early associated factors (Fig. 4) but the completion of all samples collected by early 2025 is awaited. The TEDDY study successfully screened and recruited, depending on the country, between 4.5% and 8.0% of eligible newborns with high-risk HLA. The follow-up from age 4 months to 15 years of age showed high retention and compliance. The end points of appearance of IAA, GADA, IA-2A and ZnT8A revealed genetic and environmental factors (including enterovirus infection and gastroenteritis) that were associated with either IAA (1–3 years of age) or GADA (≥3 years) as first-appearing autoantibodies. Serious life events during pregnancy, infant growth and the effects of either probiotics or high protein intake affect the two phenotypes differently. Studies thus far have not been able to fully explain the mechanisms between genetic risk, environmental exposures and the lag phase before the appearance of either IAA or GADA; however, major studies involving omics approaches are in progress to further dissect possible mechanisms

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