Original Article

The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design

The TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design.
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Abstract: The primary objective of this multicenter, multinational, epidemiological study is the identification of infectious agents, dietary factors, or other environmental exposures that are associated with increased risk of autoimmunity and type 1 diabetes mellitus (T1DM). Factors affecting specific phenotypic manifestations such as early age of onset or rate of progression or with protection from the development of T1DM will also be identified. The Environmental Determinants of Diabetes in the Young (TEDDY) is an observational cohort study in which newborns who are younger than 4 months and have high-risk human leukocyte antigen alleles in the general population or are first-degree relatives (FDRs) of patients affected with T1DM will be enrolled. Six clinical centers in the USA and Europe will screen 361 588 newborns, of which it is anticipated that 17 804 will be eligible for enrollment with just over 7800 followed. Recruitment will occur over 5 yr, with children being followed to the age of 15 yr. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay, or reverse T1DM.

The TEDDY Study Group*

Key words: dietary factors – environmental triggers – epidemiological study – HLA – infectious agents factors – islet autoimmunity – psychosocial factors – T1DM

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Type 1 diabetes mellitus (T1DM) is one of the most common and serious chronic diseases in children and is also often diagnosed in adults, affecting up to 1% of the general population during their life span (1, 2). The incidence of T1DM is highest in Scandinavia (30–50/100 000), intermediate in the USA (15–25/100 000 in 1998), and somewhat lower in Central and Eastern Europe (5–15/100 000). These geographic differences may reflect variation in the genetic susceptibility pool or in the prevalence of causal environmental factors, or both. The etiology of T1DM remains unknown, and the incidence is increasing by 3–5% per year, particularly in young children (2). While there is a strong familial clustering of the cases, approximately 90% of the patients have no FDR with T1DM (3). Genetic variability in the human leukocyte antigen (HLA) region explains ∼50% of the familial clustering (4, 5); other genes have also been identified as providing more modest contributions to risk (5, 6). Additional factors are important because only 1/15 people in the general population with the highest risk HLA genotypes develops

T1DM. The cause(s) of T1DM have not been definitively identified.

Several studies have shown that gestational events contribute to an increased risk of T1DM. The most prominent example is exposure to rubella during pregnancy. About 20% of children born with congenital rubella develop T1DM (7, 8). More recent studies have shown an increased risk for childhood T1DM if the mother has had an infection with enteroviruses during pregnancy (9, 10). Other events during pregnancy or at delivery such as pre-eclampsia also confer T1DM risk (3, 11, 12). High birth weight and children born large for gestational age have a higher risk of T1DM than controls (13, 14). Neither of these phenomena is understood, and it may be necessary to analyze them in relation to genetic incompatibilities between mother and child such as non-inherited maternal haplotypes (15) or blood incompatibility such as ABO incompatibility was related to an increased risk for T1DM (16).

The risk that a child will develop T1DM is increased when born to a T1DM mother compared to the

general population. However, the risk of the child developing the disease is higher when born to a T1DM father (17). Little is known about the consequences for islet autoimmunity or T1DM development when born to a mother with subclinical organ-specific autoimmunity such as a mother with thyroid or islet auto-antibodies but not necessarily an autoimmune disease. In most cases, overt diabetes is preceded by the presence of autoantibodies to IAs such as glutamic acid decarboxylase (GAD65), insulin autoantibodies (IAA), and tyrosine phosphatase autoantibodies (IA-2). This preclinical period, ranging from months to years, provides an opportunity for prevention, which has been unsuccessful to date.

Current understanding of T1DM etiology and the preliminary intervention data originate almost exclusively from studies of FDRs of T1DM patients. These data may not be directly applicable to the causes and prevention of T1DM in the general population where 85–90% of the patients occur (3). The presence of gene–environment interactions may explain the observed weak effects of candidate environmental agents and genes on T1DM risk. Without accounting for these interactions, we may not detect the true main effects of either the environmental agent or the gene.

Approximately 90% of all T1DM patients have either the DRB1*03,DQB1*0201 or the DRB1*04, DQB1*0302 haplotype. While the DRB1*0301, DQB1*0201/DRB1*04,DQB1*0302 heterozygotes account for only about 3% of the general population, this genotype is present in 30–40% of T1DM patients and in up to 52% of those who develop diabetes in the first 10 yr of life (18–20). Thus, a great deal could be learned about the causes of T1DM by studying the interactions between plausible environmental causes and the HLA-DR and -DQ genotypes.

T1DM has been associated with enteroviral infections, rotavirus, and herpes viruses (21–31). However, there is a lack of consistency in previous reports, which have been underpowered for the most part, and it is plausible that non-diabetogenic strains of a virus may induce immunity to antigenically similar diabetogenic strains and protect from T1DM. To test these hypotheses, large groups of young children at risk for T1DM need to be followed prospectively with collection of appropriate samples at frequent intervals. In addition, state-of-the-art techniques must be used for sensitive and specific detection of both microbial nucleic acids (to demonstrate current acute or persistent infection) and antibodies (to document previous infection).

No specific bacterial agent has been linked with onset of T1DM or with diabetes-associated autoimmunity. However, bacterial superantigens have been suggested as possible non-specific immune stimuli that could play a role in development of prediabetic autoimmunity (32). A number of bacteria have been proposed as sources of superantigens that might be relevant to onset

of T1DM, including *Mycobacterium tuberculosis*, *Mycoplasma* species, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, and *Yersinia enterocolitica*.

Lack of breast-feeding and early exposure to cow's milk or wheat have been associated with T1DM (33–36). However, the findings from prospective studies have been inconsistent. Relative deficiencies of vitamin D and E and omega-3 fatty acids have been reported to play a role but needs to be evaluated prospectively using both intake information and biomarkers (37–39). *N*-Nitroso compounds may increase the risk of diabetes, but the effect on human T1DM risk is less clear (40). Exposure to mycotoxin has been recently suggested as another candidate environmental cause of T1DM (41).

Psychosocial factors may also contribute to appearance of T1DM. Stress has long been considered a potential trigger for TIDM (42–51). Furthermore, screening for high-risk genes associated with T1DM could induce anxiety and distress in family members (52). As the children grow older, they too may become concerned about their vulnerability to TIDM. It is important that we assess the psychological impact of genetic screening and long-term follow-up of at-risk children on both the children and their families.

Unfortunately, results from previous studies have been confounded by imprecise assessment of exposure, recall bias, failure to account for genetic susceptibility, failure to assess exposures at very early ages, or the inability to follow a sufficient sample of children long term with high intensity. The present multicenter study will provide an opportunity to fill important gaps in our understanding of the events leading to T1DM by studying from birth high-risk general population children and relatives and by systematic screening of candidate environmental and genetic factors. In addition, samples collected by the Environmental Determinants of Diabetes in the Young (TEDDY) will create a valuable resource for investigators proposing innovative hypotheses concerning candidate environmental and genetic factors.

Study organization

The TEDDY consortium, comprising six clinical centers located in the USA and Europe: Washington (Seattle), Colorado (Denver), and Georgia (Augusta); Finland (Turku); Sweden (Malmo); and Germany (Munich), and a data coordinating center in Tampa, Florida, will allow for a coordinated, multidisciplinary approach to this complex disease. Collection of information and samples in a standardized manner will achieve greater statistical power than smaller independent investigations. The TEDDY study will establish a central repository of data and biologic samples for subsequent hypothesis-based research.

Study design

Hypotheses

(i) Initiation of persistent beta-cell autoimmunity and progression from beta-cell autoimmunity to diabetes is increased with:

   (a) Exposure to a trigger factor during pregnancy, such as infections, pre-eclampsia, blood incompatibility, or birth weight;
   (b) Differences in the timing of the introduction and/or the type of dietary constituents that include exposure to cereals or gluten, exposure to cow's milk during infancy and/or childhood, and short duration of breast-feeding;
   (c) Lower intake of serum 25-hydroxyvitamin D in early infancy, vitamin E, and antioxidants (e.g., carotenoids, ascorbic acid, selenium, or omega-3 fatty acids);
   (d) Higher frequency of specific (e.g., enterovirus, rotavirus, or bacterial) infections or non-specific childhood infections including those that exhibit molecular mimicry;
   (e) Increased exposure to routine childhood immunizations and their timing;
   (f) Environmental factors that may be contained in drinking water (e.g., low concentrations of zinc or high concentrations of nitrates, or lower pH levels);
   (g) Exposure to household pets and various allergies;
   (h) Excessive weight gain;
   (i) Increased psychological stress.

(ii) The risk of persistent beta-cell autoimmunity is lower in children from the general population than in offspring or siblings of T1DM patients when stratifying for the HLA-DR-DQ genotype and exposure to environmental triggers.
(iii) The interaction of HLA-DR-DQ genotype with exposure to dietary or infectious factors leads to increased incidence of beta-cell autoimmunity and T1DM.
(iv) Study participation will be associated with affective (anxiety, depression) and behavioral responses (e.g., actions to prevent possible T1DM).

Subject population

A cohort of children with increased genetic risk for T1DM will be established by screening newborns from the general population and from families with FDRs diagnosed with T1DM.

Infants are eligible for screening if they:

- Are younger than 4 months.
- Have a parent or primary caretaker who has given informed consent for screening.

Infants are excluded if they:

- Have an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes (e.g., steroids or insulin).

Infants from the general population are eligible for enrollment and long-term follow-up if they:

- Have any one of the following HLA genotypes:

   (i) DR4[1]-DQA1*030X-DQB1*0302[2]/DR3-DQA1*0501-DQB1*0201
   (ii) DR4[1]-DQA1*030X-DQB1*0302[2]/DR4[1]-DQA1*030X-DQB1*0302[2]
   (iii) DR4[1]-DQA1*030X-DQB1*0302[2]/DR8-DQA1*0401-DQB1*0402
   (iv) DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201

Note: [1]For general population subjects, DR4 subtyping must exclude DRB1*0403. [2]Acceptable alleles in this haplotype include both DQB1*0302 and *0304.

Infants who are FDRs are eligible for enrollment and long-term follow-up if they:

- Have any one of the following HLA genotypes:

   (i) DR4-DQA1*030X-DQB1*0302[1]/DR3-DQA1*0501-DQB1*0201
   (ii) DR4-DQA1*030X-DQB1*0302[1]/DR4-DQA1*030X-DQB1*0302[1]
   (iii) DR4-DQA1*030X-DQB1*0302[1]/DR8-DQA1*0401-DQB1*0402
   (iv) DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201
   (v) DR4-DQA1*030X-DQB1*0302[1]/DR4-DQA1*030X-DQB1*020X
   (vi) DR4-DQA1*030X-DQB1*0302[1]/DR1[2]-DQA1*0101-DQB1*0501
   (vii) DR4-DQA1*030X-DQB1*0302[1]/DR13-DQA1*0102-DQB1*0604
   (viii) DR4-DQA1*030X-DQB1*0302/DR4-DQA1*030X-DQB1*0304
   (ix) DR4-DQA1*030X-DQB1*0302[1]/DR9-DQA1*030X-DQB1*0303
   (x) DR3-DQA1*0501-DQB1*0201/DR9-DQA1*030X-DQB1*0303

Note: [1]Acceptable alleles in this haplotype include both DQB1*0302 and *0304. [2]In this DQB1*0501 haplotype, DR10 must be excluded. Only DR1 is eligible.

Study procedures

HLA typing (Fig. 1)

HLA screening. Genotype screening will be performed using either a dried blood spot punch or
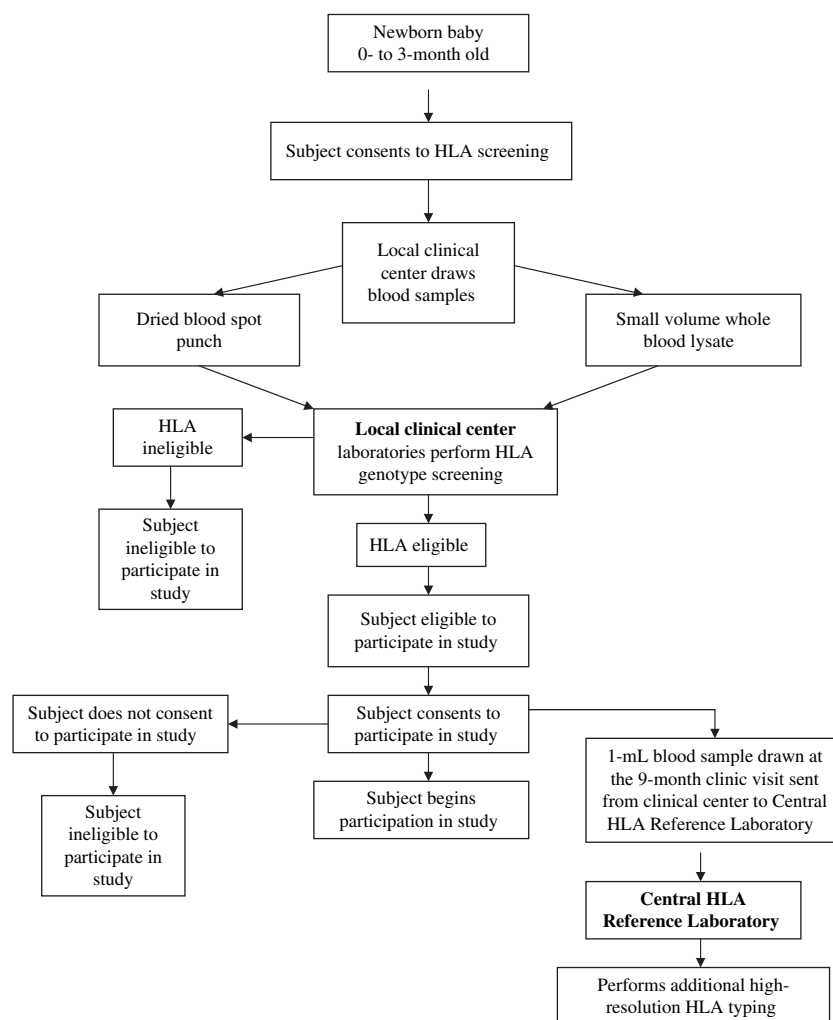
Fig. 1. TEDDY study procedures. HLA, human leukocyte antigen.

a small volume whole blood lysate specimen format. Screening blood sample will be obtained generally at birth as a cord blood sample, but potential participants, especially FDRs of T1DM patients, can be screened using heel stick capillary sample up to the age of 4 months. This exception is made to maximize the number of newborn relatives participating in this study. After polymerase chain reaction amplification of exon 2 of the HLA class II gene (DRB1, DQA1, or DQB1), alleles will be identified by direct sequencing, oligonucleotide probe hybridization, or other genotyping techniques. Additional typing to sufficiently identify certain DR-DQ haplotypes is as specified above.

HLA additional genotyping. Better definition of the HLA genotypes will be performed by a central HLA Reference Laboratory on 100% of the eligible subjects at 9 months of age. Additional high-resolution HLA genotyping will be performed. High-resolution HLA genotyping will occur at DRB1, DQA1, and DQB1 and may also occur at DPB1, HLA-A, HLA-B, MIC-A and/or other MHC loci determined by the study

group. The insulin 5′VNTR using the −23 Hph single nucleotide polymorphism will be typed by the HLA Central Laboratory.

Enrollment/follow-up

Maternal enrollment

At some sites, pregnant women, will be approached for blood samples at 12–14 wk and 25–28 wk of the pregnancy and at delivery. These blood samples will be available for retrospective analysis of mothers of children who develop islet autoimmunity or T1DM, or both. Samples will be obtained for HLA, islet cell autoantibodies, infectious agent antibodies, and infectious agent nucleic acid analyses.

Follow-up schedule for children with increased genetic risk

Eligible children will be followed for environmental exposures and dietary evaluation at a clinic visit every

3 months for the first 4 yr of life and then biannually until age 15 yr. Stool samples will be collected to assess the viral exposures at monthly intervals for the first 4 yr and then biannually until age 15 yr. The schedule for samples/visits/questionnaires is described in Table 1.

Clinic visits

Demographic and family history

Abbreviated demographic and tracking questionnaire will be completed at the first visit at the age of 3 months. However, comprehensive demographic and family history questionnaires will be undertaken at 9 months.

Medical

Medical information will be obtained by interview or questionnaires at each of the clinical visits at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 months of age and biannually thereafter. In addition, the parents will be asked to consent to allow TEDDY personnel to access the child's medical record in the event that the child has been hospitalized or has any outpatient treatments.

Clinical measurements

Accurate weight and length/height measurements will be taken at each clinic visit.

Specimen collection

To the extent possible, specimens will be collected, processed, and stored in such a manner as to be compatible with both immediate and future testing requirements. Additional aliquots will be sent to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) repository.

(i) Venous/capillary blood draws: Venous blood will be drawn for processing into serum, plasma, erythrocytes, buffy coats, and messenger RNA (mRNA). Plasma, erythrocytes, and buffy coat cells or mononuclear cells will be removed separately and aliquoted into tubes for analyzing enterovirus and rotavirus, additional infectious agents, vitamin D, alpha-tocopherol, gamma-tocopherol, carotenoids, ascorbic acid, and red blood cell membrane fatty acid. If venous blood is not available, capillary blood will be drawn.

(ii) The mRNA samples will be used to identify novel disease markers and environmental triggers as well as potential gene expression markers of inflammation, infection, and immunity.

(iii) Stool samples: At least 5 g of the child's stool each month (up until 48 months of age and biannually thereafter) will be collected in plastic stool containers. In the USA, these samples will be sent immediately to the NIDDK repository. In Europe, they will initially be sent to the local centers and then sent in bulk shipments monthly to the NIDDK repository.

(iv) Toenail clippings: These will be collected at the age of 2 yr to measure selenium.

(v) Drinking water: Tap water samples will be tested in all households at 9 months and every two years beginning at 3 years of age.

Maternal nutrition

The maternal diet will be assessed with a short food frequency questionnaire, concentrating on the intakes of fish and fish products, milk and milk products, and cereal and cereal products during the eighth (Finland and Germany) or ninth (USA and Sweden) month of pregnancy (53). The use of dietary supplements will be gauged, as well as the source of drinking water.

Dietary evaluation in children

In addition to food consumption, the diet will be assessed by mailed questionnaire to be completed prior to the first clinic visit. A structured interview will be conducted at each clinic visit, and records kept by the mother. The duration of total and exclusive breast-feeding, age at introduction of various foods during the first 2 yr of life, type of infant formulas used, source of drinking water (local waterworks, bottled water, and private wells), elimination diets, and use of dietary supplements will be recorded.

Primary caretakers (usually mothers) will be trained during the 3-month clinic visit to keep 3-day food diaries of the child's dietary intake at 3 month intervals during the first year of life and biannually thereafter. A 24-h recall of the child's diet will be obtained at the first (3-month) visit. The collection of this 24-h recall will have two purposes: (i) to assist in training the primary caretakers in what types of food items they will need to record when they complete the 3-day diet records and (ii) the dietary data from the 24-h recall will be used to reflect the infant's diet at 3 months of age. The nutritional factors of interest in the TEDDY study are described in Table 2.

TEDDY book

At the 3-month clinic visit, primary caretakers (usually mothers) will be introduced to the TEDDY book. This is a notebook that is to be used by the primary caretaker to record events in their child's life that are of interest to the study. Primary caretakers are instructed to write down things such as when foods are introduced in their child's diet, use of food and vitamin supplements, medications, vaccinations,

Table 1. Follow-up schedule

Sampling frequency	Screening Birth	Screening <4	Follow-up 2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	27	12–48 month monthly Test	24–48 month every 3-month tests	24–48 month every 6-month tests	>48 month Every 6-month Tests	>48 month Annual Tests
	Inform parents of child's HLA risk		Mail initial enrollment and questionnaire packet																				
Blood*	X†	X†		X‡	X	X	X‡	X	X	X‡	X	X	X‡	X	X‡	X	X‡	X	X‡	X‡		X‡	
Stool				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	
Tap water																							
Toenail clippings														Collected every 2 years beginning at 36-month visit									
Weight and length/height measurements				X			X			X	X	X	X	X	X	X	X	X	X	X		X	
Diet questionnaires																							
Maternal pregnancy diet			X																				
3-d diet record				X			X			X	X	X	X		X		X			X	X	X	
Environmental exposure questionnaires																							
Maternal pregnancy/birth questionnaire			X																				
Parent questionnaire			X				X			X			X		X		X		X		Annually after 27 months		
Child questionnaire																							X§
Demographic/family history/other questionnaire										X													
TEDDY book extraction				X			X			X	X	X	X	X	X	X	X	X	X	X		X	

HLA, human leukocyte antigen.
*A blood sample will be obtained by the 24-month visit from mothers who have type 1 or 2 diabetes or gestational diabetes as well as from a mother whose child is shown to be autoantibody positive at 3 or 6 months of age. An optional venous blood draw of the mother is obtained at 12–14 wk of pregnancy and at the birth of the baby.
†If cord blood is not available at birth for HLA typing, then capillary blood should be drawn.
‡If venous blood is not available at every 3-month office visit, then capillary blood should be taken.
§Beginning when the baby reaches 10 yr of age.

The TEDDY Study Group

Table 2. Nutritional factors of interest in the TEDDY study

Foods	Nutrients	Other nutritional factors
Cow's milk	Caloric intake	Nitrates, nitrites and *N*-nitroso compounds
Cereals, wheat (gluten)	Proteins	Patulin
Soy	Vitamins C, D and E	Bafilomycin
Meat	Nicotinamide	Increased weight and/or height gain (fetal period, infancy, childhood)
Coffee and tea	n-3 fatty acids	
Breast milk	Zinc	
Cod liver oil	Carotenoids and selenium	

TEDDY, the Environmental Determinants of Diabetes in the Young.

length and weight history of the child, illnesses and symptoms of the child, doctor's visits and hospitalizations, and life events of the child. The primary caretakers will be asked to bring in the TEDDY book to each clinic visit. At each visit, study personnel will go over the book with the primary caretaker and extract pertinent information using standardized study forms. The TEDDY book the primary caretaker first receives will be used up until the age of 2 yr. After that, a more age-appropriate book will be distributed.

Infectious/immunization questionnaires

At each clinic visit, information on infectious illnesses and immunizations since birth or the last visit will be recorded.

Table 3. TEDDY expected accrual

	Screening/year		Eligible/year	
	General population	FDR	General population	FDR
Center				
Colorado	13 369	165	661	38
Finland	11 288	133	627	46
Georgia/Florida	13 604	148	465	24
Germany	5717	319	220	61
Sweden	8972	204	665	36
Washington State	18 249	150	680	38
Total	71 198	1119	3318	243

	Over 5 yr	
	General population	FDR
Screened	355 992	5596
Follow-up eligible	16 588	1216
Enroll	7013	788
Cases – autoantibodies by age 6	281 (4%)	105 (13.3%)
Cases – T1DM by age 15	281 (4%)	105 (13.3%)

FDR, first-degree relative; T1DM, type 1 diabetes mellitus; TEDDY, The Environmental Determinants of Diabetes in the Young.

Psychosocial questionnaires and interviews

Assessing the psychological impact of study participation. A questionnaire will be mailed prior to the 3-month clinical visit and will be followed by self-completed questionnaires at the 6-, 15-, and 27-month study visits and annually thereafter. Should a dropout occur, a structured telephone interview will be conducted to assess the participant's experiences in the TEDDY study and reasons for dropout. Data will be obtained from the child's primary caretaker and spouse or partner. Once the child reaches 10 yr of age, the psychological impact of study participation on the child will be added to the protocol as a part of the annual assessment.

Evaluating parental distress (anxiety and depression) in response to notification of infant's at-risk status. The 20-item state portion of the State-Trait Anxiety Inventory (STAI) (54) is a reliable and well-tested instrument for assessing situation-specific anxiety in the USA and internationally. A six-item short form of this instrument as a self-completed questionnaire filled out prior to the initial 3-month clinic visit as well as at the 6-, 15-, and 27-month visits is used. In a sample of over 400 mothers whose infants were genetically at risk for diabetes, the six-item short form correlated highly with the STAI full scale (r = .95) and showed excellent internal consistency (α = .92) (55).

In addition, at any time, a child shows evidence of persistent autoimmunity (positive autoantibodies on two consecutive occasions), parental reactions to the news of the child's increased diabetes risk will be assessed using the six-item short form STAI at the child's next clinic visit.

At the 6-month clinic visit, parental depression will be assessed by the Edinburgh Postnatal Depression Scale administered as part of the self-completed questionnaire (56). In a recent study of 192 mothers with at-risk infants, Edinburgh Postnatal Depression Scale scores were reliable (α = .89) and predictive of the mother's understanding of risk (higher depression scores were associated with underestimating risk), anxiety (higher scores were associated with higher anxiety), and study dropout (higher scores were

associated with early study dropout) (57). A brief, six-item Depression Scale from Bradley's Well-Being Questionnaire will be included in the self-administered parent questionnaire completed at the 15- and 27-month study visits. After 27 months, measures of parental psychological stress will be collected annually.

At 39 months, questions to the parental/primary caretaker's annual assessment will be added to address the parent's or primary caretaker's perceptions of the child's function and well-being (e.g., does the care-taker overprotect, stigmatize, or treat the child differently because the child is at risk for diabetes).

Child reactions to study participation and at-risk status. At the age of 10 yr, children will be evaluated annually for their reactions to their increased risk status, general psychological function, and reactions to study participation. Reactions to their increased risk status will be assessed using strategies previously employed with children who were islet cell antibodies (ICA) positive in the Diabetes Prevention Trial (DPT-1) and other studies (58, 59). General functioning will be assessed by Harter's Self-Perception Profile for Children or Adolescents (60).

Behavior changes families may make in an effort to prevent the disease in the child. Data suggest that individuals who believe they are at risk for diabetes report behavior changes in an effort to prevent the disease (61, 62). Behavior changes initiated by parents in an effort to prevent diabetes in the child will be assessed as part of the self-completed question-naire assessment at the 6-, 15-, and 27-month study visits and annually thereafter. A TEDDY Participant Survey will be administered at the completion of TEDDY or at the time the parent leaves the study to also assess possible behavior changes.

Family satisfaction with participation in the study protocol. Parental satisfaction with study participa-tion will be assessed on the self-completed question-naire administered at 6, 15, and 27 months and annually thereafter. At study end, parents will be given a detailed participant survey evaluating all components of the study. Dropouts will be given this survey, by telephone if necessary, at the time they leave the study. Child satisfaction with study partici-pation will be assessed on an annual basis on all participants over 10 yr.

Psychosocial stress as a potential trigger for T1DM. Psychological stress will initially be prospec-tively measured in two ways: (i) negative life events documented in the TEDDY study book by the parent and updated at each study visit and (ii) paternal or primary caretaker anxiety and depression measured by self-completed questionnaire. Once the child reaches 10 yr of age, measures of stressful life events and child functioning will be obtained from the child.

Parental anxiety and depression. Parents or primary caretakers who are anxious and depressed create a stressful environment for the child. As stated previously, parental anxiety will be measured using the six-item short from of the STAI. Post-partum depression will be evaluated at 6 months using the Edinburgh Postnatal Depression Scale and general depression at 15 and 27 months using the six-item depression scale of the Well-Being Questionnaire. After 27 months, parental or primary caretaker psychosocial functioning will be assessed annually.

Identifying family characteristics that discriminate study completers from dropouts. Demographic and psychosocial measures will be gathered by question-naires.

Study end-points

Islet autoantibodies

The first primary end-point is the appearance of per-sistent, confirmed anti-islet autoantibodies (GAD65, IA-2, or IAA). There are two TEDDY Central Auto-antibody Laboratories, one in the USA and one in Europe. All samples identified as positive in one central laboratory will be sent to the other laboratory for confirmation.

Diabetes

The second primary outcome is the development of diabetes defined using American Diabetes Association criteria (63).

Data management and statistical analyses

Two different types of analysis, depending on the nature of the factor being studied, will be employed: For those factors whose values are known on the en-tire cohort (e.g., family history, haplotype, and breast-feeding.), we will perform log rank tests and Cox's proportional hazards regressions. For these analyses, the dependent variable will be the age at which the event being studied (development of autoimmunity or diagnosis of T1DM) occurred. Those not achieving the event when the analyses are being performed and those lost to follow-up without achieving the event will be considered censored as of the date last known to be event free. The following are examples of factors to be studied in this manner: amounts of certain nutrients consumed, duration of breast-feeding, maternal anxiety and depression as measured by the STAI and the Edinburgh Postnatal Depression Scale.

Proportional hazards regression will be used in both a univariate and multivariate manner and reported both ways. For each factor studied, estimated hazard ratios and their 95% confidence intervals will be com-puted. When a set of factors that predict conversion to T1DM or autoimmunity is determined as described

above, we will compute estimated 'survival' curves for subjects having specific factor profiles.

The following is a non-exhaustive listing of planned statistical analyses for the prospective part of TEDDY:

(i) Exposure to cereals or gluten in the diet (vs. those receiving only breast milk for the first 3 months) will be modeled as a time-dependent covariate and tested for significance using a proportional hazards regression.

(ii) Levels of antioxidants, such as carotenoids, ascorbic acid, and selenium, consumption will be analyzed with respect to the development of T1DM and autoimmunity.

(iii) Drinking water will be analyzed according to source and concentrations of zinc and nitrate and as low or high pH. Groups will be compared using the log rank test.

(iv) Cox's regression will be used to study the association of the level of psychosocial stress with the development of T1DM and autoimmunity.

For those factors whose determination is costly (e.g., assays of collected samples), we will employ a nested case–control design. At the time at which a cohort subject converts to autoimmunity or T1DM (referred to as a case), we will randomly select subjects who did not convert to autoimmunity or T1DM (controls). The sampling for the selection of matched controls is based on incidence density sampling that allows the comparison of cases with a subset of the cohort at risk of being cases at the time when each case occurs, or equivalently matches cases and controls for the duration of follow-up. Because controls selected in this way may become cases over time, we will employ oversampling of controls and may select different controls at different points in time.

We will then compare these cases with controls as a matched case–control study using conditional logistic regression. The number of controls will be determined to have at least 80% power, taking into consideration the number of cases available for the analysis. Thus, these expensive determinations will be made only on the cases and their chosen matched controls. Matching will be based on HLA type, study center, duration of follow-up, and completeness of data including serial biological samples. Every effort will be made to use the same controls for multiple case–control studies. This will allow inclusion of all key exposures simultaneously in the analytical model and exploration of confounding, effect modification, and interactions between exposures. The standard set of controls will include only those with complete data/samples for all components of the protocol. These analyses will also be performed in both a univariate and a multivariate fashion. Odds ratios for each factor

will be computed, as will their 95% confidence intervals. Receiving operator characteristic curves for sensitivity vs. $1 -$ specificity based on combinations of these factors will be computed. Here, sensitivity refers to the ability of the factors to predict conversion to the study end-point among those who do convert and specificity refers to ability to predict conversion-free survival.

Similar analyses will be performed for the development of autoimmunity and T1DM. Because the cases for T1DM will be a subset of the cases for autoimmunity, we will attempt to use the same controls.

The following analyses will be performed in the nested case–control portion of the study:

(i) The association between the number of enterovirus infections a child has and the development of T1DM and islet autoimmunity will be studied using Cox's regression. Using 0 as the reference, dummy variables will be created to represent 1, 2, etc. infections. The hazard ratios of these values relative to 0 will be estimated and p values of the estimates computed. The same type of analyses will be performed for the number of rotavirus infections.

(ii) Low levels of omega-3 fatty acids, eicosapentaenoic acids, and docosahexaenoic acids in children's erythrocyte membranes have been associated with increased risk of islet autoimmunity. The odds ratio for each of these exposures will be estimated.

(iii) Low levels of alpha-tocopherol have been associated with increased risk of islet autoimmunity. The odds ratio for each of this exposure will be estimated.

Plan and timeline of proposed analyses

In general, the study is designed to have 80% power or greater for detecting hazard ratios of 2 or greater for exposures 10% or greater, based on the expectation of being able to enroll 7013 subjects from the general population and 788 relatives in 5 yr, with 15 yr of post-accrual follow-up (Table 3). The actual study experience may be different and it is prudent to provisionally plan for interim analyses. In doing so, we consider the following caveats: (i) laboratory determinations made for interim analysis of stored samples need to be identical to the laboratory methods of the same determinations to be made at the end of the study if the data are to be aggregated and (ii) some longitudinal testing of stored samples is prudent to ensure sample integrity and quality.

Protocol monitoring

Protocol compliance in terms of screening, recruitment, and collection of protocol defined biological samples, questionnaires, and diaries will be monitored monthly.

Accrual, the demographic distribution of the subjects on study, HLA distributions, and other baseline variables will be monitored. Accrual rates will be contrasted with expected or planned rates. Monthly reports will also be prepared from the data accumulating on laboratory monitoring quality assurance programs as specified by the Laboratory Monitoring Committee.

Exposure monitoring

Because most exposures are measured from the analysis of biological samples, little will be available in the interim to assess exposure rates. Yet, we believe that it is prudent to ensure that sample collection procedures are adequate. To this end, we will target samples in which we may have more than enough volume. For example, current sample collection procedures suggest that volume will not be a problem for stool specimens and we may periodically sample the cohort to conduct interim analyses of viral exposures. In that we project collecting in excess of 26 000 stools samples in the first year, we would plan to sample the 1-yr cohort to conduct these preliminary analyses. We cannot expect to have surplus blood volumes to conduct interim analyses because all blood volume study requirements were based on the minimal amounts needed for the study analyses.

Where exposure rates can be estimated from diaries, questionnaires, psychological assessments (e.g., anxiety, depression, behavior changes, and stress), and food frequency instruments will be tabulated cumulatively and as a function of subjects' age. These tabulations will also be made monthly. Risk factors with unanticipated exposure rates will be discussed and adjustments to power calculations made as appropriate.

Retention of study participants is a high priority, and we will provide continuous assessment of study dropouts. These analyses will include baseline demographics and environmental exposures for comparison with subjects continuing the study cohort.

Outcome analysis

After 5 and 10 yr of accrual, interim analyses of the prospective portion of the study will be performed and reported to the participating investigators. These analyses will address the relationships of the triggers being studied to the development of T1DM using the same Cox's proportional hazards regressions planned for final analyses. A 4% conversion rate at 15 yr for those unexposed implies conversion rates of 1.4 and 2.7% at 5 and 10 yr, respectively, assuming exponential conversion.

As the study progresses, we will have a more accurate picture of accrual and follow-up rates and estimates of some exposure rates based on the diaries and ques-

tionnaires. Also, we will be able to observe cases of autoimmunity and T1DM and base our planned analyses on these rather than on projections. For some environmental triggers, assessed from the entire prospective cohort, we will be able to schedule interim analyses. Our first priority will be to confirm, or not, previous reports of risk factors that have been reported in the literature. For example, the study will have an early picture of diet. Literature reports of risk factors in the first 4–6 yr of life with hazard ratios of 3 or greater can be tested in interim analyses with reasonable power. Examples of these might be as follows:

- Food supplementation with gluten-containing foods before the age of 3 months (reported hazard ratio 4.0, 95% CI 1.4–11.5).
- Children initially exposed to cereals between the ages of 0 and 3 months (reported hazard ratio 4.3, 95% CI 2.0–13.8).
- Vitamin D supplementation (2000 IU daily) compared with those who regularly received less (relative risk 0.22, 95% CI 0.05–0.89).
- Coxsackievirus B5 in maternal sera collected in the first trimester of pregnancy (OR 10, 95% CI 1.4–43.4).

For other hypotheses, the duration of follow-up will be the rate-limiting factor, as many of the studies in the literature report T1DM risk in children up to 15 yr of age. TEDDY investigators will propose additional hypotheses to be tested, and prior to conducting interim analyses, each will be evaluated with respect to the detectable hazard ratio at a minimum of 80% power. Although it is recognized that this leads to increased chances of finding associations as a result of increasing study-wide type 1 error, as a hypothesis-forming epidemiological study, we will balance this against the calculated hazard ratios and exercise caution in interpretation.

Sample size and power determination

Subjects from the general population and the relatives are expected to have about 4 and 13.3% conversion to signs of autoimmunity (ICA) at 6 yr, respectively. The study has 80% power for a log rank test at a two-sided 0.01 significance level for the general population subjects, the relatives, and the pooled sample accrued over 4 yr with 15 yr of post-accrual follow-up (64, 65).

Informed consent

A two-step consent process will be used. The first consent will be specific for screening newborns for high-risk genotypes at the HLA and other loci in the general population or in families having an FDR affected with T1DM (phase 1). The second consent will cover the procedures that will be used in the

follow-up of the risk for T1DM (phase 2). Children will also be assented when they reach the age of 7.

Should a child develop persistent positive antibody test results, parents will be informed of other prevention trials that are available for which they might qualify. Should testing reveal the presence of T1DM, participants' parents/primary caretakers will be informed immediately and guided to proper treatment.

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References

1. GREEN A, PATTERSON CC. Trends in the incidence of childhood-onset diabetes in Europe 1989-1998. Diabetologia 2001: 44 (Suppl. 3): B3–B8.
2. ONKAMO P, VAANANEN S, KARVONEN M, TUOMILEHTO J. Worldwide increase in incidence of type I diabetes – the analysis of the data on published incidence trends. Diabetologia 1999: 42: 1395–1403.
3. DAHLQUIST G, BLOM L, TUVEMO T, NYSTRÖM L, SANDSTRÖM A, WALL S. The Swedish Childhood Diabetes Study – results from a nine year case register and one year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders. Diabetologia 1989: 32: 2–6.
4. RISCH N. Genetics of IDDM: evidence for complex inheritance with HLA. Genet Epidemiol 1989: 6: 143–148.
5. DAVIES JL, KAWAGUCHI Y, BENNETT ST et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature 1994: 371: 130–136.
6. COX NJ, WAPELHORST B, MORRISON VA et al. Seven regions of the genome show evidence of linkage to type 1 diabetes in a consensus analysis of 767 multiplex families. Am J Hum Genet 2001: 69: 820–830.
7. MENSER MA, FORREST JM, BRANSBY RD. Rubella infection and diabetes mellitus. Lancet 1978: 1: 57–60.
8. GINSBERG-FELLNER F, WITT ME, FEDUN B et al. Diabetes mellitus and autoimmunity in patients with congenital rubella syndrome. Rev Infect Dis 1985: 7: 170–176.
9. DAHLQUIST G, IVARSSON S, LINDBERG B, FORSGREN M. Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. Diabetes 1995: 44: 408–413.
10. HYÖTY H, HILTUNEN M, KNIP M et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study. Diabetes 1995: 44: 652–657.
11. JONES M, SWERDLOW A, GILL L, GOLDACRE M. Pre-natal and early life risk factors for childhood onset diabetes mellitus: a record linkage study. Int J Epidemiol 1998: 27: 444–449.
12. DAHLQUIST GG, PATTERSON C, SOLTESZ G. Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group. Diabetes Care 1999: 22: 1698–1702.
13. DAHLQUIST G, BENNICH SS, KALLEN B. Intrauterine growth pattern and risk of childhood onset insulin dependent (type I) diabetes: population based case-control study. BMJ 1996: 313: 1174–1177.
14. STENE LC, MAGNUS P, LIE RT, SOVIK O, JONER G. Birth weight and childhood onset type 1 diabetes: population based cohort study. BMJ 2001: 322: 889–892.
15. KOCKUM I, WASSMUTH R, HOLMBERG E, MICHELSEN B, LERNMARK A. Inheritance of MHC class II genes in IDDM studied in population-based affected and control families. Diabetologia 1994: 37: 1105–1112.
16. DAHLQUIST G, KÄLLEN B. Maternal-child blood group incompatibility and other perinatal events increased the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1992: 35: 671–675.
17. ZIEGLER AG, HUMMEL M, SCHENKER M, BONIFACIO E. Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: the 2-year analysis of the German BABY-DIAB Study. Diabetes 1999: 48: 460–468.
18. VEIJOLA R, REIJONEN H, VAHASALO P et al. HLA-DQB1-defined genetic susceptibility, beta cell autoimmunity, and metabolic characteristics in familial and nonfamilial insulin-dependent diabetes mellitus. J Clin Invest 1996: 98: 2489–2495.
19. SANJEEVI CB, LYBRAND TP, DEWEESE C et al. Polymorphic amino acid variations in HLA-DQ are associated with systematic physical property changes and occurrence of IDDM. Diabetes 1995: 44: 125–131.
20. BAISCH JM, WEEKS T, GILES R, HOOVER M, STASTNY P, CAPRA JD. Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. N Engl J Med 1990: 322: 1836–1882.
21. GAMBLE DR, KINSLEY ML, FITZGERALD MG, BOLTON R, TAYLOR KW. Viral antibodies in diabetes mellitus. BMJ 1969: 3: 627–630.
22. YOON J-W, AUSTIN M, ONODERA T, NOTKINS AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med 1975: 300: 1174–1179.
23. ROIVAINEN M, RASILAINEN S, YLIPAASTO P et al. Mechanisms of coxsackievirus-induced damage to human pancreatic beta-cells. J Clin Endocrinol Metab 2000: 85: 432–440.
24. WAGENKNECHT LE, ROSEMAN JM, HERMAN WH. Increased incidence of insulin-dependent diabetes mellitus following an epidemic of coxsackie virus B5. Am J Epidemiol 1991: 132: 1024–1031.
25. GRAVES PM, NORRIS JM, PALLANSCH MA, GERLING IC, REWERS M. The role of enteroviral infections in the development of IDDM: limitations of current approaches. Diabetes 1997: 46: 161–168.
26. HYÖTY H, TAYLOR KW. The role of viruses in human diabetes. Diabetologia 2002: 45: 1353–1361.
27. HONEYMAN MC, COULSON BS, STONE NL et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. Diabetes 2000: 49: 1319–1324.
28. BANATVALA JE, SCHERNTHANER G, SCHOBER E et al. Coxsackie B, mumps, rubella and cytomegalovirus specific IgM response in patients with juvenile-onset diabetes mellitus in Britain, Austria and Australia. Lancet 1985: 2: 1409–1412.
29. PAK C, MCARTHUR RG, EUN H-M, YOON J-W. Association of cytomegalovirus infection with autoimmune type I diabetes. Lancet 1988: 2: 1–4.
30. IVARSSON S-A, LINDBERG B, NILSSON KO, AHLFORS K, SVANBERG L. The prevalence of type 1 diabetes mellitus at follow-up of Swedish infants congenitally infected with cytomegalovirus. Diabet Med 1993: 10: 521–523.

31. LAN MS, MASON A, COUTANT R et al. HERV-K10s and immune-mediated (type 1) diabetes. Cell 1998: 95: 14–16; discussion 16

32. CONRAD B, WEIDMANN E, TUCCO G et al. Evidence for superantigen involvement in insulin-dependent diabetes mellitus aetiology. Nature 1994: 371: 351–355.

33. VIRTANEN SM, RASANEN L, ARO A et al. Feeding in infancy and the risk of type 1 diabetes mellitus in Finnish children. The 'Childhood Diabetes in Finland' Study Group. Diabet Med 1992: 9: 815–819.

34. BORCH-JOHNSEN K, MANDRUP-POULSEN T, ZACHAU-CHRISTIANSEN BZ. Relation between breast-feeding and incidence rates of insulin-dependent diabetes mellitus. Lancet 1984: 2: 1083–1086.

35. ÅKERBLOM HK, SAVILAHTI E, SAUKKONEN TT, PAGANUS A, VIRTANEN SM, TERAMO K. The case for elimination of cow's milk in early infancy in the prevention of type 1 diabetes. Diabetes Metab Rev 1994: 9: 456–462.

36. KIMPIMAKI T, ERKKOLA M, KORHONEN S et al. Short-term exclusive breastfeeding predisposes young children with increased genetic risk of type I diabetes to progressive beta-cell autoimmunity. Diabetologia 2001: 44: 63–69.

37. EURODIAB. Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. Diabetologia 1999: 42: 51–54.

38. STENE LC, ULRIKSEN J, MAGNUS P, JONER G. Use of cod liver oil during pregnancy associated with lower risk of type I diabetes in the offspring. Diabetologia 2000: 43: 1093–1098.

39. KNEKT P, REUNANEN A, MARNIEMI J, LEINO A, AROMAA A. Low vitamin E status is a potential risk factor for insulin-dependent diabetes mellitus. J Intern Med 1999: 245: 99–102.

40. DAHLQUIST GG, BLOM LG, PERSSON L-Å, SANDSTRÖM AI, WALL SGI. Dietary factors and the risk of developing insulin dependent diabetes in childhood. BMJ 1990: 300: 1302–1306.

41. MYERS MA, MACKAY IR, ROWLEY MJ, ZIMMET PZ. Dietary microbial toxins and type 1 diabetes – a new meaning for seed and soil. Diabetologia 2001: 44: 1199–2000.

42. DANOWSKI TS. Emotional stress as a cause of diabetes mellitus. Diabetes 1963: 12: 183–184.

43. SLAWSON PR, FLYNN WR, KOLLER EJ. Psychological factors associated with the onset of diabetes mellitus. JAMA 1963: 185: 313–316.

44. STEIN SP, CHARLES ES. Emotional factors in juvenile diabetes mellitus: a study of early life experience of adolescent diabetics. Am J Psychiatry 1971: 128: 700–704.

45. KISCH ES. 1985: Stressful events and the onset of diabetes mellitus. Isr J Med Sci 1985: 21: 356–358.

46. ROBINSON N, FULLER JH. The role of life events and difficulties in the onset of diabetes mellitus. J Psychosom Res 1985: 29: 583–591.

47. ROBINSON N, LLOYD CE, FULLER JH, YATEMAN NA. Psychosocial factors and the onset of type 1 diabetes. Diabet Med 1989: 6: 53–58.

48. VIALETTES B, OZANON JP, KAPLANSKY S et al. 1989 Stress antecedents and immune status in recently diagnosed type 1 (insulindependent) diabetes mellitus. Diabete Metab 1989: 15: 45–50.

49. DAHLQUIST G, BLOM L, LONNBERG G. The Swedish Childhood Diabetes Study - A multivariate analysis of risk determinants for diabetes in different age groups. Diabetologia 1991: 34: 757–762.

50. HAGGLOF B, BLOM L, DAHLQUIST G, LONNBERG G, SAHLIN B. The Swedish childhood diabetes study: implications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood. Diabetologia 1991: 34: 579–583.

51. THERNLUND GM, DAHLQUIST G, HANSSON K et al. Psychological stress and the onset of IDDM in children. Diabetes Care 1995: 18: 1323–1329.

52. JOHNSON SB. Screening programs to identify children at risk for diabetes mellitus: psychological impact on children and parents. J Pediatr Endocrinol Metab 2001: 14: 653–660.

53. ERKKOLA M, KARPPINEN M, JAVANAINEN J, RÄSÄNEN L, KNIP M, VIRTANEN SM. Validity and reproducibility of a food frequency questionnaire during pregnancy. Am J Epidemiol 2001: 154: 466–476.

54. SPIELBERGER CD, GORSUCH RI, LUSHENE R. Test Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970

55. JOHNSON SB, RILEY WJ, HANSEN CA, NURICK MA. Psychological impact of islet cell-antibody screening for IDDM in children, adults and their family members. Diabetes Care 1990: 13: 93–97.

56. ROTH R, SCHNEIDER P, SCHOBER E, SCHWINGSHANDL J, BORKENSTEIN M. Life-Events, Angst, Coping und Familienstruktur zum Zeitpunkt eines Diabetes-Risiko-Screenings von Geschwistern diabetischer Kinder – Erste Ergebnisse. In: Janig H, ed. Psychologische Forschung in Österreich. Carinthia: J.H. Klagenfurt, 1994: 187–191.

57. JOHNSON SB, TERCYACK KP. Psychological impact of islet cell antibody screening for IDDM on children, adults, and their family members. Diabetes Care 1995: 18: 1370–1372.

58. JOHNSON SB, CARMICHAEL S. At-risk for diabetes: coping with the news. J Clin Psychol Med Settings 2000: 7: 69–78.

59. HUMMEL M, ZIEGLER AG, ROTH R. Psychological impact of childhood islet autoantibody testing in families participating in the BABYDIAB study. Diabet Med 2004: 21: 324–328.

60. HARTER S. Manual for the Self-Perception profile for Children. Denver, CO: University of Denver, 1985.

61. HENDRIECKX C, DE SMET F, KRISTOFFERSEN I, BRADLEY C. Risk assessment for developing type 1 diabetes: intentions of behavioural changes prior to risk notification. Diabetes Metab Res Rev 2002: 18: 36–42.

62. BAUGHCUM A, JOHNSON SB, SHE J et al. High rates of maternal behavior change resulting from newborn genetic screening for risk of type 1 diabetes. Diabetes 2003: 52 (Suppl. 1): A410.

63. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997: 20: 1183–1197.

64. LAKATOS E. Sample sizes based on the log rank statistic in complex clinical trials. Biometrics 1988: 44: 229–241.

65. CANTOR AB. SAS Survival Analysis Techniques for Medical Research, 2nd edn. Cary, NC: SAS Institute Inc, 2003.

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