Participation in prospective studies of children with high risk for type 1 diabetes. Psychological effects, experience, and study compliance

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Psychological effects, experience, and study compliance

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CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

Participation in prospective studies of children with high risk for type 1 diabetes

Psychological effects, experience and study compliance

New-born screening for genetic risk for type 1 diabetes, longitudinal follow up, and screening for islet autoantibodies among young children within research is getting more and more common. The decision to participate with your child is not always an easy decision. The focus of this thesis has been to examine the psychological effects and families' reactions of participation in longitudinal studies with their children at high risk for type 1 diabetes and to investigate factors associated with parental anxiety, study satisfaction and study visit compliance. We also describe the development of a shorter questionnaire for children to measure their own anxiety when they participate in type 1 diabetes studies.

JESSICA MELIN is a nurse and research coordinator in The Environmental Determinants of Diabetes in the Young (TEDDY), an observational international multicentre study, following children with high genetic risk for type 1 diabetes from birth, during their childhood until age 15. Her main research interest has been to examine the families' reactions and experiences of study participation.

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Participation in prospective studies of children with high risk for type 1 diabetes: Psychological effects, experience, and study compliance

Participation in prospective studies of children with high risk for type 1 diabetes

Psychological effects, experience, and study compliance

Jessica Melin

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine Lund University, Sweden.

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Title and subtitle: Participation in prospective studies of children with high risk for type 1 diabetes – Psychological effects, experience, and study compliance

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Methods: We used parental questionnaires from the five-year visit in the Diabetes Prediction in Skåne study (DiPiS) to investigate parental anxiety when participating with their high-risk child. Anxiety was measured using the 6-item short State Anxiety Inventory (SAI) form, and logistic regression was used to examine factors associated with parental anxiety. The TEDDY cohort was used to develop a reliable and valid short form of the State Anxiety Subscale (SAI-CH) by using item-total correlation. The TEDDY cohort was also used to investigate parental study satisfaction and study visit compliance. Paper III identified factors associated with study satisfaction at two timepoints using multiple linear regression. In the last paper, we used variables collected in the first year of the study to identify, through multiple linear regression, those factors associated with study visit compliance in the subsequent three years.

Results: In the DiPiS study, we found that most of the parents were not anxious when thinking about their child's risk of type 1 diabetes. Anxiety levels were higher in mothers of children with islet autoantibodies and parents with a family history of type 1 diabetes, those with accurate risk perception, and those who experienced higher frequencies of worry. In the second paper, we described the development of a reliable and valid short 6-item form, which was subsequently chosen for continued use in the TEDDY study. Paper III revealed high overall parental study satisfaction in the TEDDY study, with mothers reporting higher mean satisfaction scores than fathers. Country of residence, staff consistency, the accuracy of parents' perception of their child's type 1 diabetes risk, and beliefs that something can be done to prevent diabetes in the child were all associated with higher study satisfaction for both mothers and fathers. In Paper IV, we identified modifiable and non-modifiable variables collected in the first year of TEDDY that were associated with study visit compliance in the three subsequent years. Mothers who completed fewer visits were likelier to be smokers and experience anxiety about their child's type 1 diabetes risk. On the other hand, mothers who completed more visits were older, participating with their first-born child, had actively participating fathers, and were more satisfied with their study participation.

Conclusion: Understanding the family's reactions and experiences during participation in longitudinal screening studies can enhance our understanding of the study's impact on the family. Attending to the collected information throughout the study can help provide families with the appropriate support, and information, and ultimately improve study satisfaction and visit compliance.

Keywords: Children, Type 1 diabetes, Study satisfaction, Anxiety, Study visit compliance

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To all the brave children in our research studies

Table of Contents

Abstract

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study can help provide families with the appropriate support, and information, and ultimately improve study satisfaction and visit compliance.

Thesis at a glance

Paper	Aim	Methods	Results	Conclusion
I	Investigate parental anxiety after 5 years of participation in the DiPiS study and factors associated with parental anxiety.	The short form of the SAI measured parents' anxiety, and logistic regression was used to examine factors associated with parental anxiety.	The majority of the parents did not have an increased anxiety level. Factors associated with higher anxiety were islet auotantibody positive child, having a family member with type 1 diabetes, low education level, accurate risk perception, and frequency of worry.	Knowledge of the impact on families of screening and study participation can be useful when creating supporting stategies to reduce anxiety.
II	To develop a reliable and valid short form of the State Anxiety Subscale of the State-Trait Anxiety Inventory for children (STAI-CH) in the TEDDY study.	Total-item correlation was used to identify the best six items out of the original 20, and coefficient alpha was used to assess the reliability. An additional number of questionnaires were collected to be used for validation.	Six items were identified, three anxiety absent and three anxiety present. Item-total correlation for the total sample was ≥0.71. Factors associated with anxiety were identified in the development sample, and the same result was found in the validation sample.	A shorter form measuring children's anxiety may increase the number of children completing the questionnaire and the knowledge of anxiety among children participating in type 1 diabetes studies.
III	Identify factors associated with parental study satisfaction in the TEDDY study. The role of staff consistency to study satisfaction was of particular interest.	Multiple linear regression was used to identify factors associated with study satisfaction at two time-points: at child-age 15 months and child-age 4 years. The regression was done stepwise.	High overall study satisfaction was found among the parents. Most factors associated with satisfaction were similar at both timepoints and for both parents. Country of residence, staff consistency, accuracy of parent's perception of the child's type 1 diabetes risk, and beliefs that something can be done to prevent diabetes in the child were all associated with higher study satisfaction.	Identifying and paying attention to modifiable variables associated with study satisfaction may increase parents' satisfaction with their participation.
IV	Identify variables collected in the TEDDY study's first year associated with study visit compliance in the subsequent three years of this longitudinal study.	Multiple linear regression was used to identify factors correlated with study visit compliance. The regression was done stepwise.	The mothers who completed fewer visits were those mothers who smoked, belonged to an ethnic minority group, and were anxious. Those who completed more visits were older mothers, mothers whose first child was participating, where fathers were active in the study, and mothers satisfied with their participation.	Modifiable factors - mothers' anxiety and satisfaction - associated with study visit compliance collected early in a study may serve as targes in efforts to improve study visit compliance.

Populärvetenskaplig sammanfattning

Typ 1 diabetes är en kronisk sjukdom, där det idag inte finns något botemedel eller ett sätt att förhindra att sjukdomen bryter ut. Idag anser man att det är en autoimmun sjukdom. Med det menas att kroppens eget immunförsvar angriper och förstör de celler i bukspottskörteln som tillverkar det livsnödvändiga hormonet insulin. Anledningen till att denna process startar i kroppen är okänt men när angreppet på kroppens celler startar bildas markörer i blodet, så kallade autoantikroppar. Dessa kan upptäckas med ett blodprov och idag vet man att individer med autoantikroppar har en betydligt högre risk att utveckla typ 1 diabetes. För barn med flera autoantikroppar, drabbas 70% av typ 1 diabetes inom 10 år.

I Sverige är typ 1 diabetes en av de vanligaste kroniska sjukdomarna bland barn, och varje år insjuknar ca 900 barn och ungdomar. Forskningsstudier har under flera år följt barn från födseln med förhöjd risk för typ 1 diabetes för att undersöka vilka riskfaktorer i barnets omgivning som triggar i gång den autoimmuna processen som leder till att autoantikropparna bildas och i vissa fall sjukdom bryter ut. Bland dessa screeningstudier finns den svenska Diabetes Prediction in Skåne (DiPiS) och den internationella The Environmental Determinants of Diabetes in the Young (TEDDY). Båda dessa studier screenade barn vid förlossningen för genetisk risk och andra riskfaktorer. De barn som ansågs ha en förhöjd risk för typ 1 diabetes bjöds in och följs sedan under barnets uppväxt tills de fyller 15 år. Protokollen för de båda studierna skiljer sig åt, med besök 1–4 gånger per år som inkluderar blodprovstagning, intervjuer och frågeformulär. Denna typ av longitudinella studier, som följer barn under flera år, är viktiga för att ha möjlighet att förstå och kartlägga omgivningsfaktorer som påverkar den autoimmuna processen. Det är viktigt att så många som möjligt av de familjer som deltar fullföljer sitt studiedeltagande - avhopp eller missade besök betyder förlust av forskningsdata och den går aldrig att ta igen. För familjerna, både föräldrar och barn, är det ett långt åtagande som tar mycket tid och kräver ett stort engagemang.

Är det då självklart för föräldrar att låta screena sitt nyfödda barn för en sjukdom som idag inte går att förebygga eller bota? Hur påverkas föräldrar och barn av att deltaga i screeningstudier? Tidigare forskning visar att deltagande i genetiska screeningstudier kan skapa ökad oro och ängslan. Föräldrar överbeskyddar sina barn och relationen mellan föräldrar och barn kan påverkas. Andra har visat på att kunskapen om att barnet har förhöjd risk och deltagandet i en forskningsstudie leder till att de känner sig trygga, får kunskap om sjukdomen och i flera fall kommer tidigare under vård när det behövs.

Denna avhandling består av fyra olika projekt där det övergripande målet har varit att undersöka hur familjer reagerar, upplever och påverkas av att deltaga i studier där barnet screenats vid födseln för ökad risk för typ 1 diabetes och följt dem under uppväxten, tills barnet fyller 15 år.

I det första projektet ville vi undersöka föräldrars oro och ängslan efter att de medverkat i DiPiS studien med sitt barn i fem år samt vilka faktorer som påverkar oron. Föräldrarnas oro för deras barns risk för att utveckla typ 1 diabetes mättes med en förkortad version av frågeformuläret State- Trait Anxiety Inventory scale (STAI). Den förkortade versionen av State Anxiety Inventory scale (SAI) består av sex frågor vilka räknades om så att scoren motsvarar det ursprungliga frågeformuläret innehållande 20 frågor. En score över 40 räknas som förhöjd oro. Vi fann att majoriteten av föräldrarna i DiPiS inte hade förhöjd oro men att mammor oroade sig mer än pappor. En ökad risk för oro fann vi bland föräldrar i familjer där någon redan har typ 1 diabetes, vars barn utvecklat en eller flera markörer (autoantikroppar) innan fem års ålder, bland föräldrar som ansåg att deras barn hade en högre risk för sjukdomen än andra barn och bland föräldrar med lägre utbildningsnivå.

Andra projektets syfte var att utveckla och validera ett liknade förkortat frågeformulär för barn, för att mäta deras oro för att utveckla typ 1 diabetes i TEDDY studien. Det ursprungliga frågeformuläret, State Anxiety Inventory scale for children (SAI-CH), innehåller 20 frågor och ansågs vara tidskrävande, svårt och det var vanligt att barn hoppade över vissa frågor. Barn, 10 år gamla från USA, Finland, Tyskland och Sverige svarade på de ursprungliga frågorna och totalt 842 frågeformulär samlades in. Genom analys valdes sex av frågorna som vars svar kunde motsvara de ursprungliga 20 ut. Den förkortade versionen, av State Anxiety Inventory scale for children (SAI-CH-6) utvärderades genom att jämföra den med ytterligare insamlade frågeformulär. Det förkortade frågeformuläret ansågs vara tillförlitligt och från februari 2017 används det i TEDDY studien för att årligen mäta barn och ungdomars oro när de tänker på sin risk för att utveckla diabetes. Förhoppningsvis kan detta även användas i framtida typ 1 diabetes studier för att utvärdera barns och ungdomars oro och ängslan.

I de två sista projekten användes information från TEDDY studien. Syftet i projekt tre var att undersöka hur nöjda föräldrarna var med sitt deltagande i TEDDY studien efter ett och fyra års deltagande samt vilka faktorer som hade betydelse för deras nöjdhet. I det fjärde projektet, undersökte vi vilka faktorer som påverkar om de deltagande familjerna fullföljer studien och genomför alla sina besök de först fyra åren med fokus på faktorer som går att påverka som till exempel föräldrars nöjdhet. Vi fann att majoriteten av föräldrarna är nöjda med sitt deltagande i TEDDY studien, mammor något mer nöjda än pappor och svenska föräldrar mer nöjda än föräldrar från de övriga länderna i TEDDY. Föräldrar som anser att deras barn har en högre risk för typ 1 diabetes och de som tror att de kan göra något för att förhindra att deras barn utvecklar sjukdomen var mer nöjda. De med högre utbildningsnivå och de med depression var mindre nöjda med sitt studie deltagande. Bland europeiska föräldrar var man mer nöjd om man träffade samma personal vid majoriteten av sina besök men detta var inget som påverkade föräldrar från USA. I de fjärde projektet, fann vi både påverkbara och icke påverkbara faktorer som inverkar på vilka

deltagare som fullföljer och genomför alla sina besök på forskningsmottagningen fram tills att barnet fyller fyra år. Mammor som genomför färre besök är rökande mammor, mammor som drabbats av depression efter förlossningen och de som är oroliga när de tänker på sitt barns risk att utveckla typ 1 diabetes. Mammor som genomförde fler besök är äldre mammor, de som deltar i studien med sitt första barn, där pappan är delaktig i studien och de som är nöjda med sitt studie deltagande.

Screeningstudier för olika kroniska sjukdomar däribland typ 1 diabetes blir allt vanligare. Kunskapen om hur föräldrar reagerar och påverkas kan användas för att i framtida studier skapa de bästa förutsättningarna för familjerna genom att ge personal som arbetar i forskningsstudier information om vilka familjer som behöver extra stöd och information samt vilka strategier som kan användas för att hjälpa familjer att fullfölja studien och öka deras nöjdhet med sitt deltagande.

Ytterligare studier behövs för att undersöka hur barn och ungdomar upplever sitt studiedeltagande. Hur ser de på sin risk att drabbas av typ 1 diabetes, är de oroliga och hur nöjda är de med sina föräldrars beslut att de skulle deltaga i en longitudinell forskningsstudie under sin uppväxt?

List of Papers

The thesis is based on the following papers, referred to by their Roman numerals I-IV.

Paper I

Parental anxiety after 5 years of participation in a longitudinal study of children at high risk of type 1 diabetes.

Jessica Melin, Marlena Maziarz, Carin Andrén Aronsson, Markus Lundgren, Helena Elding Larsson.

Pediatric Diabetes. 2020; 21: 878-889

Paper II

SAI-CH-6: Development of a short form of the State Anxiety Inventory for children at-risk for type 1 diabetes.

Kimberly A Driscoll, **Jessica Melin**, Kristian F Lynch Laura Smith, Suzanne Bennett Johnson.

Accepted for publication in Journal of Pediatric Psychology August 2023

Paper III

Is staff consistency important to parents' satisfaction in a longitudinal study of children at risk for type 1 diabetes: the TEDDY study.

Jessica Melin, Kristian F Lynch, Markus Lundgren, Carin Andrén Aronsson, Helena Elding Larsson, Suzanne Bennett Johnson, and TEDDY Study group.

BMC Endocrine Disorders. 2022; 22:19

Paper IV

Parent study satisfaction associated with subsequent study visit compliance in a longitudinal study of children at increased genetic risk for type 1 diabetes.

Jessica Melin, Kristian F Lynch, Markus Lundgren, Carin Andrén Aronsson, Helena Elding Larsson, Suzanne Bennett Johnson, and TEDDY Study group.

Submitted July 2023. Under review.

Author's contribution to the papers

Paper I

In the first paper, my responsibilities included developing the manuscript proposal and conducting the literature search and review. The questionnaires used in the paper had already been collected and entered into a local database. I retrieved and cleaned the data before proceeding with the data analysis. I conducted initial analyses, such as creating the descriptive tables and calculating the SAI scores. The analysis plan was discussed with Dr Marlena Maziarz, who performed the logistic and multinomial regression. I took charge of writing the manuscript draft, and throughout the process, all co-authors reviewed the draft and provided feedback and suggestions. After incorporating the feedback and gaining approval from all co-authors, I handled the manuscript's submission and acted as the corresponding author.

Paper II

In the second paper, my responsibilities included co-developing the manuscript proposal and conducting the literature search and review in collaboration with the first author, Dr Kimberly Driscoll. Additionally, I worked alongside Dr Åke Lernmark, to complete the Swedish ethical application requested for collecting questionnaires from Swedish children at 10 years of age. Once the application was approved, I participated in Sweden's data collection and data entry. Dr Kristian F Lynch, a statistician in the TEDDY study, conducted all statistical analyses. Through conference calls, the results were discussed and interpreted by all authors. While Dr Kimberly Driscoll served as the main writer and was responsible for the submission, I contributed to part of the background and method sections and assisted with other sections of the paper.

Paper III and Paper IV

In the third and fourth papers I was responsible for developing the manuscript proposals and conducting the literature search and review. The questionnaires and data in these papers had already been collected from various countries. As a member of the Swedish site, I have been actively involved in data collection in Sweden since 2007. The analysis plans formulated in collaboration with Dr Kristian F Lynch, a statistician in the TEDDY study, and Dr Suzanne B Johnson. I conducted all the statistical analyses for both papers, with guidance and assistance from Dr Kristian F Lynch and Dr Suzanne B Johnson, through conference calls and by visiting the data coordinator center in Tampa. I authored the drafts for both manuscripts and during the process, all other authors reviewed the drafts and provided feedback and suggestions. After receiving approval from all co-authors, I assumed responsibility for the manuscript submissions and acted as the corresponding author for both papers.

Abbreviations

DiPiS	Diabetes Prediction in Skåne
ENDIA	Environmental Determinants of Islet Autoimmunity study
FDR	First Degree Relative
HLA	Human Leukocyte antigen
GAD65A	islet autoantibodies to Glutamic Acid Decarboxylase
IA-2A	islet autoantibodies to Insulinoma-Associated protein
IAA	islet autoantibodies to Insulin
OGTT	Oral Glucose Tolerance Test
SAI	State Anxiety Inventory scale
STAI	State- Trait Anxiety Inventory scale
SAI-CH	State Anxiety Inventory scale for children
SAI-CH-6	State Anxiety Inventory scale for children short form
STAI-CH	State- Trait Anxiety Inventory scale for children
TEDDY	The Environmental Determinants of Diabetes in the Young
WHO	World Health Organization
ZnT8A	islet autoantibodies to Zinc Transporter 8

Background

Introduction

During my years as a research nurse in a longitudinal multinational study focused on children born with a genetic high risk for type 1 diabetes, I have had the opportunity to interact with many families, both during the screening process and during follow-ups. It is an incredibly meaningful experience to inform parents of a newborn baby about their child's increased risk for a disease that currently has no cure. Additionally, it has been a privilege to accompany them from their first visit, through their child's growth and development and share their experiences, emotions, and thoughts. Witnessing these children grow into adolescents and eventually graduate from their studies at the age of 15 years, brings me satisfaction and joy.

I have also been fortunate to serve as the Swedish coordinator for one of the studies included in this thesis, where my responsibilities involved developing and implementing new protocols in collaboration with colleagues from other countries. Additionally, I have been actively creating informative materials for children and parents and have worked on strategies to ensure participant retention, compliance, and engagement.

This experience has been truly inspiring, but it has also raised questions regarding the family's reactions and experience as research participants. As part of this thesis, I have sought answers to some of these questions.

Type 1 diabetes

Type 1 diabetes is a chronic autoimmune disease and one of the most common chronic diseases in children (1-3). The most common age for children to be diagnosed is between 5-7 years of age and during puberty. Type 1 diabetes is considered to be caused by an autoimmune process; wherein the body's immune system targets and attacks the insulin-producing beta-cells in the pancreas. Insulin, a vital hormone, facilitates the entry of glucose from the bloodstream into the body's cells. When the beta-cells in the body are not able to secrete sufficient insulin, blood glucose levels rise, leading to hyperglycemia, a key indicator of type 1 diabetes.

Hyperglycemia leads to symptoms such as excessive thirst, frequent urination, lack of energy, and weight loss (2) (Figure 1).

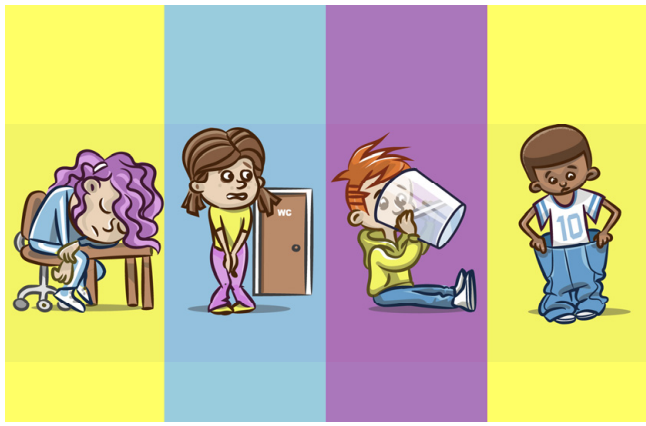

Figure 1. Sypmtomcard Type 1 Diabetes
This card is used in The Environmental Determinants of Diabetes in the Young (TEDDY) study to educate children and their parents about the signs and symptoms of type 1 diabetes.

Diagnosis criteria.

Type 1 diabetes in children is diagnosed based on criteria proposed by the World Health Organization (WHO) and the American Diabetes Association (ADA).

1. Symptoms of diabetes with a plasma glucose concentration ≥11.1 mmol/L,

   or

2. Fasting plasma glucose ≥7.0 mmol/L,

   or

3. Plasma glucose ≥11.1 mmol/L 2 hours after an oral glucose tolerance test (OGTT)[1].

If the child has any of the criteria above but is asymptomatic, the child cannot be diagnosed with type 1 diabetes without a confirmatory test another day (2, 4-6).

[1] An OGTT is performed in the morning and the patient needs to be fasting for at least 10 hours. After a blood glucose test, the patient drinks a maximum of 75g glucose, at timepoint 0. For children the glucose dose is based on their weight. After 120 minutes (2 hours) a new blood glucose value is measured. During the OGTT the patient are supposed to be sitting or lying down to rest.

Treatment and complications

Currently, there is no cure for type 1 diabetes and the treatment is lifelong, involving daily insulin injections multiple times a day or insulin administration through an insulin pump. The insulin treatment requires regular and frequent monitoring of blood glucose levels though capillary blood glucose measurements or continuous glucose monitoring (CGM). Insulin doses are adjusted based on the amount of carbohydrate intake. Well managed and controlled blood glucose levels help reduce the risk of acute complications (such as hypoglycemia, hyperglycemia, and the risk of ketoacidosis), as well as long-term complications (2).

Hypoglycemia occurs when blood glucose levels drop below 3.9 mmol/L. The initial symptoms of low blood glucose levels include shaking, sweating, rapid heartbeat, irritability, and confusion. If the condition is not treated it can lead to unconsciousness, seizures, and, in rare cases, death. Experiencing hypoglycemia can be extremely unpleasant and traumatic for individuals with type 1 diabetes and those who witness it. Parents of children with type 1 diabetes may find it stressful and can lead to anxiety, changes in daily routines, and decreased quality of life (7, 8).

On the other hand, ketoacidosis is a condition that occurs when blood glucose levels rise above 11 mmol/L, blood ketone levels increase above 3 mmol/L, and pH drop below 7.30. Ketoacidosis is caused by insulin deficiency, and the initial symptoms include excessive thirst, frequent urination, and a dry mouth, followed by stomach pain and nausea. If left untreated, it can lead to unconsciousness and death The most common reason of ketoacidosis are non-compliance with insulin therapy, insulin pump failure, other illnesses or the onset of type 1 diabetes in undiagnosed individual (9).

Complications that may occur later in life due to type 1 diabetes include heart and vascular disease, nerve damage, kidney damage, eye disease, and an increased risk of premature death (2, 10).

Incidence of type 1 diabetes

The incidence of type 1 diabetes varies among different countries worldwide. In 2021, approximately 108,200 children between the age of 0 to 14 years were diagnosed with type 1 diabetes, and these numbers continue to rise annually, particularly among children below the age of 5 years. Sweden and Finland, experiences one of the highest incidences of type 1 diabetes, with nearly 900 children being diagnosed in Sweden every year (11). The reason behind the increasing number of newly diagnosed children remains unknown, but genetic risk factors and environmental triggers are thought to play a role. Some examples of environmental factors include early infant diet practices, vitamin D deficiency, rapid growth, psychological events, and viral infections (2, 6, 12).

Genetic risk for type 1 diabetes

Several genetic factors contribute to an increased risk of developing type 1 diabetes. Approximately 50% of the genetic contribution is linked to the human leukocyte antigen (HLA) region on chromosome 6. HLA class II exhibits the strongest association with type 1 diabetes. In the longitudinal studies in this project, the child's HLA genotype was the only genetic risk factor, among others, that was part of the inclusion criteria (2, 13, 14).

Islet autoantibodies

The factors that trigger the autoimmune process leading to the destruction of beta-cells in the pancreas are not fully understood. However, it is believed to be a combination of genetic susceptibility and triggers from the environment. Biomarkers called islet autoantibodies, i.e., autoantigens towards intracellular targets in the beta-cells, can be detected in the blood during the autoimmune process. The most common islet autoantibodies include Glutamic Acid Decarboxylase (GADA), Insulinoma-Associated protein 2 (IA-2A), Insulin (IAA), and Zinc transporter 8 (ZnT8A). When one or several of these islet autoantibodies are detected in the blood, the risk for develop type 1 diabetes has increased (2, 15). For children with one islet autoantibody the risk is approximately 15% while for those with several islet autoantibodies, the risk reaches 70% of developing type 1 diabetes within ten years. Subjects with more than one islet autoantibody have a lifetime risk of almost 100% (16). At diagnosis, over 90% of children test positive for one or several islet autoantibodies (2).

The age at which a child develops their first islet autoantibody, and which specific islet autoantibody appears first seem to be important factors. Children who later developed type 1 diabetes were significantly younger at the time of seroconversion than those who did not develop the disease (15, 17, 18). Among the youngest children, IAA was the most common first-appearing islet autoantibody, peaking at one year of age and declining the following year. On the other hand, GADA, as the first islet autoantibody, was more common at later stages and continued to be the most common first-appearing islet autoantibody during childhood (17).

While it is evident that most children who test positive for multiple islet autoantibodies will develop the disease, the time frame for its onset varies significantly from months to years. This period can be stressful for the child and the family, especially when they know the child has developed islet autoantibodies.

As mentioned earlier, the diagnosis of type 1 diabetes occurs when an individual exhibits symptoms, elevated blood glucose levels, and requires insulin therapy. However, the presence of islet autoantibodies may precede the onset of the disease by several months to years. To divide this period into three different stages allows

researchers to explore various interventions aimed at delaying or preventing type 1 diabetes (4, 19) (Figure 2).

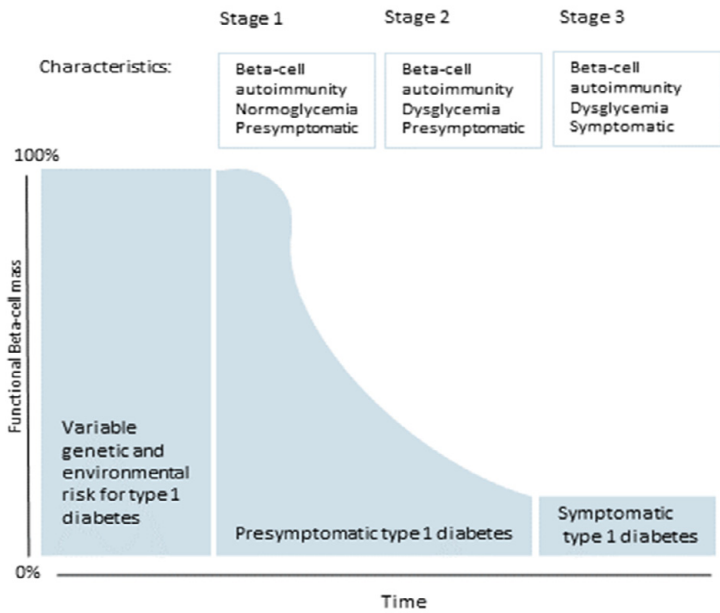

Figure 2.
Stages of type 1 diabetes pathogenesis according to the 2015 statement by JDRF, ADA, and the Endocrine Society, adapted from Insel et al. (4).

Stage 1 type 1 diabetes

This stage includes individuals with multiple islet autoantibodies, with normal blood glucose levels and no symptoms of type 1 diabetes.

Stage 2 type 1 diabetes

In stage 2, individuals are multiple islet autoantibody positive and asymptomatic. However, in contrast to stage 1, these individuals exhibit dysglycemia due to loss of beta-cell function. Dysglycemia is defined as fasting plasma glucose $\geq$ 5.6 mmol/L or impaired glucose tolerance with plasma glucose $\geq$ 7.8 mmol/L after an OGTT or an HbA1C $\geq$ 39 mmol/mol. The risk of developing type 1 diabetes is significantly increased, and approximately 75% of these individuals will progress to the disease within 5 years.

Stage 3 type 1 diabetes

At this stage, individuals exhibit the typical signs and symptoms of type 1 diabetes and have elevated glucose levels consistent with type 1 diabetes (4).

Screening studies for type 1 diabetes

In order to find the causes of type 1 diabetes and to be able to prevent or delay the disease, screening studies involving children with or without a high risk for type 1 diabetes are essential. Several longitudinal observational screening studies have or are following at-risk children from birth through childhood. These studies collect biological samples and other data to be able to identify potential environmental triggers of autoimmunity (19-22). Other research aim to prevent type 1 diabetes by screening newborn children for high genetic risk and enrolling them in randomized controlled trials (23, 24). Recently, screening for islet autoantibodies among the general population has started to identify children at high risk for type 1 diabetes. The Autoimmunity Screening for Kids (ASK) study screens children in Colorado for islet autoantibodies and follow those with multiple islet autoantibodies and educates families about the signs and symptoms of type 1 diabetes (25).

Similarly, the German screening study Fr1da seeks to assess the feasibility of screening for islet autoantibodies in the general population, aiming to prevent severe ketoacidosis and reduce anxiety through information, education, and care (26). Recently, screening for islet autoantibodies and autoantibodies for celiac disease and autoimmune thyroiditis was conducted in the general pediatric population in the southern part of Sweden in two different age groups (TRIAD). The purpose was to examine the presence of autoantibodies in a randomly selected group, assess the feasibility of home capillary blood sampling and compare two different analysis methods. Children positive for any antibodies were asked for a confirmatory sample, and persistently positive children were referred to a pediatrician with the option to participate in a prevention study.

For this project, data from the longitudinal observational screening studies Diabetes Prediction in Skåne (DiPiS) and The Environmental Determinants of Diabetes in the Young (TEDDY) have been used. Both studies screened newborn children and followed at-risk children until 15 years of age, involving 1-4 visits per year, including blood draws, interviews, and questionnaires. Detailed descriptions of these studies can be found in the section on study populations.

Ethical guidelines

As a researcher, it is important to consider and reflect on ethical questions that can impact the research and the research participants both before the start of the study and during the research process. This is even more important when the research involves children, since the children are more vulnerable, have limited control over their circumstances, and rely on their parents and other adults. In studies with a pediatric cohort, researchers must engage with the child and the entire family, taking their perspectives into account. Establishing mutual respect with the child has been

found to be important and crucial, which can have implications for the relationships with the child and the parents (27). Various laws and guidelines regulate and provide recommendations for research involving children, such as the Belmont Report and the Declaration of Helsinki (described below).

Ethical Review of research involving Humans (2003:460)

This Swedish law aims to protect the individual and uphold human dignity in research. The law encompasses research involving personal data, physical interventions on research subjects, and biological material from human beings. All research must be approved by an ethical board, which will approve only if the research can be conducted with respect for human dignity, if the scientific value outweighs the risks, and if the researchers have good knowledge and competence. All research subjects need to be informed and consent to the study. For children under 18 years of age, their guardians are informed and provide consent for the study. If a child expresses objections to participating, this should be respected (28).

Belmont Report

This report was originally developed in 1979 but has since undergone updates. Its purpose is to provide ethical guidelines for protecting the rights of research participants and human subjects. The report includes three fundamental principles:

Respect for persons: This principle emphasizes that individuals have the right to make their own decisions regarding participation in a research study or trial which must be respected. Children are considered more vulnerable individuals and require additional protection.

Beneficence: This principle encompasses the obligation to do no harm and to maximize the benefits for the research participants while minimizing the risks of their involvement. Before participating, subjects must be fully informed about all study aspects and provide informed consent. The information shared should include, aim of the study, procedures, potential benefits, risks, and that the participation is voluntary.

Justice: The principle, entails treating all research participants equally and fairly (29, 30).

Declaration of Helsinki

The first declaration was developed by the World Medical Association in 1964 and has been updated several times since then. The declaration includes ethnical principals and guidelines for medical research conducted on human subjects. The

important message is to act in the participant's best interest. It emphasizes respecting human subjects while safeguarding their health, integrity, privacy, and rights. The research should be conducted by staff members with scientific education, training, and qualifications. Research involving vulnerable groups, including children, is only justified if it cannot be conducted on non-vulnerable groups and if the children benefit from the results and new knowledge. All studies must be submitted and approved by the ethics committee, and participants must provide their informed consent (31).

Parental reactions to the child's type 1 diabetes risk and study participation

The decision to participate in a research study with your child is not an easy decision to make. It can depend on the type of study; a clinical trial where your already diagnosed child is randomized to test a new medication or treatment or a screening study to identify children with genetic risk for a disease that lacks prevention or cure. The pros and cons of genetic screening studies have been debated in the literature for years. Those not in favor of genetic screening studies believe that the risks outweigh the benefits if there is no treatment or cure. Previous studies have indicated that parents may treat their child as ill, overreact to normal behaviors and interpret them as symptoms of type 1 diabetes, which could impact the parent-child relationship (32, 33). Research studies that follow at-risk children have found an increased anxiety particularly among mothers, however the anxiety seems to decrease over time for most parents (34-37).

On the other hand, there are advantages to participating in genetic screening studies. Parents can be prepared and educated about the signs and symptoms of type 1 diabetes, and the child can thereby be diagnosed earlier and avoid serious complications such as ketoacidosis. Moreover, screening studies allow families to participate in prevention studies that may help avoid or delay the onset of the disease (19, 26, 32, 38, 39). Previous studies have also shown that parents participating in follow-up studies feel reassured (21), and the reasons for continuing participation include having someone monitor their child if the child developed type 1 diabetes (40). Families' psychological adjustment to their child's type 1 diabetes diagnosis, when the child have been participating in screening studies before the diagnosis, have also been investigated. Compared to families from the community, these families reported lower parenting stress after their child was diagnosed with the disease (41).

Anxiety

Anxiety, worry, concern, doubt, and fear all describe emotions, but do they all convey the same meaning for everyone? Is anxiety identical for all individuals? In the literature, anxiety is defined as an emotion characterized by feelings of tension and worried thoughts (42).

Sometimes, feeling anxious, worried, or concerned is a normal and a natural part of life. These emotions can be good for us, the feelings can help us pay attention to potential dangers and threats and they may prove helpful in challenging situations. However, if anxiety becomes overwhelming and characterizes one's entire life, it can significantly impact daily functioning and even elevate the risk of developing other diseases and syndromes (42).

Experiencing worry or anxiety directly after receiving information about your child's increased risk of type 1 diabetes while participating in a research study may be natural. However, from a researcher's perspective, it is crucial to minimize risks for the participants and ensure that the scientific value and benefits for them outweigh any potential risks.

As a result, parental, primary mothers' anxiety, when participating in type 1 diabetes screening studies with their newborn child has been investigated, discussed, and debated in the literature. Several studies have found an initial increase in anxiety among parents after receiving information about their child's risk for type 1 diabetes, however, in most of these studies, the anxiety tended to decrease over time (34, 36, 43, 44). On the other hand, a few studies did not find significant difference in anxiety levels among parents of at-risk children compared to those with low-risk children after receiving the screening results (45-47).

Studies following children's islet autoantibody status have observed an increased anxiety after receiving positive test results (37). Like the increased anxiety experienced after genetic risk information, this anxiety tends to decrease over time (36, 44, 48). However, Johnson et al. discovered that three years after the first positives test result, 43% of the mothers and 34% of the fathers of children with several islet autoantibodies still reported increased anxiety (34).

In studies that analyze anxiety separately among both parents, mothers appear to experience higher anxiety levels than fathers (36, 46). Moreover, parents with a family member having type 1 diabetes (FDR) tend to be more anxious than parents from the general population (35, 44). Few studies have investigated the anxiety levels of the participating children before and after receiving risk notifications. Johnson et al. compared the children's anxiety levels with those of their parents and found a correlation between children's anxiety and that of their parents. Similarly, like their parents, children experienced higher levels of anxiety after receiving information about positive islet autoantibody test results. However, in a follow-up conducted 4 months later, the children's anxiety levels decreased to normal levels (44).

Anxiety among parents with a child participating in type 1 diabetes screening studies is not associated with study withdrawal or as a predictor of early or later study dropout (49-51), or compliance with a specific protocol (52, 53). However, lifestyle changes, such as dietary and activity modifications, have been reported to be associated with anxiety among parents and children (44). Paying attention to factors associated with parental anxiety may be important to be able to provide appropriate support to participating families. Previous studies have identified several factors related to parental anxiety, including belonging to an ethnic minority group, low parental education, underestimation of the child's type 1 diabetes risk, employment status, having a family member with type 1 diabetes, and being a single parent (34, 37, 44, 54, 55).

Kerruish et al. did not find any increase in anxiety among the participating mothers; however, mothers of children with a high genetic risk for type 1 diabetes reported more frequent worries compared to mothers of low-risk children. In a follow-up, conducted 12 years later, the levels of worry concerning their child's risk of developing type 1 diabetes had decreased (43, 45). Other studies have also examined the frequency of parental worry. Similar to anxiety, mothers tend to worry more than fathers (46), and factors associated with worry include belonging to an ethnic minority, low parental education level, having a family member with type 1 diabetes, younger parental age, parents underestimating the child's type 1 diabetes risk, and dissatisfaction with the information about the study (21). Parents who expressed less worry about their child's risk of developing the disease, were found to communicate and discuss the research study more with their children, and they were also more willing to participate in another research study (56).

Few of the factors associated with anxiety and worry are modifiable, and only risk perception and dissatisfaction may be areas where staff members and researchers can intervene. However, understanding the factors related to increased anxiety and worry and any differences between mothers' and fathers' anxiety and worry can be beneficial when developing strategies to support parents and families.

Satisfaction

Satisfaction can be described as the pleasant feeling you experience when you receive something you wish for or want. It can also be described as something you feel when doing or have accomplished something you desire. However, the meaning of satisfaction can vary for different individuals, making it difficult to measure and describe accurately. In research, it is common to measure satisfaction for a specific item, such as the information provided about the study, the consent process (21, 57-59), or the treatment, intervention, or program in which you participate with your child (57, 58, 60).

Regardless of the study or clinical trial's duration, overall study satisfaction is typically measured at the end as part of the evaluation (46, 60-62). In addition to asking participants and parents about their satisfaction with specific aspects of the study, questions related to whether they would recommend the current study to others or if they are willing to participate again in a similar study are used to measure overall study satisfaction. Several studies have reported a very high percentage, over 90% of the participants, expressing willingness to participate again or recommend the study to a friend (57, 60, 61).

In the Diabetes Prevention Trial, participants, including children and their parents at high risk for type 1 diabetes, tested oral and insulin injections in order to prevent the disease. Their overall study satisfaction was measured by three questions combined to create a satisfaction score. The study found high overall study satisfaction, though differences were observed among the participants. Both mothers and fathers reported higher satisfaction levels than the children, with mothers being more satisfied than fathers (63, 64).

This methodology, to measure study satisfaction with a score was adopted by the TEDDY study and is described in greater detail in the methods section.

Most studies investigating parents' study satisfaction do not examine factors related to or associated with this feeling. However, previous publications have identified some non-modifiable factors. For instance, parents with lower education levels and those from ethnic minority groups tend to express higher satisfaction with their overall study participation than those with a university degree and families from the majority culture (60, 65).

In a clinical trial involving children and adolescents with neurofibromatosis type 1, Martin et al. found that families facing transportation problems and other study-related financial difficulties were less satisfied with their participation (66). Few pediatric studies have explored modifiable factors related to satisfaction. In a hearing screening program for children, researchers discovered that overall high study satisfaction correlated with specific items within the study, such as the information provided, the staff, and factors related to the study visit. When participating parents felt that the staff cared for them and exhibited high competency, their satisfaction with the program increased (58). Similar results have been observed in studies involving adult participants. Factors such as the staff's attitude, knowledge, if they have enough time, showed respect and friendliness were crucial for participants' study satisfaction (67-69).

However, it has been observed that overall study satisfaction is associated with study withdrawal and compliance with specific items included in the study protocol. In a study, it was found that mothers who expressed lower satisfaction with their participation were more likely to withdraw from the study whereas those who reported higher satisfaction were more likely to bring their high-risk child to the

research study for an OGTT (50, 52). Conversely, in the same study, study satisfaction was not found to be associated with food record compliance (53).

Measuring satisfaction in a research study or clinical trial is not uncommon, however, in the published literature, most studies have conducted it only once, at the end of the study, as part of the evaluation. Whether parents' satisfaction is measured for a specific item or their overall study participation, it is necessary to further investigate factors related to this feeling to improve it.

Risk perception

The definition of risk perception is "Beliefs about potential harm or the possibility of a loss and it is a subjective judgment that people make about the characteristics and severity of a risk" (70). The assessment and perception of risks can be influenced by various factors, including emotions (both negative and positive), past experiences, and knowledge (71).

One of the most important aspects for a researcher is to ensure that the participant fully understands the purpose and any potential risks associated with the study before consenting to participate in the study or clinical trial. In screening studies for type 1 diabetes information about the genetic risk for the disease and the increased risk due to the development of islet autoantibodies needs to be carefully explained and, in a way, that the participants easily can understand. Providing effective information and communication to participants can be challenging. In addition to oral and written information, other methods like pictures, videos, and stories may be necessary (71).

The level of understanding parents have about statistical information and how they interpret it can depend on various factors, including personal and cultural preferences and ethical background (45). According to Slovic et al. describing the risk for disease in numbers rather than percentages can lead to better comprehension. For instance, it is easier to understand that the risk is one out of 100 compared to 1%, since percentages make us think of a small number (71).

In studies monitoring children with an increased risk for type 1 diabetes, several investigators have asked the parents to estimate their child's risk of developing type 1 diabetes compared to other children using questionnaire. Some publications describe high accuracy in risk perception among parents (45). Conversely, others have found a high percentage of parents underestimating their child's risk (72). Additionally, some studies show how risk perception accuracy decreases over time, with parents underestimating their child's risk after several months or years following the initial information (43, 44, 73, 74).

Studies that have measured risk perception at more than one timepoint have reported varying results depending on the duration since the risk information was provided.

Swartling et al. and Kerruish et al. measured risk perception at two time points early in their respective studies, and the results remained consistent. However, Kerruish et al. followed up after 12 years and found that the number of parents with accurate risk perception had decreased from 92% at child-age 1 year to 50% 12 years after receiving the risk information (43, 45, 72).

To be able to increase the participants' knowledge and improve risk communication, it is crucial to investigate factors associated with risk perception. Previous publications have identified factors that may be important to consider when providing risk information and developing educational material. Parents who underestimate their child's risk are more likely to be from an ethnic minority group and have lower level of education (72-74). On the other hand, parents who have a family member with type 1 diabetes (21, 36, 72) and those who are anxious about their child's type 1 diabetes risk are more likely to have accurate risk perception (34, 74).

Furthermore, differences between parents have also been investigated. For instance, Swartling et al. found that mothers were more accurate in their risk estimates compared to fathers, while conversely, Lernmark et al. found the opposite result - mothers tended to underestimate the risk of type 1 diabetes in their child compared to fathers in the DiPiS study (21, 72).

Parents' risk perception has also been found to be important for retention and compliance in research studies. Parents who underestimate their child's risk are more likely to withdraw from the study (49, 50) whereas mothers with accurate risk perceptions comply more with specific items in the study protocol (40, 52). Furthermore, parents with accurate risk perception were more willing to participate in future studies (75).

Parents seem to be positive to receiving information about their child's type 1 diabetes risk (37, 46). However, it is essential to carefully consider how, when, and how often the information is given. When participants underestimate the risk, it could be due to lack of information and knowledge, but it may also serve as a coping mechanism in response to the potentially stressful information.

Children as research participants

In a systematic literature review conducted in 2017, which included 23 studies, researchers investigated children's perspective of participation in research studies (27). The findings revealed that most children held a positive outlook towards participating in research, citing reasons such as the opportunity to learn something new and a desire to help others. Only a few children reported experiencing negative emotions, such as anxiety, feeling upset, boredom, and worry.

The review further indicated that children preferred being actively involved in decision-making processes and being well-informed about the study's benefits, risks, and results. Additionally, they valued feeling safe and respected throughout the research process (27).

The question of involving children and adolescents in the consent process for research studies has been discussed and debated. The existing literature supports obtaining both assent and consent from children together with their parents' consent (27, 76, 77). Informed consent represents a legally binding approval, while informed assent is an agreement from a child who cannot provide legal consent due to their age. Many parents agree with their children that a shared decision is the best way. However, some argue that children should not bear such responsibility, as they might lack the necessary comprehension to make such decision (76, 78).

When a child participates in a longitudinal screening study from birth, parents initially provide consent for their child's participation. However, out of respect for the child's integrity and their right to decide about their participation, it becomes crucial to inform the child about the study's purpose and voluntary participation at a certain point (59).

In the studies used for this project, children in DiPiS did not provide assent or consent for their study participation. In contrast, in the TEDDY study it was site specific. The different sites acted based on their local laws or regulations. The age at which assent or consent was sought ranged from 7 to 10 years old, but regardless of whether assent or consent was obtained, all children participating in the TEDDY study received the same information.

To inform the child at different timepoints and to repeat the information has been found to be important in another longitudinal study with children at risk for type 1 diabetes. This practice is crucial in ensuring understanding and participation. It becomes even more pertinent in studies where children are enrolled as infants and have grown up during participation (79).

Previous publications have primarily focused on examining children's positive feelings, such as satisfaction, and the burdens they might experience in hospital care, treatment, medical procedure, or specific items like information. However, these studies have not explored the children's experience regarding screening studies and their overall study participation in observational longitudinal studies (27, 79-83). Few studies have investigated factors associated with the positive or negative aspects of a child's participation in research (27).

Research regarding children's worry and anxiety during their participation in genetic screening studies and followed with islet autoantibodies is limited. Johnson et al. found that at-risk children react similar to their mothers after receiving information about their increased risk of developing type 1 diabetes. Initially, their anxiety increased but it decreased shortly after (48).

In the Swedish All Babies In Southeast Sweden (ABIS), a study screening for type 1 diabetes and other autoimmune diseases, the majority of the children expressed feelings of being calm or very calm about participating, with only 26% reporting feelings of worry (84).

In this thesis, our primary aim was to investigate and describe families' reactions and experiences during their participation in longitudinal follow-up studies when participating with their child who have been screened at birth for high risk of type 1 diabetes. Our investigation focused on the negative and positive aspects of participation and the associated factors. Additionally, we sought to develop a short, valid, and reliable questionnaire for children to self-assess their anxiety related to their risk of developing type 1 diabetes during their involvement in type 1 diabetes studies, as such a tool was currently unavailable.

Aims of the thesis

The overall aim of the thesis was to examine the psychosocial effects and families reactions of participation in longitudinal studies with their children at high risk for type 1 diabetes.

The specific aims of this thesis were to:

Paper I — Investigate parental anxiety level after five years participation in the DiPiS study and factors associated with parental anxiety.

Paper II — To develop a reliable and valid short form of the State Anxiety Subscale of the State- Trait Anxiety Inventory for children (STAI-CH) in the TEDDY study.

Paper III — Identify factors associated with parental study satisfaction in the TEDDY study. The role of staff consistency to parent study satisfaction was of particular interest.

Paper IV — Identify modifiable variables collected in the first year of the TEDDY study that were associated with study visit compliance in the subsequent three years of this longitudinal study.

Study population

Study cohorts

DiPiS

The Diabetes Prediction in Skåne (DiPiS) study is a prospective, longitudinal research study focusing on children at high risk for type 1 diabetes. The aim of the study was to follow children from 2 to 15 years of age, to identify environmental risk factors with type 1 diabetes.

Children were screened with a cord blood sample at all five maternity clinics in Skåne between 2000 and 2004, following parental consent. The blood sample was analyzed for HLA genotype and cord blood islet autoantibodies. Children's risk score for type 1 diabetes was calculated based on the HLA genotype, presence of maternal infections during pregnancy, maternal diabetes, cord blood islet autoantibodies, and high or low birthweight for gestational age.

Between September 2000 and August 2004, a total of 48,058 children were born in Skåne, out of which 35,683 children were screened at birth. At child-age 2 month their parents were invited to participate in the study. They were requested to provide written consent and to complete a questionnaire, which gathered information about family demographics, family medical history of diabetes, pregnancy details, the child's first month of life, and parental reactions to the child's risk for type 1 diabetes. At child-age 2 years parents to children with high risk for type 1 diabetes based on the risk score, who agreed to participate (n = 7,826), were contacted again, and invited to participate in the follow-up. In total, 3,889 parents participated in the annual follow-up (Figure 3).

The follow-up includes an annual questionnaire and a blood draw. The questionnaire included questions regarding the child, but the parents also answered some questions separately. For instance, they answered questions regarding their anxiety when thinking about their child's risk of developing type 1 diabetes, frequency of worries and their perception of the risk. The blood sample collected were analyzed for islet autoantibodies. Parents of children who developed islet autoantibodies were informed about the child's increased risk for the disease. For those with multiple islet autoantibodies, follow-ups occurred every third month, including HbA1c and blood glucose tests, along with an Oral Glucose Tolerance

Test (OGTT) annually. At child-age 3 years, all parents were offered the option to receive information about their child's HLA genotype and the corresponding risk of type 1 diabetes. This information was communicated to the parents via letter.

All data are stored in a local database at Lund University, while all blood samples are kept in a repository at the study coordinator centre in Malmö (21).

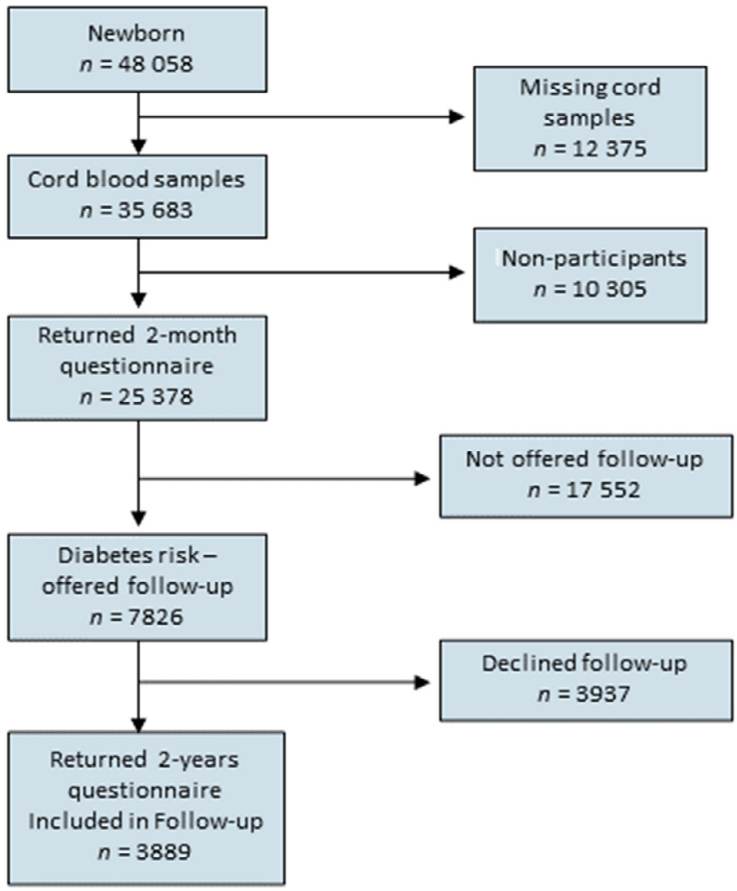

Figure 3.
Flowchart DiPiS study population.

TEDDY

The Environmental Determinants of Diabetes in the Young (TEDDY) study is a longitudinal, observational study focusing on children with an increased genetic risk for type 1 diabetes. The aim of the study was to follow at risk children to identify environmental triggers of type 1 diabetes related to autoimmunity and the progression to type 1 diabetes.

Children from the United States (with sites in Colorado, Georgia/Florida, and Washington), Finland, Germany, and Sweden were screened (n = 434,620) at birth, between September 2004 and February 2010, to identify HLA genotypes associated with a high risk for type 1 diabetes. Parents were informed about their newborn child's high genetic risk for type 1 diabetes over phone and written information. A total of 8,676 out of the 21,321 eligible children were enrolled before reaching 4.5 months of age, and they were followed every three months until four years of age and after that, twice per year until the age of 15. Subjects who developed islet autoantibodies after four years of age continued with a quarterly schedule.

Table 1.
Data collection in the TEDDY study

Collection	Sampling frequency at age
Blood	Every clinical visit
Stool	Monthly up to 4 years, four time per year up to 10 years of age
Tap water	Child-age 9 month, every two years from child-age 3 years
Toenails	Child-age 2 years, annually thereafter
Nose swab	Every clinical visit
Urine	Every clinical visit
Activity meter	Child-age 5 years, annually up to 10 years of age
Weight and height	Every clinical visit
Tree-day food record	Every 3 month up to 1 years, biannually up to 10 years of age
Parental questionnaire	Child-age 3, 6, 15, 27 month, annually thereafter
Child questionnaire	Child-age 10 years, annually thereafter
TEDDY book extraction	Every clinical visit

The protocol includes standardized interviews, questionnaires, food records, activity data, and various biological samples, including a venous blood draw. The interview (TEDDY book extraction) includes questions regarding the child's allergies, vaccinations, illnesses, medications, supplements, and life events. Both parents independently complete an annually questionnaire including information about their anxiety when thinking of their child's type 1 diabetes risk, risk perception, depression, beliefs if something can be done to reduce their child's risk for type 1 diabetes, and their overall study satisfaction. The blood draw is analyzed for islet

autoantibodies, and parents of children testing positive for one or several islet autoantibodies are informed about their child's increased risk for type 1 diabetes (Table 1).

After the initial first oral and written information regarding the child's increased genetic risk for type 1 diabetes, the clinical staff members have consistently repeated this risk information annually, using both oral and written information and pictographs. The information provided is based on both the child's increased genetic risk and the results from the blood draw, specifically the status of islet autoantibodies.

Children over three years of age and positive for more than one islet autoantibody are eligible for an OGTT two times per year.

Already at the age of two the children in TEDDY received a small book with pictures describing a research visit at the clinic. The purpose was that the family could talk and prepare the child for the visit. This book was then followed by two other books and videos distributed at the age between 5-7, and at age 10. The purpose was to inform and educate the children about the study, the blood draw, islet autoantibodies, increased risk, and type 1 diabetes. At 10 years of age, the child gives their assent or consent depending on the laws and regulations in the different countries of the study. From the age of 10 years, the child is eligible to fill out their own annual questionnaire. The child questionnaire includes questions like the questionnaire for the parents, anxiety when thinking of their own risk for developing type 1 diabetes, frequency of worry, risk perception, and overall study satisfaction.

All data is stored in the study data coordinator centre in Tampa, US, and all samples are kept in a central repository in Washington DC, US (13, 20).

Paper I

The cohort used in Paper I consists of participants from the DiPiS study. Both mothers' and fathers' annual questionnaires, collected at child-age five were used in the analysis. Out of the 3,889 enrolled children, 2,088 questionnaires were collected at child-age five years (mothers: n = 2,059 and fathers: n = 1,933). Among the included 2,088 children, the majority (n = 2,026) tested negative for islet autoantibodies, while n = 80 had one islet autoantibody, and n = 23 had several islet autoantibodies. (Figure 4).

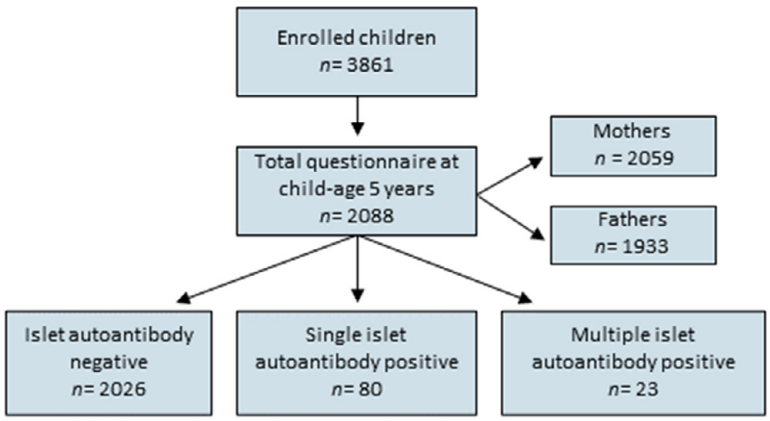

Figure 4.
Flowchart Paper I.

Paper II

In Paper II, the first annual child questionnaire in TEDDY, collected at child-age10 years, was used, and divided into three different cohorts:

Development sample. Child questionnaires containing the full 20-item SAI-CH form collected between December 2014 and September 2016 at child-age 10 years, were included (n = 842) in the analysis to develop the six-item short SAI-CH form (SAI-CH-6).

Validation sample. Between October 2016 and January 2017 an additional 257 10-year-old child questionnaires with the full 20-item SAI-CH were collected. This sample was used to validate the new short SAI-CH-6 form.

Application sample. The new SAI-CH-6 form replaced the full 20-item SAI-CH form in TEDDY in February 2017. Children who completed the new form from

February 2017 to November 2020 (n = 2,710) were included in the application sample. This sample was used to test if the SAI-CH-6 results from the development and validation sample could be replicated.

The characteristics of participants from the development sample, validation sample, and the application sample are described in Table 2.

Table 2.
Characteristics of participants

Variable	Development sample *n* = 842 (%)	Validation sample *n* = 257 (%)	Application sample *n* = 2,710 (%)
Country:			
US	325 (38.6)	84 (32.7)	1214 (44.8)
Finland	300 (35.6)	72 (28.0)	588 (21.7)
Germany	46 (5.5)	21 (8.2)	126 (4.7)
Sweden	171 (20.3)	80 (31.1)	782 (28.9)
Child sex:			
Female	445 (52.9)	125 (48.6)	1318 (48.6)
Child ethnic minority:			
Yes	102 (12.5)	30 (12.2)	379 (14.5)
First-degree relative with T1D:			
Yes	102 (12.1)	44 (17.1)	301 (11.1)

Paper III

In Paper III, the TEDDY cohort was used to measure study satisfaction at two time points: at child-age 15 months and child-age four years. Out of the total 8,676 enrolled children in the TEDDY cohort, we included mothers and fathers with completed annual questionnaires at the two time points. At child-age 15-months, we had questionnaires from n = 6,576 mothers and n = 5,859 fathers, while at child-age four years, from n = 4,744 mothers and n = 4,063 fathers.

Children meeting any of the following criteria were excluded from the analysis: having maternal islet autoantibodies at birth, not being HLA eligible, or having developed islet autoantibodies. After applying these exclusion criteria, the final sample size for the analysis at the first time point, 15 months of age, included 5,579 mothers and 4,942 fathers. Similarly, the final sample size for the analysis at the second time point, four years of age, included 4,010 mothers and 3,411 fathers (Figure 5).

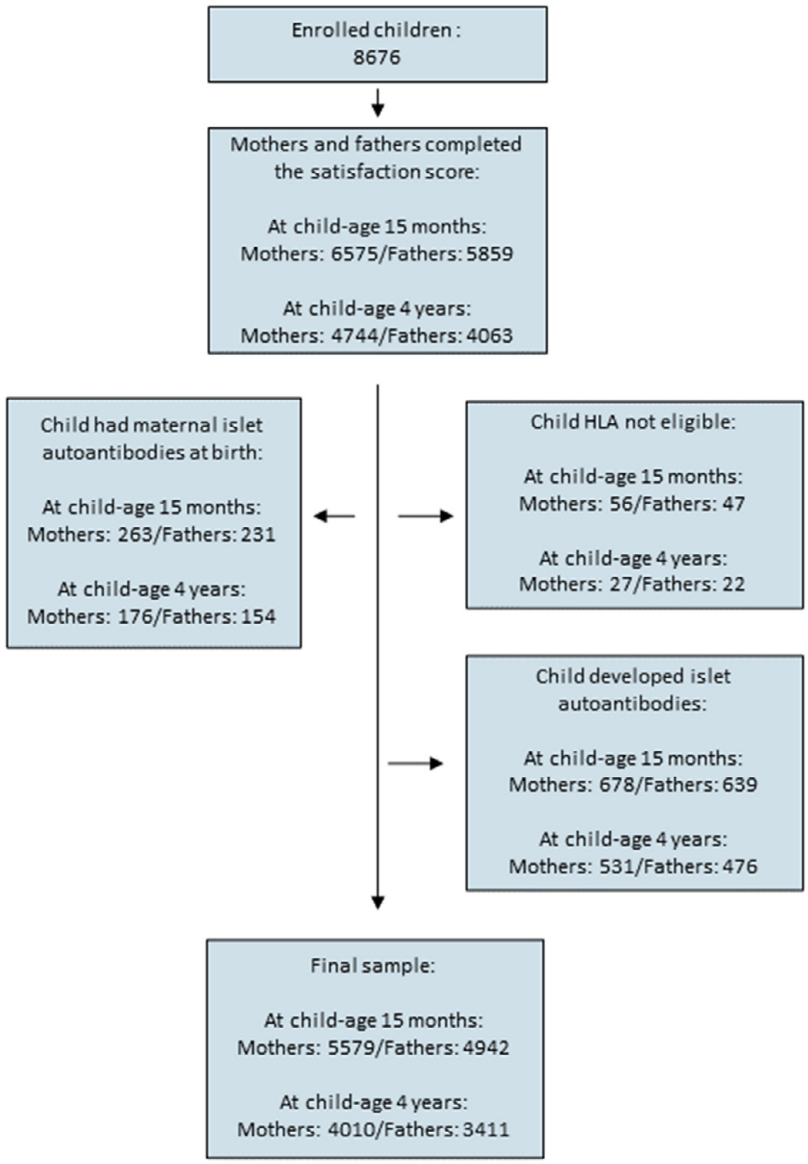

Figure 5.
Flowchart Paper III.

Paper IV

The TEDDY cohort was used to examine variables collected during the first year of study participation, which might be associated with study visit compliance in the subsequent three years. Out of the total 8,676 enrolled children we specifically selected those children remained enrolled in the study, were never withdrawn, and remained active (i.e., having attended at least one visit per year) at child-age four years, resulting in total of n = 4,916 children meeting these criteria. Additionally, we excluded children who developed islet autoantibodies before reaching four years of age, excluding n = 316 subjects. Consequently, the final sample included 4,600 subjects.

Methods

STAI - Anxiety

Spielberg and colleagues developed the original State- Trait Anxiety Inventory[2] (STAI) scale for adults in 1970, and it is still one of the most frequently used scales to measure anxiety both in clinics and in research. The questionnaire contains 40 items, where 20 measure state anxiety (SAI) and 20 measure trait anxiety (STI) and can be used as it is or separately. State anxiety can be described as how you feel at the moment and trait more how you generally feel on a day-to-day basis. Both scales have equal numbers of anxiety-absent and anxiety-present items and are respondents by a 4-point Likert scale. The score ranges from 20-80, were higher scores indicate greater anxiety (85). When using SAI in type 1 diabetes research to measure anxiety, the scale has been used both as a continues variable (34, 37) and a binary variable, and participants with scores > 40 have then been considered as highly anxious (86). The original version has been translated into several different languages.

Based on the same concept, Spielberg developed a child version in 1973, the State-Trait Anxiety Inventory[3] (STAI-CH) (87). The instrument is developed for children 9-12 years of age.

The strength of the STAI is that it is considered to be a reliable and sensible measure of anxiety, and since many researchers have used it, the results can be compared to others. However, the length of the questionnaire has been described to be both time-consuming and a barrier for patients and participants with reading difficulties. As a result, several researchers have tried to develop a shorter form to reduce unanswered items, minimize errors, and save time for the patients and participants when answering the questionnaire (74, 88).

Marteau at al. conducted a study using healthy pregnant women and students to identify the most suitable items for a short form of the State Anxiety Inventory (SAI)

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[3] Copyright © 1970 by Charles D. Spielberger. State- Trait Anxiety Inventory for Children requires license purchase and is a trademark of Mind Garden, Inc

that would highly correlate with the scores obtained with the full form. It resulted in a six-item short form with an equal number of anxiety-absent and anxiety-present items, that produced similar scores to those obtained using the full 20-item form (88). Hood et al. also developed a short six-item short form of the SAI to use in type 1 diabetes research, based on the original SAI. Participants were asked to think about their own or their child's risk of developing type 1 diabetes while responding to the six items. There was a high correlation between the six-item version and the full 20-item version (r = 0.95). To allow comparisons with other researchers using the full 20-item version, the shorter version was calculated by a regression equation to convert to the full-scale score (74). This short six-item SAI has then been used in several type 1 diabetes studies.

Similarly, a need for a shorter version of the STAI-CH has been recognized for children. Some research studies involving children have used the adult version (89) to measure anxiety in children, while others have tried to identify the best 10 items from the SAI-CH for use in Chinese pediatric cohorts. Although this version showed a strong correlation between the 10-item and 20-item scales, it was only validated with Chinese populations (90, 91). No short form specifically designed for children at risk for type 1 diabetes has been developed.

For this project, the short six-item form for adults has been used in all papers. Parents were asked to answer the six questions while thinking about their child's risk of developing type 1 diabetes. At least three or more items needed to be completed, and any missing items were replaced with the mean of the non-missing items. The scores obtained from the six-item form were converted to the full 20-item score using the following equation: total score = 2.80 [six-item total score] + 6.89.

Paper I

In Paper I, we considered parents with a score > 40 as being highly anxious, and when examining factors associated with parental anxiety, we treated the scores in two different ways. Firstly, we treated the score as a binary variable, distinguishing between low and high anxiety. Secondly, we used a three-level variable approach, categorizing parents into the following groups: lowest anxiety (SAI 22.05), moderate anxiety (SAI 22.1–40), and higher anxiety (SAI > 40). The rationale behind dividing parents into three groups was that a significant number of parents (22.8% of mothers and 30.4% of fathers) had the exact lowest score of 22.05, and we wanted to investigate whether they differed in any meaningful ways from the others. In the main analysis for this paper, we used the three-level SAI score and presented the results accordingly in the relevant section. Additionally, we employed the binary SAI score for sensitivity analysis.

Paper III and IV

In Paper III and IV, the SAI score was used as a continuous variable, where higher scores indicated a higher level of anxiety experienced by parents when thinking of their child's risk for developing type 1 diabetes.

Paper II

In Paper II, the aim was to develop and validate a short form of the State Anxiety Inventory for Children (SAI-CH) specifically for use in the TEDDY study. Children participating in TEDDY at the age of 10 years completed the full 20-item SAI-CH questionnaire. The questionnaire was distributed in both English, Finnish, Swedish, and German languages, with the goal of collecting at least 100 questionnaires in each language. We called this the development sample, and it consisted of 842 questionnaires. Psychometric methodology was used to identify the best six items, with three anxiety-absent and three anxiety-present items.

First, children who completed fewer than 10 items were excluded. Then, items skipped by over 20% of the children in any country were removed from the analysis. For the remaining 15 items an item-total scale score correlation was calculated and those with the highest correlation were selected to be included in the new short six-item SAI-CH. After the 842 questionnaires were collected, an additional 257 20-item questionnaires were completed, these were used for validation.

The new short six-item form replaced the full 20-item form in the child questionnaire from February 2017. To ensure that the shorter form measures the same, the remaining 10-year-old children in TEDDY who completed the short form (n = 2,710) were used to examine whether the results from both the development and validation samples could be replicated.

In Paper II, when investigating the correlation between the children's and parents' scores, the parents' SAI score was used as described above (in Paper III and IV).

Frequency of worry

Parents' frequency of worry was measured through questionnaires administered annually, separately for mothers and fathers as part of the DiPiS study. Data from the questionnaire at child-age 5 years was used for analysis in Paper I. Parents were asked following question:

"How often do you worry that your child will develop type 1 diabetes?"

The five possible responses were grouped into 1 = never worried, 2 = rarely worried, and 3 = sometimes, often, and very often worried.

In Paper I, never worried was used as the reference group.

Children's worry about developing type 1 diabetes was measured by questionnaire at child-age 10 years and used in Paper II. Children in the TEDDY study were asked the following question:

"Do you worry about getting diabetes?"

The three possible responses were grouped into 0 = I never worry and 1 = I worry sometimes, and I worry a lot.

Risk perception

Parents

Parents', both mothers' and fathers', risk perception about their child's risk of developing type 1 diabetes was measured by questionnaires annually in both the DiPiS and TEDDY studies. Parents were asked to answer the following question:

"Compared to other children, do you think that your child's risk of developing type 1 diabetes is": Much lower, somewhat lower, about the same, somewhat higher, and much higher.

In Paper I, using data from the DiPiS study, the answers were divided into three groups as follows: lower risk (much lower and somewhat lower), the same risk (about the same), and higher risk (somewhat higher and much higher risk). The lower risk group was used as the reference group.

In the three other papers, data from TEDDY was used and when analysing risk perception, the variable was divided into two groups: parents underestimating their child's risk for type 1 diabetes (much lower, somewhat lower, and the same risk) and parents with accurate risk perception (higher and much higher risk).

Children

Children's perception of their risk of developing type 1 diabetes is only measured in the TEDDY study, not in the DiPiS study. It its measured by questionnaires annually from the age of 10 years. Similar to the parents, the children are asked:

"Risk is the chance that something may or may not happen. What do you think about your risk of getting diabetes?" I think I have: a smaller risk of getting diabetes than my friends who are not in TEDDY, the same risk of getting diabetes as my friends who are not in TEDDY, a higher risk of getting diabetes than my friends that are not in TEDDY, and I am not sure about my risk of getting diabetes.

Children were considering to be accurate if they chose the option: “I have a higher risk of getting diabetes.” All others were considered to be underestimating their risk of developing the disease.

Children’s risk perception was used in Paper II.

Study Satisfaction score

Parents’ overall study satisfaction was measured separately for mothers and fathers, through questionnaires in the TEDDY study at enrollment, at the six-month visit, the 15-month visit, and annually thereafter. The questions used to measure overall study satisfaction in TEDDY have been used in previous publications to measure participant or parental study satisfaction in the Diabetes Prevention Trial. This trial investigated if insulin injections and oral insulin could be possible prevention strategies in children at high risk for type 1 diabetes (63, 64).

The three questions used were:

1. Overall, how do you feel about having your child participating in the TEDDY study? Scored 2 = like it a lot, 1 = like it a little, 0 = it is ok or dislike it
2. Do you think your child’s participation in TEDDY was a good decision? Scored: 2 = a great decision, 1 = a good decision, 0 = an ok decision or bad decision
3. Would you recommend the TEDDY study to a friend? Scored: 2 = yes, 1 = maybe, 0 = no

The three items mentioned above were highly correlated, and their scores were summed up to calculate a total study satisfaction score. This score ranged from 0 to 6, with a score of 6 indicating absolute study satisfaction.

The overall study satisfaction score was used as a continuous variable in Paper III and IV.

Staff consistency

To be able to measure staff consistency in Paper III we developed this specific variable for the TEDDY study. We wanted to be able to find out if the families met the same staff member during their study visits or if there were frequent staff changes throughout their participation.

During all study visits in the TEDDY study, the staff member responsible for the visit and the interview of the family added their specific staff code to all forms. We used this information to measure consistency by the number of staff changes.

In Paper III, we examined factors associated with overall study satisfaction at two different time points: at child-age 15 months and child-age 4 years. The number of staff changes was one of the independent variables used in the model. By child-age 15 months the families had completed five visits since enrollment, and the number of staff changes ranged between 0-4. At child-age 4 years, we used the number of staff changes in the last year, which ranged between 0-3 (as four visits were expected to be completed between 3 and 4 years).

Study visit compliance

There is no common definition for compliance among research studies, as it may vary depending on each study's different aims, protocols, and duration. For a prospective longitudinal study as TEDDY, complete visits are important for the quality of data collection.

In Paper IV, while examining factors associated with study visit compliance, we defined compliance as having a complete physical exam form. This form includes the child's height, weight, and blood draw, which the staff members record. For the analysis, we used early variables collected before or at child-age 15 months and counted the number of completed study visits between child-age 18 months and four years. Children who missed four or more visits in a row were considered withdrawn from the study. The number of study visits ranged between 3-11.

Statistical methods

Comparison of mean between independent groups was done using ANOVA for continuous variables and chi-square test for categorical variables in all papers. Paper III used paired t-tests to compare mothers' and fathers' study satisfaction scores at a given time. Several of the outcome variables evaluated in the papers were developed based on questionnaires containing several questions which were then combined into a score using various methods (details are described here or in the manuscripts). We calculated the Pearson correlation coefficient (r) to quantify pairwise correlations between covariates of interest. We used the reliability coefficient α, also known as Cronbach's α, to quantify the consistency when comparing different approaches of measuring the same thing. For example, the

anxiety score based on the 6-item and the full 20-item questionnaire. For all papers, a *p*-value of < 0.05 was considered to be statistically significant.

The analyses were performed using R (r-project.org) version 3.5.0 (Paper I), SPSS (IBM SPSS Statistic for Windows, Armonk, NY: IBM Corp) version 24 and 27 (Paper I, III and IV), and SAS (Statistical Analysis Software) (Paper II).

Logistic Regression

We used logistic regression in Paper I to estimate the association between a binary outcome (1 if parents are anxious, 0 otherwise) and the main covariates of interest (islet autoantibody status, risk perception, and frequency of worry) while adjusting for confounders (details provided below) (92).

Multinomial Logistic Regression

Multinomial logistic regression generalizes logistic regression to outcomes with more than two levels. We used it in Paper I to estimate the association between a three-level outcome and the main covariates of interest.

Specifically, in Paper I, we used logistic and multinomial logistic regression to estimate the association between the binary and three-level outcomes, respectively, and the main covariates of interest. We fit three logistic and three multinomial models for mothers and fathers separately, with the outcome coded as a binary and three-level outcome, respectively.

Model 1, examined the association between parental anxiety (coded as three-level outcome in the main analysis and as a binary outcome in the sensitivity analysis) and the child's islet autoantibody status, adjusting for FDR status, sex of the child, and the child's HLA risk genotype.

Model 2, examined the association between parental risk perception, adjusting for covariates as in model 1 as well as islet autoantibody status and the parental education level.

In the third model, we examined the association between parental anxiety and frequency of worry, adjusting for covariates as in model 2, as well as risk perception, working status, level of support, and whether the parents lived in the same household as the child or not.

The models presented in the publication includes all variables regardless of significance.

Multiple Linear Regression

In Papers III and IV we used multiple linear regression to estimate the association between a continuous outcome and the predictors of interest. In Paper III, parent's study satisfaction score was the main outcome of interest, while in Paper IV, it was study visit compliance. In both papers we used forward selection to identify independent variables (predictors) associated with study satisfaction in Paper III and study visit compliance in Paper IV. Variables with a p-value > 0.10 at a given step were excluded from further analysis. In the final model only variables with a p-value < 0.05 were kept, while all others were removed. In Paper III the final model for mothers and fathers includes the same variables.

Multiple linear regression was also used in Paper II to estimate the association between the short 6-item SAI and the full 20-item form for children and a variety of factors hypothesized to be associated with anxiety. The main covariates of interest for those two models were the country of residence, gender of the child, member of a family with type 1 diabetes, risk perception accuracy, and worry of developing type 1 diabetes.

Ethical approvals

DiPiS

The study was approved by the Ethics Committee at Lund University, Lund, Sweden (Dnr 490-99). Parents were informed about the study during pregnancy at the maternity clinics, and written consent was obtained from the parents at child-age 2 months.

TEDDY

The local ethics boards in each respective country approved the study following the Declaration of Helsinki. For Sweden, it was approved by the Ethics Committee at Lund University, Lund (Dnr 217/2004). TEDDY is monitored by the National Institutes of Health in the US, and regular site visits have been conducted over the years. All staff members working with the TEDDY study must complete the Protecting Human Research Participants Course every other year.

Parents were informed during pregnancy, and oral or written consent was obtained before the child was born. Subsequently, written consent was then obtained from the parents at the first study visit, at child-age 3-4.5 months. For children participating in TEDDY at child-age 7-10 years, an assent or consent was obtained, depending on the laws and regulations in the different countries. In the case of Swedish children, written assent was obtained at child-age 10 years, following both written and oral information provided by the study nurses. The Swedish children consented to completing their annual questionnaires and answering questions about special life events. A separate ethical approval was obtained for the process of the Swedish children (Dnr Ö39-2015).

The clinical trial registration number for the study is NCT00279318.

Result

Paper I

This paper aimed to examine parental anxiety when participating with their child in the DiPiS study and factors associated with anxiety. Parents' anxiety levels were measured when thinking of their child's risk of developing type 1 diabetes at child-age 5 years. We hypothesized that there would be differences in anxiety levels between mothers and fathers. Additionally, we expected that anxiety would be associated with the child's islet autoantibody status, parental risk perception, and frequency of worry.

A total of 2,088 children were included in the analysis, of which 1,053 were girls. Among these children, 2.8% had a family member with type 1 diabetes, and 4.9% of the children had developed one or several islet autoantibodies. Both mothers and fathers had the opportunity to complete their questionnaires in the DiPiS study. At child-age 5 years, a total of 2,059 mothers and 1,933 fathers completed the questionnaire. The majority of the parents had no SAI score above 40, indicating a higher anxiety level. However, 20.4% of mothers and 14.8% of fathers reported higher anxiety levels when thinking of their child's risk for developing type 1 diabetes.

For the main analysis for this paper, we used the three-level SAI score. We compared parents with the lowest anxiety score (SAI score = 22.1) to those with moderate anxiety (SAI scores > 22.1-40), and we also compared parents with the moderate anxiety to those with higher anxiety (SAI score > 40). The analysis was conducted in three different models.

The results are presented separately for mothers (Figure 6) and fathers (Figure 7). In the first model, we examined parents' anxiety levels related to the child's islet autoantibody status while adjusting for having a family member with type 1 diabetes, the child's gender, and the HLA risk genotype.

Having a child with one or several islet autoantibodies was associated with higher anxiety levels for mothers but not fathers than parents whose children had not developed any islet autoantibodies. For mothers, their child's islet autoantibody status remained associated with higher anxiety levels in both model 2 and model 3 when adjusting for other potential confounding factors.

Additionally, having a family member with type 1 diabetes was found to be associated with higher anxiety for both parents in this first model. However, this association was not observed in the subsequent two models.

In the second model, we examined mothers and fathers anxiety levels in relation to their risk perception while adjusting for the child's islet autoantibody status, HLA risk genotype, FDR status, and parental education level.

Among the parents, 20.4% of mothers and 14.5% of fathers perceived their children to have an increased risk of developing type 1 diabetes. Parents who believed that their child had a higher risk of developing type 1 diabetes seemed to be more anxious compared to other parents.

Mothers' risk perception, but not fathers', was also found to be associated with anxiety in model 3 when adjusting for other potential confounders.

In model 2, parental education level was also associated with anxiety, apart from the child's islet autoantibody status and FDR status. Parents without a university degree (49.6% of mothers and 61.7% of fathers) appeared to experience higher anxiety levels than parents with a higher education level.

In the last model, we examined parent's anxiety in relation to their frequency of worry regarding their child's risk of developing type 1 diabetes. The analysis was adjusted for the child's islet autoantibody status, HLA risk genotype, FDR status, parents' risk perception, parents' education level, if they were working or not, level of support, and whether the parent was living with the child or not.

A large proportion of the participating parents (31.0% of the mothers and 47.4% of the fathers) reported never worrying about their child's risk of developing type 1 diabetes. However, parents who worried often or sometimes about their child's risk of type 1 diabetes exhibited higher anxiety levels among mothers and fathers.

Furthermore, in this model, we observed that fathers needing more support were more likely to experience moderate anxiety levels than those with low anxiety levels. However, this association was not found among mothers nor in fathers when comparing those with moderate anxiety to those with higher anxiety levels.

As a sensitivity analysis, we examined parental anxiety using SAI score at a binary level. This result is presented in detail in the published article. When comparing the binary results with the results from the three-level analysis, we found consistent outcomes, particularly when comparing parents with higher anxiety levels to those with moderate anxiety levels in the main analysis.

The primary difference was observed among fathers of children who had developed islet autoantibodies. In the sensitivity analysis, fathers with children with one or several islet autoantibodies appeared to be more anxious than fathers whose children had no islet autoantibodies. However, this difference was not found in the main analysis when fathers were divided into three groups based on anxiety levels.

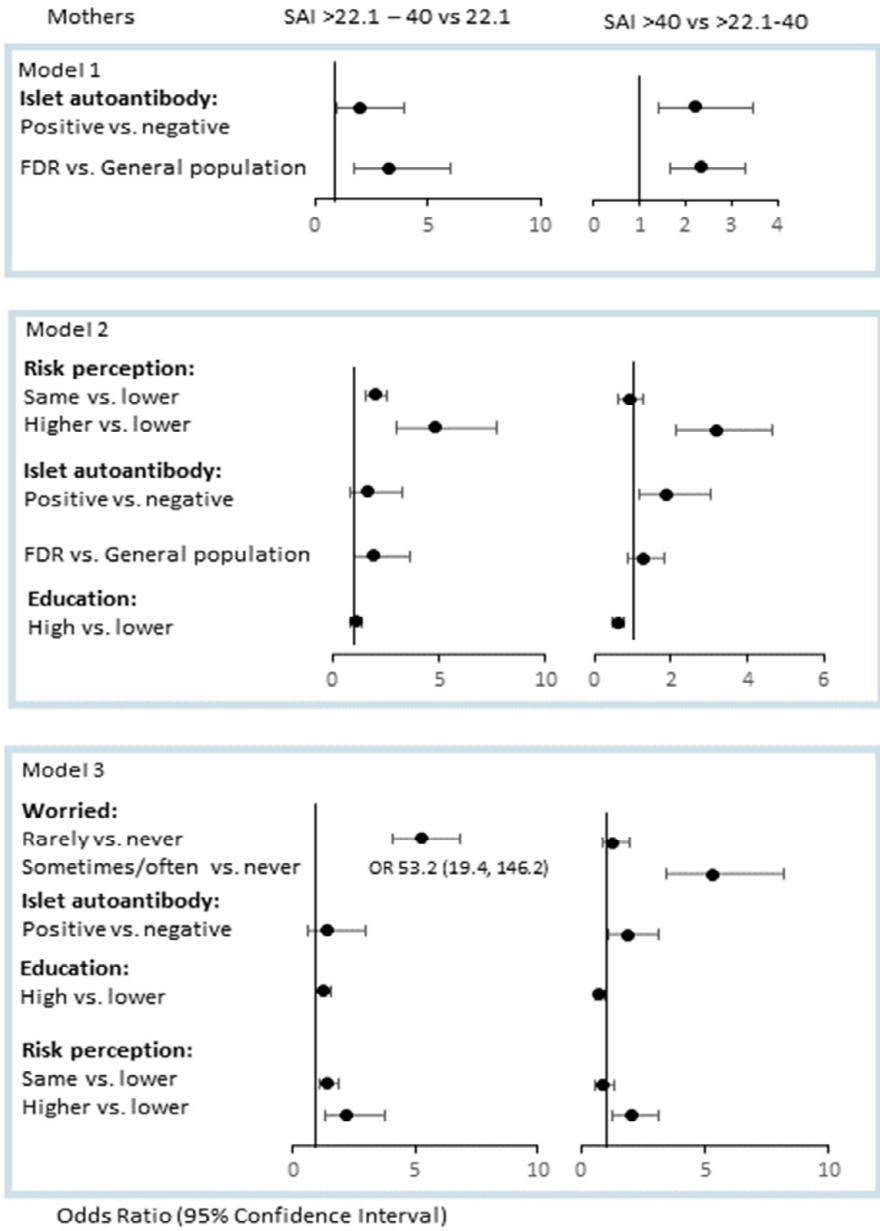

Figure 6.
The mothers' SAI score modelled as a 3-level variable (lowest anxiety = 22.1, moderate anxiety >22.1-40, and higher anxiety >40). Only the significant vaiables are presented in the figure. In model 1 we also adjusted for HLA genotype and gender. Model 2 also for HLA genotype. In model 3 also for HLA genontype, FDR status, working or not, level of support, if mother living with the child or not.

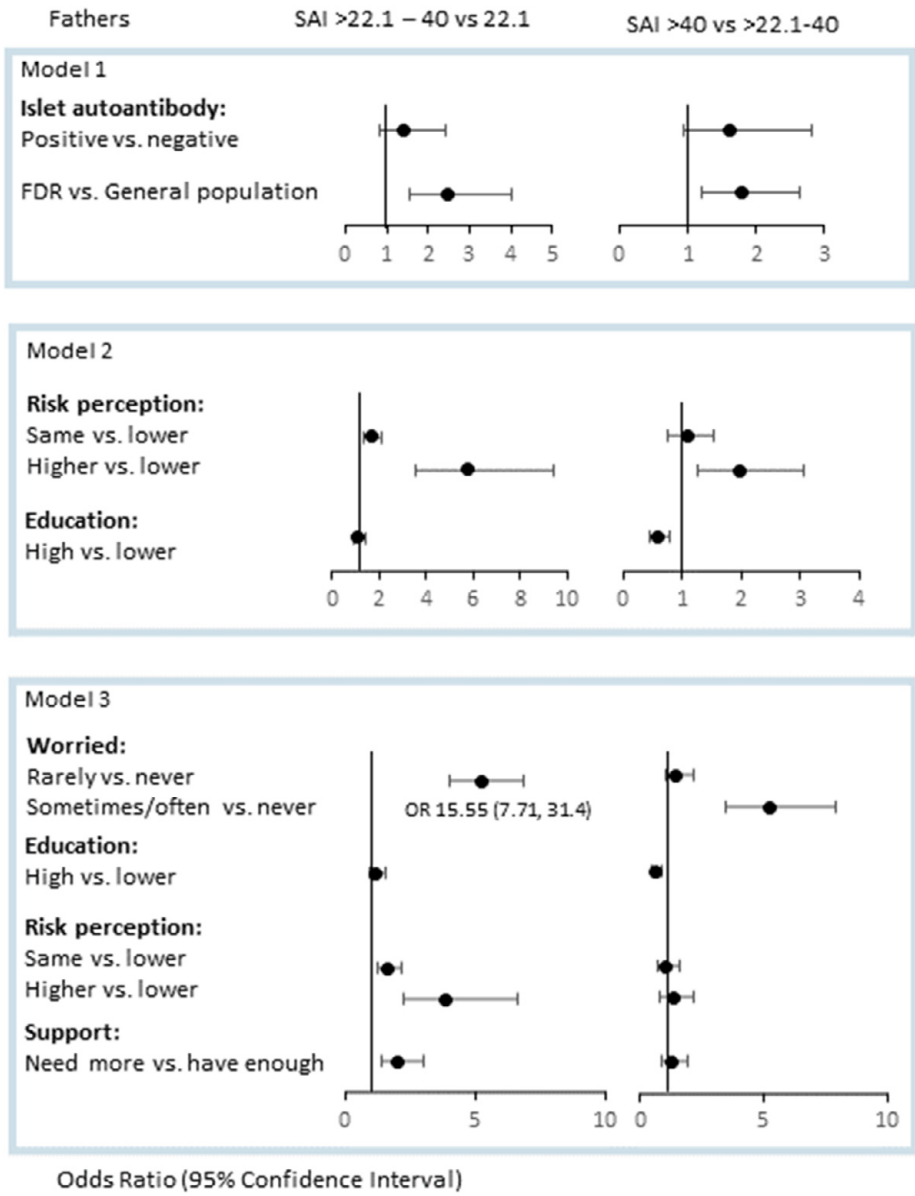

Figure 7.
The fathers' SAI score modelled as a 3-level variable (lowest anxiety = 22.1, moderate anxiety >22.1-40, and higher anxiety >40). Only the significant vaiables are presented in the figure. In model 1 we also adjusted for HLA genotype and gender. Model 2 also for HLA genotype, islet autoantibody status, FDR status. In model 3 also for HLA genontype, islet autoantibody status, FDR status, working or not, if mother living with the child or not.

Paper II

The second paper aimed to develop a reliable and valid short form of the State Anxiety Subscale (SAI-CH) of the State- Trait Anxiety Inventory for children (STAI-CH), to be used in the TEDDY study. From the initially collected 842 questionnaires (development sample), 7.6% (n = 64) were excluded as they had answered less than 10 of the original 20 items.

At the next step, five out of the original 20 items were removed from the analysis due to more than 20% of the children in any country skipping those items. Following this, the remaining 15 items, item-total correlations were examined, and the six items with the highest item-total correlations were selected (three anxiety present and three anxiety absent).

Due to copyright and license agreement, the six selected items are not presented here or in the publication. For more detailed information about the selected items, contact Mind Garden, Inc. (Table 3).

Table 3.
Item-total correlatios from the State Anxiety subscale of the STAI-CH

Item	Overall	US	Finland	Germany	Sweden
Anxiety present item 1	0.73	0.77	0.72	0.65	0.64
Anxiety present item 2	0.70	0.74	0.71	0.61	0.61
Anxiety present item 3	0.73	0.73	0.76	0.69	0.71
Anxiety absent item 1	0.75	0.76	0.77	0.78	0.71
Anxiety absent item 2	0.75	0.76	0.83	0.62	0.63
Anxiety absent item 3	0.71	0.70	0.76	0.72	0.68

When comparing the original 20 item SAI-CH and the new short form SAI-CH-6 in the development sample, we found both good reliability and a strong correlation between the two scales. The coefficient alfa was 0.94 for the SAI-CH and 0.87 for SAI-CH-6, with a correlation of 0.94 between both scales. In the validation and application sample, the coefficients alfa for the SAI-CH-6 was slightly lower, at 0.84 and 0.81, respectively, compared to the development sample.

After estimating the SAI-CH-6 scale score and the SAI-CH scale score using a special regression equation, we compared the two scores and examined the association of different variables with anxiety. The results were similar for the SAI-CH-6 and the SAI-CH in all three samples. Children who had a family member with type 1 diabetes were found to be more anxious than those with no family member with the disease. Additionally, children who worried more about developing type 1

diabetes were more likely to be anxious compared to those who were not worried. Moreover, children with an accurate risk perception were more likely to be anxious compared to those who underestimated their type 1 diabetes risk. Lastly, children from US sites were more anxious compared to children from Finland, Germany, and Sweden.

Differences between children's SAI-CH and SAI-CH-6 and parents' SAI-6 anxiety scores were examined in the development, application, and validation sample. We found a significant correlation; although it was low, the correlation ranged between 0.09 to 0.16.

The validation sample (n = 257) and the application sample (n = 2, 710) confirmed the results from the development sample.

Paper III

In this paper, we examined mothers' and fathers' overall study satisfaction and factors associated with their satisfaction at two time points: child-age 15 months and child-age 4 years. All the variables used in the model are described in detail in the publication, and only the variables found to be associated with study satisfaction are presented here. We found an overall high study satisfaction among the participating parents; 45% of the mothers and 38% of the fathers reported the highest possible satisfaction score at child-age 15 months and 48% respective 40% at child-age 4 years (Table 4).

Table 4.
Distribution of study satisfaction score for mothers and fathers at child-age 15 months and 4 years.

The score rage between 0-6, were a score of 6 is consider to be absolutely satisfied with the study.

Study satisfaction score:	Mothers at child-age 15 month *n* (%)	Fathers at child-age 15 month *n* (%)	Mothers at child-age 4 years *n* (%)	Fathers at child-age 4 years *n* (%)
0	37 (0.7)	63 (1.3)	30 (0.7)	72 (2.1)
1	433 (7.8)	612 (12.4)	304 (7.6)	427 (12.5)
2	419 (7.5)	464 (9.4)	301 (7.5)	278 (8.2)
3	688 (12.3)	679 (13.7)	402 (10.0)	405 (11.9)
4	721 (12.9)	704 (14.2)	521 (13.0)	440 (12.9)
5	788 (13.9)	551 (11.1)	513 (12.8)	418 (12.3)
6	2503 (44.9)	1869 (37.8)	1939 (48.4)	1371 (40.2)

Non-modifiable factors

Country of residency, parental education level, and parental depression were all variables associated with study satisfaction for both mothers and fathers at both time points. Specifically, parents from Sweden expressed higher satisfaction levels than parents from other countries. Additionally, parents with lower education levels reported higher satisfaction than those with a university degree. Conversely, parents with depression indicated lower satisfaction with their participation.

Furthermore, there were some differences between mothers and fathers. Mothers living alone with their children were less satisfied at both time points, and older mothers were more study satisfied at child-age 15 months, though this association was not observed at 4 years.

Among fathers, those with a family member with type 1 diabetes were more likely to be satisfied at the first time-point. However, smoking fathers were less satisfied at the second time point.

Modifiable factors

We identified fewer modifiable factors associated with study satisfaction. Parents who had an accurate risk perception when thinking of their child's risk for type 1 diabetes and those who believed they could do something to prevent their child to develop the disease were more likely to be satisfied with their participation at both time points.

However, there were some differences between mothers and fathers. Mothers who were anxious when thinking of their child's risk to develop type 1 diabetes were more likely to be less satisfied at child-age 15 months and 4 years.

Interestingly, at the first time point (child-age 15 months), fathers who experienced a higher frequency of staff changes during study visits were less satisfied compared to those with fewer staff changes. However, this association was not found in the final model at child-age 4 years, and it did not appear in any of the final models for mothers.

Staff consistency

At both time points, there were significant differences in staff changes within the last year when comparing the participating countries in the TEDDY study. Sweden had the smallest numbers of staff member changes, at child-age 15 months with an average of 0.3 and at child-age 4 years 0.1 staff changes. In contrast, the US had the largest number of staff changes, with an average at child-age 15 months of 2.5 changes and at 4 years 1.6 changes (mothers' data) (Table 5).

Table 5.
Number of staff member changes within the last year at two time-points (mothers data)

Staff member change ranges between 0-5 at child-age 15 months and 0-4 at child-age 4 years

	US Mean (SD)	Finland Mean (SD)	Germany Mean (SD)	Sweden Mean (SD)
Staff member changes:				
Child-age 15 months	2.5 (1.3)	1.1 (1.3)	0.8 (0.8)	0.3 (0.6)
Child-age 4 years	1.6 (1.1)	0.5 (0.7)	0.4 (0.6)	0.1 (0.4)

Only in fathers' final model at child-age 15-months, the number of staff changes was associated with study satisfaction. Fathers were less satisfied if there were several staff changes since their child was enrolled in the study (-0.07, 95% CI -0.11, -0.02, $p = 0.007$).

Due to the large differences between the countries, we further investigated if there were any difference between the US and Europe. The interaction between country and staff changes was significant at both time points for both mothers and fathers. Consequently, we rerun the final models for these two groups separately. We found that staff consistency was important for European parents at both time points, while this association was not seen among parents from the US. Specifically, a higher number of staff changes within the last year was associated with lower study satisfaction among parents from Europe, even after adjusting for all other variables included in the final model (Table 6).

Table 6.
Association of staff consistency with parents study satisfaction at child-age 15 months and 4 years

	US				Europe			
	n	B°	95% CI	*p*	*n*	B°	95%CI	*p*
Numbers of staff changes at 15 months:								
Mothers:	2089	0.01	-0.04, 0.06	0.591	3135	-0.30	-0.36, -0.24	<0.001
Fathers:	1692	-0.04	-0.11, 0.02	0.195	2873	-0.28	-0.34, -0,21	<0.001
Number of staff changes at 4 years:								
Mothers:	1474	0.06	-0.01, 0.13	0.085	2375	-0.41	-0.53, -0.29	<0.001
Fathers:	1058	0.02	-0.06, 0.10	0.626	2059	-0.35	-0.48, -0.21	<0.001

°= B is the linear model coefficient and is interpreted as difference in mean satisfaction compared to the reference group for categorical variables or difference in mean satisfaction per 1 unit change in parental measure for continuous variables when adjusting for all other variables in the final models for mothers and fathers.

Paper IV

This paper aimed to identify variables collected during the first year of the TEDDY study participation associated with study visit compliance in the subsequent three years of the study. Study visit compliance between the 18 month and four years visits ranged between 3 to 11, and we found a high percentage (60.5%) among the included families who completed all 11 visits.

Several variables were used in the multiple linear regression analysis, and only the significant ones in the final model are presented here. The mean, standard deviation of numbers of completed visits or their correlation with number of completed visits for these significant variables are presented in the table below (Table 7).

Table 7.
Univariate associations between study variables collected on or before the child-age 15-month study visit and subsequent number of study visits completed between 18 and 48 months of age.

Variable	Mean (SD) of number of completed visits or correlation (r) with number of completed visits. From 18-48 months of age	*p*-value
Country:		< 0.001
Sweden	10.49 (1.03)	
US	10.11 (1.42)	
Germany	8.30 (2.26)	
Finland	9.92 (1.57)	
Ethnic minority:		0.001
No	10.16 (1.42)	
Yes	9.93 (1.56)	
Firsit born child:		0.003
No	10.08 (1.47)	
Yes	10.21 (1.39)	
Mother smokes:		< 0.001
No	10.16 (1.42)	
Yes	9.72 (1.63)	
Post-partum depression:		0.081
No	10.17 (1.41)	
Yes	9.92 (1.61)	
Mother's age at child's birth:	r = 0.06	0.005
Mother's anxiety:	r = 0.06	0.050
Mothers' study satisfaction:	r = 0.13	< 0.001
Fathers' study satisfaction:	r = 0.07	0.001
Father participate:		< 0.001
No	9.42 (1.93)	
Yes	10.22 (1.35)	

Non- modifiable factors

We found significant country differences, with mothers from Sweden completing more visits than mothers from the other three countries. Additionally, several factors were associated with the number of study visits completed by mothers.

Older mothers, mothers participating in the TEDDY study with their first-born child and mothers were the child's fathers actively participated in the study were all more likely to complete more study visits.

On the other hand, certain factors were associated with completing fewer study visits. Mothers who smoked when their child was newborn, and mothers belonging to an ethnic minority group were more likely to complete fewer study visits in the TEDDY study.

Modifiable factors

Few modifiable factors were associated with study visit compliance in the TEDDY study. Mothers who were anxious when thinking of their child's risk of developing type 1 diabetes were more likely to complete fewer visits and mothers who were more satisfied with their study participation in the TEDDY study completed more visits between 18 months and four years.

Figure 8 illustrates the relationship between mothers' satisfaction level, based on the satisfaction score ranging from 0-6, and the percentage of completed visits. Among mothers with the highest satisfaction score (5 and 6), 65% completed all visits. In contrast, among those who were unsatisfied with their study participation, only 48% completed all 11 visits. (Figure 8).

Figure 8.
Mother's study satisfaction score at child-age 15 months and completed study visits. Study satisfaction score range between 0-6, where 6 is completely satisfied.

Fathers impact on study visit compliance

The results in the final model are based on data and variables from the participating mothers. Mothers whose child's father actively participated, i.e. completed his annual questionnaire at child-age 15 months, completed more study visits. Including fathers' study satisfaction in the mothers' final model did not contribute significantly, as no significant variable changed. Although we run a separate model using fathers' data, the results were similar to those observed for mothers. Fathers' study satisfaction was important for study visit compliance (p = 0.029); fathers satisfied with the participation completed more study visits. At child-age 15 months, the correlation between mothers' and fathers' study satisfaction was r = 0.413.

Discussion

Genetic screening for type 1 diabetes in newborns and longitudinal follow-up in research studies have been ongoing for several years and screening for islet autoantibodies in the general population is becoming more and more common. Better screening tools have been developed, allowing us to identify children with over 10% genetic risk of developing the disease early in life (23, 93).

This study aimed to investigate families' reactions and experiences when participating in type 1 diabetes screening studies with their children. The impact on and reactions from the participating families have been discussed and debated over the years. Both negative (32) and positive aspects (32, 46) have been presented. Several researchers consider, based on ethical aspects, that providing information about an increased risk for a disease with no cure or prevention can potentially harm the child and the family more than it benefits them. Parents may feel more anxious, stressed, and worried, treating the child differently and potentially disrupting the relationship between parents and child (32, 33).

On the other hand, families informed about their child's increased genetic risk or islet autoantibody positivity can be informed and educated about the signs and symptoms of type 1 diabetes. In some cases, they may also be eligible for enrollment in prevention studies (19, 46). Without these screening studies the research cannot move forward. However, we must pay close attention to the parents' and child's reactions to minimize the risk of negative effects and improve positive feelings and reactions.

Moreover, screening for type 1 diabetes may become more clinically relevant if we have tools to delay or stop the development of the disease.

Anxiety

Increased anxiety is one of the negative aspects that has been found among parents, particularly mothers, participating in screening studies with their child at risk for type 1 diabetes (34, 36, 37, 44, 46, 48, 55). Parents' anxiety has increased after receiving information about their child's genetic risk for type 1 diabetes or when the child has developed islet autoantibodies, although, several publications have reported that the anxiety is decreasing over time (48, 55). In the TEDDY study,

researchers investigated parents' anxiety levels when thinking of their child's risk of developing type 1 diabetes over time, before and three years after receiving information about the child's positive islet autoantibody status. Notably, the anxiety levels of mothers increased and remined elevated for several years after receiving the information (34).

In this thesis, examining parents' reactions to study participation, anxiety has been an important factor to investigate. This was done as a dependent variable in the first paper, where we examined parents' anxiety after five years participation in the DiPiS study. Furthermore, we explored anxiety as an independent factor when investigating factors associated with study satisfaction and study visit compliance.

In the first paper, we found an increased anxiety level among some of the parents, although the majority of the parents were not anxious when thinking about their child's risk of developing type 1 diabetes. Notably, more mothers than fathers had an anxiety score above 40. Various factors were associated with increased anxiety in both parents, including belonging to a family with a member with type 1 diabetes, risk perception accuracy, lower parental education level, and a higher frequency of worry. In addition, for mothers, the child's positive islet autoantibody status was also associated with increased anxiety. In other studies, many of these factors have been found to be associated with increased anxiety levels among parents, particularly mothers (34, 36, 44, 54, 55). Moreover, the study uncovered differences between mothers and fathers anxiety levels, a finding supported by previous research (34, 36, 44, 46).

While we can only speculate about the reasons for these differences, one possibility could be that, in most cases, the mothers have served as the primary contact person for the study. Consequently, they may have been the one's study staff contacted by mail and phone to inform about the child's risk and islet autoantibody status. This might explain why mothers, but not fathers, experienced increased anxiety associated with the child's islet autoantibody status.

In Paper III and IV, among other factors, we aimed to interested if parents' anxiety when thinking about their child's risk of type 1 diabetes had any impact on study satisfaction and study visit compliance in the TEDDY study. We found that anxious mothers in the TEDDY study were less satisfied with their study participation, both at child-age 15 months and at child-age 4 years. Additionally, they completed fewer study visits. Few previous publications have reported any associations between anxiety and study satisfaction or study visit compliance. Notably, Tercyak et al. found that parents who were less worried had a more positive attitude to the research study and were more willing to be recontacted to participate in another study (75) which is in line with our results.

However, the association between mothers' anxiety and study visit compliance had not been investigated before, and previous publications did not find any association between anxiety and compliance for specific items in the study protocol (52, 53).

Most of the factors found to be associated with higher levels of anxiety are not modifiable. Parents' perception of their child's type 1 diabetes risk is the only modifiable factor that was found to be associated with anxiety in the DiPiS study. Although we as staff cannot influence certain factors, increasing knowledge and awareness of which parents may be at risk for increased anxiety is important. This understanding can improve the staff's possibility to support the families throughout their study participation. More and repeated information, using various reading levels and different communication approaches, and allowing parents more time to ask questions, are strategies to reduce parents anxiety, increase their study satisfaction, and improve study visit compliance. For example, the TEDDY study coordinators have developed different pictographs (Figure 9 and Figure 10) to inform families about the increased risk of type 1 diabetes, in addition to written information.

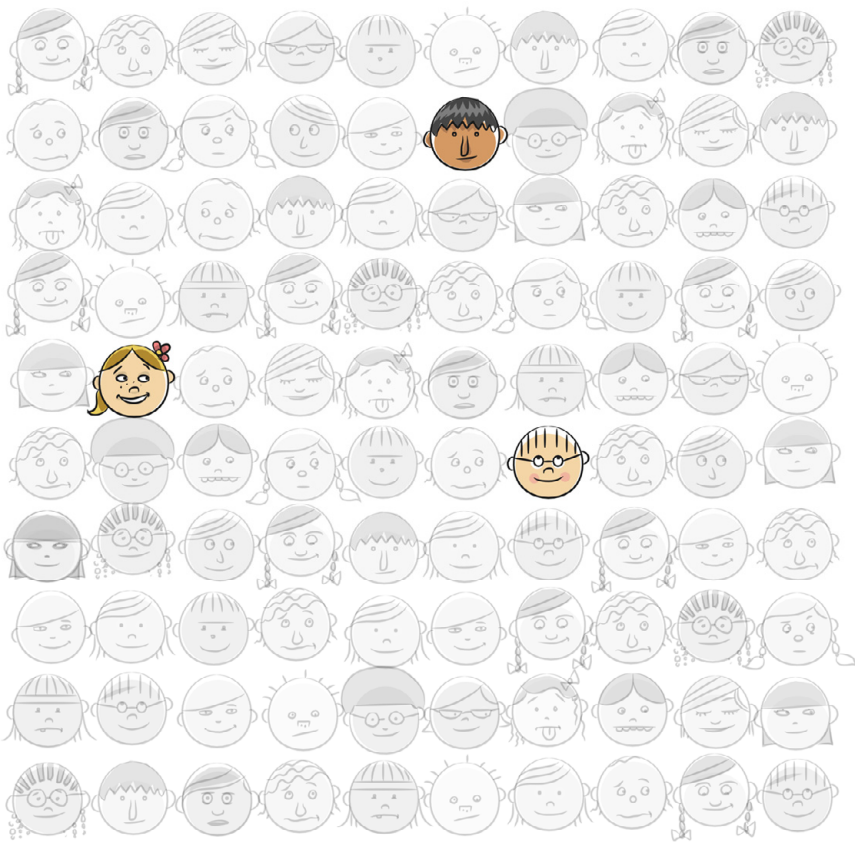

Figure 9.
Risk pictograph explaining the 3% risk for developing type 1 diabetes before 15 years of age and the gentic risk of children participating in TEDDY.

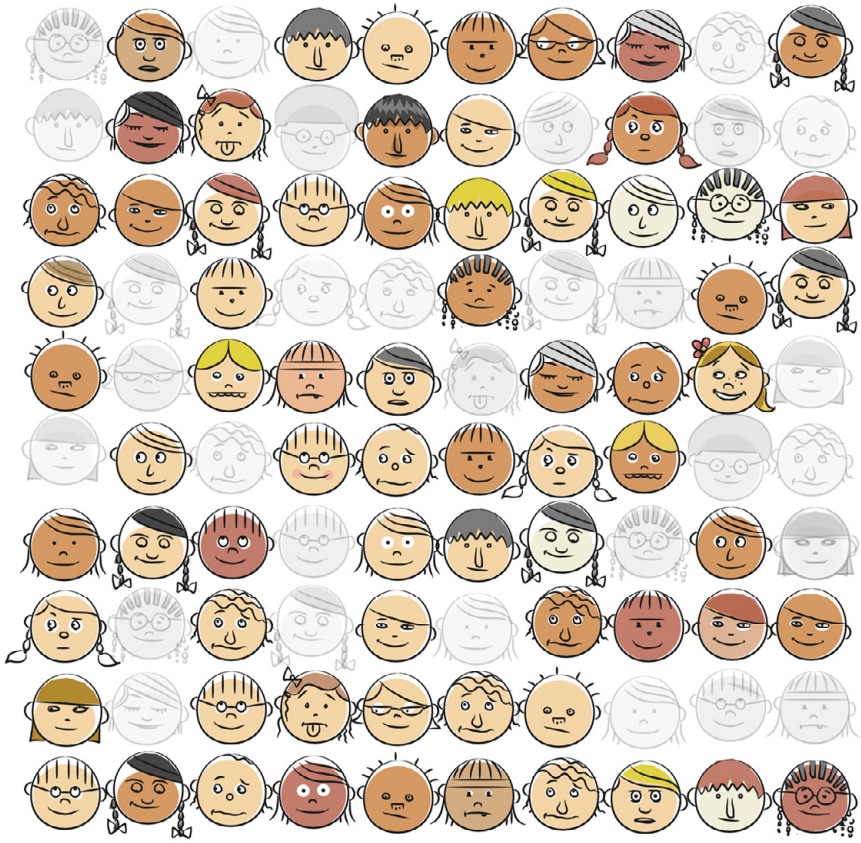

Figure 10.
Risk pictograph explaining 70% risk of developing type 1 diabetes, the risk with multiple islet autoantibodies in the TEDDY study.

In research studies including children, the child's perspective is important to consider. However, only a few studies following children at increased risk for type 1 diabetes have evaluated the participating child's anxiety when thinking of their own risk of developing type 1 diabetes. Interestingly, some studies that examined the child's anxiety levels after receiving information about islet autoantibody positivity found an increase in anxiety levels among the children. Additionally, these studies found a correlation between the children's anxiety and that of their parents (44, 48).

As part of the TEDDY protocol, children from the age of 10 years were asked to complete an annual questionnaire, which included questions about their anxiety, risk perception, and overall study satisfaction. However, the researchers were lacking a

short questionnaire similar to the one used for parents, specifically designed to measure children's anxiety related to their type 1 diabetes risk. A shortened questionnaire would increase compliance and reduce the burden on the child.

Previous research had used the longer original SAI-CH questionnaire; however, it was considered to be too long, time-consuming, and there was a risk that the children would skip certain questions. Thus, in Paper II we wanted to develop a reliable and valid short form, SAI-CH-6, to be used in the TEDDY study. Part of the development of the short form, we examined how different factors are associated with the child's anxiety and compared the results from the original 20-item form with the newly developed short 6-item form.

The results were in line with our hypothesis. Moreover, interestingly, no differences in anxiety levels were found between girls and boys. One possible explanation could be the regular clinical visits with a strong focus on child engagement, which may have mitigated the sex differences observed in other research studies (94-96).

The existing literature describes a strong connection between parents and children's anxiety. However, in Paper II, the correlation between the child's and parents' anxiety scores were significant but lower than expected. Once again, the long relation with the staff which provide information and support specifically for the children may mitigate the impact of the mothers and fathers anxiety on the child anxiety.

Satisfaction

Parents' satisfaction in a research study has been deemed crucial for retention and compliance, as highlighted in previous publications (50, 52). However, the methods of measuring satisfaction vary, both the questions used, when satisfaction is measured, and how often during the research study. Many publications measure study satisfaction only once, often at the end of the study as part of the evaluation (57, 60, 61). Only a few studies have examined factors associated with parental study satisfaction.

We believe that it is important to investigate study satisfaction while the study is still ongoing. In line with this belief, the TEDDY study conducted annual assessments of study satisfaction throughout the research. By doing so, researchers gained valuable insights into parental satisfaction, which could help enhance participation and adherence to the study protocol.

At two different time points, parental study satisfaction and factors associated with satisfaction were investigated separately for mothers and fathers (Paper III) and in the last paper (Paper IV), study satisfaction was used as an independent factor to examine factors associated with study visit compliance. The findings revealed a

high level of overall study satisfaction among the participating parents in the TEDDY study, both early in the study and after four years of involvement.

Mothers mean scores were higher than fathers (Paper III) a result that have been presented in previous publications (21, 63, 64). However, it is noteworthy that their satisfaction scores showed a significant correlation (Paper IV). The observed differences between the parents may be explained by the fact that mothers generally take on more responsibility for their child's healthcare and assume a more active role in the study participation, particularly when the child is young. This could potentially account for the variations in their satisfaction levels.

Both non-modifiable and modifiable factors were found to be associated with overall study satisfaction (Paper III). Notably, one of the non-modifiable factors was the parents' education level, which has been described previously as important for overall study satisfaction (60, 65). Interestingly, parents with lower education levels seems to be more satisfied than those with a university degree.

One possible explanation for this finding is that study participation provides a sense of security to parents. They may feel that someone is monitoring their child for signs and symptoms of a disease, and to meet the study staff regularly offer them opportunities to ask questions and get support. Moreover, this may also be the reason why mothers living alone seems to be more satisfied than those married or living together with someone who have someone to share the burden of being part of a study and the knowledge of their child's risk for type 1 diabetes.

The more modifiable factors include study-related aspects. For instance, parents with an accurate risk perception are more satisfied than those underestimate their child's risk for type 1 diabetes. Additionally, parents who believe that something can be done to prevent the disease are more satisfied than those who do not hold such beliefs.

Moreover, within the European families, those who meet the same staff member during their study participation are more satisfied than those who see several different staff members. The continuity of meeting the same staff member on most visits may increase the opportunity to create trust between the staff, parents, and the child, and increase the families' sense of security. Furthermore, this approach benefits the staff by allowing them to become more acquainted with the family's needs, providing tailored support and information accordingly.

Differences in satisfaction between the countries in TEDDY may be explained by how the study was initially presented to the families. In the US sites, compared to the EU sites, the case-management approach was not introduced to the families at the beginning of the study, and therefore, it was not something the US families expected. Nevertheless, the approach of connecting a specific staff member to a family is something the has been done more and more often at the US sites, particularly upon request from the families.

Both mothers and fathers overall study satisfaction measure early in the TEDDY study was found to be associated with study visit compliance between 18 month and 4 years. As a participating parent, to feel that the decision to participate with your child was right, to feel overall satisfied with the study certainly increases the motivation to continue participating and to complete as many visits as possible.

However, it may be important to measure study satisfaction and ask for participants' feedback not only at the end of a study, but also during the participation. Investigating factors associated with study satisfaction increases our knowledge and gives us an opportunity to find ways to maintain and improve study satisfaction among parents in pediatric research studies, and it can even lead to increased study visits compliance. Compliance is important for observational longitudinal research studies, prevention studies and clinical trials trying to find a cure to type 1 diabetes and other chronical diseases among children. Satisfied families may be more compliant with the study visits and the intervention part of the study or trial, such as a supplement, medication, or other recommendations.

Measuring study satisfaction among parents of chronically ill children at regular intervals at the health care clinic or the hospital may be of importance to improve visit compliance and compliance to the treatment and care. Information about factors related to dissatisfaction and satisfaction may increase the staff's possibility of improving the parents' satisfaction.

Staff consistency

Staff consistency was found to be important for overall study satisfaction, particularly among European parents participating in the TEDDY study (Paper III). Surprisingly, few other studies have investigated the relationship between staff consistency and study satisfaction. Although, staff consistency seems to be important for study retention in some research (40, 97, 98).

A survey conducted among parents who had participated in TEDDY for 1 to 5 years revealed that Swedish parents rated "Being seen by the same TEDDY staff" as one of the most important reasons for staying in the study (40). More recently, the Environmental Determinants of Islet Autoimmunity (ENDIA) study in Australian, a study similar to both DiPiS and TEDDY, presented similar findings in their survey. The majority of the parents in the ENDIA study considered seeing the same staff at every visit as important or very important for staying in the study (97).

However, publications examine the importance of research staff in relation to study satisfaction report increased participation satisfaction if the staff was friendly, listen to them, had enough time for them, and showed respect (58, 67-69, 99). In the ENDIA study, 84% of the parents reported that the interaction between their child

and the study staff was very important for the overall experience of the study participation (97).

In our study, only European parents, mothers and fathers, consider staff consistency important for their study satisfaction. We can only speculate about the reason; however, the clinics in the TEDDY study are organized in different ways. Parents from the European countries were, to a greater extent, assigned to their own study staff from the beginning of the study, and they may have been more negatively affected by frequent staff changes. Another reason could be the varying healthcare systems in the different countries, where families from Europe in most cases are used to having the same nurse at the healthcare clinic following their children for many years, from birth until the child starts school.

The importance of study staff consistency should not be underestimated. Dias et al. compared parents' and staff's opinions regarding the influence of the study staff on participation and retention. Interestingly, the staff underestimated their qualities; 89% of parents, compared to 66% of the study staff, responded with "liked a lot" to the item "seeing the same staff at each visit" (100).

Unfortunately, we could not use the variable of staff consistency when examining factors associated with study visit compliance (Paper IV). Previous publications have found staff consistency to be important for retention (40, 97, 98, 100), and we can only speculate that it might be important also for study visit compliance, particularly in longitudinal research studies.

Our results suggest that families highly value meeting the same staff as much as possible. This knowledge may be important to consider when planning new research studies and may also be important in the care of chronically ill children.

Study visit compliance

We observed a high study visit compliance among the participating families in TEDDY (Paper IV). Over 60% of the families completed all 11 visits between 18 months and 4 years; however, we found differences between the participating countries. Swedish families completed more visits, followed by families from the US compared to the others.

As mentioned, even though the TEDDY participants follow the same protocol, the clinics are set up differently. Factors such as traveling distance to the clinic, use of satellite clinics, staff turnovers, and case management approach can differ and may affect study visit compliance. Previous studies have also described differences in compliance between sites within a study. For instance, Hamstra et al. found that sites using more strategies, had lower staff turnover, and had more staff resources had higher study visit compliance (101).

We identified both modifiable and non-modifiable factors associated with visit compliance. Among them, belonging to an ethnic minority group is the only factor that we found that has been described before in the literature to be associated with lower visit compliance in pediatric research (101). This group is vulnerable and may need more support and tailored information to effectively manage a demanding research protocol.

Study satisfaction and anxiety were modifiable factors found to be associated with study visit compliance in TEDDY. Mothers and fathers who were satisfied with the study participation completed more visits, while mothers anxious when thinking of their child's risk of developing type 1 diabetes completed fewer visits. Our results are in line with previous publications that found that high study satisfaction among mothers was associated with better compliance for a specific item in a study protocol (52) and that mothers who were less satisfied with the study were more likely to drop out of the study (50).

One possible explanation for these findings is that individuals who are satisfied with their decision to participate want to continue participating and contribute to the research as much as possible. Previous research has not found anxiety among mothers in TEDDY to be associated with study drop out (49, 50). Instead, anxious mothers seem to continue their participation despite missing some study visits.

Compliance in research studies is crucial to reach the study's goals and ensure enough statistical power. In longitudinal research studies like DiPiS and TEDDY, missed visits is missed information about the participants, and this data can never be replaced. To pay attention to participants at risk of being less compliant and focusing on factors that you as a research staff can influence may be one effective approach to improving study visit compliance.

Fathers roll in pediatric research

Few studies report on mothers' and fathers' experience and involvement in research separately; the most common is to report the mothers' views or the parents' all together. Nevertheless, it is getting more and more common to take fathers' experiences and views in research into account and understanding their importance (102).

In a literature review comparing fathers' participation with mothers' in observational studies on parenting and childhood obesity, 36% of the studies only reported data from the mothers, 50% included results from at least one father, and 8.5% reported fathers and mothers result separately (102). Costigan et al. examined the characteristics of families in which the fathers participated or not and found that participating fathers were more often higher educated, married, with the child being

the first or second-born, and had an older mother. There were no significant differences related to the gender of the child (103).

In both the DiPiS and TEDDY studies, mothers and fathers have had the opportunity to complete their questionnaires, which include questions about their risk perception, anxiety, and study satisfaction. Additionally, sociodemographic variables are collected for both parents in these studies. This provided us with the possibility to investigate various aspects, such as both mothers' and fathers' anxiety levels in the DiPiS study, their anxiety levels in TEDDY in correlation with their child's anxiety, their study satisfaction, and the impact of fathers' participation on study visit compliance.

Previous publications have reported differences between parents regarding their anxiety levels, study satisfaction, and risk perception accuracy when participating in screening studies with their children (21, 36, 46, 63, 64, 72). This is in line with our results, as we observed that more mothers had anxiety levels above 40 compared to fathers in the DiPiS study, and mothers had a higher mean satisfaction score than fathers in TEDDY. However, we also found that the factors associated with anxiety and study satisfaction were similar among mothers and fathers. This highlights the importance of consider both parents' experiences and views and emphasizes the need for study staff to provide information and support to both parents regarding their participation.

Fathers' participation has previously been found to be important for study retention (49, 50). Our findings in Paper IV of the TEDDY study also demonstrate that fathers' involvement is crucial for study visit compliance. Specifically, mothers whose children's fathers completed their questionnaire were likelier to complete more study visits. Longitudinal studies like TEDDY, with demanding protocols, may benefit significantly from having both parents actively involved, as it provides shared support in coping with the demands of participation and dealing with their child's increased risk of type 1 diabetes. For further research studies, it may be of importance to find ways to engage and encourage both parents to remain committed to the study participation.

Strengths and Limitations

The strength of the papers in this thesis is the large size of the cohorts, both the DiPiS and the TEDDY studies used for analysis. Additionally, TEDDY is a multinational cohort with subjects from four different countries, which allows the results to be applied in different parts of the world. When examining families' experiences and reactions, the questionnaire of both mothers and fathers were used and analyzed. The large amount of data collected through these questionnaires and

interviews with the families gives a valuable opportunity to investigate various factors associated with anxiety, study satisfaction, and study visit compliance.

Reliable measures were used to assess anxiety, depression, post-partum depression, and study satisfaction in the various papers. Both adults and children were assessed using the SAI to measure anxiety. The SAI-CH was used to develop a short 6-item form for children. The questionnaire is a common, valid, and reliable measure, available in multiple languages, including English, Swedish, German, and Finnish and has been used in many other research studies.

There are limitations regarding the selection of the cohorts, the design of the studies, data collection, and analysis methods. Both the DiPiS and TEDDY cohorts was selected due to the child's risk for type 1 diabetes, meaning the findings may not directly apply to the general population or other cohorts. The research protocol with visits several times per year, with follow-up until the child reaches 15 years of age is demanding and the reactions and experience may differ compared to other pediatric research studies. Both studies had families who withdrew from participation or families with lower compliance, leading to missed study visits or questionnaires. Consequently, the results are based on active participants still in the study and it may differ from those who chose to withdraw.

In Paper I, the number of islet autoantibody positive children was quite small, which might have affected the outcome of our analyses, particularly the results derived from the fathers' model. Due to the small sample size, we were not able to dividing the children with islet autoantibodies into two groups, single and multiple, which would have been interesting for comparing the anxiety levels among parents, since this have been shown in other research publications (34). Furthermore, in this paper, we treated the anxiety variable as a binary variable in the regression model instead of using it as a continuous variable, which is more commonly done when investigating increased anxiety among parents in type 1 diabetes studies. This approach may have led to a loss of information and sensitivity in our analysis.

In Paper II, we developed a short 6-item form for children to be used to examine children's own anxiety when thinking of their risk of developing type 1 diabetes. However, it is important to note that the development of this form was based solely on questionnaires from 10-year-old children at risk for type 1 diabetes. Therefore, further research is needed to determine the questionnaire's applicability and effectiveness in other cohorts or among healthy children. Additional studies would be beneficial to validate its use beyond the specific group it was initially designed for.

In Paper III and IV, we excluded the islet autoantibody positive children from the analysis. The rationale behind this decision was the possibility that parents of these positively identified children might experience different levels of overall study satisfaction and study visit compliance compared to parents of children who tested negative for islet autoantibodies. Additionally, we excluded children who had

withdrawn from the study before the child-age 4 years from some or all of our analysis. This exclusion could affect the results, as parents who decided to withdraw from the study might have different overall study satisfaction and study visit compliance compared to those who remained in the study.

Conclusions

The four papers included in this thesis confirm existing findings and provide new insights into factors influencing parents' anxiety, study visit compliance, and their perception of participation in screening and follow-up studies for children at risk of type 1 diabetes. Developing a short questionnaire for children to measure their own anxiety facilitates the collection of the child's experiences and increase our knowledge and understanding of how children are affected by participation. These findings can help us when designing and implementing future studies, and they may be of importance in the future in population-based screening for type 1 diabetes if new drugs that can delay or prevent the disease are approved.

- Longitudinal follow-up of children at high risk of type 1 diabetes in the DiPiS study does not increase anxiety in most parents. (Paper I)
- In the DiPiS study, parents from families with first degree relatives, especially mothers whose children tested positive for islet autoantibodies, parents who think their child to be at risk for type 1 diabetes, parents who sometimes and/or often worried about type 1 diabetes, and parents with lower education levels are overall more anxious. (Paper I)
- Developing a reliable and valid short 6-item questionnaire for children (SAI-CH-6) proved beneficial for investigating children's anxiety in type 1 diabetes research. The shorter form reduced the burden on children and potentially improved compliance rates. (Paper II)
- High levels of study satisfaction were found among mothers and fathers in the TEDDY study, and the factors associated with study satisfaction were similar for both parents at two different time points. (Paper III)
- Staff consistency was found to be important for European parents' study satisfaction, while this association was not found among parents from the US. (Paper III)
- In the TEDDY study, mothers with greater anxiety regarding their child's risk for type 1 diabetes completed fewer study visits. (Paper IV)
- Mothers who were more satisfied with their TEDDY participation after one year of involvement, completed more study visits over the subsequent three years. (Paper IV)

- Potentially modifiable variables related to study visit compliance, collected early in a research study, may serve as targets in efforts to improve study visit compliance. Our results suggest that paying greater attention to mothers' study satisfaction and mothers' anxiety levels could be an important way to improve compliance. (Paper IV)
- Continuous attention to parents' opinions and experiences throughout the study participation, not just at the study's end, may enhance the opportunity for staff to provide the right support, reduce anxiety, increase satisfaction, and improve study visit compliance.

Future directions

The work with the papers included in this thesis has raised several new questions and a curiosity to continue investigating how families, both children and parents, are affected by their participation in screening studies.

We found high overall study satisfaction among the parents in TEDDY at child-age 15 months and 4 years. However, does parents' study satisfaction change as children age? Given that satisfaction is measured annually in the TEDDY study, it would be possible to investigate this aspect further.

In paper III and IV, we excluded parents of children positive for islet autoantibodies. However, it is important to note that the information and knowledge of their child's increased risk of type 1 diabetes may influence the parents' study satisfaction and the families' study visit compliance. This aspect would be of great interest to investigate further.

The children's perspective, reactions, and experiences are important factors. Johnson et al. found lower study satisfaction among children participating in a clinical prevention trial compared to their adult participants. Therefore, it is crucial to determine how satisfied the children are with their study participation in TEDDY when they reach 10, 13, or 15 years of age. Investigating differences between children's and parents' study satisfaction and examining potential changes in children's study satisfaction over time is worth considering.

Clinical implementations

Pros and cons for new-born screening for genetic risk for type 1 diabetes and screening for islet autoantibodies during childhood have been subject to debate, but they are here to stay. The screening has become better at finding children at high risk for the disease. As a result, children will continue to be followed through observational studies and participate in prevention studies or clinical trials. Recently, Teplizumab®, was approved in the US designed to delay the onset of type 1 diabetes in adults and children over 8 years of age with multiple islet autoantibodies in stage 2. This is a step forward, and hopefully just the beginning. To advance further and find prevention or cure for type 1 diabetes, we need to continue screening in the general population. However, we must also prioritize the well-being of participating families. This involves offering support to help them cope with the increased risk for type 1 diabetes and providing the right information to alleviate anxiety and enhance their satisfaction with their decision to participate in research. Our findings have given us valuable insights into identifying families most at risk of experiencing worry and anxiety, allowing us to offer tailored support and strategies to minimize the risk of increased anxiety.

The importance of staff consistency may also be something to consider in future research studies, and it may also be important in the care of chronically ill children. Having the same research staff, nurse, paediatrician, or other clinical team members present at all visits could improve the satisfaction levels regarding study participation and the care at the hospital. Research has indicated that satisfied parents tend to be more compliant, which is of importance both in research studies and in the care of chronically ill children.

Our results about factors associated with study satisfaction, anxiety and study visit compliance can help future research to ensure that parents and children feel less anxious, more satisfied and to help the research staff to improve study visit compliance.

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