Exploring Heterogeneity in Paediatric Type 1 Diabetes

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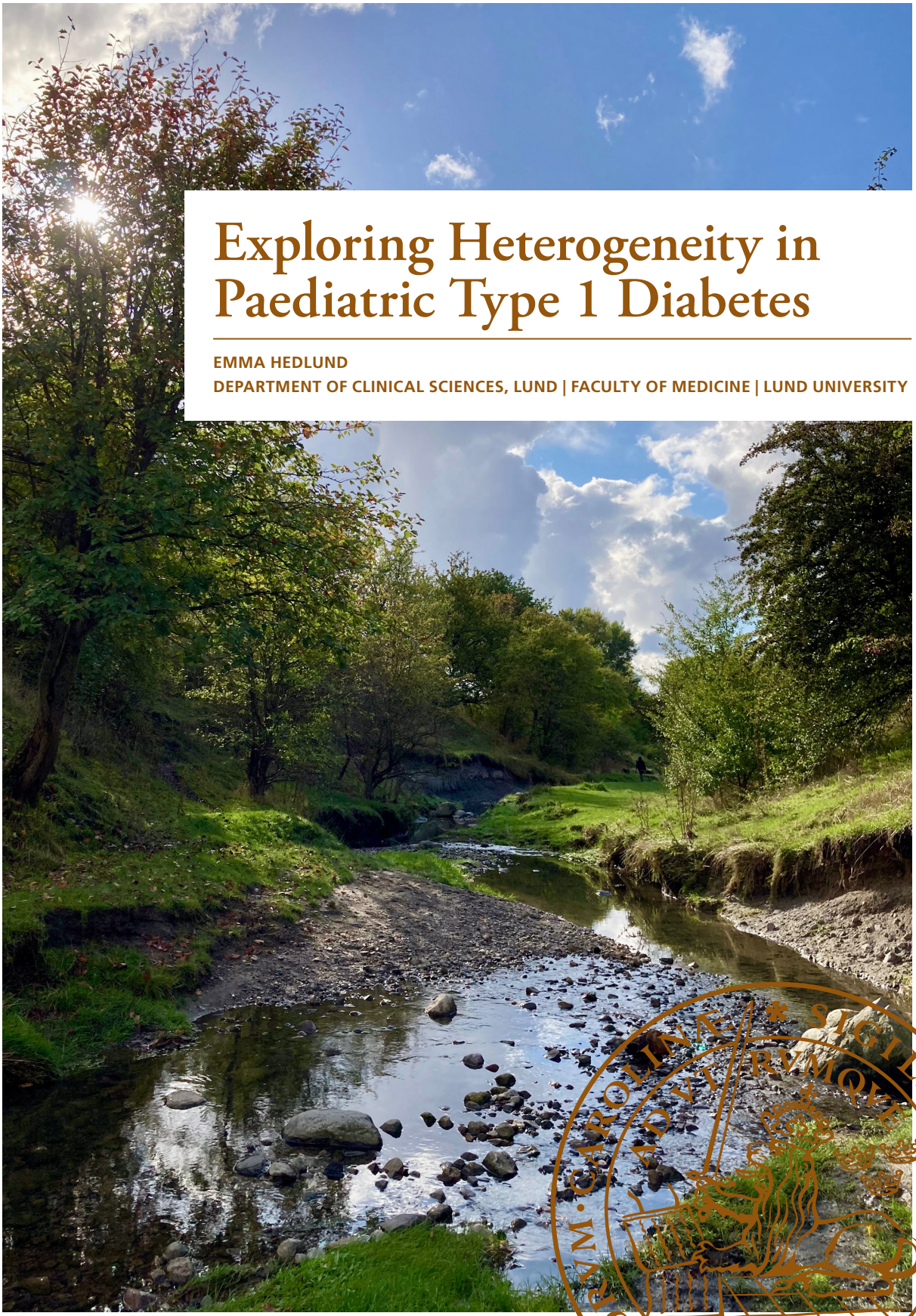

Exploring Heterogeneity in Paediatric Type 1 Diabetes

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Abstract:

Background and aim: Children with type 1 diabetes (T1D) represent a heterogeneous group of children with varying genetic backgrounds and different numbers of autoantibodies at diagnosis. The latter may reflect an interaction between genetic susceptibility and environmental triggers that contribute to the onset of the disease. However, the specific triggers remain unknown. The overall aim of this thesis was to increase our understanding of the heterogeneity of T1D in children.

Methods: To address our specific research questions, we used data from the Better Diabetes Diagnosis (BDD) cohort in combination with the Swedish National Diabetes Register (NDR). The overall study cohort, used for all papers, comprised 3,647 children diagnosed between 2005 and 2010. Blood samples, clinical data, and family history information were collected at diagnosis. Analyses included age at diagnosis, sex, autoantibodies (GAD65, IAA, IA-2, ZnT8A), and HLA genotype (Papers I-IV), as well as month of birth (Paper I), family history, body mass index (BMI), diabetes ketoacidosis (DKA) and HbA1c (Papers II-IV), and c-peptide (Papers III-IV). Paper IV also included follow-up data on BMI and HbA1c after diagnosis.

Results: In Paper I, boys diagnosed before the age of 5 were more often born in May. In Paper II, a family history of T1D or T2D was more common among children with T1D than among those without, and clinical presentation varied by family history. A family history of T1D was associated with younger age at diagnosis and lower HbA1c, whereas a family history of T2D was associated with higher BMI. In Paper III, children without autoantibodies at diagnosis differed from those with autoantibodies: they were more often boys, had higher HbA1c, less DKA, and more frequently a family history of T2D, suggesting a more slowly progressing disease. In Paper IV, follow-up data showed that differences in HbA1c and BMI observed at diagnosis persisted over time.

Conclusion: These findings suggest that there are subgroups of children with T1D that differ according to family history, sex, and autoantibody status. Understanding this heterogeneity may be crucial for improving risk prediction for poorer metabolic management and long-term complications, ultimately supporting the development of precision medicine approaches for children with T1D.

Keywords: Type 1 diabetes, heterogeneity, autoimmunity, family history of diabetes, autoantibodies, HbA1c, BMI, childhood obesity

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Utan tvivel är man inte klok

Tage Danielsson

Preface

During my early studies and at the beginning of my career, I didn't imagine myself doing research. In fact, I was quite convinced that I did not want to pursue it – at least not for the sake of the research itself. If I were to do research, it would have to be in a field that mattered to me and where I truly wanted to find answers.

Earlier in my medical training, diabetes was not a field I found particularly exciting. During on-call nights at the internal medicine rotation, I dreaded questions about insulin dosage. One of my first real encounters with childhood diabetes as a medical student came during my paediatrics rotation in Lund, when I shadowed Annelie Carlsson as she spoke with a family whose child had just been diagnosed. I remember not fully understanding at the time why the mother was so upset—until I gradually realised what the diagnosis meant for a child and a family's life. That moment stayed with me and was probably the beginning of the change in my view of diabetes.

I continued along my path in paediatrics and specialised, and during this time, I eventually joined the paediatric diabetes team, which opened the door to this field. At a specialist course on paediatric diabetes, I met Annelie Carlsson again and asked if I could do a research project with her. That step marked the beginning of my research journey, one that has since grown into this thesis.

Working as a clinical paediatrician while also conducting research has given me a unique perspective. Reporting patients to the Better Diabetes Diagnosis (BDD) study has strengthened my understanding of the challenges of data collection and also improved my ability to explain to families why their participation matters. Meeting children and families with diabetes every week has deepened my understanding of the disease and the challenges the families face, while research has allowed me to bring new insights back to the clinic. Knowing the patients personally has also made the work more meaningful to me, providing me with an added motivation to understand the field and why research matters. Attending conferences and presenting my work has been a privilege, not least because I could bring knowledge home to improve care for our patients. Being able to share new findings, or information about what's on the horizon, with my patients and their families brings me great joy. Today, my colleagues would likely describe me as someone who does find diabetes exciting.

My ambition was never to do research for its own sake, but rather to contribute, if only in a small way, to knowledge that can benefit patients in the long run. Along my research journey, the field has evolved, both clinically, with the introduction of continuous glucose monitors, smart pumps, and scientifically, with new discoveries that shape our understanding of diabetes. At the same time, I have learned not only about research and medicine but also much about myself. I am grateful that I found this field, which truly matters to me.

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Publications included in the thesis

I. Hedlund E, Ludvigsson J, Elding Larsson H, Forsander G, Ivarsson S, Marcus C, et al. Month of birth and the risk of developing type 1 diabetes among children in the Swedish national Better Diabetes Diagnosis Study. *Acta Paediatr*. 2022;111(12):2378–83.

II. Hedlund E, Tojjar J, Lilja L, Elding Larsson H, Forsander G, et al. Family history of diabetes and clinical characteristics in children at diagnosis of type 1 diabetes. *Diabetes Care*. 2024;47(11):1–5.

III. Hedlund E, Maziarz M, Lindahl T, Elding Larsson H, Forsander G, Persson M, et al. Clinical characteristics in Swedish children with and without autoantibodies at the time of type 1 diabetes diagnosis. *Diabetes Care*. In press.

IV. Hedlund E, Bladh M, Elding Larsson H, Forsander G, Persson M, Pundziute-Lyckå A, et al. Persistent differences in HbA1c and BMI by family history in children with type 1 diabetes. *Manuscript.*

Author contributions

I contributed to the conception and design of the studies together with my supervisors and the Better Diabetes Diagnosis (BDD) study steering group, who were responsible for data acquisition. I participated in the formulation of research questions and hypotheses (Papers I–IV) and was responsible for preparing and analysing the data. For Paper I, I also collected the control data from Statistics Sweden.

I performed the statistical analyses myself, with guidance from statisticians and bioinformaticians, including Fredrik Norström (Paper II), Marlena Maziarz (Paper III), and Marie Bladh (Paper IV). I created the figures and tables for all papers, except for Figure 2 in Paper III.

I wrote the first draft of all four manuscripts and revised them after comments and suggestions from my co-authors. I submitted Papers I-III and handled the correspondence with the scientific journals, acting as the corresponding author, and revised Papers I-III according to reviewers' comments with guidance from my supervisor and statisticians.

I helped acquire funding for the research in all four papers.

Publications outside of the thesis

Tojjar J, Cervin M, Hedlund E, Brahimi Q, Forsander G, Elding Larsson H, et al. Sex differences in age of diagnosis, HLA genotype, and autoantibody profile in children with type 1 diabetes. Diabetes Care. 2023;46(11):1993-6.

Thesis at a glance

	Aim	Methods	Results	Conclusions
I	- To assess whether month of birth influences the risk of T1D. - To explore potential patterns between month of birth, age, sex, HLA type, and autoantibody profile at diagnosis.	We compared 8,761 children with T1D from the nationwide Better Diabetes Diagnosis (BDD) study to the general population with respect to month of birth, sex, and age at diagnosis. In a subset of 3,647 children, HLA-type and autoantibodies at diagnosis were also analysed in relation to month of birth.	We found no overall association between month of birth and T1D incidence. However, boys diagnosed before age 5 were more often born in May (p=0.004) and showed different autoantibodies profiles compared with peers born in other months.	The impact of month of birth on T1D diagnosis was generally weak, except for boys diagnosed before the age of 5, suggesting that distinct triggers may operate in different subgroups of patients with T1D.
II	- To compare the prevalence of parental diabetes between children with and without T1D. - To compare clinical characteristics at T1D diagnosis in children with and without a family history of diabetes.	Parental diabetes among children with T1D in the BDD was compared with a general population cohort. Clinical characteristics were compared by family history of diabetes in parents and grandparents of 3,603 children with T1D using relative risk and ANOVA.	Children with T1D were more likely to have parents with T2D than children without diabetes. At diagnosis, those with a family history of T2D were more often overweight or obese and less frequently carried high-risk HLA genotypes.	Family history of T2D was more common among children with T1D, and the association with overweight an onset may contribute to an increased risk of developing T2D.
III	- To analyse clinical and hereditary characteristics of children with and without autoantibodies at T1D diagnosis.	Data from 2,753 Swedish children in the BDD cohort were analysed. Children were grouped by autoantibody status (aAb+ vs aAb-) and compared for sex, age at diagnosis, HLA genotype, DKA, BMI, HbA1c and C-peptide.	In total, 169 children (6%) lacked aAbs. At diagnosis, these children were more often boys, had higher HbA1c, were less likely to present with DKA, and were more likely to have parents with T2D.	Clinical differences between children with and without autoantibodies highlight potential heterogeniety in the disease's pathogenesis across subgroups.
IV	- To investigate whether family history of diabetes is associated with differences in HbA1c and BMI at follow-up.	Using data from the National Diabetes Register, we compared HbA1c and BMI at 1, 2, 5, and 10 years after diagnosis in 3,329 children from the BDD cohort, stratified into four family history groups. Differences in trajectories and values at specific timepoints were assessed using repeated measures ANOVA.	Children with family history, especially for T2D or combined T1D and T2D, had higher HbA1c and BMI levels throughout follow-up. Although both HbA1c and BMI changed significantly over time, these trends were similar across the family history groups.	Differences in HbA1c and BMI by family history persisted over time. These findings may underscore the impact of genetic predispositions on baseline metabolic markers.

Abstract

Background and aim: Children with type 1 diabetes (T1D) represent a heterogeneous group of children with varying genetic backgrounds and different numbers of autoantibodies at diagnosis. The latter may reflect an interaction between genetic susceptibility and environmental triggers that contribute to the onset of the disease. However, the specific triggers remain unknown. The overall aim of this thesis was to increase our understanding of the heterogeneity of T1D in children.

Methods: To address our specific research questions, we used data from the Better Diabetes Diagnosis (BDD) cohort in combination with the Swedish National Diabetes Register (NDR). The overall study cohort, used for all papers, comprised 3,647 children diagnosed between 2005 and 2010. Blood samples, clinical data, and family history information were collected at diagnosis. Analyses included age at diagnosis, sex, autoantibodies (GAD65, IAA, IA-2, ZnT8A), and HLA genotype (Papers I-IV), as well as month of birth (Paper I), family history, body mass index (BMI), diabetes ketoacidosis (DKA) and HbA1c (Papers II-IV), and c-peptide (Papers III-IV). Paper IV also included follow-up data on BMI and HbA1c after diagnosis.

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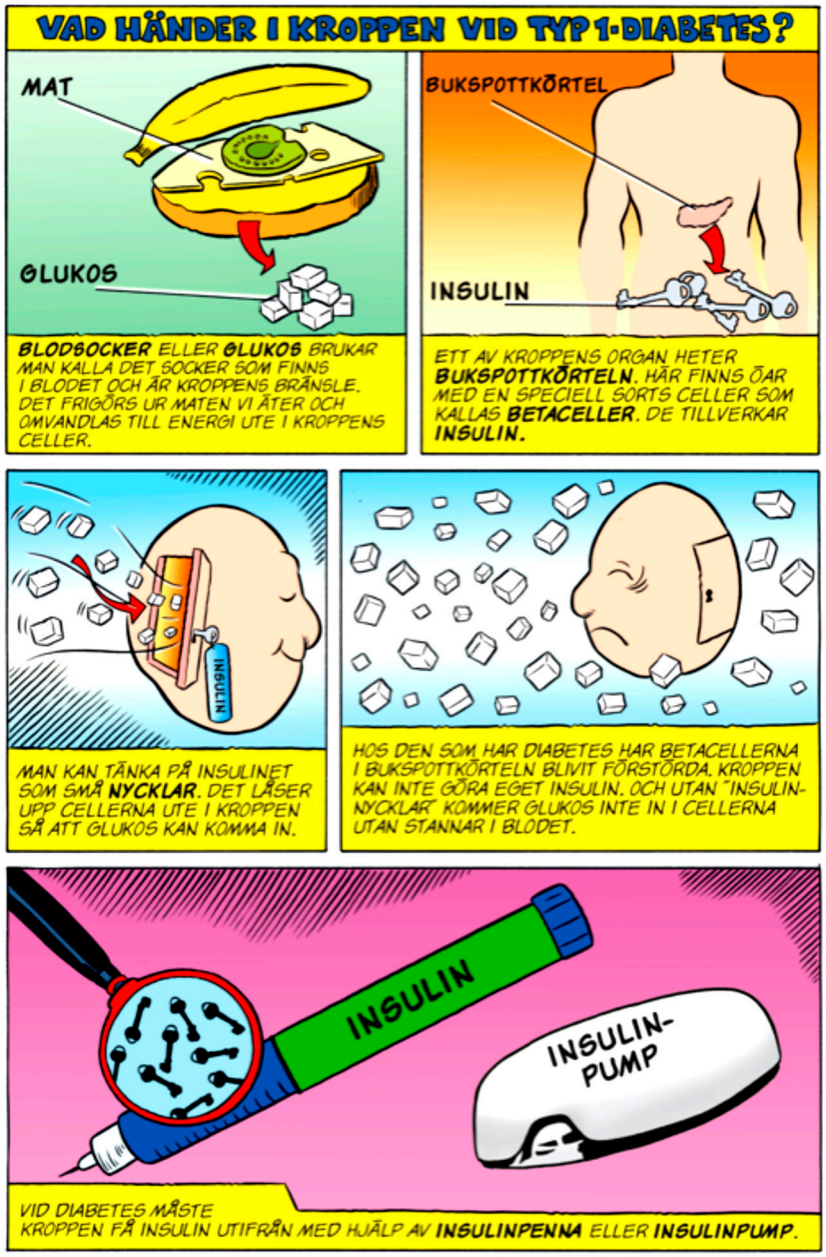

Figure 1: Illustration from Bamse och Lillmickel – en specialtidning om diabetes [1]. Reproduced with permission.

Populärvetenskaplig sammanfattning

Antalet personer med diabetes ökar, både för barn och vuxna, i Sverige och i världen. Nästan 10% av jordens befolkning lider nu av diabetes. Av dem är det bara 5–10% som har typ 1 diabetes, och även om det traditionellt har kallats ”barndiabetes” är det nästan hälften av patienterna som insjuknar i vuxen ålder. Typ 1 diabetes är den vanligaste kroniska sjukdomen hos barn och ungdomar i Sverige. När folk i allmänhet pratar om eller tänker på diabetes handlar det ofta om typ 2 diabetes, då det är klart vanligare i samhället och i världen. Det är två olika sjukdomar, där man vid typ 1 diabetes har total brist på insulin och vid typ 2 har en minskad känslighet för insulin. Sjukdomarna har alltså stora skillnader, trots sitt gemensamma namn, men man börjar mer och mer se att det finns vissa likheter också, och ibland kan det vara svårt att skilja mellan dem i kliniken.

Trots att typ 1 diabetes är en vanlig sjukdom, och att mycket forskning har gjorts på området, är kunskapen om dess uppkomst och sjukdomsmekanismer fortfarande till stora delar okända, och det finns än idag inget botemedel för typ 1 diabetes. Det är känt att det finns en ärftlig komponent som påverkar risken att få diabetes, även om de flesta med dessa gener aldrig får diabetes. Vi vet också att de flesta personer som får typ 1 diabetes har antikroppar mot de insulinproducerande cellerna i bukspottskörteln. Dessa antikroppar är en viktig del i händelseförloppet, men det är inte känt varför just de som utvecklar antikroppar gör det, eller varför de utvecklas just då.

Typ 1 diabetes innebär att kroppen inte längre kan producera insulin, ett hormon som behövs för att sockret i det vi äter ska nå cellerna i kroppen, där det används som bränsle. Insulin brukar liknas vid en nyckel, som ”låser upp” cellerna för att kunna släppa in sockret. Anledningen till att kroppen inte kan producera insulinet är för att cellerna som producerar insulinet har blivit förstörda av kroppens egna immunförsvar. Processen att bryta ner de insulinproducerande cellerna sker över lång tid, från månader till år. Symtomen vid klinisk debut, när insulinproduktionen är väldigt låg, kan ändå vara livshotande när kroppen inte längre kan ta hand om blodsockret. Symtomen är ökad törst och urinproduktion, trötthet, viktnedgång och ibland magsmärtor och kräkningar. Vid uttalad insulinbrist är risken stor att man utvecklar en livshotande syraförgiftning, så kallad ketoacidos.

Att få en typ 1 diagnos innebär en livslång behandling med insulin, via sprutor eller pump, och ständig blocksockerkontroll. Behandlingen är komplex, och insulinbehovet för att upprätthålla en god blodsockerkontroll påverkas av många olika faktorer i vardagen. En välreglerad blodsockernivå, och ett lågt HbA1c (långtidssocker) är viktigt, eftersom sämre kontroll ökar risken för så kallade senkomplikationer – skador på både små och stora blodkärl, vilket kan leda till ögon- och njurproblem samt hjärt-kärlsjukdomar.

I denna avhandling undersöker jag skillnader inom gruppen av barn med typ 1 diabetes. Jag använder mig av en studie som heter Bättre Diabetes Diagnostik (BDD), som är en nationell studie där man samlat in information om alla barn som insjuknat i diabetes i Sverige sedan 2005 (som vill delta), för att kunna använda till forskning med syfte att få ökad kunskap om varför barn insjuknar i typ 1 diabetes. Det är en fantastisk tillgång, eftersom det är en spegling av hela landet och hela populationen med diabetes, inte bara en utvald grupp, vilket gör den representativ och därmed lämplig för forskning.

Det man märker när man jobbar med barn med typ 1 diabetes, är att det kan verka orättvist. Såklart är det mycket som skiljer barnen, familjerna och dess förutsättningarna åt, men trots det finns det skillnader man inte riktigt förstår. Vi vet också att det är en otrolig påfrestning för en familj med ett barn med diabetes, och att även de som inte har perfekt blodsockerkontroll anstränger sig mycket för att få till det. Det finns skillnader som vi ser men inte riktigt kan förklara, varför vissa utvecklar ketoacidos ganska snabbt, och vid relativt låga HbA1c (bra diabeteskontroll), varför det finns skillnader i utveckling av komplikationer hos olika individer med till synes samma metabola kontroll, varför vissa barn behöver mycket högre eller lägre doser av insulin än andra barn i deras ålder. Det gör att man undrar om det finns underliggande mekanismer som vi inte förstår. Vad är det vi missar? Finns det subgrupper med olika risk och olika aggressivitet i sjukdomen? Hur kan vi hitta dem? Hur kan vi följa dem? Därför ville vi undersöka om vi i vårt studiematerial kunde hitta några skillnader som skulle kunna hjälpa oss att identifiera olika undergrupper, och i förlängningen individer med olika riskfaktorer eller till och med olika orsaker till att de får sjukdomen, baserat på hur de ser ut vid debut. På sikt skulle det kunna bidra till en mer individanpassad vård.

I den första artikeln undersökte vi om födelsemånad spelade någon roll för risken att utveckla diabetes. Detta gjorde vi genom att jämföra barn i BDD-studien med friska barn födda under samma period och se om de skiljde sig i födelsemånad, om de skiljde sig i vilka antikroppar de hade när de insjuknade och om det fanns någon skillnad mellan olika åldrar och mellan flickor och pojkar. Vi såg ingen skillnad för hela gruppen avseende födelsemånad jämfört med bakgrundspopulationen, men vi kunde se en skillnad bland pojkar under 5 år; de var oftare födda i maj. Bland dessa pojkar kunde man också se att de hade andra antikroppar vid insjuknande än pojkarna under 5 år som var födda under de andra månaderna.

I den andra studien undersökte vi om det fanns någon skillnad i ärftlighet för diabetes mellan barn med och utan typ 1 diabetes. Vi ville också undersöka om barnen i BDD-studien med olika ärftlighet hade olika klinisk bild vid insjuknandet avseende kön, ålder, antikroppar, HbA1c (långtidssocker), HLA-typ (riskmarkör för ärftlighet) samt övervikt och fetma. Det är känt sedan tidigare att det är vanligare för barn med diabetes att ha en förälder med typ 1 diabetes, och det kunde vi bekräfta, men vi kunde också visa att det var vanligare med typ 2 diabetes hos föräldrarna till barnen med typ 1 diabetes jämfört med de utan. Vad gäller

skillnaderna i klinisk bild såg man skillnad i ålder, HbA1c och att det var större risk för barn med ärftlighet för typ 2 diabetes att vara överviktiga än barn utan ärftlighet.

I den tredje studien undersökte vi barn i BDD studien som saknar antikroppar vid diagnos. Som nämnt ovan så är autoantikroppar en del av den klassiska bilden vid typ 1 diabetes, ett immunologiskt svar på vad som händer i kroppen, men det förekommer fall där man inte kan hitta några vid insjuknandet. Det kan röra sig om att det faktiskt inte är typ 1 diabetes, utan till exempel typ 2, eller att de har haft antikroppar som sedan försvunnit, men det finns också fall där sjukdomen i alla andra avseende är typisk för typ 1 diabetes, där de saknas, och det är dessa vi fokuserar på. Det vi ville göra var att se om de barnen skiljde sig från barnen med antikroppar vid diagnos avseende klinisk bild och vi tittade därför på kön, ålder, BMI, HLA-typ, HbA1c, c-peptid, ketoacidos och ärftlighet för typ 1 eller typ 2 diabetes. Vi kunde visa skillnader för kön, BMI, ärftlighet för typ 2 diabetes och ketoacidos vid diagnos i jämförelsen mellan de två patientgrupperna med och utan antikroppar. Det var vanligare med pojkar i gruppen som saknade antikroppar. Vidare fann vi att barn utan antikroppar vid debuten hade ett högre HbA1c-värde och mer sällan hade ketoacidos vid diagnostillfället. De antikroppsnegativa barnen hade oftare en förälder mer typ 2 diabetes, men inte med typ 1.

I den sista studien undersökte vi om ärftlighet för diabetes påverkade HbA1c och BMI över tid, vid mätpunkter efter 1, 2, 5 och 10 år. Uppföljningsdata fick vi från Nationella Diabetesregistret, där det samlas information från patienterna när de kommer på återbesök. Här ser vi att grupperna utifrån ärftlighet fortfarande skilde sig åt avseende HbA1c och BMI långt efter diabetesdiagnosen, vilket talar för att vi redan vid diagnos behöver göra en mer individanpassad vård, till exempel utifrån om individen har ärftlighet för diabetes.

Sammantaget ger dessa studier ytterligare belägg för att diabetes bör betraktas som en komplex och mångfacetterad sjukdom, där olika undergrupper kan ha olika sjukdomsprocess. Det finns undergrupper inom populationen av barn med typ 1 diabetes, vilket kan bero på att olika barn får sjukdomen av olika orsaker, och att skillnaden i metabol kontroll och ärftlighet kan vara av värde att beakta redan vid diagnos. Detta skulle kunna motivera olika rådgivning och eventuellt även behandling för olika grupper eller individer, något som i sin tur kan påverka både prognos och behandlingsstrategi. Det är dock viktigt att detta område fortsätter att utvecklas och att nya och större studier genomförs över tid, och i olika populationer, för att bättre beskriva och förstå dessa grupper.

Abbreviations

aAb	Autoantibody
ADA	American Diabetes Association
ANOVA	Analysis of Variance
BDD	Better Diabetes Diagnosis
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
DKA	Diabetic Ketoacidosis
ETICS	Exploring The Iceberg of Celiacs in Sweden
GADA	Glutamic Acid Decarboxylase 65 Autoantibodies
GLP-1	Glucagone-Like-Peptide-1
HbA1c	Glycated Haemoglobin A1c
HLA	Human Leukocyte Antigen
IAA	Insulin Autoantibody
IA-2A	Insulinoma-associated Protein 2 or Islet Antigen-2 Autoantibodies
ISPAD	International Society of Paediatric and Adolescent Diabetes
MODY	Maturity Onset Diabetes of the Young
NDR	National Diabetes Registry
OGTT	Oral Glucose Tolerance Test
SNP	Single Nucleotide Polymorphism
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEDDY	The Environmental Determinants of Diabetes in the Young
ZnT8A	Zink Transporter 8 Islet Autoantibodies

Introduction

History of diabetes

As history is always important in whatever we do, I will begin there.

Diabetes was first mentioned in the Ebers Papyrus of ancient Egypt (approximately 1550 BC) [2]. The earliest clear recognition of the disease, however, came from Aretaeus of Cappadocia around 100 AD, who also coined the term *Diabetes*, derived from the Greek "to run through," referring to the excessive urination that characterises the disease [3].

> Diabetes is a remarkable affliction, not very frequent among men… The course is the common one, namely, the kidneys and the bladder; for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts… The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst, unquenchable; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouth becomes parched and their body dry; the viscera seems as if scorched up; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire. [3]

Similar descriptions can be found in Arabic, Indian, and Chinese medical writings [4, 5]. A major historical milestone came in the 17th century, when Thomas Willis 'rediscovered' the sweetness of the urine and added *mellitus* ('like honey') to the name [5]. In 1776, Matthew Dobson confirmed this by boiling down diabetic urine, leaving a residue he described as resembling brown sugar [6].

The 19th century brought further insights: Claude Bernard demonstrated the roles of the liver and glycogen in glucose metabolism [7]. A few years later, von Mering and Minkowski discovered that removing the pancreas in dogs induced diabetes, establishing the central role of the pancreas [8]. The greatest breakthrough came in 1921, when Frederick Banting and Charles Best succeeded in isolating insulin, building on the earlier work of many others [9]. The first patient was treated with insulin in 1921, and in 1923, insulin became available for clinical use [5]. The

discovery of and treatment with insulin has dramatically improved the life expectancy of patients with diabetes, especially for children [10].

Before insulin, treatment options were extremely limited and often relied on severe dietary restrictions, such as starvation or diets avoiding carbohydrates, though their mechanisms were poorly understood at the time. Even after the introduction of insulin, the role of diet has been discussed and explored as an additional/ complementary treatment, with varying results [4].

The distinction between different types of diabetes emerged in the 1930s, when it was recognised that patients could present with different phenotypic characteristics [11]. In 1936, Harold Himsworth proposed that some patients had insulin resistance rather than insulin deficiency, laying the foundation for later subclassification [12]. Formal classifications were not introduced until the 1970s, when the terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) were adopted [13]. These were later revised in the late 1990s, when the current terminology of type 1 and type 2 diabetes was established [11].

Diabetes research has been extensive, and several Nobel Prizes have been awarded for discoveries related to insulin and diabetes. These include the 1923 prize to Banting and Macleod for the discovery of insulin, the 1958 prize to Sanger for determining the structure of insulin, and more recent prizes recognising work on insulin signalling and incretin hormones [12].

Despite these major achievements and more than a century of research, a cure for diabetes has not yet been found. Nevertheless, the past few decades have brought remarkable technological advances: improved insulin formulations, automated insulin pumps, and continuous glucose monitoring systems that have provided people with diabetes far greater freedom and flexibility in everyday life.

Diagnosis and classification of diabetes

The diagnosis of diabetes is primarily based on elevated blood glucose levels, the common denominator across all diabetes types and the reason they share the same name. Hyperglycaemia is typically characterised by symptoms such as polydipsia, polyuria, fatigue and weight loss. Once diagnosed, diabetes is further classified into specific clinical categories, or types.

Elevated blood glucose can be defined in several ways, as summarised in Figure 2. If there are no clear symptoms, the diagnosis should be confirmed with repeated testing. The American Diabetes Association (ADA), the International Society for Paediatric and Adolescent Diabetes (ISPAD), and the World Health Organisation (WHO) define diabetes similarly [14-16], with HbA1c added as a diagnostic option in 2010 [17].

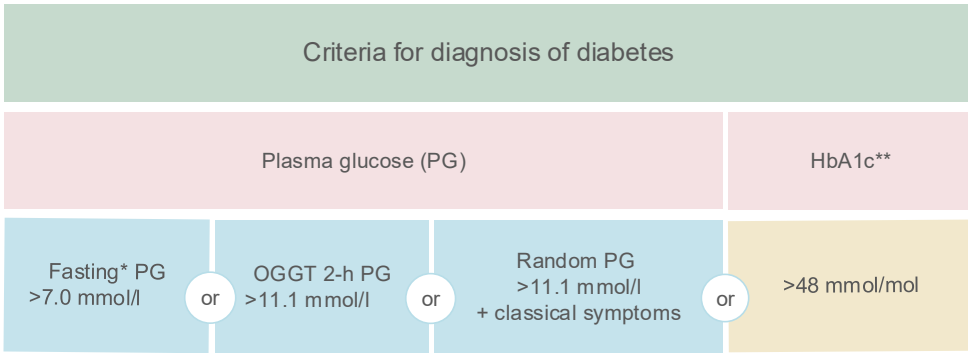

Figure 2: Classification of diabetes according to WHO, ISPAD and ADA.
*Fasting: 8 h without caloric intake.
** Test should be performed with an NGSP (nationally certified method, requires a standardised test, by an authorised laboratory).
OGTT: Oral glucose tolerance test.

Subclassification into different types

The most predominant forms of diabetes are type 1 and type 2, and most patients can be classified into one of these categories. Traditionally, type 1 diabetes has been considered a childhood disease and type 2 an adult disease. While this distinction still holds overall, the boundaries are becoming increasingly blurred. As obesity and overweight become more prevalent at younger ages, type 2 diabetes is being diagnosed more frequently in children.

Type 1 diabetes

Type 1 diabetes is an autoimmune condition that results in absolute insulin deficiency due to immune-mediated destruction of pancreatic β-cells. Although traditionally defined as childhood diabetes, it can occur at any age. Recent studies indicate that approximately 50% of all individuals with type 1 diabetes are diagnosed after the age of 18 [18-20]. The onset is typically rapid and acute, sometimes presenting with diabetic ketoacidosis (DKA) at the time of diagnosis. Once symptoms appear, the condition is usually easily recognisable.

Type 2 Diabetes

Type 2 diabetes is characterised by a progressive loss of adequate β-cell insulin secretion, typically occurring against a background of insulin resistance, often related to obesity or ageing. It is not an autoimmune disease. While more common in adults, it is increasingly diagnosed in younger individuals, likely due to the rising prevalence of childhood obesity. Management often begins with lifestyle modifications and oral glucose-lowering agents, with insulin therapy added if needed. The condition reflects an inadequate insulin response in the presence of increasing insulin resistance.

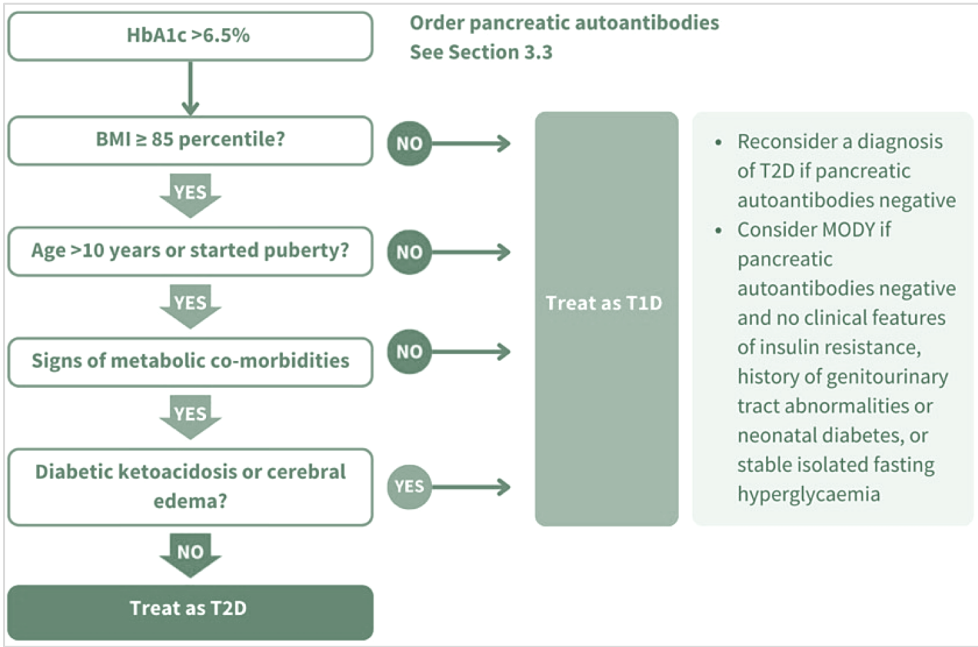

Figure 3: ISPAD's guidelines for diagnosing type 1 and type 2 diabetes (T1D, T2D) in unclear cases. Adapted from Shah et al. [21], licenced under CC BY 4.0.

Monogenic diabetes

Monogenic forms of diabetes, caused by mutations in a single gene, are rare and include maturity-onset diabetes of the young (MODY), specific syndromes that include diabetes, and neonatal diabetes, the latter typically diagnosed before six months of age [22]. While uncommon, these forms are important to recognise, as their treatment, prognosis, and inheritance patterns differ from those of type 1 and type 2 diabetes. Accurate identification can enable more targeted therapy, genetic counselling, and prevent unnecessary insulin use in some cases.

Other specific types of diabetes

Other specific types of diabetes include gestational diabetes, mitochondrial diabetes, and secondary diabetes due to other causes such as pancreatic diseases (e.g., cystic fibrosis, pancreatitis) or pancreatic surgery, drug- or chemical-induced diabetes, tumours, mitochondrial disorders, and other endocrine diseases. Recognising these less common forms is essential for accurate diagnosis, appropriate treatment, and a more nuanced understanding of the overall heterogeneity of diabetes in children.

Dilemmas regarding clinical definition

Distinguishing between diabetes types in children is not always straightforward, and in clinical practice, not all cases can be neatly defined. A patient may present with features of more than one condition – for example, having type 1 diabetes while also being overweight or obese, leading to insulin resistance.

With earlier detection through screening programmes or participation in research studies, overlapping presentations have become more apparent. These include cases of DKA in individuals with type 2 diabetes, autoantibody positivity in type 2 diabetes, and autoantibody negativity in type 1 diabetes. Coupled with the rising prevalence of obesity in young people, these overlaps make the distinction between diabetes types increasingly difficult.

Epidemiology

The incidence of both type 1 and type 2 diabetes has increased worldwide in recent decades [23, 24]. For type 1 diabetes, incidence has risen both in Sweden and globally since the second half of the 20th century, with an average annual increase of about 3-4%, and with a particularly marked rise among younger children [23, 25-28]. Globally, in 2021, 529 million people, or 6.1% of the population, were living with diabetes, of whom 96% were diagnosed with type 2 diabetes [24].

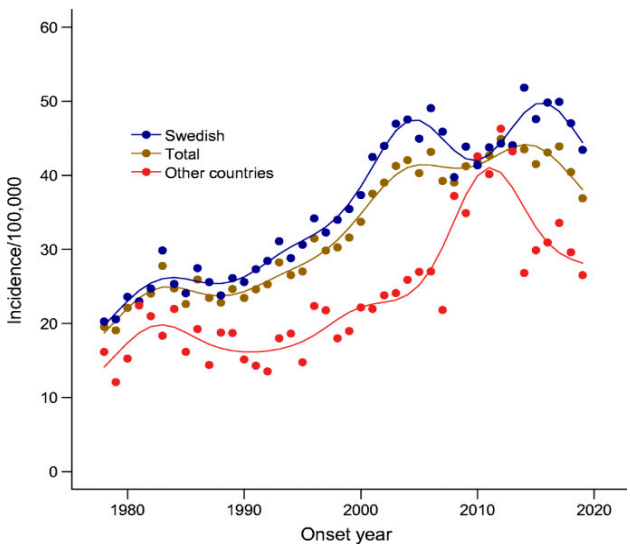

Figure 4: Incidence of type 1 diabetes over recent decades**.** Reproduced from Waerenbaum et al. [28], licensed under CC BY 4.0.

In 2025, an estimated 9.5 million people are living with type 1 diabetes, and of these, 1.9 million are under the age of 20 [27]. The highest incidences of type 1 diabetes are seen in Finland and Sweden (and, intriguingly, in Sardinia). In recent years, new countries are approaching a similar level to Sweden, such as Saudi Arabia [27]. However, the largest relative increase is seen in low-incidence countries, such as China [29].

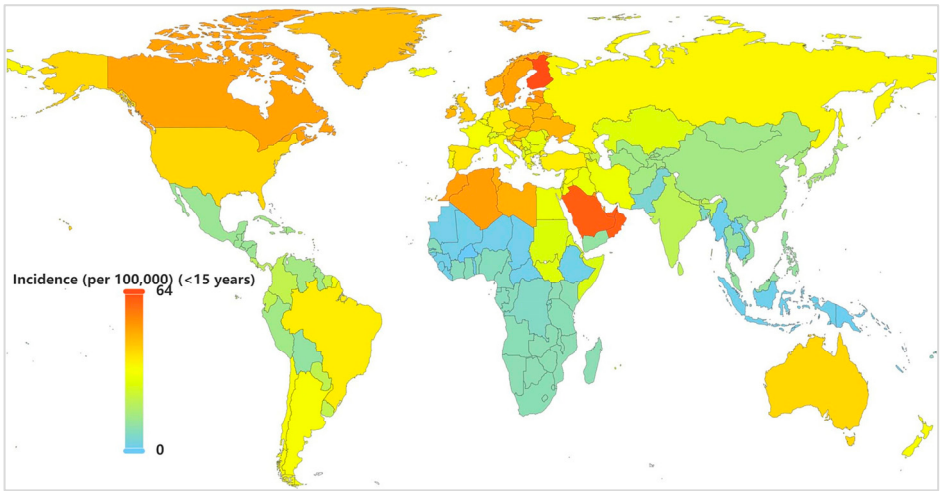

Figure 5: Worldwide distribution of type 1 diabetes in children <15 years. Reproduced from Ogle et al. [27], licenced under CC BY-NC-ND.

Large global differences remain in both incidence and access to, as well as quality of, care. Life expectancy after a diagnosis of type 1 diabetes varies widely, ranging from 6 to 66 years in different regions, reflecting a loss of 8-49 years compared with the general population [30].

For type 2 diabetes in children, the data are much more scarce and less reliable, but the highest numbers are reported in China, India and the United States [31]. The highest prevalence has been reported as 520 per 100,000 in China and 212 per 100,000 in the US, whereas some European countries report rates as low as 0.6-1.2 per 100,000 [32].

In Sweden, the overall prevalence of diabetes in 2024 was 6.2% across both children and adults, including all types combined. Among children alone, a total of 8,712 were living with diabetes, and the incidence in 2023 was 38 per 100,000 children. In contrast to the global adult pattern, 96.9% of Swedish children with diabetes have a type 1 diabetes diagnosis [33].

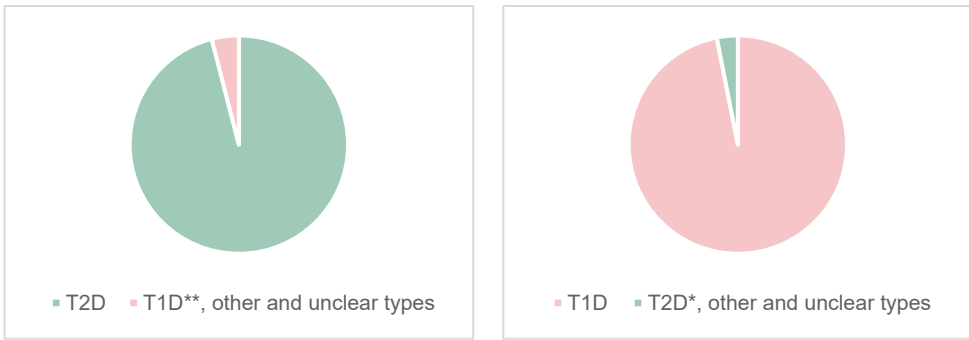

Figure 6 a + b: Comparison of the ratio of type 1 and type 2 diabetes (T1D, T2D). Global ratio of type 1 diabetes (T1D) to type 2 diabetes (T2D) across all ages compared with the ratio of T1D to T2D in Swedish children, illustrating the inverse relationship.

In conclusion, while in most contexts the term 'diabetes' refers to type 2 diabetes due to its predominance in the global population, the focus of this thesis will, from this point onward, be directed toward type 1 diabetes.

Type 1 diabetes

Pathophysiology

The β-cells are located in the Islets of Langerhans in the endocrine part of the pancreas. They are insulin-producing cells, and their destruction leads to an insulin deficiency and subsequently hyperglycaemia.

At the onset of disease development, a trigger – likely involving a combination of genetic susceptibility and environmental factors – initiates the autoimmune process. This trigger causes the β-cells to release antigens, which activate autoreactive lymphocytes that have escaped the negative selection in the thymus. CD4+ helper T cells recognise these β-cell antigens and recruit both T and B cells. The B cells produce autoantibodies, which serve as biomarkers of the autoimmune process, while CD8+ cytotoxic T cells directly attack the β-cells. In parallel, both B and T cells release cytokines, driving local inflammation that further contributes to β-cell destruction. Regulatory T cells, which normally suppress autoreactive immune responses, are impaired and do not exert their normal protection.

Autoantibodies

Autoantibodies are a well-established component of the autoimmune process leading to pancreatic β-cell destruction. They can be detected years before the onset of clinical diabetes. The presence of at least two diabetes-associated autoantibodies,

in combination with an HLA risk genotype, confers a 10-year risk of about 70% and a lifetime risk approaching 100% for progression to type 1 diabetes [34]. More than 90% of patients with type 1 diabetes present with at least one autoantibody, most commonly directed against glutamic acid decarboxylase (GADA), insulinoma antigen-2 or islet antigen-2 (IA-2A), insulin (IAA), or zinc transporter 8 (ZnT8A) [35, 36].

Autoantibodies have been recognised since the 1970s, when islet cell antibodies were first described. Subsequent discoveries included IAA, GADA, IA-2A and, more recently, ZnT8A. Initially thought to be directly pathogenic, later histopathological studies demonstrated insulitis and highlighted the central role of T cells in β-cell destruction. Today, autoantibodies are primarily regarded as biomarkers of ongoing disease activity, with a central role in prediction studies and as a valuable diagnostic tool.

Despite this, the role of autoantibodies in the pathogenesis of type 1 diabetes is not fully understood, and around 10% of patients present without detectable autoantibodies at diagnosis [35, 36]. Explanations for autoantibody negativity include the disappearance of previously present antibodies, antibody levels below detection thresholds, misclassification, or the involvement of not yet identified autoantibodies or other biomarkers [37]. Reversion of autoantibody positivity has also been reported, particularly in children with a single antibody, and is associated with lower risk compared to persistent positivity, though still higher than in those who never developed autoantibodies [38].

Beyond their role as biomarkers of autoimmunity, autoantibodies also reflect disease heterogeneity and progression. Both the type and number of autoantibodies, especially when combined with age at first seroconversion, are strongly predictive of progression. This underlines their importance in defining heterogeneity prior to clinical diagnosis and justifies their inclusion in precision staging frameworks for type 1 diabetes. More recently, autoantibody profiles have been incorporated into risk scores alongside age and genetic background, further refining prediction [39].

Stages of type 1 diabetes

The idea of different stages of type 1 diabetes, acknowledging that the disease process begins before clinical diagnosis and that onset is not always equal to clinical symptoms, emerged alongside the discovery of diabetes-associated autoantibodies and the spread of prediction studies. These studies demonstrated that the presence of two or more autoantibodies confers a very high risk of developing type 1 diabetes, with around 70% progressing within 10 years and more than 80-90% over a lifetime [34, 40]. In 2015, Insel et al. proposed a framework that has since formed the basis of staging. This describes a progression from stage 1, when two or more autoantibodies have appeared but blood glucose remains normal, to stage 2, when dysglycaemia is present but not usually clinically apparent, and finally to stage 3,

when symptoms develop and a diagnosis is made [41]. More recently, revisions to this model have been suggested, introducing subdivisions such as stage 2a/b and 3a/b, although their definitions are not yet clearly established [42]. This staging system has become a key foundation for considering population-based screening programmes, identifying individuals at risk of developing the disease.

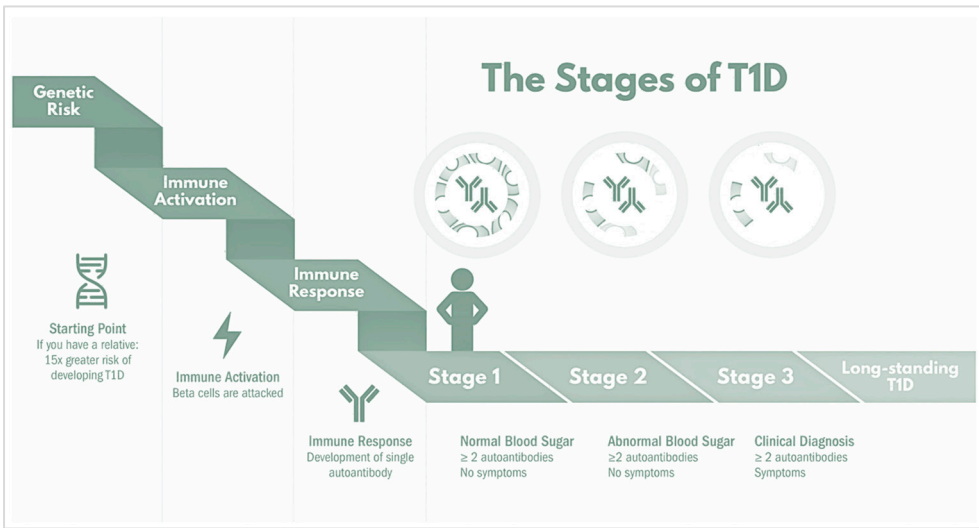

Figure 7: The stages of type 1 diabetes. Reproduced with permission from Greenbaum et al. [43] © Springer Nature. Minor modifications made for stylistic consistency.

Aetiology

The aetiology of type 1 diabetes has been extensively studied, and although important insights have been gained, uncertainty remains regarding why the disease develops and why onset occurs at a particular time. Multiple risk factors and theories have been proposed, and while convincing evidence supports the role of several contributing factors, no single unifying explanation has been identified. Important pieces of the puzzle are still missing. In this section, I will present some of the current theories and established findings.

Genetics

The human leukocyte antigen (HLA) complex, located on the short arm of chromosome 6, represents the primary region of susceptibility for type 1 diabetes. It encodes the DR, DQ, and DP loci and has long been recognised as the main genetic contributor to disease risk [44, 45]. The highest risk is conferred by carrying the HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes, either alone or in combination [46]. The role of HLA molecules is to present antigens to helper T cells and thereby stimulate the immune response [47].

There is increasing evidence that genome-wide association studies are a powerful approach for identifying genes involved in human diseases. The tag single-nucleotide polymorphism (SNP) genotyping approach captures most of the genetic variation in the HLA region by using representative SNPs that serve as markers for nearby variants, offering a simpler alternative to classical HLA typing. To date, more than 40 SNPs outside of the HLA region have been associated with type 1 diabetes, and over 69 SNPs with type 2 diabetes [48].

Based on these findings, Oram et al. have developed a genetic risk score that integrates HLA-risk alleles, non-HLA genes, and 30 SNPs, enabling the prediction of children at high genetic risk of developing type 1 diabetes-associated autoantibodies – about 1 in 10 children identified by this risk score develop autoantibodies [49, 50]. This risk score has been applied both for screening children at risk and, in ambiguous cases, for distinguishing between type 1 and type 2 diabetes [49, 51, 52].

Epigenetics refers to changes in gene expression without alterations in the DNA sequence itself. Epigenetic regulation provides a molecular link between genetic susceptibility and environmental exposures, shaping cellular phenotypes [53, 54]. Prolonged inflammatory stimuli can imprint epigenetic memory through methylation changes, amplifying immune responses and influencing disease onset and severity [55]. As an example of epigenetic influences and the modification of genetic risk, studies have shown that individuals who move from a low-incidence area to a high-incidence area have an increased risk of developing type 1 diabetes. This suggests that environmental exposures can interact with genetic predisposition to alter disease risk [56, 57].

Family history

For decades, it has been recognised that family history plays a role in the development of diabetes. In general, a family history of diabetes increases the risk. Traditionally, the focus has been on type 1 diabetes being inherited within families with type 1 diabetes, type 2 diabetes within families with type 2 diabetes and MODY within families with MODY. More recently, evidence suggests an overlap, showing that children with type 1 diabetes are more likely to have parents or grandparents with type 2 diabetes compared to children without diabetes [58-62]. Studies of family history in patients with type 1 diabetes have found that both type 1 and type 2 diabetes are more common among relatives of type 1 diabetes patients than in the general population [58, 60, 61]. However, it is important to note that most children who develop diabetes do not have a family history of the disease at all, which should be considered when assessing risk and targeting prevention efforts. One consistent finding is that children of mothers with type 1 diabetes have a lower risk than children of affected fathers [63].

Hygiene hypothesis

The hygiene hypothesis, first introduced by Strachan in 1989 in relation to allergic diseases, suggests that children in industrialised countries experience significantly fewer infections in early childhood than in the past, leading to less immune system training and a tendency for stronger immune reactions later [64]. The concept was later linked to diabetes by Kolb et al., discussing it as a possible explanation for the rise in incidence of type 1 diabetes [65], and viruses have been discussed as a contributor to this [56]. This aligns with studies showing that daycare attendance is a protective factor that decreases the risk of developing diabetes [66, 67].

Over time, the hygiene hypothesis has been modified and expanded to incorporate factors from multiple biological levels, including the human microbiome [68, 69].

Viruses

There are hypotheses that viral exposure, particularly to enterovirus, may play a role both in initiating the immune response leading to the destruction of the pancreatic β-cells, and also that they might be a part in the progression to clinical diabetes [70, 71]. It has also been suggested that intrauterine viral exposure could contribute to this process [57, 72-75]. Some studies report that maternal enteroviral infection during pregnancy increases the risk of type 1 diabetes in the offspring [72, 76], but others have not confirmed this association [74, 75, 77]. Beyond the prenatal setting, enterovirus infections are more frequently observed in children who later develop type 1 diabetes [78].

The COVID-19 pandemic brought new insights, as children infected with the virus were found to have a higher risk of developing autoimmunity [79, 80], and ongoing trials are investigating whether COVID-19 vaccination may help prevent or delay the onset of type 1 diabetes [81].

Interestingly, certain viral exposures may even be protective and reduce the risk of islet autoimmunity [82, 83].

Perinatal period

The perinatal period has been widely discussed as an influential window for the risk of developing type 1 diabetes. Maternal respiratory infections and gastroenteritis during pregnancy have been identified as risk factors for type 1 diabetes in the offspring [84, 85]. Epigenetic modifications established early in life, including those triggered by maternal enteroviral infections, may create lasting vulnerabilities that increase later-life disease risk [54]. In addition, perinatal factors such as maternal obesity [86] and the child's birthweight may contribute to the child's risk of developing diabetes. The role of Caesarean delivery has been debated, and some studies show an increased risk of type 1 diabetes in the offspring [87, 88] while others do not [89].

Seasonality

Studies have been conducted in several countries examining the association with birth month and seasonality. These show that in high-incidence areas, such as Finland, Sweden and Sardinia, there is a clear difference in the distribution of birth months among individuals with type 1 diabetes compared with the background population [90-94]. However, in low-incidence countries, such as Japan and China, no clear differences have been observed [95, 96].

The finding that people with type 1 diabetes are more often born during certain times of the year compared with the background population supports the hypothesis that viral infections play a role as a trigger for the autoimmune process [91, 97]. Similar patterns have been reported for other autoimmune diseases, such as inflammatory bowel disease, celiac disease, and multiple sclerosis, which also show seasonal variation similar to that observed in type 1 diabetes [98-100].

Seasonal variation has also been observed for disease diagnosis and clinical onset, with diagnosis being more common during the colder months. This is thought to be related to the higher frequency of infections during this period, with the stress of an infection potentially tipping pre-existing dysglycaemia into overt diabetes [101].

Overweight & obesity

The acceleration hypothesis proposes a link between type 1 and type 2 diabetes, suggesting that the rising incidence of type 1 diabetes may partly be explained by the parallel rise in overweight and obesity among children. According to this model, three accelerators drive disease progression: the intrinsic rate of β-cell loss, insulin resistance (associated with obesity, rapid growth, and puberty) and, specific to type 1 diabetes, the autoimmune attack [102, 103]. The TEDDY study has shown that faster growth and higher BMI in children are associated with earlier seroconversion to autoantibody positivity and a more rapid progression to type 1 diabetes [104, 105].

Other environmental factors

In addition to the environmental factors mentioned above, a range of other potential contributors to the development of type 1 diabetes have been discussed, including gluten, cow's milk, vitamin D, and the human microbiome. Apart from breastfeeding during infancy, which appears to have a protective effect, the findings from these studies have been largely inconsistent and inconclusive [57]. The role of the gut microbiota has also received attention, with evidence suggesting that dysbiosis may play a role in the development of type 1 diabetes [54, 106, 107].

Recently, results from the large, long-running TEDDY (The Environmental Determinants of Diabetes in the Young) study were published, providing new insights into both protective and risk factors for the development of type 1 diabetes. They found that persistent viral infections, particularly with enterovirus B, are

thought to play a role in triggering islet autoimmunity. Beyond viral exposure, a range of nutritional and metabolic factors may influence disease progression in genetically susceptible children. Protective factors that have been suggested include adequate levels of vitamin D, vitamin C, n-3 fatty acids, probiotics, and regular physical activity. In contrast, excessive weight gain and high protein intake have been linked to accelerated progression toward clinical diabetes, while psychosocial stress may also contribute, although the underlying mechanisms remain unclear [108]. See Figure 8.

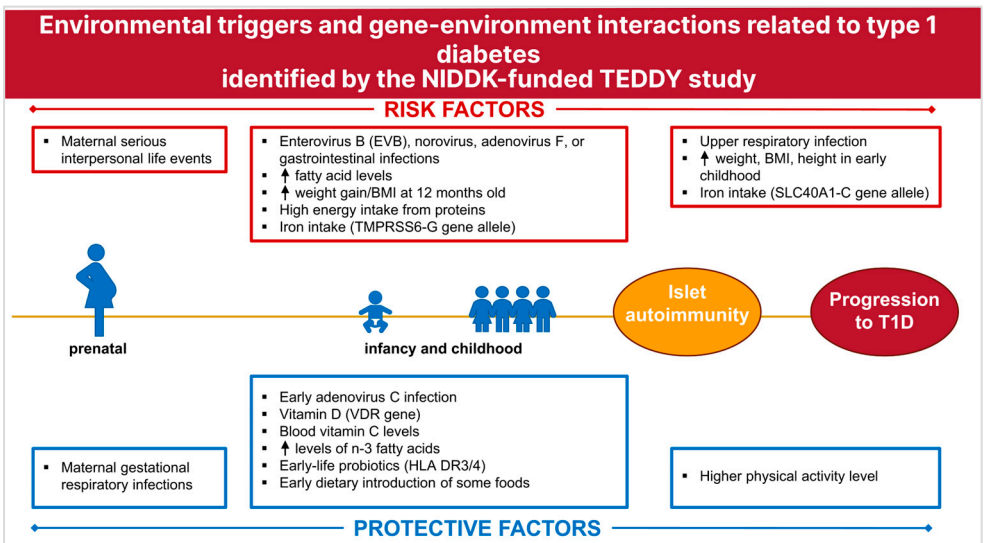

Figure 8: Risk factors and protective factors for type 1 diabetes from TEDDY (The Environmental Determinants of Diabetes in the Young) study. Reproduced with permission from Rewers et al. [108]. © 2025 John Wiley & Sons.

Sardinia

Sardinia represents a unique epidemiological setting and is often described as a 'natural laboratory' for type 1 diabetes. As a relatively isolated island population with limited genetic variability and more easily controlled environmental factors, Sardinia offers particular insights. The incidence of type 1 diabetes in Sardinia has long been among the highest in the world, second only to Finland. Studies suggest that Mycobacterium avium paratuberculosis infections, high levels of heavy metals, and common viral exposures contribute to the island's exceptionally high incidence, supporting the idea that multiple interacting environmental agents contribute to disease risk [109].

Clinical presentation

The typical symptoms of type 1 diabetes at diagnosis in children are polydipsia, polyuria, weight loss, and fatigue, with additional potential symptoms including blurry vision, enuresis, mood changes or irritability and abdominal pain. Characteristic clinical findings include elevated blood glucose and HbA1c, often accompanied by weight loss. Boys are generally diagnosed at a younger age and with lower HbA1c levels, and the disease is more common among boys, especially after puberty [110]. A serious complication of clinical onset is diabetic ketoacidosis (DKA), the risk of which increases with delayed diagnosis.

Management

Treatment

There is currently no curative treatment for type 1 diabetes. While this is true for most autoimmune diseases, many have seen the development of disease-modifying therapies, such as biologics and immunomodulators, that can alter the disease course. In contrast, replacement of the missing insulin with exogenous insulin remains the only established therapy for type 1 diabetes. Insulin can be delivered through multiple daily injections or via pumps, most often sensor-augmented and including hybrid closed-loop systems, so-called 'smart pumps' [111]. Over recent decades, treatment has been further enhanced by the development of continuous glucose monitoring (CGM) systems [112], which measure interstitial glucose levels and reduce the need for frequent finger-prick testing.

Additional treatments include glucagon for the management of acute hypoglycaemia. For individuals with signs of insulin resistance or a double diagnosis, adjunctive therapies such as metformin or GLP-1 receptor agonists may be considered in certain cases [113].

Teplizumab, recently approved in the US, can be offered to individuals at risk (genetic predisposition and two or more autoantibodies at screening) to delay the onset of type 1 diabetes by up to two years [114, 115].

Pancreas transplantation is an option for some patients but requires lifelong immunosuppressive therapy, which carries significant risks. On the research horizon are novel approaches using genetically modified allogeneic donor islet cells designed to evade immune detection, thereby eliminating the need for immunosuppression. A recent breakthrough demonstrated that such transplanted insulin-producing cells can survive and function for at least three months in a person with type 1 diabetes without the need for anti-rejection medication [116]. This marks the first successful proof of concept for this approach and represents an important step forward in cell-based treatment research.

Glucose control & complications

Glycaemic management is central to diabetes management. It influences daily well-being, guides the evaluation of treatment effectiveness, and is critical for long-term outcomes, including the risk of developing diabetes-related complications. The standard measure of glycaemic management is glycated haemoglobin (HbA1c), which reflects the proportion of haemoglobin molecules bound to glucose and provides an estimate of average blood glucose levels over the preceding 2-3 months. HbA1c is associated with diabetes-related complications, with higher levels increasing the risk of microvascular complications and intensive treatment delaying the onset of long-term complications [117]. The greatest morbidity related to type 1 diabetes is due to chronic microvascular complications, including retinopathy, nephropathy, and neuropathy [117, 118]. Importantly, this is already relevant early after diagnosis and in adolescence, as it has been shown that early poor metabolic management and higher HbA1c is associated with a higher HbA1c later and also with earlier development of complications such as microalbuminuria and retinopathy [119]. Years of poor glycaemic management in adolescents confer elevated risk even if improved later [120].

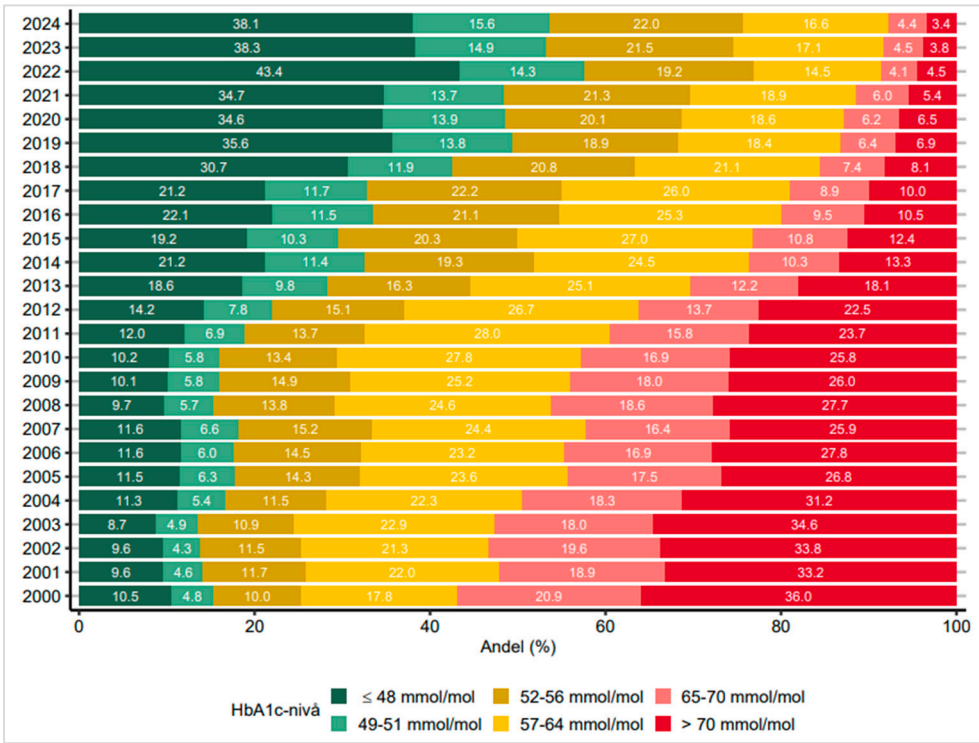

Figure 9: Distribution of HbA1c over time among children with type 1 diabetes at paediatric diabetes clinics in Sweden, expressed in mmol/mol. Andel = proportion (%). Source: National Diabetes Register (NDR), Annual Report 2024 Results [33].

Diabetes duration and prolonged hyperglycaemia are the main risk factors for late complications in children with type 1 diabetes. Although some studies suggest that diabetes duration itself – independent of glycaemic management – acts as a risk factor for complications [121, 122], these findings can be difficult to interpret because glycaemic management and treatment outcomes have improved considerably over the years, making it challenging to fully adjust for historical differences in management when assessing risk.

While persistent hyperglycaemia is the main driver of complications, additional contributing factors have been identified. Several studies suggest that genetic predisposition may play a role [123-127], with specific HLA alleles conferring either increased risk or protection [124]. Overweight and obesity have also been linked to increased risk of complications [128]. Socioeconomic factors are also significant, with higher levels of maternal education and household income being associated with lower HbA1c levels [129].

Over time, as treatment and technology have advanced and enabled more precise diabetes management, overall glucose and HbA1c levels have shown a decline. In Sweden, the target HbA1c has been set at <48 mmol/mol since 2017, whereas in the US, the recommended target remains <53 mmol/mol [14].

In parallel, increasing collaboration among diabetes teams across Sweden, the use of quality registers, and lowering of national HbA1c goals have raised awareness of risks and contributed to systematic improvements. Together, these developments, mirrored by international advances, have led to improved glucose management in Sweden and worldwide over recent decades [130]. Sweden stands out for its excellent glycaemic management and lower incidence of severe hypoglycaemias compared to other high-income countries [131, 132]. The use of CGMs in Sweden is widespread, and over 90% of children with type 1 diabetes have some sort of sensor [33, 133].

A large international study reported a decline in mean HbA1c among children with type 1 diabetes between 2013 and 2022, from 66.5 to 59.4 mmol/mol, accompanied by reductions in both hypoglycaemia and diabetic ketoacidosis (130). In Sweden, mean HbA1c levels in children under 7 years decreased from 58 to 50 mmol/mol between 2008 and 2018 (115). Data from the NDR shows that the mean HbA1c among Swedish children has decreased from 64.4 in 2008 to 51.9 in 2024 [33, 134]. See Figure 10.

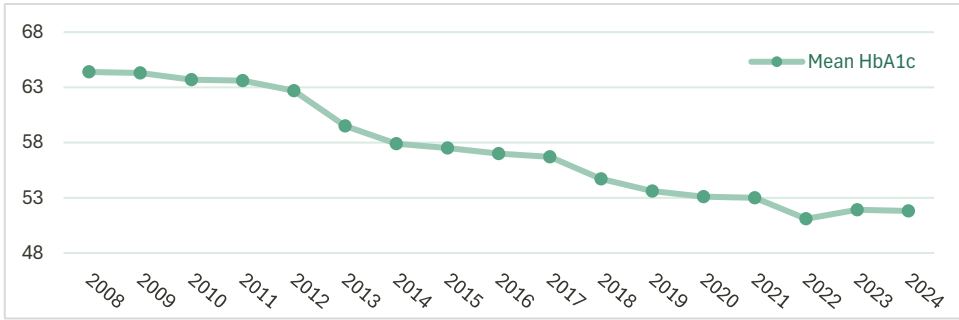

Figure 10: Mean HbA1c over time (2000–2024) among children with type 1 diabetes in Sweden, expressed in mmol/mol. Source: National Diabetes Register (NDR), Adapted from Annual Report 2024 Results [33] and Annual Report 2012 [134].

Acute complications

The main acute adverse events in diabetes are hypoglycaemia and diabetic ketoacidosis (DKA). DKA is a life-threatening condition that develops when there is an absolute or relative deficiency of insulin, which may occur due to poor treatment adherence, technical problems, or other factors. It can present at diagnosis but may also arise later in the course of the disease. In Sweden, 27% of children with type 1 diabetes present with DKA at diagnosis, but among those under 2 years of age the rate is as high as 55% [33]. Globally, the frequency of DKA varies widely, reaching up to 70% in some settings [135].

Hypoglycaemia, on the other hand, results from excess insulin relative to physiological needs and is a common day-to-day challenge for people living with diabetes. Severe episodes can lead to seizures or loss of consciousness, and recurrent hypoglycaemia has been associated with an increased risk of cognitive impairment. Beyond the physical risks, fear of hypoglycaemia greatly affects quality of life; many patients, particularly adolescents, adopt strategies to avoid it, which may contribute to higher HbA1c levels and overall suboptimal glucose control.

Living with type 1 diabetes

Living with a chronic disease such as type 1 diabetes is demanding, requiring constant attention and daily self-management. These challenges become particularly evident during the teenage years, a complex and challenging period already marked by continuous physical and psychological change. To face this while also managing diabetes, which limits independence and makes a young person stand out among peers, adds an extra layer of difficulty that should not be underestimated.

Beyond age-related challenges, social and economic circumstances also influence outcomes. In Sweden, diabetes care, medications, and technical aids are provided free of charge. However, even with universal and free healthcare, children from families with lower socioeconomic status have poorer glycaemic outcomes [136]

and a higher risk of cardiovascular disease [137]. In other parts of the world where healthcare is not readily available or affordable, the burden is even greater, regardless of the structure of the healthcare system.

A considerable proportion of children and adolescents with type 1 diabetes also experience what has been termed diabetes distress. Hislop et al. report that one-third of young adults experience such stress [138], and Gillani et al. describe a higher prevalence in women [139]. Distress can be amplified by healthcare encounters, where the pressure to achieve perfect glucose values may unintentionally reinforce feelings of inadequacy. Although diabetes distress is clearly associated with poorer metabolic outcomes, it remains unclear whether it also increases the risk of long-term complications [140].

While new technologies such as insulin pumps and CGMs have improved diabetes management and outcomes, they can also bring new forms of stress, with constant data and higher expectations for near-perfect management. Much of this is linked to self-esteem and the feeling of being 'good' or 'bad' at clinic visits. Socioeconomic disadvantage often adds to these challenges, as limited access to healthy foods and higher rates of obesity can contribute to poorer glycaemic management, greater distress, and a vicious cycle of worsening outcomes.

Parental distress is also a concern. It is associated with an increased risk of depression in both parents and children and with higher HbA1c levels in the child, as well as more family conflicts and reduced quality of life among parents [141].

A recent Swedish study showed that the parental income of children with type 1 diabetes is negatively affected for both parents, with a greater impact on mothers, and most pronounced when the child was diagnosed before the age of 6 [142].

Heterogeneity in diabetes

Type 1 diabetes is a multifactorial disease influenced by both genetic and environmental factors. Risk appears to be shaped by the contribution of multiple genes in combination with a variety of environmental exposures.

Several frameworks have been proposed to explain the heterogeneity observed within and between diabetes types, including the palette model, the threshold hypothesis [143] and, more recently, the concept of endotypes. Endotypes refer to distinct subtypes defined by underlying disease mechanisms – for example, more aggressive immune responses and rapid β-cell loss in children diagnosed at younger ages compared with slower progression and different autoantibody profiles in those diagnosed later [144-147]. Although promising, this remains a developing field that requires further refinement before it can reliably guide clinical care [144, 146]. In parallel, a Swedish data-driven cluster analysis proposed a reclassification of adult-onset diabetes, mainly type 2 diabetes, based on its heterogeneity, with the aim of

identifying distinct risk profiles for complications [148]. Together, these approaches highlight overlapping mechanisms and may provide a basis for more precise and individualised treatment strategies. Together, these approaches highlight overlapping mechanisms and may provide a basis for more precise and individualised treatment strategies.

Over time, the population of children with type 1 diabetes has become increasingly diverse, as environmental factors play a greater role [149]. One example is the shift in HLA genotypes over time, compared with 30-50 years ago. Children diagnosed today are less likely to carry the highest-risk genotypes, while low- and moderate-risk genotypes have become more common, particularly among those diagnosed at older ages [150-152]. The rising incidence of type 1 diabetes, together with the growing proportion of lower-risk genotypes and differences in risk in people migrating from low-risk to high-risk countries, highlights the importance of environmental contributions [153].

Several studies have described factors that explain the heterogeneity in the paediatric type 1 diabetes population, including age at onset, HLA genotype, residual β-cell function, and autoantibody patterns [61, 145, 154-159]. The diversity of the disease is further reflected in differences in autoantibody patterns, which vary by sex [154, 156] and by age at onset [145, 160].

Other contributors to heterogeneity have also been described. Seasonality is one such example: some HLA types show pronounced seasonal patterns, others display age-dependent variation [161], and regional differences have been reported [101]. Interestingly, the distribution of diagnoses shifted during the COVID-19 pandemic, with more cases in summer and autumn instead of the usual winter peak [162].

Another example is that overweight and obesity might play a role, as children with a low-risk HLA genotype are more likely to present with higher BMI at diagnosis [163], and increasing BMI has been associated with a higher risk of islet immunity and type 1 diabetes [164].

Longitudinal studies of children at increased genetic risk have added further nuance. The TEDDY study has shown that the identity of the first appearing autoantibody – IAA or GADA – is associated with the underlying HLA genotype, and that predictors and rates of progression vary according to the first-appearing autoantibody [157]. Young age at seroconversion predicted progression both to multiple autoantibodies and from autoantibodies to diabetes, except in children whose first autoantibody was GADA. A family history of type 1 diabetes and carrying the HLA-DR4 allele were associated with progression to multiple autoantibodies but not to diabetes. While sex did not influence the development of multiple autoantibodies, females progressed faster from multiple autoantibodies to clinical diabetes [165]. Viral exposure early in life may also trigger β-cell destruction [57, 72-75], and maternal respiratory or gastrointestinal infections

during pregnancy have been identified as risk factors for type 1 diabetes in the offspring [84, 85].

Finally, heterogeneity extends to complications. Genetic differences appear to influence complication risk, and younger children have been shown to have a lower likelihood of developing microalbuminuria [166].

Taken together, these findings suggest that the paediatric type 1 diabetes population has become increasingly diverse, with environmental factors playing a greater role.

Aims

The overall aim of the thesis is to gain a better understanding of the heterogeneity among Swedish children with type 1 diabetes and to identify potential subgroups, using data from the Swedish BDD Cohort, which comprises children born between 2005 and 2010.

Specific aims:

- Does the month of birth influence the risk of type 1 diabetes? (Paper I)
- Can patterns be found between the month of birth, age at diagnosis, sex, HLA-type and type of autoantibody at diagnosis? (Paper I)
- What is the prevalence of parental diabetes among children with and without type 1 diabetes? (Paper II)
- Are there any clinical differences at diagnosis of type 1 diabetes dependent on family history? (Paper II)
- Do clinical characteristics differ at type 1 diabetes diagnosis between children with or without autoantibodies? (Paper III)
- Is a family history of diabetes associated with differences in HbA1c and BMI levels at follow-up? (Paper IV)

Materials and methods

In Sweden, all children diagnosed with any type of diabetes are referred to paediatric diabetes teams and clinically classified at diagnosis according to the American Diabetes Association (ADA) criteria [167], with a re-evaluation of diagnosis at follow-up. They are subsequently registered and followed in the National Diabetes Register (NDR) [168].

Healthcare in Sweden is subsidised by the government, and all care related to diabetes, such as hospital visits, insulin and even insulin pumps and continuous glucose monitors (CGMs), is free of charge to the paediatric patients. This provides a unique opportunity to study the entire population without exclusions, unlike studies limited to specific regions, hospitals, racial or age groups, or different socioeconomic groups. However, despite equal access to healthcare, families still differ in their approach and capabilities to support their children in managing this chronic disease, indicating that these differences cannot be attributed to lack of care.

Population

All the papers in this thesis are based on cohorts consisting of children from the Better Diabetes Diagnosis (BDD) study.

From May 2005 until December 2010, 4,088 patients were diagnosed with diabetes and included in the BDD study. After exclusions (see statistical analysis section), the cohort comprised 3,647 children who were clinically classified as having type 1 diabetes.

This cohort has been extensively tested for the common MODY variants (GCK, HNF1A, and HNF4A) according to Carlsson et al. [169]. This was one of the reasons we have limited our analysis to this earlier period, when more comprehensive clinical follow-up and genetic testing were available.

Overall, the same cohort was used across the papers in the thesis (except for parts of Paper 1 that used a larger cohort), but variations in data handling – such as exclusions, missing data, and differences in the variables used and analysed – led to some differences in the final study populations. For details on this, see the Statistical Analysis Section and Figure 11.

Paper I: We analysed 8,641 children diagnosed between 2005 and 2016 to examine month of birth, sex, and age, and a subset of 3,647 children diagnosed between 2005 and 2010 to compare antibody and HLA profiles.

Paper II: We compared the BDD cohort with children without type 1 diabetes from the ETICS study, restricting the analysis to BDD children aged 11-13 years and to first-generation family history of diabetes, to ensure comparability for age and period of birth. We then stratified the children by family history (first and second generation) and compared the clinical characteristics at diagnosis.

Paper III: We analysed 2,753 children diagnosed between 2005 and 2010, stratified by autoantibody positivity versus negativity, and compared clinical characteristics at diagnosis.

Paper IV: We analysed 3,329 children diagnosed between 2005 and 2010, stratified by family history, and compared HbA1c and BMI at diagnosis and follow-up after 1, 2, 5, and 10 years of diabetes duration. Data from NDR were linked with data from the BDD study.

Data sources

BDD

Background

The Better Diabetes Diagnosis (BDD) study is a nationwide, population-based study of paediatric diabetes in children aged 0 to 18 years at diagnosis. It was started in May 2005 and is ongoing, and currently holds information on more than 16,000 children and adolescents. The main aim of the study is to facilitate a more precise classification of diabetes and to increase the understanding of factors contributing to the development and increased incidence of diabetes in children and adolescents, primarily by focusing on genetic risks and clinical phenotypes [170].

The BDD study is divided into two phases, BDD1 and BDD2. BDD1, conducted between 2005 and 2010, corresponds to the cohort included in Papers II-IV, during which 40 of the 42 paediatric diabetes clinics in Sweden participated.

As a result of the BDD study, analyses performed in the BDD1 study, such as HLA genotyping, autoantibody measurement, and C-peptide assessment, demonstrated significant value in improving the accuracy of diabetes classification in children and adolescents. Based on these results, in December 2010, the National Diabetes Society in Sweden recommended incorporating several of these analyses into routine clinical practice for newly diagnosed patients.

Accordingly, BDD2 was launched in 2011 with full nationwide participation (all clinics, with >99% of patients agreeing to take part [170]) and slightly modified protocols; only GADA and IA-2A are analysed initially (further autoantibodies tested if negative), and HLA typing is simplified to the the detection of the DQ2 and DQ8 alleles.

The BDD setting

At the time of diagnosis of diabetes, blood samples are collected along with information on clinical characteristics, family history of diabetes and other autoimmune diseases. Blood samples are also collected in a research setting and are kept in a biobank for potential later analysis, but no further tests are required from the patient.

All children are initially classified by experienced diabetes care teams using a combination of clinical features (e.g., age at onset, HbA1c, BMI, presence of DKA), autoantibodies, C-peptide, and HLA typing. Those children who are autoantibody-negative undergo further clinical and/or genetic evaluation to rule out MODY and type 2 diabetes. Diagnoses should be re-evaluated after one year as part of standard clinical follow-up.

Other data sources

ETICS

The ETICS study (Exploring the Iceberg of Celiacs in Sweden) is a cross-sectional study of healthy Swedish 12-year-olds in two cohorts, born in 1993 and 1997 (total n=11,050). The children were asked about parental (first-degree) family history for type 1 and type 2 diabetes when screened for celiac disease [171].

In Paper II, this cohort was used as a reference group for comparison of the family history of diabetes to individuals from the general population.

National Diabetes Register

The National Diabetes Register (Nationella Diabetes Registret, NDR) is the Swedish national diabetes register (formerly Swediabkids), which holds data from all the Swedish paediatric diabetes clinics that have been registered since 2000. NDR also holds data on more than 90% of adult patients with type 1 diabetes in Sweden since 1996. It was introduced to gather data on clinical characteristics and risk factors for late complications in patients with diabetes. The register has the status of a national quality registry, and the patients are informed about the register before agreeing to inclusion [130].

According to the Swedish guidelines, children with diabetes visit a diabetes centre at least four times per year. At these visits, HbA1c and other clinical parameters

such as type of treatment, insulin dose, physical activity, weight and height are measured and reported online to the register by trained nurses or physicians.

Statistics Sweden

Statistics Sweden (Statistiska Centralbyrån) is a government agency responsible for official population-based statistics and for coordinating the system for official statistics in Sweden.

Data on the distribution of birth months for the general population were retrieved from Statistics Sweden. Comparisons between individuals in the BDD cohort and individuals from the general population were made, covering all births between 1987 and 2015. The average number of births was 105,214 yearly, with a range from 88,173 to 123,985.

Variables

Age

Age was calculated on the basis of date of diagnosis and birth date.

In Paper I, participants were grouped into two categories: under 5 years and 5 years and older. This approach was chosen to isolate the youngest children as a distinct subgroup and to evaluate the influence of birth month on the risk of developing type 1 diabetes.

For Papers II and III, the cohort was stratified into three age groups: 0-6 years, 6-12 years, and 12-18 years. This approach allowed for a clearer separation between younger children and adolescents while also avoiding the creation of too many subgroups with limited sample sizes. The most diverse group was the 6-12 years, encompassing both children still in early childhood and those entering prepuberty and puberty. Studying different age groups is particularly relevant given the recent increase in type 1 diabetes among younger children, indicating that there are distinct or specific risk factors for this subgroup.

Sex

In all papers, I examined sex differences and subgroups. Although such differences have been shown previously, I was surprised by how often they are overlooked in studies exploring the heterogeneity in type 1 diabetes. In this cohort, sex differences have also been reported [35]. While not the primary focus of my analyses, exploring sex-specific patterns remains relevant for identifying meaningful subgroups. In this thesis, I have aimed to balance this interest with the need to maintain analytical clarity, avoiding an excessive number of subgroup analyses that could complicate interpretation and increase the risk of type I errors due to multiple comparisons.

Family history

In the BDD study, information on family history was collected and recorded at diagnosis by a diabetes nurse or physician. Inquiries about first-degree (parents) and second-degree (maternal and paternal grandparents) relatives regarding diabetes of different types, cardiovascular diseases, and other autoimmune diseases were made.

For Papers II and IV, family history among both parents and grandparents was considered, and the cohort was categorised into four groups: only type 1 diabetes, only type 2 diabetes, both type 1 and type 2 diabetes, or no family history of diabetes.

This broader approach was chosen to increase the number of children classified with a family history of type 2, since family history was a key variable in these papers. As information was recorded at the time of the child's diagnosis, when the child is still young, the parents are also young, typically in their 30s or 40s, and therefore less likely to have developed type 2 diabetes, even if prone to do so.

For Paper III, only parental family history was assessed: children were classified as having a parental history of type 1 diabetes if at least one parent was affected; otherwise, they were considered to have no parental history, with the same classification applied for type 2 diabetes. In this study, however, family history was not a central variable.

Month of birth

From the BDD study, we collected data on the date of birth, from which we extracted the month of birth and later season of birth.

There are limitations in comparing month of birth as a risk factor for type 1 diabetes because it is a narrow measurement that does not consider whether a child is born prematurely and because being born on the last day of one month or the first of the next can affect the outcome, so we also compared seasons of birth by categorising birth months into seasons as December–February, March–May, June–August, and September–November and into warm or cold periods as April–September and October–March to capture larger periods.

Autoantibodies

Blood samples for autoantibody analysis were collected on the first or second day after diagnosis, in most cases before the first dose of insulin was given. Analyses were performed at the Clinical Research Centre, Skåne University Hospital, Malmö. For the 4,088 children diagnosed with type 1 diabetes during the years 2005-2010, the GADA, IAA, IA2A, and ZnT8RA, ZnT8WA, and ZnT8WQA autoantibodies were analysed. The cut-off points for positive values (not including the threshold values) were IAA ≥1.0 U/ml, GADA ≥50 U/ml, IA2A >10 U/ml, ZnT8WA >75 U/ml, ZnT8RA >75 U/ml, and ZnT8WQA >100 U/ml. A detailed description of the

antibody analyses has been described previously [170]. The autoantibodies were all analysed by in-house radioimmunoassays [172, 173].

For Papers I and II, the autoantibodies were considered individually and were treated as separate variables. A child was considered positive for a given autoantibody if the level was above the positive cutoff, and negative if below (including the threshold value).

For Paper III, the children were classified as autoantibody positive if they were positive for at least one of the six autoantibodies and negative otherwise. A sub-analysis comprised 3 comparisons: (1) autoantibody-negative vs single autoantibody (single as reference), (2) autoantibody-negative vs multiple autoantibodies (multiple as reference), and (3) single autoantibody vs. multiple autoantibodies (multiple as reference).

BMI

Data on weight and height, measured at a mean duration of three months post-diagnosis, were collected from NDR, and body mass index (BMI) was calculated and measured in kg/m2.

In Paper II, we examined the outcome using relative risk, applying ISO-BMI to categorise children as normal weight, overweight, or obese, based on age-adjusted values for those over two years of age [174]. The results were presented as relative risks for overweight or obesity.

In Paper III, in order to account for age- and sex-related variations in BMI, we used the BMI standard deviation scores (BMI-SDS), computed using Swedish reference values [175]. Overweight and obesity were defined as >+1 SDS and >+2 SDS, respectively, following established paediatric criteria [174].

In Paper IV, BMI was assessed both as a continuous measure (raw BMI) and as a categorical variable (normal weight vs. overweight/obese) at diagnosis (baseline) and after 1, 2, 5, and 10 years of follow-up. For the categorical variable, age- and sex-standardised BMI-SDS values were calculated for children (<18 years) using Swedish reference data [175], as above. For participants aged ≥18 years during follow-up, adult BMI cut-offs (25 and 30 kg/m^2) were applied. These measures were combined to classify participants as normal-weight or overweight/obese. Using both continuous and categorical BMI approaches ensured that differences were captured across the full cohort while also allowing evaluation against clinically relevant cut-offs.

HLA

The determination of HLA-DQA1 and HLA-DQB1 has been previously described [173, 176]. The HLA genotypes were classified into risk groups according to the specific aim of each paper. See Table 1.

In Paper I, the HLA genotypes were classified into three risk groups: high risk (DQ2–DQ8, DQ8–DQ8, and DQ2–DQ2), medium risk (DQ8–DQX), and low risk (DQ2–DQX), where X indicates all alleles other than DQ2 or DQ8. For some analyses, genotypes were further dichotomised into high risk and not high risk, with the latter including both medium- and low-risk groups.

In Papers II–IV, HLA genotypes were first grouped as follows: (1) HLA-DQ2/DQ8, (2) HLA-DQ8/X (where X ≠ 2), (3) HLA-DQ2/X (where X ≠ 8), and (4) HLA-DQX/X (where X ≠ 2 or 8) [172]. For analyses, these were further classified into two categories: high risk, defined by the presence of HLA-DQ2/DQ8, and lower risk, comprising all other genotypes [62].

Table 1: HLA classification used in the papers.

Papers	Original Grouping	Risk Group	Definition	Dichotomised Group
I	Three groups	High risk	HLA-DQ2/DQ8, DQ8/DQ8, DQ2/DQ2	High risk
		Medium risk	HLA-DQ8/DQX (X ≠ 2 or 8)	Not high risk
		Lower risk	DQ2/DQX (X ≠ 8)	Not high risk
II-IV	Four groups	1	HLA-DQ2/DQ8	High risk
		2	HLA-DQ8/X (X ≠ 2)	Not high risk
		3	HLA-DQ2/X (X ≠ 8)	Not high risk
		4	HLA-DQX/X (X ≠ 2 or 8)	Not high risk

HbA1c

HbA1c was analysed at different hospitals according to different laboratory methods. These are quality assured through Equalis (External Quality Assurance in Laboratory Medicine in Sweden), which makes it possible to compare HbA1c values across different clinics [177]. HbA1c is presented as International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol), and as a percentage according to the National Glycohaemoglobin Standardisation Program (NGSP).

C-peptide

Serum c-peptide levels were determined at clinical diagnosis before insulin treatment was started, using a non-fasting blood sample. Analyses of c-peptide were performed for all included patients at Linköping University in Sweden, as described previously [170].

Diabetic ketoacidosis

The pH value at diagnosis was used to identify diabetic ketoacidosis (DKA), defined as venous pH<7.30 combined with hyperglycaemia, according to ISPAD guidelines [135].

Statistical analysis

Calculations and statistical analyses were performed using SPSS Version 25.0-29.0 (IBM Inc., Armonk, NY, USA) and Microsoft Excel. A p-value of less than 0.05 was generally considered statistically significant.

Paper I

Month of birth was analysed by comparing children in the BDD cohort with the general population, both overall and stratified by sex and by age at diagnosis (<5 years or >5 years). This was performed by comparing observed values, the BDD data, to expected values calculated from the birth distribution in the general population, using chi-square tests. Each month was compared with all other months, followed by comparisons across seasons and between the warm and cold periods of the year.

For the autoantibody and HLA analyses, comparison with the general population was not possible due to the lack of available data on these variables. Instead, for autoantibodies, we compared the presence at diagnosis in each birth month with all other months within the same group, using a chi-square test. For HLA, we compared the frequency of high-risk genotypes with other genotype groups across different birth months, stratifying the analysis by age at diagnosis and sex.

We considered multiple comparisons according to Bonferroni by adjusting the alpha level to 0.004 to compensate for the 12 months of comparison.

Paper II

For Paper II, we used relative risk, with a 95% confidence interval (RR, 95% CI), to compare family history for children with and without type 1 diabetes using the reference group from the ETICS study.

Relative risk was also used for analyses of autoantibodies, DKA and overweight or obesity at diagnosis of type 1 diabetes, comparing children with a family history of diabetes to those without. Three different age groups were used to minimise age-related effects: 0-5.99 years, 6-11.99 years, and 12-17.99 years.

We used analysis of variance (ANOVA) to compare mean age at diagnosis, and the Kruskal-Wallis test for comparisons of HbA1c between different family history groups and age groups. Bonferroni correction for multiple testing was used for both tests.

We used chi-square tests to compare HLA genotypes in the different family history groups and the prevalence of diabetes among parents and grandparents.

Paper III

To explore the differences between the children with and without autoantibodies, we used t-tests for the continuous variables (age at diagnosis, c-peptide, BMI, HbA1c), and chi-square tests for the binary variables (sex, DKA, HLA-risk group, parental history of type 1 and type 2 diabetes).

We used logistic regression to examine the association between autoantibody status and the variables of interest, with sex as the main predictor. In Model 1, we adjusted for age at diagnosis, BMI, HbA1c, c-peptide, HLA, and DKA, while in Model 2, we additionally adjusted for parental history of type 1 and type 2 diabetes.

Paper IV

We compared HbA1c and BMI at 1, 2, 5, and 10 years after type 1 diabetes diagnosis across four family-history groups. We used repeated-measures ANOVA to evaluate (1) overall temporal trends, (2) mean values across all visits, and (3) point-specific differences at each time point.

Analyses were conducted crude (unadjusted), adjusted for each covariate individually, and fully adjusted using all covariates.

BMI was analysed both as a continuous variable (raw BMI, repeated-measures ANOVA) and as a categorical variable (normal weight vs. overweight/obese). We used chi-square tests and odds ratios (ORs) with 95% confidence intervals (CIs) to compare family history groups at each time point, and Cochran's Q test to assess within-group changes over time.

A Bonferroni correction was used to adjust for multiple comparisons.

Missing data & exclusions

In the period 2005-2010, 4,088 children were diagnosed with diabetes and included in the BDD study. Patients with other types of diabetes than type 1 were excluded in these papers, as well as those who no longer participated and patients with incomplete data. For details on this, see Figure 11.

Paper I: Complete data on month of birth, age at diagnosis, sex, and autoantibodies were available for 3,647 children.

Paper II: Exclusion of 44 children with more than two missing variables resulted in a final sample of 3,603 children. Sensitivity analyses in those with partial missing data yielded results similar to the main cohort.

Paper III: Exclusion of 894 patients with incomplete data resulted in a final sample of 2,753 children.

Paper IV: Exclusions due to missing data were 321 for the HbA1c analyses and 703 for the BMI analyses, leaving final analytic samples of 2,626 and 3,008 children, respectively.

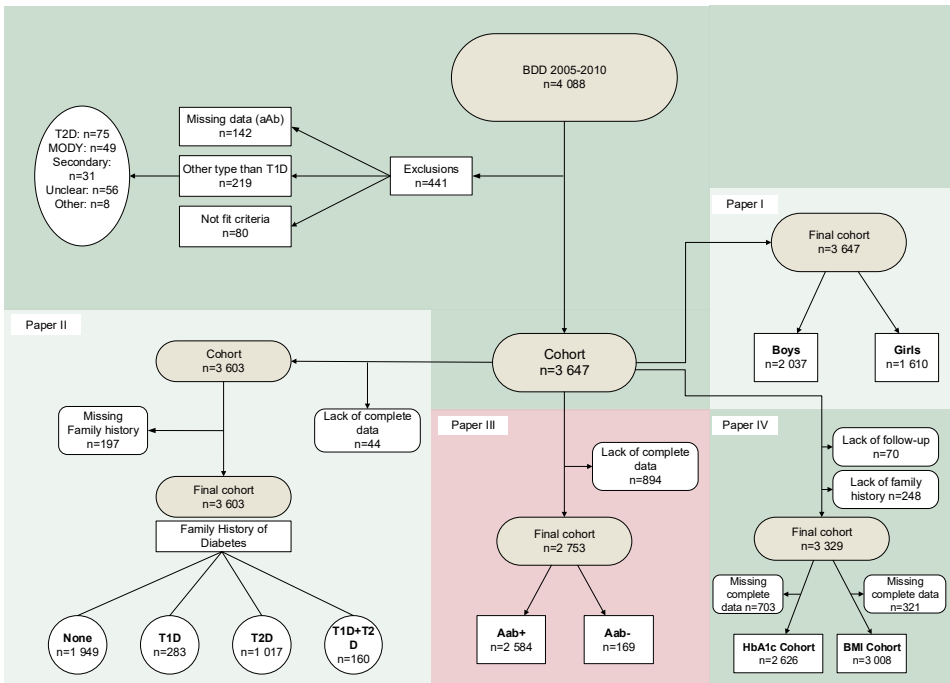

Figure 11: Flowchart illustrating participant selection before study initiation and during data preparation for Papers I-IV.

Ethical considerations

This thesis is based on data from the BDD study, including background variables such as family history of diabetes and weight and height of children and parents, as well as parameters characterising the diabetes onset, such as presenting symptoms, laboratory results, and stored blood samples that allow for future analyses.

All participants – or, in the case of minors, their legal guardians – have provided informed consent to participate in the study. Initially, the blood samples were obtained solely for research purposes; however, most of these laboratory tests are now incorporated into routine clinical practice. Consequently, the existing ethics approval governs only the use of these samples and associated data for research, rather than the act of obtaining the samples themselves. The BDD study exclusively captures data related to the time of diagnosis and baseline characteristics; no follow-up data are added to this registry. Instead, longitudinal information is collected in a separate system known as the National Diabetes Register (NDR).

In most cases, informed consent was obtained in the paediatric emergency department at the time of initial blood sampling. This practice may raise ethical questions regarding (1) ensuring that families are fully informed and (2) verifying that consent is genuinely voluntary. When a child arrives and is identified as eligible for the study, it is often immediately apparent to clinical staff that the child has diabetes. However, it cannot be assumed that the family is already fully aware of, or has fully comprehended, the diagnosis and its implications. This raises concerns about whether consent can genuinely be considered informed. To mitigate this risk, families receive verbal information from a physician or nurse and are subsequently provided with written information and a consent form, which they are not required to sign on the spot. This procedure allows families to review materials at their own pace and to sign the consent form later, thereby helping to ensure comprehension and minimising pressure to decide in the immediate presence of healthcare personnel.

The study information explicitly states that participation is voluntary and that families may withdraw at any time. Nonetheless, it must be acknowledged that families might feel compelled to consent because the request comes from a member of the healthcare team; they may want to be perceived as good parents or patients, want to secure optimal care, or they may fear possible reprimands. To address this,

the patient information leaflet clearly states that the child will receive the same quality of care regardless of participation.

Whether obtaining consent in the paediatric emergency department is optimal can be debated, given the considerations outlined above. However, an important counterpoint, at least from a data-quality perspective, is that the well-established routine of asking all newly diagnosed children to participate virtually guarantees a high inclusion rate. This, in turn, strengthens the registry and arguably serves the participants' interests, assuming they would have agreed under less stressful circumstances.

Because the BDD study captures only baseline data at diagnosis and collects no subsequent information, many families may not recall their agreement to participate. The emergency setting, combined with the emotional impact of receiving a diabetes diagnosis, means that consent to join the study is often not a central memory of their hospital visit. Younger children lack the cognitive capacity to remember or understand the process, and parents may not see the need to explain to a toddler that a sample has been stored for research. Given that no further reminders occur after the acute phase, the likelihood that participants fully grasp their ongoing right to withdraw is low. Of course, families can request withdrawal at any time.

The study in its entirety has received approval from the appropriate regional ethics review board. Any substantial future project arising from this work will be subject to a separate application for ethical clearance.

Ethical approvals

The studies included in the thesis were approved by the Central Ethical Review Board at Karolinska Institute; no 04-826/1 with amendments 2006/108-32/1 and 2007/1383-32/1, 2009/1684/32 and 2011/1069-32, and no 2019-03600 with amendment 2023-00365-02.

Results

Paper I

Does the month of birth influence the risk of type 1 diabetes?

We did not find any difference in terms of month of birth in the cohort in its entirety between the BDD cohort and the general population. Since our hypothesis was that birth month might primarily influence the risk of developing diabetes at an early age, we divided individuals with type 1 diabetes into different age categories at diagnosis. We observed that for boys diagnosed before the age of 5, being born in May was more common (p=0.004).

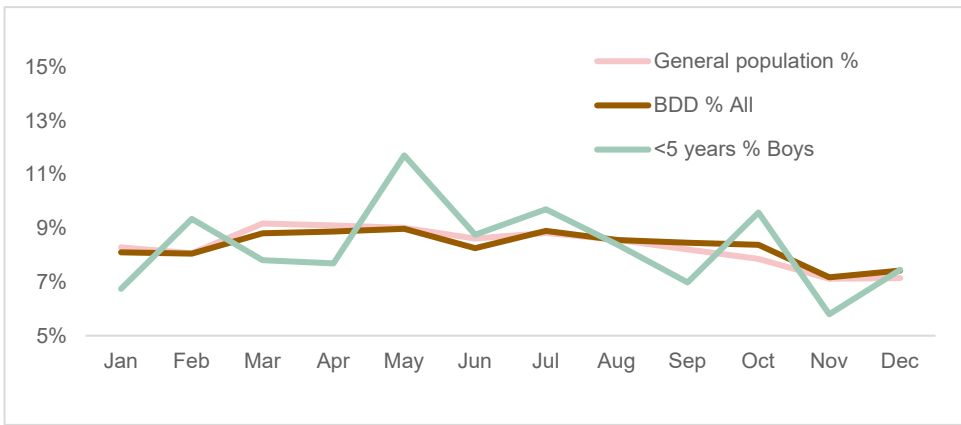

Figure 12: Distribution of month of birth in the general population, the entire Better Diabetes Diagnosis (BDD) cohort, and boys in the BDD study diagnosed before the age of 5 years, expressed as percentages (%).

The children were also stratified according to season of birth to reduce the risk of overlooking seasonal trends that might not be apparent when analysed by month. Among girls diagnosed with type 1 diabetes after the age of 5, birth during the autumn was more common compared with the general population (p=0.01), although this did not reach statistical significance after adjustment for multiple comparisons (Bonferroni-corrected threshold, p>0.004). No seasonal pattern was observed in younger girls (under 5 years) or in boys. Birth during the warmer half

of the year (April–September) did not influence the risk of type 1 diabetes compared with the colder half (October–March).

Exploring patterns between month of birth, age at diagnosis, sex, HLA-type and type of autoantibody at diagnosis

We examined boys diagnosed before the age of 5 who were born in May, and found that they differed in their autoantibody profile compared with boys of the same age group born in other months. Specifically, they were more likely to present with ZnT8A (p=0.006) or IAA (p=0.023), although this association did not remain significant after Bonferroni correction.

When analysing the distribution of birth months across different HLA risk groups in comparison with the general population, we observed a modest overrepresentation of children with high-risk HLA genotypes born in August. This finding, however, also lost statistical significance after adjustment for multiple comparisons using the Bonferroni correction (p=0.02).

Table 2: Autoantibody profiles in boys before the age of 5 years diagnosed with type 1 diabetes: comparison between those born in May and those born in other months.

	Month of birth			
	May		Other months	
	n	%	%	p-value
GADA	11	38%	39%	0.880
IAA	12	41%	63%	0.023
IA-2A	18	62%	76%	0.102
ZnT8RA	20	69%	42%	0.006
ZnT8WA	13	45%	37%	0.394
ZnT8QA	10	35%	22%	0.123

Paper II

In Paper II, we explored the differences and commonalities between children in the BDD cohort with different family histories of diabetes, and we also compared these children in the BDD with a reference cohort consisting of children without type 1 diabetes, but with available information on family history of diabetes.

In the BDD cohort, 40% of children had a first- or second-degree family history of diabetes. Specifically, 12% had a family history of type 1 diabetes and 33% had a family history of type 2 diabetes, with some children reporting both. Among first-degree relatives, 8.3% had type 1 diabetes and 2.5% had type 2 diabetes.

Analysis of familial relationships revealed that children with type 1 diabetes were significantly more likely to have an affected father than mother ($p<0.0001$). This pattern was also observed for type 2 diabetes, with paternal transmission being more common ($p<0.0001$). Similarly, diabetes was more commonly reported in grandfathers than in grandmothers, for both type 1 ($p=0.003$) and type 2 diabetes ($p<0.001$).

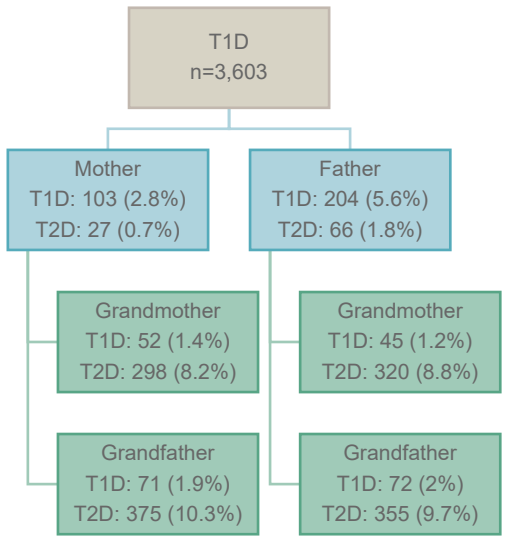

Figure 13: Family history of diabetes among children with type 1 diabetes (T1D), grouped by first- and second-generation relatives and stratified by parental sex. Data are presented as n (%).

What is the prevalence of parental diabetes among children with and without type 1 diabetes?

In the BDD cohort, having a parent with type 1 diabetes was more common than in the reference groups (8.4% vs. 2.1%). Similarly, parental type 2 diabetes was also more frequent among children with type 1 diabetes compared with the reference group (3.5% vs. 1.9%).

Children with type 1 diabetes were nearly four times more likely to have a parent with type 1 diabetes (crude RR 3.93; 95% CI 3.03-5.11), and nearly twice as likely to have a parent with type 2 diabetes (crude RR 1.88; 95% CI 1.27-2.76). These differences were seen independent of sex. Among girls, the crude RR for parental type 1 diabetes was 3.51 (95% CI 2.29-5.39), and for type 2 diabetes, 2.03 (95% CI 1.18-3.50). Among boys, the crude RR was 4.16 (95% CI 2.98-5.80) for type 1 diabetes and 1.77 (95% CI 1.02-3.08) for type 2 diabetes.

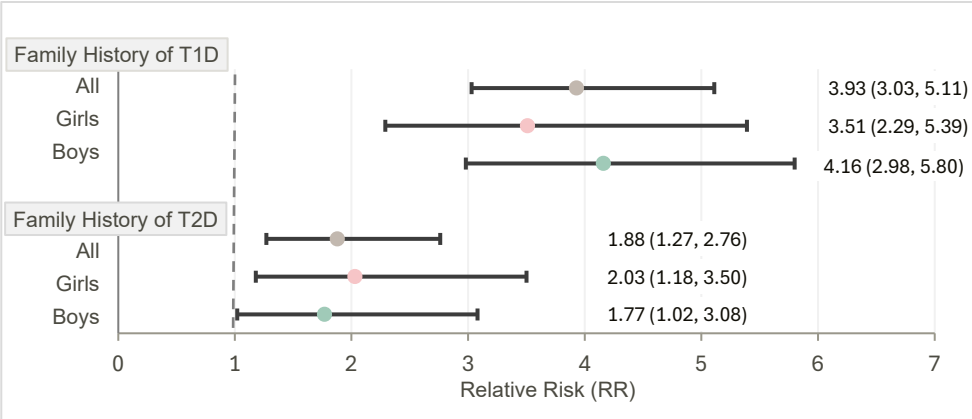

Figure 14: Comparison of type 1 diabetes (T1D) risk by family history of T1D or type 2 diabetes (T2D), stratified by sex. Risk estimates are presented as relative risks (RR) with 95% confidence intervals.

Are there clinical differences at diagnosis of type 1 diabetes dependent on family history?

Family history and HbA1c

When comparing HbA1c values at diagnosis across family history groups, the lowest HbA1c was found in children with a family history of type 1 diabetes, particularly those before the age of 6, while the highest levels were seen in children with a family history of type 2 diabetes, especially those diagnosed after the age of 12. Overall, boys had a lower HbA1c than girls ($p<0.0001$).

Children with a family history of type 1 diabetes had significantly lower HbA1c compared with those with a family history of type 2 diabetes ($p<0.0001$) and those without a family history ($p<0.0001$). In contrast, HbA1c did not differ significantly between children with a family history of type 2 diabetes and those without ($p=0.408$). These patterns were consistent across all age groups.

Family history and age

Children with a family history of type 1 diabetes were, on average, one year younger at type 1 diabetes diagnosis than those with a family history of type 2 diabetes ($p<0.0001$). Children with a family history of type 1 diabetes were also younger than those with no family history of diabetes ($p<0.0001$).

Family history and BMI

In the BDD cohort, 8.4% of children were overweight and 2.0% were obese at the time of type 1 diabetes diagnosis. Among those with a family history of type 1

diabetes, 9.9% were overweight and 2.8% were obese. The corresponding proportions for children with a family history of type 2 diabetes were 8.8% and 3.1%, respectively.

Children with a family history of type 2 diabetes had a significantly increased risk of being overweight or obese at diagnosis compared with those without a family history (RR 1.42; 95% CI 1.14–1.78; p=0.002). In contrast, no significant difference was observed for children with a family history of type 1 diabetes compared with those without (RR 1.35; 95% CI 0.94–1.94).

When stratified by sex, the association for type 2 diabetes family history remained significant in boys (RR 1.50; 95% CI 1.15–1.97) but not in girls.

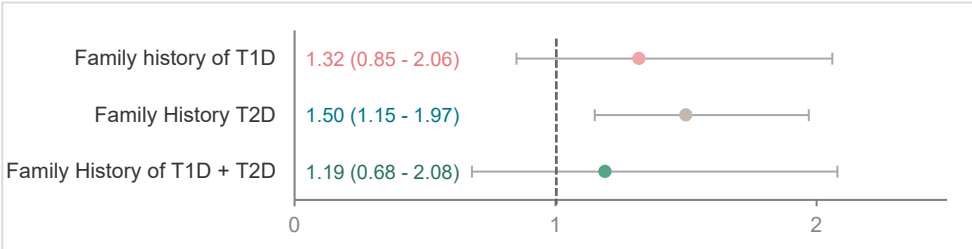

Figure 15: Comparison of risk for overweight and obesity by family history. Risk estimates are presented as relative risks (RR) with 95% confidence intervals.

Family history and DKA, antibodies, and HLA

The prevalence of diabetes ketoacidosis (DKA) at clinical onset was 16% (n=527) in the entire cohort and was most common among children under 6 years of age (18%).

We found no significant difference in the relative risk of DKA between children with a family history of type 1 or type 2 diabetes and those without a family history. However, children with a combined family history of both type 1 and type 2 diabetes had a lower risk of DKA (RR 0.58; 95% CI 0.35–0.96) compared with those without.

No significant differences in the distribution of autoantibodies were found between the groups with a family history of diabetes and those with no family history.

Children with a family history of type 2 diabetes were less likely to carry the high-risk DQ2/DQ8 genotype than those without a family history (p=0.02), but this association was not statistically significant after adjustment for multiple comparisons (adjusted p=0.32).

Table 3: Presentation of clinical characteristics at diagnosis of type 1 diabetes (T1D) in children from the Better Diabetes Diagnosis (BDD) cohort.

Family History			
None	**T1D**	**T2D**	**T1D+T2D**
n=1,949 Mean Age: 9.6 Mean BMI: 16.9 Mean HbA1c: 95 Boys: 55 % High-risk HLA: 31 % DKA: 16 % GAD-ab: 56 % IAA-ab: 34 % Overweight/obesity: 8.9 %	n=283 Mean Age: 9.4 Mean BMI: 17.5 Mean HbA1c: 82 Boys: 58% High-risk HLA: 29% DKA: 17 % GAD-ab: 57% IAA-ab: 35% Overweight/obesity: 12%	n=1,017 Mean Age: 10.5 Mean BMI: 17.7 Mean HbA1c: 97 Boys: 57% High-risk HLA: 27% DKA: 16 % GAD-ab: 58% IAA-ab: 31% Overweight/obesity: 13%	n=160 Mean Age: 10.5 Mean BMI: 17.9 Mean HbA1c: 86 Boys: 63% High-risk HLA: 27% DKA: 10 % GAD-ab: 60% IAA-ab: 32% Overweight/obesity: 13%
Girls			
(n=874) Age: 9.4 BMI: 17 HbA1c: 97 DKA: 17 %	(n=125) Age: 8.6 BMI: 17 HbA1c: 81 DKA: 20 %	(n=443) Age: 10 BMI: 17 HbA1c: 100 DKA: 17 %	(n=60) Age: 9.3 BMI: 18 HbA1c: 82 DKA: 9 %
Boys			
(n=1,075) Age: 9.9 BMI: 17 HbA1c: 93 DKA: 17 %	(n=158) Age: 9.9 BMI: 18 HbA1c: 83 DKA: 14 %	(n=574) Age: 11 BMI: 18 HbA1c: 94 DKA: 18%	(n=100) Age: 10.6 BMI: 18 HbA1c: 87 DKA: 10 %

Grouped by family history (first- and second-generation) of T1D, type 2 diabetes (T2D), both T1D and T2D, or no family history of diabetes, and stratified by sex. GADA=glutamic acid decarboxylase autoantibody; IAA=insulin autoantibody.

Paper III

Among the children in our cohort, 169 children (6.2%) lacked autoantibodies at the time of type 1 diabetes diagnosis. When grouped by number of autoantibodies, 428 children (15%) had one autoantibody and 2,156 (78%) had multiple autoantibodies (two or more).

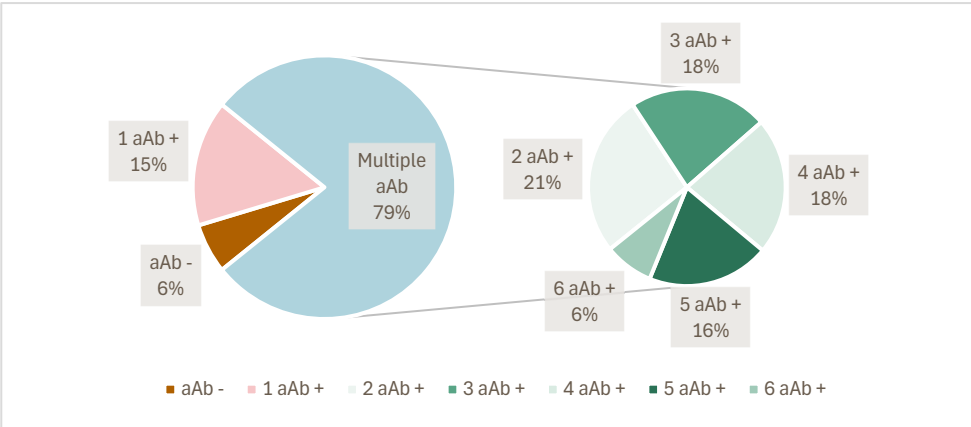

Figure 16: Number of autoantibodies, ranging from all negative to all 6 positive.

For the whole cohort, the mean age at diagnosis was 10 years, mean HbA1c was 94.6 mmol/mol, mean C-peptide was 0.27 nmol/L, and mean BMI-SDS was –0.44.

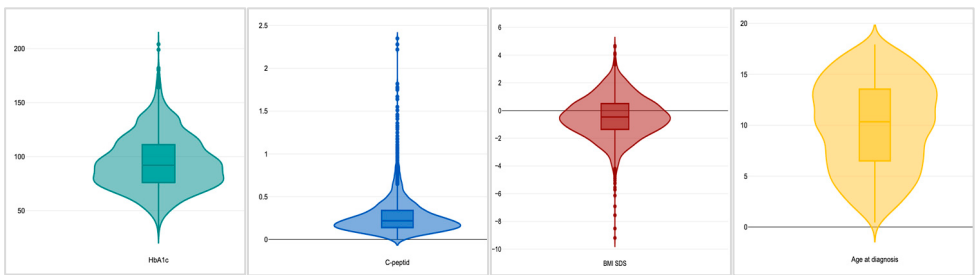

Figure 17: Violin plots showing the distribution of HbA1c, C-peptide, BMI-SDS, and age at diagnosis for the whole cohort.

Do clinical characteristics differ at type 1 diabetes diagnosis between children with or without autoantibodies?

Autoantibody negativity was more common in boys. Additional differences at diagnosis included a higher frequency of DKA among children with autoantibodies, higher HbA1c levels in those without autoantibodies, and a greater prevalence of type 2 diabetes family history among those without autoantibodies. No significant differences were observed between children with and without autoantibodies regarding age, BMI, HLA or family history of type 1 diabetes.

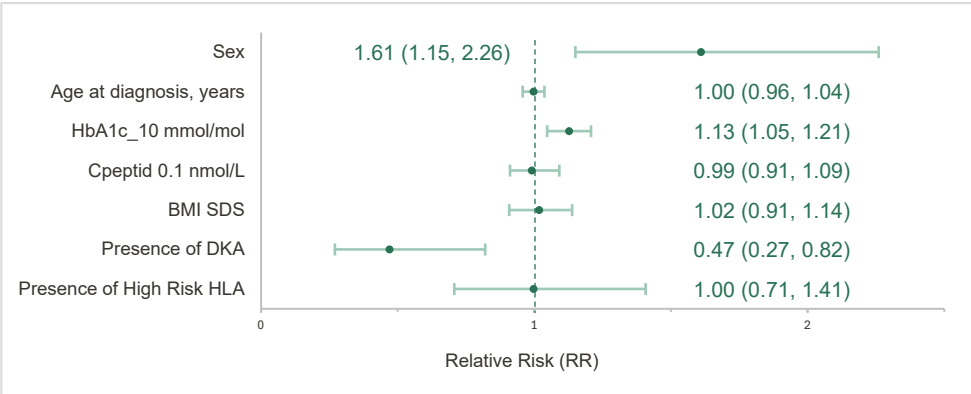

Figure 18: Forest plot summarising odds ratios (ORs) with 95% confidence intervals (CIs) for the association between autoantibody positivity and five covariates: sex (male vs. female), age at diagnosis, HbA1c, C-peptide, BMI, diabetic ketoacidosis (DKA), and high-risk HLA genotype. Units for each continuous covariate are indicated in the figure. The adjacent table shows each OR (95% CI).

When stratified by number of autoantibodies, children with a single autoantibody resembled those without autoantibodies. No statistically significant differences were observed between these two groups, apart from a higher prevalence of family history of type 2 diabetes. Comparisons between children without autoantibodies and those with multiple autoantibodies (excluding the single-autoantibody group) yielded results consistent with the main analysis. This suggests that their overall clinical profiles are similar.

Table 4: Comparisons by autoantibody status at type 1 diabetes (T1D) diagnosis.

n (%) or mean (SD)	aAb- 169 (6%)	aAb+ 2,598 (94%)	p-value	1+ aAb 428 (15%)	Multiple aAbs 2170 (78%)	aAb- vs 1+ aAb p-value	aAb- vs Multiple aAbs p-value
Sex, male	112 (66%)	1451 (56%)	**0.008**	247 (58%)	1204 (56%)	0.054	**0.006**
Age (years)	10.4 (4.1)	10.0 (4.4)	0.168	9.8 (4.3)	10.0 (4.4)	0.123	0.194
HbA1c (mmol/mol)	100 (27.8)	94.1 (24.7)	**0.002**	96.5 (27)	93.6 (24)	0.141	**<0.001**
C-peptide (nmol/L)	0.26 (0.18)	0.27 (0.22)	0.529	0.27 (0.22)	0.28 (0.22)	0.756	0.496
BMI (kg/m2)	17.2 (3.4)	17.2 (3.2)	0.889	16.8 (3.0)	17.2 (3.2)	0.189	0.901
Presence of DKA at diagnosis	15 (9%)	382 (15%)	**0.036**	57 (13%)	325 (15%)	0.133	**0.030**
Presence of High-risk HLA (DQ2/DQ8)	50 (30%)	784 (30%)	0.871	136 (32%)	648 (30%)	0.603	0.940
Parental heredity							
For T1D	14 (8%)	226 (9%)	0.853	41 (10%)	185 (9%)	0.622	0.914
For T2D	13 (8%)	58 (2%)	**<0.001**	12 (3%)	46 (2%)	**0.007**	**<0.001**

Comparisons between autoantibody-negative (aAb−) and autoantibody-positive (aAb+) participants, and between subgroups with a single autoantibody (1+ aAb) versus multiple autoantibodies. p-values indicate differences across groups.

Paper IV

Is a family history of diabetes associated with differences in HbA1c and BMI levels at follow-up?

Overall, the results of this paper showed that differences in HbA1c and BMI by family history persisted over time and were particularly pronounced in children with a family history of type 2 diabetes or a combined family history of type 1 and type 2 diabetes.

HbA1c

Across the four follow-up visits, HbA1c increased from baseline through years 1, 2, and 5, followed by a slight decline at year 10 ($p<0.001$).

At specific time points in the fully adjusted models, HbA1c was higher in the group with a family history of type 1 diabetes at 1 year (p=0.024). At 2 years, both the type 2 diabetes (p=0.022) and combined (p=0.033) groups differed significantly from those with no family history. At 5 years, all three family-history categories showed significantly higher HbA1c compared with the group with no family history: type 1 diabetes (p=0.033), type 2 diabetes (p=0.003), and both (p=0.016). At 10 years, only the combined group continued to differ significantly (p=0.007).

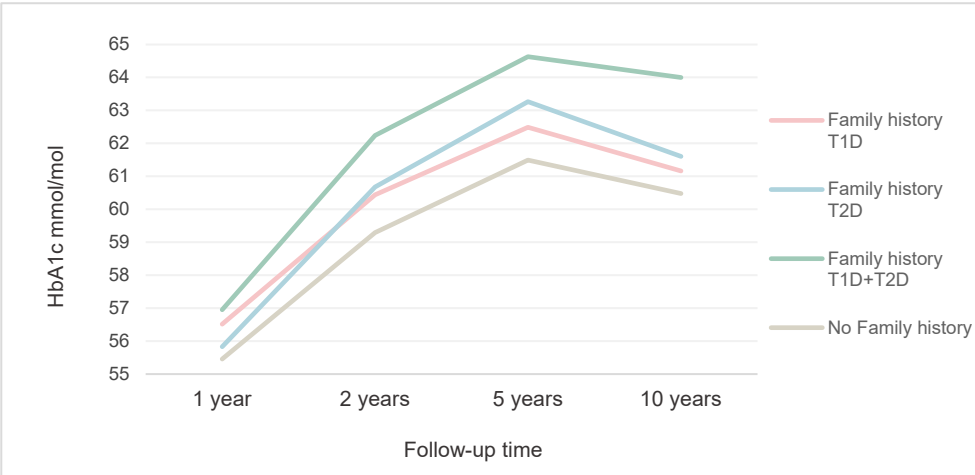

Figure 19: HbA1c over follow-up time by family history of diabetes, in children with type 1 diabetes from the BDD cohort.

In unadjusted analyses, mean HbA1c across visits was higher in children with a family history of type 2 diabetes (p=0.015) and in those with a family history of both type 1 and type 2 diabetes (p=0.010) compared with those without a family history. After adjustment, only the group with a family history of both types remained significantly different (p=0.028).

Although HbA1c levels changed over time, the trajectories were similar across family history groups. Therefore, no significant differences in change over time were observed between family history groups, neither unadjusted (p=0.313) nor adjusted (p=0.657).

BMI

Across both measurement approaches, BMI increased over time in all groups (p<0.001). Similarly to HbA1c, family history did not influence the change over time (unadjusted, p=0.519, adjusted p=0.177).

Mean BMI across visits differed significantly between family history groups, both unadjusted and after adjusting for individual covariates (p<0.001), but not when all covariates were considered (p=0.405).

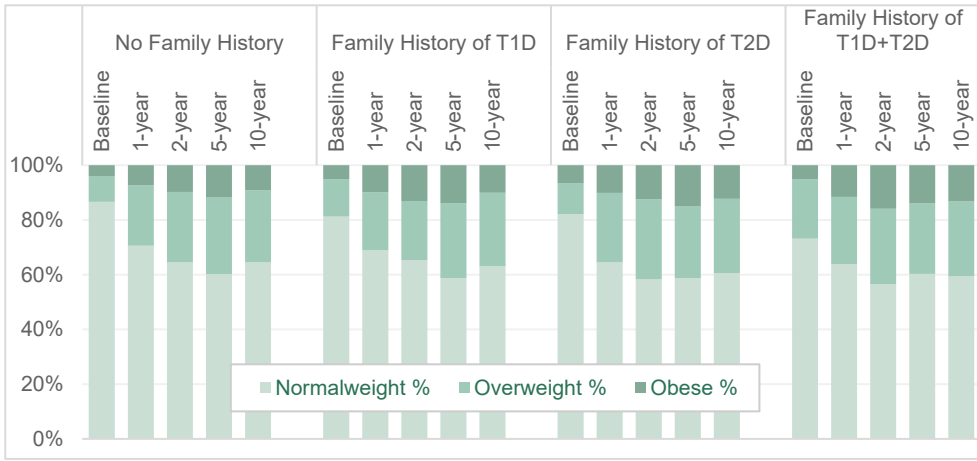

Figure 20: Comparison of BMI categories **(**normal weight, overweight, and obese) across family history groups at five timepoints over 10 years of follow-up. Data are presented as percentages (%).

Time point–specific analyses showed that, when BMI was analysed categorically, children with a family history of type 2 diabetes had higher BMI at 1, 2, and 10 years (p<0.001, p=0.001, p=0.049). When BMI was analysed as a continuous variable, unadjusted analyses showed higher BMI in the type 2 diabetes group at all time points and in the combined group at years 1 and 10 (p=0.041 and p=0.003). In the fully adjusted model, significant differences remained only at 10 years, with higher BMI among children with a family history of both type 1 and type 2 diabetes (p=0.022). See Figure 2 and Table 5.

Table 5: Comparison of BMI category across family history groups over time.

Timepoint	Comparison	OR (95% CI)	p-value	Overall p-value
Baseline	No FH vs T1D	1.49 (1.06–2.09)	0.023	<0.001
	No FH vs T2D	1.40 (1.13–1.74)	0.002	
	No FH vs Both	2.37 (1.58–3.55)	<0.001	
1 year	No FH vs T1D	1.08 (0.83–1.42)	0.561	0.005
	No FH vs T2D	1.32 (1.12–1.55)	<0.001	
	No FH vs Both	1.36 (0.95–1.96)	0.091	
2 years	No FH vs T1D	0.97 (0.75–1.26)	0.818	0.003
	No FH vs T2D	1.30 (1.11–1.52)	0.001	
	No FH vs Both	1.40 (0.99–1.99)	0.058	
5 years	No FH vs T1D	1.06 (0.82–1.38)	0.641	0.870
	No FH vs T2D	1.06 (0.91-1.25)	0.441	
	No FH vs Both	1.00 (0.70–1.42)	0.990	
10 years	No FH vs T1D	1.06 (0.80–1.42)	0.673	0.210
	No FH vs T2D	1.19 (1.00–1.42)	0.049	
	No FH vs Both	1.25 (0.83–1.86)	0.284	

BMI categories: normal vs overweight/obese. Showing prevalence of overweight/obesity in the different family history groups, the X2 and the corresponding p-values and odds ratio (OR) with 95% confidence interval (95% CI).

Discussion

In the papers of this thesis, I set out to describe heterogeneity among children with type 1 diabetes in a large, well-characterised Swedish cohort of children diagnosed between 2005 and 2010.

We found that boys under the age of 5 were more often born in May, that parental diabetes (both type 1 diabetes and type 2 diabetes) was more common among children with type 1 diabetes than among those without, and that children with different family histories showed differences in clinical characteristics both at onset and during follow-up. We also observed that children with no or only one autoantibody appeared to have a more slowly progressing form of diabetes.

Type 1 diabetes is the most common chronic disease in children, and the incidence of both type 1 and type 2 diabetes has increased worldwide in recent decades [23, 178]. Both conditions often cluster in families, suggesting shared genetic and environmental risk factors.

It has become increasingly clear that type 1 diabetes is not a single uniform disease but a heterogeneous condition with multiple possible biological pathways. Children with type 1 diabetes differ in important ways – including age at onset, HLA genotype, residual β-cell function, autoantibody profiles, and family history – and these differences help explain variation in clinical presentation, aetiology, disease progression, and treatment response. This heterogeneity suggests that type 1 diabetes may be triggered by multiple distinct factors, resulting in different endotypes. Recognising and accounting for this is crucial, particularly in light of the rising global incidence and the interplay of genetic and environmental risk factors.

Many different factors contribute to diabetes risk, ranging from genetics to environmental exposures, and are further layered by disease heterogeneity and possible endotypes. Some exposures might be triggers of the disease, while others are drivers. These influences also interact with each other, indicating that certain risk factors may only confer susceptibility in the presence of specific genetic or environmental contexts. This complexity may explain why no single piece alone can complete the diabetes puzzle, and why conclusive findings have often been elusive. Recognising and accounting for this heterogeneity is therefore essential, as it may represent the key to understanding the diverse pathways that lead to disease onset. Future progress in both research and clinical care will depend on embracing this complexity rather than searching for a single explanatory factor.

Seasonality, age and sex

Our finding that boys diagnosed before the age of 5 stood out in the cohort, being more often born in May, is consistent with other observations. Examples are the increased incidence of type 1 diabetes in boys during the COVID-19 lockdown [179] and the decreased risk among children attending day-care centres compared with those cared for at home [67]. Together, these findings suggest that distinct immunological features in young boys may influence disease risk.

The prevalence of diabetes is higher among boys than girls, especially after the teenage years [110, 180], which is noteworthy given that this contrasts with the general pattern of autoimmune diseases, where girls usually predominate. Other examples of gender differences include variations in autoantibody profiles and a higher prevalence of autoantibody negativity in boys. A Finnish study has shown that girls tend to have a more aggressive disease progression [154].

Such findings indicate significant immunological heterogeneity within the group of children with type 1 diabetes and suggest sex differences in immune response, also reflected in antibody patterns. This raises hypotheses that different risk factors may be sex-specific. The findings could also play a role in future screening programmes, both national and international, and highlight the need to design ethically and economically sustainable strategies to identify children at increased risk of developing type 1 diabetes, where sex must also be considered.

The discussion of heterogeneity is particularly important given that children are now being diagnosed with type 1 diabetes at younger ages, resulting in a longer lifetime burden of disease. Younger children represent a distinct subgroup, with characteristics that may differ from those diagnosed later. These include genetic background, autoantibody profiles, and sex distribution, as well as clinical features such as a higher risk of DKA at diagnosis. Given that type 1 diabetes is becoming more common in very young children, recognising and understanding these differences is essential for both clinical care and research.

Regarding seasonality, it is important to note that although we did not observe any differences in the overall cohort, that does not exclude the possibility that foetal risk factors may play a role. It therefore remains important to consider such influences when examining disease heterogeneity [181].

Family history

Our results showing that family history of diabetes is more common among children with type 1 diabetes confirm the findings of earlier studies [58, 60, 61]. The older Swedish study by Dahlquist et al. showed that family history of either type 1 or type 2 diabetes was more common in children with type 1 diabetes than in the healthy reference group [60]. In comparison, we found a similar prevalence of parental type 1 diabetes, but a higher prevalence of parental type 2 diabetes than 25 years earlier (2.5% vs 1.7%). This may reflect the increasing prevalence of type 2 diabetes in the

general population, but it also raises the possibility that a family history of type 2 diabetes could itself act as a risk factor for developing type 1 diabetes, and may contribute to the rising incidence observed over recent decades.

The finding that parental type 2 diabetes is more common among children with type 1 diabetes suggests that both type 1 and type 2 family histories are relevant when considering genetic and environmental contributions to disease risk. Future research should therefore not only assess the family history of type 1 diabetes but also that of type 2 diabetes, as well as their combination, particularly when designing screening programmes and evaluating risk.

In line with previous studies [59, 62, 182-185], we found that family history was associated with differences in clinical presentation. Children with a family history of type 1 diabetes tended to be younger at diagnosis and had lower HbA1c at onset, whereas children with a family history of type 2 diabetes showed clinical features that more closely resembled type 2 diabetes: they were older, more likely to be overweight or obese, and less often had the high-risk DQ2/DQ8 HLA genotype.

At follow-up, children with a family history of type 2 diabetes, or of combined type 1 and type 2 diabetes, had persistently higher HbA1c and BMI levels. One possible explanation is that these children may have reduced insulin sensitivity, and when combined with excess weight already at diagnosis, this could contribute to their elevated risk.

A further aspect, not addressed in my papers but relevant to highlight, concerns the social and metabolic consequences of having multiple family members with type 1 diabetes. It is well established that parents with type 1 diabetes who have higher HbA1c levels tend to have children with poorer glycaemic management. Several mechanisms might underlie this association. While speculative, they may include social disparities as well as psychological factors, such as the extent to which a parent has accepted and adapted to their own disease, and the potential influence this acceptance (or lack thereof) may have on the child's metabolic management.

These findings highlight the clinical value of assessing family history at the time of diagnosis. Children with a family history of diabetes, especially those with both type 1 and type 2 diabetes in their family, may represent a higher-risk subgroup that would benefit from closer monitoring, early intervention and tailored support, including guided education, nutritional counselling, and psychosocial support. Recognising these risk profiles early could not only improve type 1 diabetes outcomes but also reduce the future risk of developing type 2 diabetes, sometimes referred to as double diabetes.

It is noteworthy, however, that most children with type 1 diabetes have no family history of the disease. More than 90% lack a family history of type 1 diabetes, and even when type 2 diabetes is included, a substantial proportion still report none. When second-degree relatives are also included, around 60% of children remain

without any family history. Yet, in the context of precision medicine, family history represents a simple but powerful stratification tool.

Autoantibodies

The role of autoantibodies in the pathogenesis of type 1 diabetes is not fully understood. Notably, approximately 10 % of patients present without autoantibodies at diagnosis [36], a subgroup that warrants special attention. The prevalence of autoantibody negativity in our study was 6.2% whereas previous reports have ranged from 2.3 % to 19% [37, 169, 186-191], likely reflecting differences in study design and the range of autoantibodies assessed.

We found that children lacking autoantibodies at type 1 diabetes diagnosis were more often boys, had higher HbA1c levels, a lower frequency of DKA, and were more likely to have a parental history of type 2 diabetes. This pattern suggests heterogeneity in disease pathogenesis and potentially slower disease progression in this subgroup, particularly among those with a parental history of type 2 diabetes. Discrepancies with earlier studies may reflect differences in cohort size, age range, and exclusion criteria.

A particularly noteworthy finding was the relatively high proportion of children with newly diagnosed type 1 diabetes who either lacked autoantibodies or presented with a single one at diagnosis. When stratified into groups, we found that children with a single autoantibody closely resembled those without autoantibodies across most clinical measures. Taken together, these subgroups account for more than one-fifth of all new diagnoses. This is important, as such children are often excluded from studies and interventions, yet their inclusion is crucial when designing future screening programmes aimed at identifying those at risk of developing type 1 diabetes.

Overall, these findings highlight substantial immunological heterogeneity among children with type 1 diabetes and suggest possible sex-specific differences in immune responses, as reflected in antibody patterns.

BMI

For BMI and clinical presentation, we found that children with a family history of type 2 diabetes were more often overweight or obese, were older at diagnosis and tended to carry the high-risk-HLA genotype DQ2/DQ8 less frequently. The association between family history and overweight/obesity was observed only among boys. Previous studies have reported that boys are more likely than girls to develop type 1 diabetes, with the risk increasing with age [35], and that men develop type 2 diabetes at a lower BMI than women [192]. While increased BMI has been identified as a risk factor for type 1 diabetes in several studies [59, 102, 164, 193], sex-specific differences have rarely been addressed. Taken together, our findings

suggest that boys may be particularly susceptible to developing type 1 diabetes in the context of overweight or obesity.

It has previously been reported that an increased BMI in combination with low-risk HLA DQ2.5/DQ2.5 is associated with a higher risk of type 1 diabetes, supporting the view that obesity together with genetic susceptibility may act as a risk factor for type 1 diabetes [170]. These findings align with the accelerator hypothesis, which proposes that elevated BMI induces insulin resistance and increases β-cell stress, and thereby increasing the risk of type 1 diabetes [193, 194].

Overweight and obesity are also known to increase the risk of complications, and our study shows that BMI differences by family history – most evident in children with a family history of type 2 diabetes, alone or in combination with type 1 diabetes – persist over time. This indicates that these children are at a higher risk for developing complications and may benefit from more intensive interventions at an early stage.

HbA1c

HbA1c is a well-established predictor of diabetes complications in both children and adults [195-197], acting alongside other risk factors such as smoking, BMI, and lack of physical activity [198, 199]. Even in early life and adolescence, elevated HbA1c has been linked to increased risk of complications [119, 120, 200, 201]. Girls consistently exhibit higher HbA1c than boys at diagnosis and throughout adolescence [168, 196], placing them at greater long-term risk. Although the role of family history in these outcomes remains underexplored, these findings underscore the importance of early glycaemic management.

The lower HbA1c observed in children with type 1 diabetes and a parental history of the disease likely reflects greater awareness of clinical symptoms and, therefore, earlier detection. However, it may also indicate that a younger age at onset corresponds to a more aggressive course, similar to that reported in children with multiple autoantibodies [202]. Indeed, some studies have shown that girls are more often multi-autoantibody positive [35, 154], which aligns with the observation that boys are more frequently autoantibody-negative. Taken together, these findings highlight both the potential benefits of earlier detection in families familiar with type 1 diabetes and the possibility of a more aggressive disease phenotype in these children. In such cases, early identification is particularly important to prevent progression to more severe disease.

Over the 10-year follow-up, children with a family history of diabetes of any type had higher mean HbA1c compared to those without. The differences present at diagnosis persisted over time, becoming particularly pronounced at the 5-year follow-up, especially among those with a combined family history of both type 1 and type 2 diabetes.

Our findings suggest that, on average, individuals with a positive family history experience higher HbA1c levels over time, placing them at elevated risk for microvascular and macrovascular complications. Given the association between family history of type 2 diabetes and both increased BMI and potential insulin resistance, patients in this subgroup may benefit from targeted weight-management strategies and insulin-sensitising therapies.

Because this study spanned a period of evolving diabetes care in Sweden, including national reductions in HbA1c targets and the widespread adoption of continuous glucose monitoring and advanced insulin pumps, overall improvements in treatment undoubtedly influenced observed trends. However, these improvements likely affected children with and without a family history of diabetes in a similar way.

At the same time, psychosocial and social factors—such as socioeconomic status, education, family structure, social support, life stressors, comorbidities, and parental health behaviours—also play an important role in shaping metabolic outcomes [138, 203, 204]. As children mature and assume greater self-management responsibility, glycaemic outcomes may diverge further. Although Sweden's universal healthcare system and standardised national guidelines aim to ensure equitable care, differences in resources and expertise across paediatric diabetes centres remain, contributing to variability in metabolic management [205].

Clinical implications

We intend to describe heterogeneity among Swedish children with type 1 diabetes to improve risk stratification so that follow-up and interventions can be targeted to high-risk individuals rather than applied uniformly to all patients. Such precision in patient care is expected to benefit both families and the healthcare system, improving clinical efficiency and reducing costs.

Children with a family history of diabetes, particularly when type 2 or both type 1 and type 2 diabetes are present, represent a distinct risk profile at the time of diagnosis. These differences support the idea that subgroups can be identified already at disease onset, opening the possibility of precision medicine from the start. For example, children who are overweight, have a family history of type 2 diabetes, and retain preserved C-peptide function may benefit from additional or tailored treatment strategies beyond standard insulin therapy. Increasing evidence suggests that such insulin resistance can be addressed with adjunctive treatments, including metformin and GLP-1 receptor agonists. Assessing family history is therefore a simple yet valuable tool, offering important insights into clinical heterogeneity and helping to guide more differentiated care approaches.

Incorporating lifestyle modification programmes (nutritional counselling, structured physical activity) alongside adjunctive pharmacotherapy, such as metformin or GLP-1 receptor agonists, could mitigate weight gain, improve glycaemic management, and ultimately reduce complication risk. By routinely collecting family-history data and applying precision-based interventions from the outset, clinicians can more effectively allocate resources and optimise long-term outcomes for high-risk children and adolescents.

The finding that a high proportion of children with newly diagnosed type 1 diabetes either lacked autoantibodies or presented with a single one at diagnosis has important implications for the design of future screening programmes, as screening strategies relying solely on autoantibody status could miss a subset of at-risk children. In this context, genetic risk scores may need to play a larger role in identifying individuals at elevated risk.

Another clinical implication of these findings is that differentiation between type 1 diabetes, type 2 diabetes, and other forms of diabetes is often less straightforward than traditionally assumed. This diagnostic ambiguity highlights the importance of maintaining awareness of heterogeneity at onset and recognising that atypical presentations may occur. Even within a clearly stratified cohort restricted to children with type 1 diabetes, marked heterogeneity in phenotypes was observed. These insights emphasise the need for clinicians to remain open to alternative diagnostic considerations and to carefully evaluate individual patient characteristics when determining diagnosis and management strategies.

Strengths and limitations

The primary strength of this thesis is its exceptionally large, nationwide cohort, capturing the vast majority of paediatric diabetes cases diagnosed consecutively in Sweden over 5 years. The cohort's size and population-wide coverage enhance the generalizability of the findings and allow for robust subgroup analyses.

Linkage with the Swedish National Diabetes Register (NDR) enabled extended follow-up and more precise differentiation between type 1 and type 2 diabetes. The risk of misclassifying family members' diabetes status was further minimised by providing professional support during questionnaire completion, thereby increasing the reliability of family history data. This is particularly important given that subtype classification is often uncertain at initial diagnosis. In addition, the cohort has previously been screened for MODY [14], further strengthening diagnostic accuracy.

Finally, although data were collected from a cohort established nearly two decades ago, this could reflect both a strength and a limitation. On the one hand, its long-

term nature provides a stable foundation with possibilities to integrate with national registries and related studies, increasing its scientific value and credibility. On the other hand, some findings may be less reflective of modern diagnostic standards, treatment options, or environmental conditions.

As always, there are also some limitations to be considered when interpreting the studies.

In Paper II, the reference group provided a comparison for the family history of children without type 1 diabetes, but it was not a fully matched control group. Data for the reference group were based on self-reported questionnaires on family history and may not be as complete as those in the BDD cohort, where the families received professional support to complete them. However, since the data were limited to first-degree family history and the questionnaires were completed by the parents, we believe that the information is accurate.

Information on family history of diabetes was recorded at the time of the child's type 1 diabetes diagnosis, which may underestimate parental type 2 diabetes, as it is often diagnosed later in life.

While sibling history is an intriguing aspect of familial diabetes risk, it was not included in the present analyses. Given the complexity of the current study design, with multiple outcomes and variable exposures, focusing exclusively on sibling risk would be more appropriate in a dedicated analysis, as has been done within the broader BDD framework. We did not analyse parental BMI, which could be relevant for interpreting familial risk factors, particularly in children with a family history of type 2 diabetes.

Finally, data on socioeconomic status were not collected in the BDD, which could be relevant for interpreting the data. Similarly, while advanced glycaemic metrics such as Time in Range would have added valuable insight to the analysis, continuous glucose monitoring was not yet in widespread clinical use during the study period. However, this could provide further context in future studies.

Thesis conclusion

This thesis set out to describe the heterogeneity of type 1 diabetes among children in Sweden, with the aim of improving risk stratification so that follow-up and interventions can be targeted to high-risk individuals rather than applied uniformly to all patients. Through this work, key differences in clinical characteristics and familial patterns have been identified, representing an important step toward more personalised paediatric diabetes care.

The main findings can be summarised as follows:

1. The month of birth showed only a weak association with type 1 diabetes diagnosis overall. However, a notable exception was observed among boys diagnosed before the age of 5, who were more likely to have been born in May.
2. A family history of either type 1 or type 2 diabetes was more common in children with type 1 diabetes. Differences in family history of diabetes were associated with differences in clinical presentation of the disease, particularly overweight and obesity.
3. Differences were also observed based on family history of diabetes in follow-up data on BMI and HbA1c over 10 years.
4. Differences at clinical onset were found between the groups with and without autoantibodies at diagnosis, suggesting that the autoantibody-negative group may represent a subgroup with slower progression to diabetes. This subgroup could be particularly important to consider in overweight children, where distinguishing type 1 diabetes from type 2 can be challenging.

Taken together, these findings reflect the underlying heterogeneity of type 1 diabetes, as demonstrated across the different aspects investigated in this thesis – from temporal patterns of birth and diagnosis (point 1), to the influence of family history on disease occurrence, presentation, and follow-up outcomes (points 2 and 3), and the identification of clinically distinct subgroups based on autoantibody status (point 4). They highlight that distinct environmental and genetic factors may influence disease onset and progression in specific subgroups and emphasise the clinical value of assessing family history at the time of diagnosis.

Children with a family history of diabetes may represent a higher-risk subgroup who may benefit from intensified monitoring and early intervention. Early recognition of such risk profiles can support more personalised care strategies.

These findings make a meaningful contribution to ongoing efforts to refine classification and improve earlier, more tailored interventions, with the ultimate goal of achieving better outcomes for children with type 1 diabetes.

Future perspectives

An important future direction would be to expand this work to include siblings, particularly those with different family histories, to assess whether similar patterns are observed and to potentially identify additional meaningful subgroups. A national study is being planned to investigate the risk of type 1 diabetes among siblings of children diagnosed with the disease (the BDD-Family study). Within this framework, it would also be of interest to explore whether the same heterogeneity can be observed within families.

Building on this and on the results of this thesis in mapping overweight and obesity in children with different family histories, a valuable next step would be to connect these findings to data on overweight and obesity in their parents. This could deepen our understanding of inherited risks and the mechanisms through which they are transmitted. Further refinement could also be achieved by focusing analyses specifically on parental family history and by exploring potential sex differences.

From a precision medicine perspective, a future project could investigate how children with type 1 diabetes who also have a family history of type 2 diabetes, or of both types, and who present with overweight or obesity, respond to adjunctive treatments such as metformin or GLP-1 receptor agonists.

Complementing these family-based perspectives, another project is currently underway mapping the genetic risk score in BDD children, with a particular focus on those who are autoantibody-negative. Insights from this genetic work could provide a foundation for linking specific risk profiles to both early and late outcomes.

One such outcome of interest is the development of complications. While Paper IV was initially planned to focus on this area, the project became too large in scope, and reliable data proved difficult to obtain. Nonetheless, it would be valuable to design a study exploring whether autoantibody patterns or family history patterns influence the risk of future late complications in children with type 1 diabetes. Identifying higher-risk groups could enable earlier, targeted interventions, benefiting not only the children and their families but also the broader societal health and economic outcomes of society. Equally important, recognising groups at lower risk could help reduce unnecessary worry and stress, which are known to contribute to diabetes distress and diminished quality of life in both children and parents.

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Exploring Heterogeneity in Paediatric Type 1 Diabetes

Type 1 diabetes in children is a complex disease, influenced by both genetic and environmental factors. Its presentation varies: some children are very young at diagnosis; some have certain autoantibodies, others do not; and some carry a family history of diabetes that may shape their clinical picture.

This thesis explores that variation – the heterogeneity of type 1 diabetes in childhood. Using data from the Better Diabetes Diagnosis (BDD) study it brings together clinical information, family history, and laboratory findings from more than 3,600 children. By examining children with type 1 diabetes from several perspectives, such as month of birth, family background, autoantibodies, and patterns over time, the work aims to deepen our understanding of why the disease is not the same for every child. The ultimate goal is to support more personalised care for children with type 1 diabetes, where follow-up and interventions can be tailored to individual risk and need.

EMMA HEDLUND is a paediatric diabetologist at Kristianstad Central Hospital. Her main research focus has been exploring data from the Better Diabetes Diagnosis study, searching for pieces of the puzzle to understand why children with the same disease can differ so widely.

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