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2024

Document Version:
Publisher's PDF, also known as Version of record

Link to publication

Citation for published version (APA):
Lindgren, M. (2024). *Gluten and Celiac Disease in children with Type 1 diabetes*. [Doctoral Thesis (compilation), Department of Clinical Sciences, Lund]. Lund University, Faculty of Medicine.

Total number of authors:
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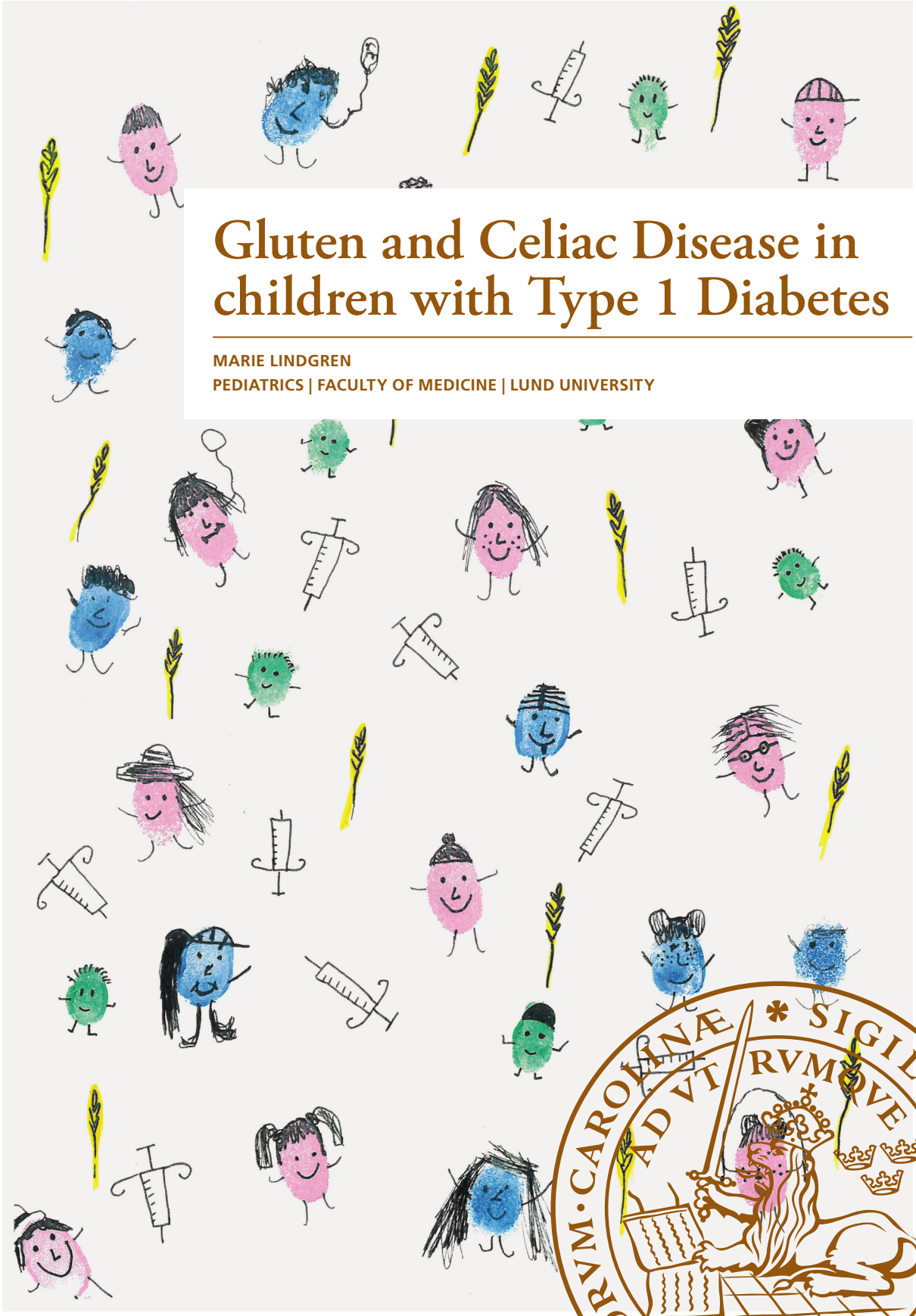

Gluten and Celiac Disease in children with Type 1 Diabetes

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PEDIATRICS | FACULTY OF MEDICINE | LUND UNIVERSITY

Gluten and Celiac Disease in children with Type 1 Diabetes

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Marie Lindgren

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University. To be publicly defended on 24 October at 13.00 in Segerfalksalen, Biomedical Center (BMC), Lund.

Faculty opponent
Professor Olga Kordonouri, Hannover

Organization: LUND UNIVERSITY

Document name: Doctoral Thesis **Date of issue** 2024-10-24

Author: Marie Lindgren

Title and subtitle: Gluten and Celiac Disease in children with Type 1 Diabetes

Abstract:

Background: Gluten is a factor thought to be involved in the pathogenesis of type 1 diabetes (T1D), however, studies have been conducted with inconsistent results. Children with T1D are screened for celiac disease (CD) and autoimmune thyroid disease (ATD), but the frequency of screening and who to screen is not well established. In addition, the effect of a CD diagnosis on growth and metabolic control in children with T1D is unclear.

Aim: The overall aim of this thesis is to determine whether variations in the introduction of gluten during infancy influence the risk of receiving a T1D diagnosis and to provide an individual-based screening recommendation for CD in children diagnosed with T1D.

Methods: We compared the cumulative incidence of T1D in two cohorts of children with different gluten recommendations during infancy. We examined the prevalence of CD prior to, at and after the diagnosis of T1D, as well as predictive variables at the time of acquiring a T1D diagnosis for being diagnosed with CD in 5,295 children with T1D from the BDD-study. HbA1C and BMI-SDS were compared between children with T1D+CD and T1D only. Finally, we analysed the risk and predictive factors of being diagnosed with both CD and ATD (triple autoimmunity) when having T1D and compared the risk with children screened for CD and ATD from the general population.

Results: The cumulative incidence of T1D differs between the cohorts, 0.77% vs 0.68%. The prevalence of CD in children with T1D was 9.8%, 58.2% diagnosed before or at T1D diagnosis and 95.9 % diagnosed within 5 years. Young age and HLA DQ2 were risk factors. Those diagnosed with CD after T1D diagnosis did not differ in BMI-SDS nor HbA1c compared to those with T1D only, but those diagnosed before or upon the diagnosis of T1D had a lower BMI-SDS. Only 0.8% had triple autoimmunity. HLA DQ2/DQ2 was a risk factor but not sex. In age-matched children from the general population, the risk for CD+ATD was only 0.02%.

Conclusion: Differences in national feeding recommendations did not affect the cumulative incidence of T1D indicating that gluten may not be part of the pathogenesis behind T1D. Screening for CD should be based on age at T1D diagnosis and time after the diagnosis of T1D. To have CD does not seem to affect metabolic control in children with T1D. Also, the risk of triple autoimmunity is low in children but much more common than in the general population without T1D.

Key words: Type 1 Diabetes, Celiac Disease, Gluten, Ethiology, Screening, Growth, glyceamic control, associated autoimmunity

Classification system and/or index terms (if any) Supplementary bibliographical information

Language English **Number of pages**: 100

ISSN: 1652-8220, Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:125

ISBN: 978-91-8021-622-7

Recipient's notes Price Security classification

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Department of Pediatrics, Clinical Sciences. Faculty of Medicine

Lund University, Sweden

ISBN 978-91-8021-622-7

ISSN 1652-8220 Lund University, Faculty of Medicine Doctoral Dissertation Series 2024-125

Printed in Sweden by Media-Tryck, Lund University

Lund 2024

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MADE IN SWEDEN

Humlan kan inte flyga för vingarna är för små. Den struntar i allt vad man säger och flyger ändå. Säg mig du lilla humla hur går den där flykten till? Men humlan den brumlar och mumlar. Man kan allt man vill.

Lennart Hellsing

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List of publications

This thesis is based on the following papers, which will be referred to by the roman numbers I-IV.

I. **Lindgren M,** Palmkvist E, Norström F, Cerqueiro Bybrant M, Myleus A, Samuelsson U, Ludvigsson J, Carlsson A. Cumulative incidence of type 1 diabetes in two cohorts of children with different national gluten recommendations in infancy. Acta Diabetologia. 2024 Jan;61(1):35-41.

II. **Lindgren M,** Norström F, Persson M, Elding Larsson H, Forsander G, Åkesson K, Samuelsson U, Ludvigsson J, Carlsson A. Prevalence and predictive factors for celiac disease in children with type 1 diabetes: Whom and when to screen? A nationwide longitudinal cohort study of Swedish children. Diabetes Care. 2024 Apr 1;47(4):756-760.

III. **Söderström H,** Lindgren M, Elding Larsson H, Forsander G, Cervin M, Carlsson A. Glycaemic control and growth in children with type 1 diabetes, with and without celiac disease. A longitudinal national cohort study. Submitted to Hormone and Research in Pediatrics, June 2024, under revision.

IV. **Lindgren M,** Norström F, Elding Larsson H, Forsander G, Ludvigsson J, Åkesson K, Myleus A, Carlsson A. Prevalence and predictive factors for being diagnosed with both Celiac disease and Autoimmune Thyroid disease in children with Type 1 diabetes. Manuscript.

Abstract

Background: Gluten is a factor thought to be involved in the pathogenesis of type 1 diabetes (T1D), however, studies have been conducted with inconsistent results. Children with T1D are screened for celiac disease (CD) and autoimmune thyroid disease (ATD), but the frequency of screening and who to screen is not well established. In addition, the effect of a CD diagnosis on growth and metabolic control in children with T1D is unclear.

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Conclusion: Differences in national feeding recommendations did not affect the cumulative incidence of T1D indicating that gluten may not be part of the pathogenesis behind T1D. Screening for CD should be based on age at T1D diagnosis and time after the diagnosis of T1D. To have CD does not seem to affect metabolic control in children with T1D. Also, the risk of triple autoimmunity is low in children but much more common than in the general population without T1D.

Thesis at a glance

Paper	Aim	Methods	Results	Conclusions
I	Investigate whether differences in gluten introduction recommendations during infancy, affected the cumulative incidence of T1D.	The cumulative incidence of T1D were compared between two cohorts of children born 1992/1993, during the CD epidemic and 1997/1998 after the CD epidemic.	The cumulative incidence of T1D was significant higher in those born 1997/1998 (after the CD epidemic).	Gluten amounts and the way gluten is introduced during infancy does not affect the risk of T1D in children as it did with the risk of CD in the same cohorts.
II	To develop individual based screening guidelines for CD in children with T1D by studying prevalence of CD in relation to the diagnosis of T1D and predictive factors at T1D diagnosis for a later CD diagnosis.	A longitudinal cohort study investigating prevalence of CD, age at T1D diagnosis, sex, HLA and diabetes-related autoantibodies in 5295 children with T1D from the BDD study.	9.8% of children had a CD diagnosis, 58.2% were diagnosed before or at T1D diagnosis and 95.9 % with both T1D and CD were diagnosed within 5 years after T1D diagnosis. Young age and HLA DQ2 were risk factors at T1D diagnosis.	New screening recommendations for CD in children with T1D based on age and time after T1D diagnosis are recommended.
III	To study the impact of a CD diagnosis on BMI and glycaemic control in children with T1D, and whether the timing of CD in relation to T1D diagnosis is of relevance.	A case control study where regression models were used to study differences in HbA1c and BMI-SDS in 3612 children with T1D from the BDD-study divided into groups based on CD status at T1D diagnosis.	Children diagnosed with CD before and at T1D diagnosis had a lower BMI than those with T1D only during two and five years follow up after T1D diagnosis. There were no differences in HbA1c or prevalence of DKA.	A CD diagnosed before or at T1D diagnosis had an impact on BMI during follow-up but the presence and timing of CD did not affect HbA1c.
IV	To study prevalence and risk factors for a child with T1D to also be diagnosed with CD and ATD in childhood. Also to study risk and sex ratio for being diagnosed with CD and ATD in children with T1D compared to children without T1D from general population.	As in Study II, but we also added ATD as a factor. The BDD cohort was compared with a age matched cohort from the general population.	0.8% had T1D and CD+ATD. HLA DQ2/DQ2 being a risk factor. The risk in general population for CD+ATD was 0.02% (0% in boys/0.05% in girls) compared to 0.8% (0.6% in boys/1% in girls) in those with T1D.	T1D+CD+ATD before 18 years of age is very uncommon, but having HLA DQ2/DQ2 means an increased risk. Children with T1D have an higher risk of having CD+ATD compared with children from general population.

Populärvetenskaplig sammanfattning

Vårt immunförsvar skyddar oss dagligen mot bakterier, virus och annat som hotar vår hälsa. Immunförsvaret kan skilja på vad som är kroppseget respektive främmande för kroppen, men ibland gör immunförsvaret fel och reagerar på kroppens egna celler. Då uppstår en autoimmun sjukdom. Typ 1 diabetes (T1D) och celiaki är två exempel på autoimmuna sjukdomar, likaså bland de vanligaste kroniska sjukdomarna barn drabbas av. Barn med T1D löper dessutom en ökad risk att få celiaki.

Vid T1D reagerar kroppen mot betacellerna i bukspottskörteln och förstör dem allt eftersom. Betacellerna har till uppgift att bilda insulin och därmed reglera blodsockret. I takt med att betacellerna förstörs, avtar kroppens förmåga att tillverka den mängd insulin som behövs för att tillgodogöra sig glukos från maten vi äter. Blodsockret stiger och kroppen reagerar med ökade urinmängder, törst och viktnedgång. Insulin är en livräddande behandling.

Att leva med T1D innebär en vardag med ständig koll på blodsocker, insulininjektioner, och kolhydraträkning samt rädsla för låga eller höga värden. Med tiden ökar även risken för att utveckla olika komplikationer.

De senaste årtiondena har antalet barn som insjuknar i T1D ökat varje år. Intensiv forskning för att förstå varför fler och fler drabbas pågår. Det är känt att vissa varianter av gener, HLA DQ2 och DQ8, som styr ett viktigt protein i vårt immunförsvar, innebär en ökad risk att utveckla T1D. Även omgivningsfaktorer påverkar risken för T1D och förändringar i dessa, tros vara en orsak till att förekomsten av T1D ökar.

Gluten är ett protein som finns i vete, korn och råg. Vid celiaki triggar gluten igång en autoimmun process i våra tarmar som gör att tarmluddet förstörs. Den drabbade kan få symtom som viktnedgång, diarréer, järnbrist eller depression, men vissa är helt symtomfria. Behandlingen av celiaki är att helt utesluta gluten ur sin kost. Genvarianterna HLA DQ2 och DQ8, som innebär en ökad risk för T1D, är också riskgener för att utveckla celiaki.

Eftersom gluten triggar igång celiaki så är det en viktig och helt avgörande miljöfaktor för att få celiaki. Man har däremot spekulerat i om det har någon betydelse hur och i vilken mängd gluten introduceras till spädbarn för att utveckla celiaki.

I Sverige hade vi under perioden 1984–1996 en epidemi av barn under 2 år som insjuknade i celiaki. Epidemin tros bero på ändrade rekommendationer kring hur gluten skulle introduceras till spädbarn. Rekommendationerna gick från gradvis vid

4 månaders ålder till mer abrupt vid 6 månaders ålder. Samtidigt ökades glutenhalten i välling. När man ändrade tillbaka till att rekommendera gluten från 4 månaders ålder och minskade på glutenhalten i vällingen, sjönk antalet barn som insjuknade i celiaki till samma nivå som tidigare.

I studie I använde jag mig av detta unika nationella experiment för att se om även risken för att insjukna i T1D ändrades, vilket då skulle tala för att gluten är en faktor som påverkar risken för att insjukna i T1D. Jag jämförde barn födda 1992/1993, under celiakiepidemin, med barn födda 1997/1998, efter celiakiepidemin och fann att T1D var vanligare hos barn som föddes efter celiakiepidemin. Vi kan därmed dra slutsatsen att glutenrekommendationerna och mängden gluten som påverkade risken för celiaki inte påverkade risken för diabetes på samma sätt. Däremot hade barnen som föddes efter celiakiepidemin högre BMI/vikt vid 12 års ålder än barn som föddes under epidemin. Vi spekulerar därför i om högre BMI är en förklaring till varför barnen som var födda 1997/1998 hade en högre risk att insjukna i diabetes och att detta kan vara en orsak till varför allt fler barn insjuknar med T1D.

Det är sedan länge välkänt att barn med T1D har en ökad risk för att få andra autoimmuna sjukdomar, främst celiaki och sköldkörtelsjukdom. När ett barn insjuknar i T1D screenar vi alla för celiaki och sköldkörtelsjukdom. I Sverige är rekommendationen att screena vid diabetesdebuten, därefter en gång per år. Som erfaren läkare blir det tydligt att majoriteten av screeningproverna kommer tillbaka helt normala. Det innebär att de allra flesta barn med diabetes inte får fler autoimmuna sjukdomar.

I studie II har jag därför försökt kartlägga vilka det är som insjuknar i celiaki genom att försöka identifiera riskfaktorer vid diabetesdebuten för en senare celiaki diagnos samt studera när i förhållande till diabetesdiagnosen som celiaki utvecklas. Syftet är att undvika onödig screening.

I studie III undersöker jag om tillväxt och metabol kontroll påverkas hos barnen med T1D och screeninggupptäckt celiaki jämfört med de som endast har T1D.

I studie IV undersöker jag en subgrupp av barn som utvecklat trippelautoimmunitet, vilket innebär att de insjuknar i de tre autoimmuna sjukdomar; T1D, celiaki och autoimmun sköldkörtelsjukdom.

Jag har använt mig av ett material från ”Better Diabetes Diagnosis” studien, en studie som pågått sedan 2005 där alla barn 0-18 år som insjuknar i diabetes i Sverige erbjuds att delta. Syftet med studien är att optimera diagnostiken av diabetes hos barn, och de allra flesta tackar ja till att delta. I studie II-IV, har jag tittat på 5 295 barn som insjuknat i T1D mellan åren 2005-2012 i Sverige och följt dem i 4-10 år.

I studie II hittade jag, precis som tidigare studier visat, att cirka 10 % av barnen med T1D även har celiaki. Majoriteten diagnostiserades innan eller i samband med diabetesdiagnosen, och mer än 90 % diagnostiserades med celiaki inom 5 år efter diabetesdiagnosen. Ung ålder vid diabetes diagnos samt att ha genkombinationen

HLA DQ2/DQ2, var riskfaktorer för att diagnostiseras med celiaki efter diabetesdiagnosen.

Vi tog därför fram ett förslag till ny screeningrekommendation som innebär betydligt färre prover och individanpassade riktlinjer som utgår från ålder vid diabetesdiagnosen samt antal år efter diabetesdiagnosen. Att glesa ut provtagningen innebär att celiaki kan upptäcks ett par år senare än med dagens årliga provtagning. I studie III kunde vi visa att det inte är någon skillnad i metabol kontroll mellan barn med både diabetes och celiaki när man jämför med de som endast har T1D. När vi tittade på tillväxten, mätt som BMI, så var det inte heller några skillnader mellan de som får celiaki efter diabetesdebuten och de som bara har diabetes. Därför känner vi oss trygga med att rekommendera glesare screeningen av celiaki vid våra diabeteskliniker.

I studie IV kan jag visa att det är en liten risk för ett barn med T1D att utveckla trippelautoimmunitet. Dock är risken betydligt högre än för ett barn som inte har diabetes. Autoimmuna sjukdomar brukar vara vanligare hos kvinnor. Därför är det lite förvånande att vi kunde visa att för de med T1D är det inte någon skillnad mellan könen i risken att insjukna i trippelautoimmunitet. Även den här studien bekräftar att genvarianten HLA DQ2/DQ2 innebär en ökad risk för att insjukna i både celiaki och sköldkörtelsjukdom.

Sammanfattningsvis kan jag utifrån mina fyra delstudier dra slutsatsen att gluten inte verkar vara en stark orsak till att barn insjuknar i T1D. På våra diabeteskliniker kan vi minska antalet screeningprover och individanpassa våra rekommendationer utan att det påverkar våra patienter negativt utifrån vare sig tillväxt eller metabol kontroll. Studien har även visat hur ovanligt det är att ett barn med diabetes får både celiaki och sköldkörtelsjukdom, vilket kan komma att påverka hur vi inom diabetesvården utför våra årliga screeningrutiner.

Preface

Twenty years ago, I moved to Lund intending to learn all about the mysterious things going on in our bodies and minds, so that perhaps, one day, I could become a paediatrician. During my medical studies, my interest was drawn towards autoimmunity, endocrinology and diabetes. How come the immune system, otherwise so smart, all of a sudden starts to produce antibodies that target the body itself?

During the last semester of medical school, I came into contact with Annelie Carlsson who became my supervisor during my Master's project. Back then, I aimed to study to what extent children with type 1 diabetes (T1D) had heredity for type 2 diabetes. During this work, I realised how little was known and this left me with more questions than answers and an urge to try to find the answers.

A few years passed and, I started my career as a paediatrician at Vrinnevisjukhuset in Norrköping where I met Lars Stenhammar. Both Annelie and Lars introduced me to "the epidemic of celiac disease (CD) in Swedish children" and the ETICS study. During the years 1984-1996, there was an epidemic of CD in Swedish children. The increase in incidence was thought to depend on changes in the way gluten was introduced during infancy and the amount of gluten introduced to the child's diet during infancy. During the work with my Master's project, I read about gluten as a potential trigger in the pathogenesis of T1D. What about the risk of T1D during the "Swedish CD epidemic"? Did it change and if so in what way? Did the changes in gluten introduction also affect the risk of T1D? The work with my first study started.

I found that differences in gluten recommendations did not affect the cumulative incidence of T1D in the same way as it affected the risk of CD during the epidemic. During the work with Study I, I started to work clinically with children with T1D and their families. The Swedish recommendation is that children with T1D should be screened annually for CD after a T1D diagnosis. Test after test came back with negative transglutaminase autoantibodies. Do we need to take all these blood tests? Can we do it in a better and more individual-based way? I then started working on Study II, where I looked at the risk of receiving a CD diagnosis prior to, at and annually following the diagnosis of T1D as well as predictive factors that might predict a CD diagnosis following T1D; the aim being, to create a more individual-based recommendation for CD screening in children with T1D.

A reason to screen for CD in children with T1D is that concomitant CD is thought to affect metabolic control negatively and, as most paediatricians are familiar with, the risk of reduced growth of children with CD. Our proposed screening recommendation in Study II means that less frequent testing with transglutaminase autoantibodies is required, could this affect the metabolic control and growth negatively in children with both T1D and CD? In Study III, we aimed to study the metabolic control and growth in children diagnosed with both T1D and CD.

Finally, in the last study, I continued work with Study II investigating the risk of being diagnosed with T1D, CD and autoimmune thyroid disease (ATD) referred to as triple autoimmunity in this thesis. We compared with an age-matched cohort from the general population, also screened for both CD and ATD. During the work with Study II, it was a bit surprising that after the diagnosis of T1D, the risk of CD was the same for both girls and boys. From the general population, we know that girls are more frequently diagnosed with CD. Therefore, we wanted to further examine gender differences between those with only T1D and those who were also diagnosed with associated autoimmune diseases.

The master project left me with more questions than answers. While working on this thesis, I have gained further knowledge of the complexity of T1D, however, still there are unanswered questions. Some years ago when I questioned my work as a PhD student, and the work at the clinic was much more fun, a colleague said: "doing research is also a part of being a physician but for the patients of the future". I hope that by writing my thesis, I have helped children today and in the future that struggle with T1D, with a small piece of the puzzle.

Abbreviations

ADA	American Diabetes Associations
Anti-EMA	Autoantibodies against endomysium
Anti-tTG	Antibodies against tissue transglutaminase
ATD	Autoimmune thyroid disease
BDD	Better Diabetes Diagnosis study
BMI	Body mass index
CD	Celiac Disease
ESPGHAN	European society for paediatric gastroenterology, hepatology, and nutrition
ETICS	Exploring the iceberg of celiac disease in Sweden
GADA	Glutamic acid decarboxylase autoantibodies
GFD	Gluten free diet
HLA	Human Leukocyte Antigen
IA	Islet autoimmunity
IAA	Insulin autoantibodies
IA-2A	Insulinoma-associated-2 autoantibodies
ISPAD	International society for paediatric and adolescent diabetes
MODY	Maturity-onset diabetes of the young.
NPR	National Patient Register
T1D	Type 1 diabetes
T2D	Type 2 diabetes
Treg	Regulatory T-cells
ULN	Upper limit of normal
ZnT8A	Zinc-transporter-8 autoantibodies

Introduction

Diabetes

"Diabetes Mellitus" describes a group of metabolic diseases characterised by hyperglycaemia due to defects in insulin secretion, insulin action or both (1).

History

Diabetes Mellitus has a long history dating back to the Ebers papyrus 1500 BC, which contains a description of patients with excessive thirst and copious urination (2). Aretaeus of Cappadocian, a physician active during the second century AD, called the disease "diabetes" from the Greek siphon meaning "to run through" (2). The name Diabetes Mellitus was stated in the 17th century by an English physician Thomas Willis, who was the first European medical writer to mention the sweet taste of the urine (2).

In the 19th century, Oskar Minkowski and Joseph von Mering, demonstrated that diabetes mellitus is caused by a disease in the pancreas (2), and in 1923 Frederick Banting and John MacLeod were awarded the Nobel Prize in Medicine for the discovery of insulin (2). Frederick Banting shared his prize with Charles Best and John MacLeod with James Collip (2). Insulin made it possible for patients with diabetes to go from a treatment with a strict fasting diet and short life after diagnosis, to survival and a better life, although the treatment is still demanding.

Diagnosis of Diabetes

In children and adolescents, diabetes often presents with characteristic symptoms, that is, polyuria, polydipsia and weight loss (1).

Diabetes is diagnosed based on HbA1c or plasma glucose, either fasting plasma glucose, 2-hour glucose value after oral glucose tolerance test or a random glucose value combined with classic hyperglycaemic symptoms described above (3).

Criteria for the diagnosis of diabetes are one of the following (1, 3)

- Classic symptoms of diabetes or hyperglycaemic crisis with a random plasma glucose concentration ≥11.1 mmol/L.
- Fasting (=no caloric intake for at least 8h) plasma glucose ≥7.0 mmol/L.
- 2-hour glucose value after an oral glucose tolerance test ≥11.1mmol/L.
- HbA1c ≥48 mmol/mol.

If there are no clear clinical symptoms, two abnormal screening tests are needed for the diagnosis of diabetes (3).

Classification of diabetes

Patients with diabetes are classified into diagnostic categories based on genetic and other characteristics and pathophysiology (3).It is important to distinguish between the various forms of diabetes because this determines therapeutic decisions (1).

Type 1 Diabetes

The hallmark of type 1 Diabetes (T1D), is the destruction of ß-cells by the immune system, autoimmune reaction, resulting in a lack of insulin production (1, 3). Of those with a diagnosis of diabetes, 5-10 % have T1D (3), and it is the most common form of diabetes in children and adolescents, although adults are also diagnosed. T1D is described in more detail in this thesis.

Type 2 diabetes

Type 2 Diabetes (T2D) where hyperglycaemia is due to insulin resistance together with relative insulin deficiency due to impaired ß-cell function, is a progressive non-autoimmune loss of adequate ß-cell insulin secretion (3, 4). Because hyperglycaemia often develops over time, T2D can often be undiagnosed for many years since the individuals do not notice any symptoms of diabetes. Although asymptomatic, individuals with T2D are still at an increased risk of both micro- and macrovascular complications (3). T2D is the most common form of diabetes worldwide. Risk factors for T2D include being overweight, but also age (3). T2D is uncommon in the paediatric population, however, during the last decade there has been a rapid increase in the incidence and prevalence of T2D in children and adolescents (3). In a study from eight paediatric diabetes centres in the USA, the majority of those with T2D were female, from racial and ethnic minority populations, had a family history of T2D and/or were obese (5).

In the early stages of T2D, insulin levels are often normal or elevated, but not enough to compensate for the insulin resistance (3). Weight loss and increased physical exercise may be enough to decrease insulin resistance; however,

pharmaceutical medications are often required to improve insulin sensitivity and endogenous insulin secretion, and also insulin is often needed(4).

Monogenic diabetes

Monogenic diabetes consists of mainly neonatal and maturity-onset diabetes of the young (MODY).

MODY results from one or more defects in a single gene or chromosomal locus affecting the function of the ß-cells. At least 14 genes have been reported to cause MODY, the three most common are GCK, HNF1α, and HNF4α (6). Often there are family members with the same form of diabetes, but it can also present spontaneously due to de novo mutations (6). MODY is uncommon, but in different studies, it still accounts for up to 6% of paediatric diabetes cases (6). In a study from Sweden, the estimated prevalence of MODY in children with diabetes was 1.4% (7). It is important to differentiate between MODY, T1D and T2D since the most common forms are not insulin-dependent. Individuals with a glucokinase mutation (GCK) regulate insulin secretion at a slightly higher set point, resulting in mild hyperglycaemia that needs no treatment (6, 8). Individuals with mutations in the transcription factors HNF-1α or HNF-4α should instead be treated with low-dose sulfonylureas (6, 8)

At the time of diabetes diagnosis, children who test negative for four islet autoantibodies, particularly those who also have low glycaemia as shown by plasma glucose or HbA1C and/or family history of diabetes, should be considered for genetic testing (7).

Neonatal diabetes is another form of monogenic diabetes affecting children below 6 months of age. Since T1D is very rare in this age group, all children diagnosed with diabetes before 6 months of age should have genetic testing for neonatal diabetes (3). Different genetic factors can result in neonatal diabetes; some can produce temporary diabetes, while others can induce persistent diabetes (3). In addition, treatment differs, some, around 50%, are insulin-dependent while others are treated with oral sulfonylureas (3).

Gestational diabetes

Gestational diabetes, which is hyperglycaemia discovered when screening pregnant women (3), normalises after giving birth.

Secondary diabetes

Secondary diabetes is caused by diseases of the exocrine pancreas (for example cystic fibrosis) and drug- or chemical-induced diabetes (3).

Sometimes, it is difficult to classify the type of diabetes in a child. Because of the rising prevalence of overweight children and adolescents, many children with newly diagnosed T1D are overweight and have the same phenotype as those with T2D. In

addition, many patients with T2D are diagnosed with classic symptoms of diabetes (5), although it is considered to be more common in children with T1D. In addition, monogenic diabetes often presents as T1D or T2D. Therefore, in order to classify diabetes, diabetes-related autoantibodies play an important role as diagnostic tools, since the presence of at least one autoantibody most often confirms T1D in children (1, 7). It has been shown that 93% of children have at least one of four diabetes-related autoantibodies at T1D diagnosis, however, 7% of children diagnosed with T1D in Sweden lack autoantibodies at diagnosis (9).

Type 1 diabetes

Epidemiology

T1D is the most common form of diabetes in children and adolescents, and it is also one of the most common chronic diseases affecting children (1). In 2021, the International Diabetes Federation Atlas estimated that 1,211,900 children and adolescents younger than 20 years around the world were diagnosed with T1D and that 108,300 children and adolescents below 15 years of age will be diagnosed with T1D in 2021 (10).

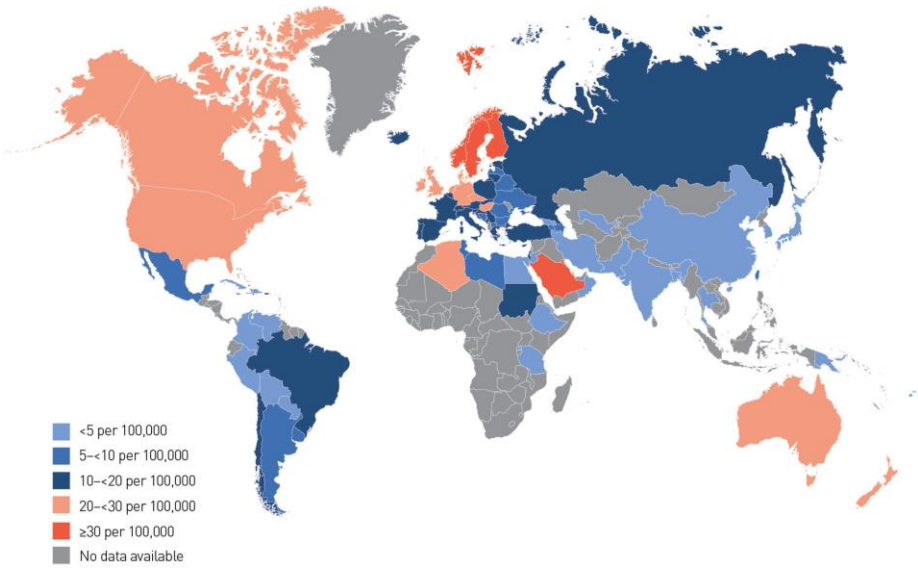

Figure 1: Incidence rates per 100 000 of type 1 diabetes in children aged <15 years 2019. Reprinted from Diabetes Research and Clinical Practice, vol 157, C. Patterson et al, "Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9te edition", 2019 (11). Reprinted with kind permission from Elsevier.

There is a large variation in the incidence of T1D, see Figure 1, thought to reflect the distribution of ethnic populations with different genetic susceptibility (12). After Finland, Sweden has the highest incidence of T1D in the world (10, 12).

The global incidence of T1D has increased in recent decades. Between 1990 and 1999, there was a 2.8% annual increase in the incidence worldwide (12). In Europe, during the period 1989-2013, the incidence rate of T1D for children increased by 3.4 % annually, but a reduced rate in the incidence increase has been seen in some high-risk countries during the last few years (13).

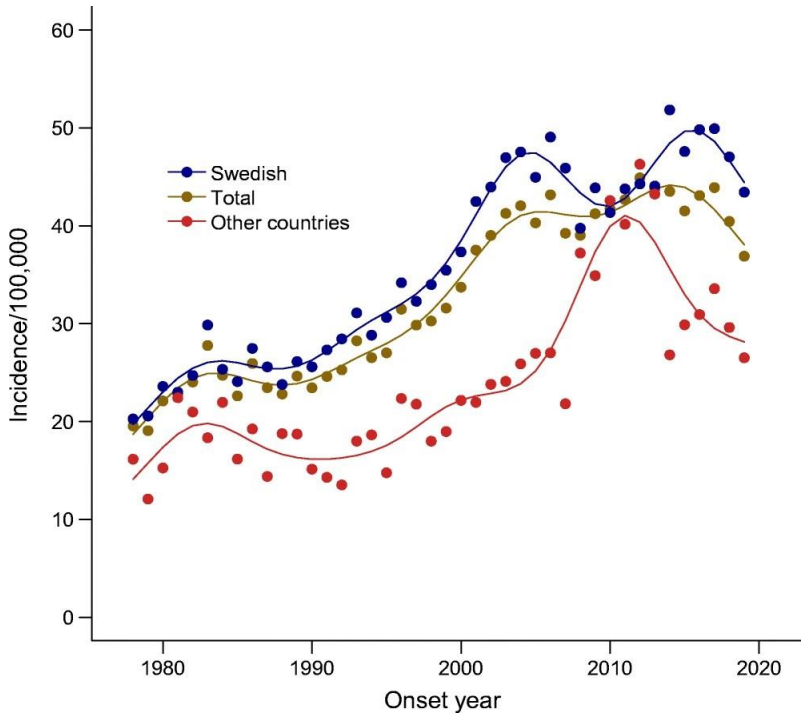

Figure 2: Incidence of type 1 diabetes per 100 000 during the years 1978-2019 in children <15 years of age in Sweden. Adapted from "The incidence of childhood-onset type 1 diabetes, time trends and association with the population composition in Sweden: a 40 year follow-up.", by I. Waernbaum et al, Diabetologia 2022 (14).

In Sweden, the incidence of T1D in children also increased during the 1980s and 1990s, however, from 2000, the increase in incidence tapered off and a plateau in incidence has been observed (15). When analysing the incidence trend in Sweden from 2000 until 2019 the incidence continues to be more stable, albeit at a very high level (14), see Figure 2. Year 2022, the incidence of T1D in Swedish children aged 0-17 years old was 45.8 per 100,000 individuals (16).

The incidence of T1D differs within countries probably affected by different race/ethnicity. Non-Hispanic whites have the highest risk of T1D, but the incidence has also increased in other races/ethnicities and the increase in incidence is higher in black and Hispanic youth than in whites (17).

The incidence peaks at puberty (18) in children and adolescents. Before puberty, the sex ratio is roughly equal, but after puberty, the incidence decreases in women but remains high in males so male excess is commonly found in populations 15-40 years of age (18, 19).

In some studies, especially from countries with marked differences between summer and winter, it has been shown that the incidence of T1D peaks during autumn and winter (18, 20), above all in children 5 years of age or older (20). The month of birth, during the warmer or colder half of the year, has not been shown to affect the risk of T1D (21).

Pathophysiology

Autoimmune diseases are a group of chronic diseases characterised by damage and dysfunction of organs due to immune response to self-antigens. The pathogenesis behind T1D is often described as autoimmune T-cells destruction of the insulin-secreting pancreatic ß-cells (22). Most probably multiple mechanisms lead to the selective destruction of insulin-secreting pancreatic ß-cells and thereby the loss of insulin production (22), but the pathogenesis is still not fully understood.

One process in the development of T1D autoimmunity is the loss of tolerance to ß-cell antigens. T-cells that are reactive with self-antigens are believed to be eliminated in the thymus by central tolerance (23). Autoreactive T-cells can still slip through the thymus, and because of this, there is a back-up mechanism, called peripheral tolerance with autoantigen-specific regulatory T-cells (Treg) (23). It has been shown that patients with T1D have defects in either the number and/or function of Treg (24).

It is thought that environmental factors affect the ß-cells leading to the release of ß-cell-antigens that autoreactive T lymphocytes recognise and react against (23). T-cells are the main contributor to the immune attack against the ß-cells (25). CD8+T-cells directly attack the ß-cells and destroy them, while the CD4+T-cells release cytokines that destroy the ß-cells and attract T and B lymphocytes to the islets leading to insulitis which further damages the ß-cells (25).

The autoimmune process is notable by the presence of autoantibodies against ß-cell autoantigens (22), insulin, glutamic acid decarboxylase 2 (GAD65), tyrosine phosphatase like protein IA-2 and zink transporter 8 (ZnT8) (26). The CD4+ T-cells assist the B-cells to produce autoantibodies (25), where the major diabetes-related autoantibodies are glutamic acid decarboxylase autoantibodies (GADA),

insulinoma-associated-2 autoantibodies (IA-2A), insulin autoantibodies (IAA) and three types of zinc-transporter-8 autoantibodies (ZnT8A). The autoantibodies are not thought to play a role in the pathogenesis, but when present they indicate that the destruction of ß-cells has and probably will happen again (27). The presence of diabetes-related autoantibodies is called islet autoimmunity (IA) hereinafter.

IA can develop at any age and has already been detected at three months of age in children (28, 29). Prospective studies that follow children with a genetic risk of T1D from birth have shown that seroconversion to IA often happens between 9-24 months of age (28). At seroconversion, the first autoantibody to appear is most often IAA, GADA or multiple autoantibodies directly. Those with IAA as the first autoantibody are often younger at seroconversion, one year of age, compared to those with GADA where seroconversion occurs over a wider age range starting at two years of age (30). Autoantibodies also differ with regard to the amount and type between sexes (31), whereas girls at diagnosis of T1D are positive for GADA more often (31, 32) and have multiple autoantibodies compared to boys (31).

When diagnosed with T1D, the pathogenesis/process towards symptomatic disease has already been ongoing for months and probably several years. This process can be detected by the presence of diabetes-related autoantibodies. The disease can be characterised into three well-defined stages (33), see Figure 3.

*Stage 1***:** individuals with two or more T1D-related autoantibodies (multiple islet autoimmunity) but who are normoglycemic (33). In a prospective study involving children with a genetic risk for T1D, the majority of children with multiple islet autoimmunity developed diabetes following a 10 years follow-up (34). The risk of T1D at 15 years of age was 0.4% in children with no autoantibodies, 12.7% in children with a single autoantibody, 61.6% in children with 2, and 79.1% in children with 3 islet autoantibodies (34).

Stage 2: As in stage 1, individuals with multiple islet autoimmunity, progress to the development of dysglycaemia as a result of losing functional ß-cell mass (33), but they do not yet exhibit symptoms of diabetes. To prevent the progression from one stage to another, many efforts have been made and during the last few years, teplizumab, an anti-CD3 monoclonal antibody has been shown to delay the progression from stage 2 to stage 3 (35).

Stage 3: occurs when the patient has developed typical clinical symptoms and signs of diabetes (33), that is, when a critical mass of ß-cells has been destroyed (22) and there is a lack of insulin that prevents cells from getting enough glucose. To protect residual ß-cell function and prevent future complications of the diabetes diagnosis, numerous attempts have been done and others are under investigation (36).

The time from the appearance of diabetes related autoantibodies in stage 1 to the diagnosis of T1D in stage 3 can be weeks to decades (27). It is thought that genetic variation influences the immune regulation and response to environmental factors,

numbers of autoantibodies and type, age at development of multiple autoantibodies and the rate of progression (33, 37).

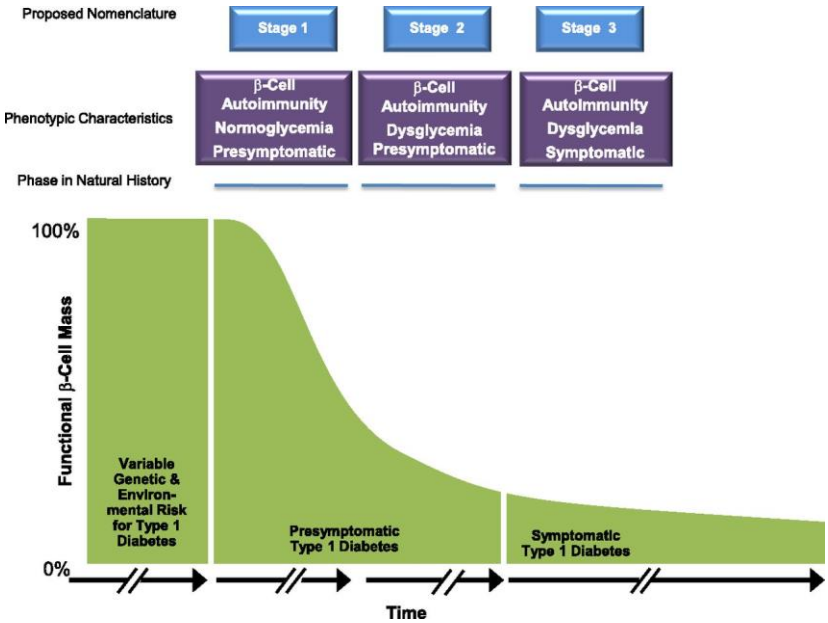

Figure 3: Stages of type 1 diabetes, adapted from ”Staging presymptomatic type 1 diabetes: A scientific statement of JDRF, the endocrine society, and the American Diabetes association” by Insel et al, diabetes care 2015 (33)

Aetiology

Most probably, individuals are born with various degrees of genetic susceptibility for T1D that together with different environmental factors, influence the process towards symptomatic disease.

Genetic

The primary risk factor for T1D is genetic, which acts as a trigger for ß-cell autoimmunity, affects the progression to clinical onset in those with IA and affects the risk of diabetes-related complications (38).

In a child with a mother diagnosed with T1D, the risk of T1D in the child is 1.3-4% compared to a risk of 6-9 % if the father were to be diagnosed with T1D (39). Siblings of patients with T1D have a risk of 6-7% (39).

The strongest genetic risk factor for T1D is the Human Leukocyte Antigen (HLA) genes on the short arm of chromosome 6 accounting for about 50 % of the genetic risk (38). These HLA genes encode for major histocompatibility complex (MHC)

cell-surface membrane glycoproteins; located at cell surfaces and are tasked to present antigens to the immune system so they can react to foreign threats. HLA DQ2 and DQ8 are risk alleles for T1D, and nearly 90% of children with T1D in Sweden are positive for one or both of these (38). The highest risk of T1D is in those positive for HLA DQ2 and HLA DQ8, the DQ2/DQ8 genotype (39). Except for HLA, more than 50 other genetic loci have been found to play a role in the development of T1D (38, 39).

T1D is considered a heterogeneous disease with differences in clinical phenotypes and genotypes. It has been shown that HLA affects which diabetes-related autoantibody appears first. HLA-DQ2 is associated with GADA, and HLA-DQ8 with IAA (26, 29, 30). This means that different genetics and perhaps also environmental factors impact in different ways. Recent studies have introduced the idea of endotypes, subtypes of T1D with distinct etiopathogenesis that might have specific treatment approaches and prognostic implications (40). Endotypes can be classified based on several factors, but age at diagnosis is commonly used and a division into three age groups <7, 7-13 and >13 years of age (41) has been proposed. The youngest, < 7 years of age, had a stronger familial clustering, higher frequency of high-risk HLA genotype and higher frequency of IAA compared to the older, ≥13 age group, who had a stronger male dominance and higher frequency of GADA (41). It was also shown that those in the youngest age group/endotype had a shorter duration of symptoms before T1D diagnosis and less severe decompensation at T1D diagnosis (41).

Environment

Genetic risk is important in the pathogenesis of T1D, but an environmental trigger is often needed for T1D to develop (38), see Figure 4. As for genetic risk factors, environmental risk factors can act as a trigger for IA to develop, act by affecting the rate of progression through the three stages described before and perhaps also protect against T1D.

The importance of environmental factors in pathogenesis is proven by the rapid increase in T1D incidence that cannot be explained solely by changes in the genetic upset (22). Additionally, individuals who migrate from a region with a low incidence of T1D to one with a high incidence of T1D increases their risk of developing T1D (42). Finally, over time it has been observed, particularly in the youngest children, that the high-risk HLA genotypes have becoming less frequent in children with T1D (43, 44), and children who in the past would not have developed T1D are nowadays diagnosed (45). These observations indicate that environmental factors must play an increased role in the pathogenesis.

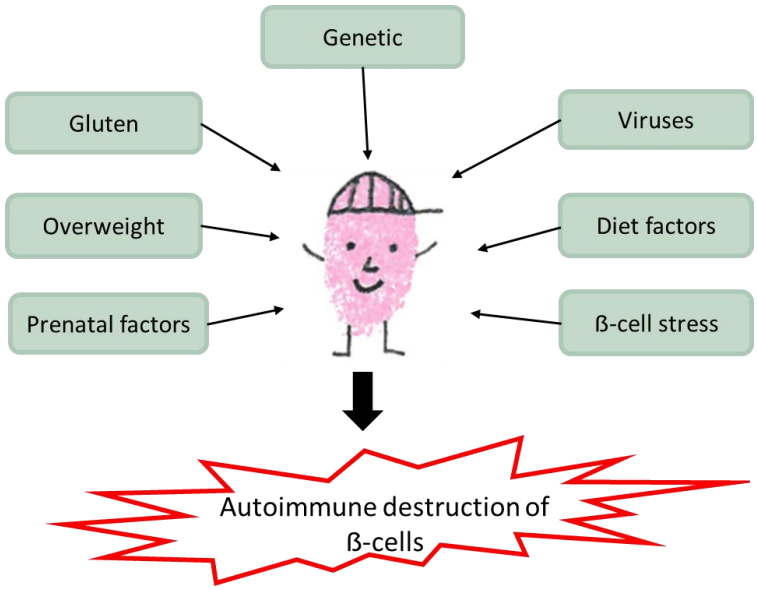

Figure 4: Environmental factors studied as being part of the pathogenesis of T1D.

Many factors in our environment have been studied as being part of the pathogenesis of T1D. There are several hypotheses, but none has been completely proven and there are studies that speak both in favour and against the different environmental risk factors proposed.

Prenatal risk factors

Since the process towards stage 3 in the pathogenesis can start early, already at 3 months of age, environmental factors affecting the foetus when in utero may affect the risk. Some studies have indicated a correlation between being born large for gestational age (46), maternal age, and intrauterine infections (47) with an increased risk of T1D.

The hygiene hypothesis

According to the hygiene hypothesis, our immune system needs to be exposed to microbes in order to develop and mature in the right direction (48). Children today are less exposed to microbes, which according to the hypothesis could lead to a reaction to self-antigens and thereby to an increase in autoimmunity (42). However, in children at genetic risk of T1D, those developing IA and progression to T1D are younger at their first infection and had a higher number of early infections than those without IA and T1D (48).

Viruses

Many studies support the idea that viruses affect the immune system or directly impact ß-cells, being a factor in the development of islet autoimmunity (49). Many different viruses have been studied, where enteroviruses have the strongest evidence of being associated with IA (50). Covid-19 has also been discussed as a potential trigger of T1D. The incidence of T1D in children and adolescents increased during the Covid-19 pandemic (51, 52). There have been different theories behind the rise in new cases of T1D during the Covid-19 pandemic, but there is no definitive explanation for the increased incidence. A large study from Finland showed a significantly increased incidence of T1D in children and adolescents, but no association with a Covid infection in the children diagnosed with T1D (53). Although the majority of studies have not been able to determine that it is the virus itself that has caused the rise in the incidence of T1D, there is some evidence to suggest that in young children with a genetic risk for T1D a Covid infection may raise the risk of developing IA (54). Another theory, supporting the hygiene hypothesis, is that the reduced amounts of other respiratory and gastrointestinal virus infections in children during the pandemic have caused the increase in incidence seen during the pandemic (53).

Diet factors

It has been suggested that some dietary elements, such as cow's milk, gluten and pollutants, may precipitate the development of T1D (50). In contrast, vitamin D and the length of breastfeeding may provide preventive effects (50). Study results for most factors are contradictory, and there is no strong evidence for a connection with the risk of T1D. The associations found between factors in diet and the risk of IA and/or T1D are often explained by effects on the gut microbiota, immune response or oxidative stress (55).

Gluten

This thesis focuses on gluten as an environmental factor that influences the clinical course and incidence of T1D. Gluten is a protein found in wheat, rye and barley. Gluten acts as an elastic network in bread for example. The two major components of gluten are gliadins and glutenins. When we eat, dietary proteins are broken down into amino acids or small dipeptides or tripeptides before they are transported across the intestinal epithelium (56). These amino acids, are often harmless and not capable of initiating any immune responses (56). Gluten is resistant to this enzymatic breakdown (56) and therefore contains peptides that are capable of triggering the immune system (57).

Many studies have been conducted both in animals and humans to find how gluten can affect pathogenesis, but the role of gluten and a gluten-free diet is unclear (58). One hypotheses is that gluten affects the intestinal flora and the immune system and is therefore a factor in the pathogenesis of T1D (56).

Various characteristics of gluten, including the amount and time of introduction, have been investigated and discussed in relation to its diabetogenic potential. A meta-analysis showed that a later introduction of gluten was associated with a reduced risk of T1D (55). In the BABYDIAB study in Germany that followed children born to parents with T1D, children who were introduced to gluten-containing foods before the age of 3 months had a higher risk of developing IA compared to children who only received breast milk during the same period of life (59). The increased risk was not an effect of shorter breastfeeding in those introduced before 3 months of age (59). In the same study, children at a genetic risk of T1D were randomly assigned to be introduced to gluten at the age of 6 months or 12 months of age. There was no effect on the prevalence of IA between the groups (60). Additionally, the risk of IA has been investigated in children with genetic risk for T1D or with parents who have T1D by the US-based Diabetes Autoimmunity Study in the Young (DAISY) (61). Children who consumed food containing gluten before the age of 4 months but also after 7 months of age had a higher risk of IA than those introduced to cereals between 4-6 months of age (61). In the TEDDY-study, they showed that a late introduction of cereals, after 9 months of age, increases the risk of IA in these children (62).

The amount of gluten in the diet during pregnancy and the risk of T1D in offspring have been studied. A Danish study showed an increased risk of T1D in the offspring of mothers with high gluten intake during pregnancy (63). In contrast, a study from Norway could not find any association between gluten intake during pregnancy and the risk of T1D (64).

A study looking at children's amount of gluten intake discovered that those who consumed more gluten early in life were more likely to be diagnosed with T1D later on (64).

Gluten-free diet

A gluten-free diet (GFD) has been shown to reduce the incidence of T1D in mice, and a cereal-based diet to promote T1D in animals (56). A lifelong GFD in mice has been shown to reduce the risk of autoimmune diabetes from 64% to 15% (57). The risk decreased further in the offspring whose mothers were subjected to a GFD throughout pregnancy (57).

It has also been shown that in individuals with both celiac disease (CD) and T1D, CD is often diagnosed after T1D instead of the other way around. Therefore, it is believed that the risk of associated autoimmune diseases after CD diagnosis may be related to the duration of exposure to gluten (65) and that a GFD may protect against other autoimmune diseases (66).

Studies in humans on the effect of a GFD on the development of diabetes as well as its effect on remission have indicated that a GFD may have a beneficial effect on the ß cells (56). In a Danish study, 13 children were given a GFD for 6 months after

a T1D diagnosis (67). At 1-year follow-up, they had better HbA1c values and a three-fold higher prevalence of partial remission compared to children on a regular diet (67). In a study of children with newly diagnosed T1D in Sweden, one group was given a GFD and another a regular diet. During follow-up, the study indicated the benefits of a GFD on the glycemic control, but because there were only a few participants, no firm conclusion could be drawn (68). Finally, in a study of patients diagnosed with CD and having diabetes-related autoantibodies at CD diagnosis, but without a diabetes diagnosis, after a 2-year follow-up on a GFD, they were no longer positive for diabetes-related autoantibodies (69).

The accelerator hypothesis

Another hypothesis is the accelerator hypothesis (70). The incidence of T1D has increased in parallel with improvements in the standard of living and factors associated with modern living. Being overweight and a sedentary lifestyle have been studied as potential risk factors in the process towards T1D. The accelerator hypothesis states that T1D as well as T2D are related to insulin resistance but occur in patients with different genetic upset. Growth and excessive weight gain are associated with an increased insulin demand and insulin resistance that accelerate ß-cell apoptosis and autoimmunity in the presence of susceptibility HLA genotypes leading to T1D (70, 71).

Another hypothesis is the ß-cell stress which states that exhausted ß-cells produce peptides that act as autoantigens and initiate ß-cell autoimmunity (50). Being overweight is one of the factors discussed that affect the incidence of T1D among children (72-76). Other factors that cause increased insulin demand and ß-cell stress such as rapid growth, puberty, low physical activity, trauma and psychological stress may play a role in the development of T1D (50). According to a recent study, fast weight gain during puberty significantly impacts the emergence of IA in children at genetic risk for T1D, but puberty itself has no significant effect (77).

Since the conversion to IA is highest around 9-24 months of age (28), the growth pattern before is of interest. It has been shown that a higher weight gain during infancy increases the risk of IA (78).

During the Covid-19 pandemic, there was an increase in body weight, body mass index (BMI) and obesity in children worldwide, probably due to lockdowns leading to lifestyle changes (79). This suggest that the rise in T1D incidence observed during the Covid pandemic may have been from the lockdown rather than the Covid-19 virus. It was also recently demonstrated that BMI and overweight increased in children with a genetic risk of T1D starting already at 9 month of age during the pandemic (80); this increase in early growth was associated with a higher risk of developing IA (80).

As previously mentioned, over the past two decades, the incidence of T1D in Sweden has plateaued (14). During the same period there was a stabilisation in the

prevalence of overweight and obesity among schoolchildren in Sweden (81, 82), which further strengthens the hypothesis that increased growth and weight may affect the incidence of T1D (14).

Treatment

The future for a child with T1D has changed dramatically since the discovery of insulin. Today, children with T1D are treated with multiple daily injections of long-lasting and rapid-acting insulin or through the use of continuous subcutaneous insulin infusions (insulin pumps) (22). Closed loop-systems, that integrate continuous subcutaneous insulin infusion with continuous glucose monitoring and an algorithm that automatically modulates insulin administration are the most recent breakthroughs in diabetes technology.

Despite the availability of new insulins and technological advancements, achieving and maintaining adequate glycaemic control can be difficult, especially in childhood and adolescence when hormonal changes, growth and social pressures are present (83).

Complications

Children with T1D are at risk of both acute- and long-term complications. The acute complications are due to the insulin treatment, where a mismatch adjusting insulin together with diet and physical activity can lead to too much insulin being administered, with the risk of hypoglycaemia. Conversely, insulin deficiency leads to hyperglycaemia and increased risk of diabetic ketoacidosis and by time late complications.

Long-term complications are rare in children and adolescents, but the process towards complications can be started already in childhood, depending on metabolic control. Microvascular complications leading to nephropathy (kidney disease), retinopathy (vascular damage to the retina) and neuropathy (nerve damage) as well as macrovascular complications leading to cardiac disease, peripheral vascular disease and stroke are among the complications (84).

In the 1990s, the Diabetes Control and Complications Trial (DCCT) research group showed that intensive insulin therapy which aimed to achieve blood glucose values close to normal delayed the onset and slowed the progression towards both micro- and macrovascular complications (85). The follow-up study, the Epidemiology of Diabetes, Interventions and Complications, showed that the beneficial effects of an period with intensive therapy persist; this phenomenon is known as metabolic memory (86).

HbA1c has long been the golden standard for assessing metabolic control; the goal to prevent complications is <48 mmol/mol or 53 mmol/mol, depending on the length of diabetes, availability of care, and use of technical aids (87). Targets for continuous glucose monitoring can also be used to estimate metabolic control (87). In Sweden, the HbA1c goal is < 48 mmol/mol and our collaboration and help from our national registries have helped us to achieve good metabolic control for children with T1D as a group, which will diminish their risk of developing complications in the future (88).

Comorbidities

Except for macro- and vascular complications, children with T1D are also at an increased risk of developing other autoimmune conditions (89, 90). The association/comorbidity between T1D and other autoimmune diseases has been contributed to shared risk HLA genotypes (91).

In a newly published Swedish study with children and adolescents diagnosed with T1D, 19.2% were diagnosed with at least one additional autoimmune disease, 2.0% with two additional autoimmune diseases and 0.3% with three or more after a mean follow-up time of 8.8±5.7 years (some were followed-up for 19 years) after a T1D diagnosis (92). In another study with the type 1 diabetes exchange clinic network in the US including individuals with T1D from 1 to 93 years of age, 27% of participants had at least one additional autoimmune disease, 5% had two additional autoimmune diseases and less than 1% had three (90). In adults without diabetes, 7.3% had one autoimmune disease and 0.7% had two (93). The risk of hypothyroidism, CD and hyperthyroidism was 3.4, 4.6 and 2.9 times higher in adults with T1D compared to adults without T1D (93).

Autoimmune thyroid disease (ATD) and CD are the two most commonly associated autoimmune diseases in T1D (90, 92, 94), but the prevalence of other autoimmune diseases such as psoriasis, vitiligo, rheumatic joint disease, Addison's disease and atrophic gastritis are also increased (92).

Risk factors for being diagnosed with an additional autoimmune disease are diagnosed with T1D late in life, longer diabetes duration independent of age at T1D diagnosis, white non-Hispanic ethnicity and female sex (90, 92, 93, 95).

Celiac Disease

CD is a disease with many faces, from typical small children with poor growth, an extended stomach and loose stools, to teenagers with depression, but some individuals have no symptoms at all, at least with no awareness of symptoms.

Specific serological markers, HLA DQ2 and/or DQ8 and enteropathy provide the diagnosis.

Epidemiology

CD has been regarded as a paediatric diagnosis but has become more often diagnosed among adults, but still, children are two times more likely to be diagnosed with CD (96, 97). In a review, the global pooled prevalence of CD serological positivity was 1.4% and of biopsy-proven CD 0.7% (97). In children, the pooled prevalence of biopsy-proven CD was 0.9% in the general paediatric population (97). However, the reported prevalence depends on whether or not the studied population is screened for CD, because most individuals with CD remain undiagnosed due to differences in symptoms, or lack of symptoms.

During the last few decades, there has been a 7.5% increase in CD incidence in the general population including CD in both children and adults (96) and the prevalence has increased from 0.6% in 1991-2000 to 0.8% in 2001-2016 (97). The incidence has increased in all geographic areas studied (mainly the Western world), all age groups and sexes (96). The increase in incidence can be attributed to better diagnostic tools and increased awareness of symptoms suggestive of CD (96). However, a 'real' increase in incidence has also been suggested due to changes in environmental risk factors (96).

CD is a common childhood disease in Sweden. During 1973-2009 there was an increase in childhood CD incidence from 10 per 100,000 person-years in children age 0-15 between 1973-1984 to 42 cases per 100,000 person-years in 2004-2009 (98), see Figure 5. The median age of CD diagnosis has increased from 1.1 years to 6.7 years over the same period (98). From 1973 until the mid-1990s almost all childhood cases were found in children under the age of two, but between 1998-2009 most new cases were in the age group 5-14.9 years (98).

Females are approximately 1.5 times more often diagnosed with CD than males (96, 97). In the paediatric population, girls have an increased risk compared to boys (98). Family members of an individual with CD are at an increased risk (10-15%) of developing CD (99). Individuals with other autoimmune diseases such as T1D are also at an increased risk of being diagnosed with CD (100-103).

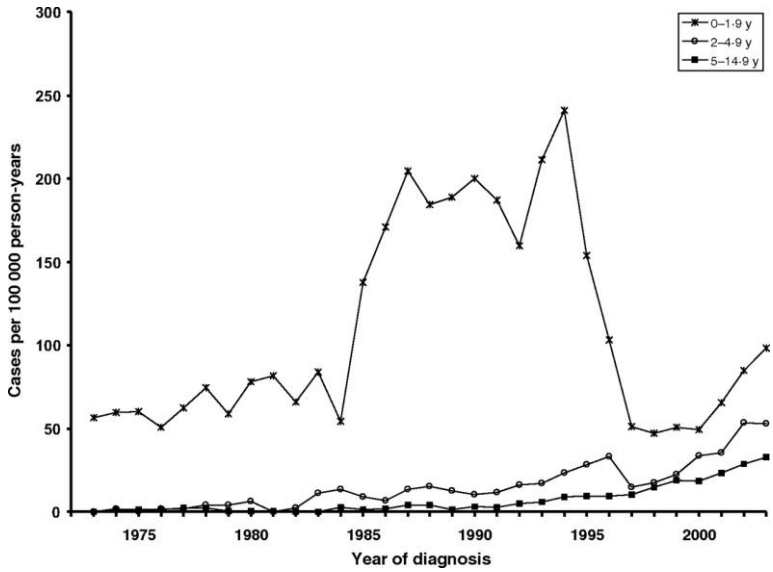

Figure 5: Annual incidence rates of celiac disease in Swedish children from 1973 to 2003 diveded into groups based on age at diagnosis. Adapted from "Difference in celiac disease risk between Swedish birth cohorts suggests an opportunity for primary prevention" by C.Olsson et al (104). Reproduced with permission from Pediatrics, vol 122, © 2008 by the AAP.

During the years 1984-1996, Sweden experienced a period with a dramatically higher incidence of CD in young Swedish children below the age of two called *the Swedish epidemic of celiac disease,* hereinafter called the Swedish CD epidemic (105), see Figure 5. During this period, the cumulative incidence of CD in children at 2 years of age increased from 1.4 cases per 1,000 births 1973-1983 to 3.7 cases per 1,000 births (105). Concomitantly with the Swedish CD epidemic, there was a national change in Swedish infant feeding recommendations to postpone gluten introduction in infancy from four to six months, which practically went from a gradual introduction of gluten at four months of age, to a more abrupt introduction of gluten at 6 months of age (105, 106). Additionally, the gluten content in the cereal-based follow-on formula was increased (105, 106). In 1996 the feeding recommendations were changed back to introduction at 4 months of age, and from 1995, the gluten content in formulas was decreased again (105). After these changes, a rapid decrease in CD incidence in young children was noticed, approaching the levels in incidence rate before the epidemic (106, 107).

This unique situation in Sweden with birth cohorts that differ in recommended gluten introduction and amount of gluten intake during infancy has been studied in the Swedish study ETICS (exploring the iceberg of celiac disease in Sweden). In this study, almost 10% of the children born 1993 and 1997 were screened for CD at 12 years of age and it was found that during the Swedish CD epidemic, the

prevalence of CD was increased significantly, 2.9% compared to 2.2% after the epidemic (106).

Pathogenesis

CD is a chronic T-cells-mediated enteropathy caused by the ingestion of gluten in individuals with a genetic susceptibility for the disease (108).

As described before, gluten and its major components glutenin and gliadin, are difficult to digest (56) and enter the intestinal lumen. Gliadin interacts with epithelial cells and triggers an innate immune response with the release of cytokines and interacts with CXCR3 receptors in the epithelium of the small intestine leading to the release of zonulin and thereby a disruption of the tight junctions (109). With an increase in intestinal permeability, gluten peptides are translocated into the lamina propria. In the lamina propria glutamine meets the enzyme transglutaminase 2, which deaminates gliadin to glutamic acid, which then binds strongly to HLA DQ2 and DQ8 on antigen-presenting cells (110). The antigen-presenting cells activate CD4+T helper cells that secrete pro-inflammatory cytokines that initiate a massive immunologic reaction with the activation of T-cells and B-cells that release antibodies against gluten and tissue transglutaminase (anti-tTG) (58, 99). The release of cytokines and activated T and B-cells increases the intestinal permeability and damage the intestinal mucosa leading to malabsorption and symptoms suggestive of CD.

Aetiology

Genetic factors

The fact that people with a family member diagnosed with CD have an increased risk of CD indicates the importance of genetic factors. As for T1D, CD has a strong association with HLA. Almost all patients with CD are positive for HLA DQ2 or DQ8 (111). In the general population, the HLA-genotype DQ2/DQ2 generates the highest risk for CD (112, 113) and is also associated with an earlier CD onset (113). A small number of patients with CD are negative for both HLA-DQ2 and DQ8, 4.8% in a large Italian study of both children and adults (114). Many of them lacking DQ2 and DQ8, are positive for one-half of the DQ2 heterodimer (DQA1*05 or DQB1*02) (115). HLA-DQ7 positivity is also more prevalent in those who are HLA-DQ2 and DQ8 negative (114). Except for HLA, other non-HLA genetic factors have been associated with CD, but each factor has a smaller contribution to the risk than HLA (99).

Environmental factors

Exposure to gluten is necessary in order to develop CD and is the most important risk factor for CD. The importance of other environmental factors in the pathogenesis of CD is supported by the Swedish epidemic of CD, and the increase in incidence over the past few years has been too rapid to be explained by changes in the genetic upset. It has also been shown that children, with a genetic risk of CD, and born in Sweden have almost twice the risk of CD compared to children born in the United States after adjusting for sex, family history of CD and HLA (113). This speaks in favour of environmental factors affecting the risk. Factors such as when gluten is introduced, the amount of gluten in the diet and the effects of breastfeeding have been discussed (58, 106, 116, 117), as well as infections (99).

Diagnosis

As said before, CD is a disease with different faces, and can, according to "the Oslo definitions for CD and related terms" be divided into classical, non-classical and subclinical forms (108). There are also other forms, not mentioned in this thesis. Classical CD is common in the youngest of children, < 5 years, with symptoms of malabsorption such as diarrhoea, weight loss, distended stomach and stunted growth (108). The non-classical CD presents with no symptoms of malabsorption, instead constipation, abdominal pain, depression, iron deficiency etc. (99, 108). Those with subclinical CD are often detected by screening. In subclinical CD the disease is below the threshold of clinical detection, meaning there are no symptoms of CD (108).

In Sweden, we use the guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) to diagnose CD in children. As described previously, autoantibodies like anti-tTG are formed during the development of CD (99). These autoantibodies are used in the diagnostic process. Today anti-tTG and total IgA in serum is the initial step in the diagnosis of patients with symptoms suggestive of CD or screening for CD (118). Patients with low IgA in serum, IgA deficiency, should be tested with an IgG-based test such as anti-tTG IgG (118). Anti-tTG has been found to have a sensitivity in children of 97.7% and a specificity of 70.2% (119). The higher levels of anti-tTG, the higher degree of villous atrophy, and a value ≥10x upper limit of normal (ULN) predict enteropathy corresponding to Marsh 2/3 (118).

In children with anti-tTG ≥10xULN, a second blood test which analyses autoantibodies against endomysium (anti-EMA) should be performed, and if positive, the child is diagnosed with CD (118). This is called the no-biopsy approach to diagnose CD. The sensitivity of anti-EMA in children is 94.5% and the specificity is 93.8% (119), that is anti-EMA has a higher specificity than anti-tTG, but is dependent on the observer; it is also more expensive (99).

In children with elevated anti-tTG, but below ≥10xULN, a gastroscopy and small intestinal biopsy with at least 4 biopsies from the distal duodenum and at least 1 from the duodenal bulb should be done (118). The histological picture of CD is characterised by the presence of crypt hypertrophy, villus atrophy and increased intraepithelial lymphocytes (99). The extent of the damage in the biopsy is classified mostly by using the Marsh-Oberhuber classification (118). If Marsh is class 2 or 3, CD is confirmed (118).

Treatment

The treatment of CD is a strict lifelong GFD to heal the intestinal damage. The individual's diet needs to be strict to avoid complications both in the short term (gastrointestinal symptoms such as diarrhoea, constipation, abdominal pain, vitamin and iron deficiencies, failure-to-thrive and fatigue), and also in the long term (T-cell lymphoma (although very rare), decreased bone mineral density, infertility and mortality) (120).

Celiac disease and Type 1 diabetes

CD is frequent in individuals with T1D with a co-occurrence rate of between 1.6% to 12.3% in different populations (100-103). In Sweden, previous studies have reported a CD prevalence of approximately 10% in children with T1D (121, 122).

There are few longitudinal studies examining the timing of a CD diagnosis in relation to the diagnosis of T1D. In a prospectively followed cohort of children with high genetic risk of both T1D and CD, IA usually precedes the development of anti-tTG in young children (123). In a Swedish study following children for five years after a diagnosis of T1D, the majority of children with CD were diagnosed after the T1D diagnosis, most often within the first two years (121). A systematic review by Pham-Short et al. demonstrated that 79 % of the children with both T1D and CD were diagnosed with CD within five years of a T1D diagnosis (100).

The reason for the increased risk of CD in children with T1D has been attributed to shared genetic risk factors (124). T1D and CD share the same HLA risk genes, HLA DQ2 and/or DQ8 (38, 111), but the co-occurrence is greater than what can be explained by shared genetic risk factors (123). The HLA-DQ2 haplotype is found in about 90% of children with CD and 55% of patients with T1D, while the HLA-DQ8 haplotype is only found in about 10% of children with CD but around 70% of children with T1D (125).

Except for HLA, age at T1D diagnosis has also been reported as a risk factor, where a younger age seems to increase the risk of CD (102, 103, 126-128). In the general

population, CD is more common in females (97), whereas in children and adolescents with T1D, some report female sex as a risk factor (102, 103, 126), but others have not found any differences among the sexes (127, 128). Delivery by caesarean section and being born during the summer are perinatal risk factors associated with being diagnosed with both T1D and CD during childhood (129). Gluten as a trigger mechanism for both T1D and CD has also been discussed. See Table 1 for a comparison between T1D and CD.

Table 1: Similarities and differences between Type 1 diabetes and celiac disease.

	Type 1 diabetes	Celiac disease
Epidemiology	Rising incidence during the last decades.	Rising incidence during the last decades.
Patogenesis	Autoimmune disease with destruction of the ß-cells in the pancrease.	Autoimmune-induced inflammation leading to damaged intestinal mucosa.
Autoantibodies	GADA, IAA, IA2A and ZnT8* are common diabetes related autoantibodies that can be detected for month up to years before diagnosis.	Transglutaminase autoantibodies, can be detected before diagnosis.
Genetics	Strongest genetic risk HLA genes on chromosome 6, but also other non-HLA genes contribute.	Strongest genetic risk HLA genes on chromosome 6, but also other non-HLA genes contribute.
High-risk HLA genotype	HLA DQ2/DQ8	HLA DQ2/DQ2
Environmental factors	Many suspected as viruses, diet factors, overweight etc	Gluten but probably also other factors as viruses
Gender	Male predominance overall after puberty	Female predominance
Age at diagnosis	Peak in incidence during puberty, but can be diagnosed at any age.	Classical CD, most common <5 years of age. Non-classical, asymptomatic, at any age.

*Glutamic acid decarboxylase autoantibodies (GADA), insulinoma-associated-2 autoantibodies (IA-2A), insulin autoantibodies (IAA) and zinc-transporter-8 autoantibodies (ZnT8A).

Screening

In 1968, the World Health Organization (WHO) stated 10 principles for screening that are still frequently referred to (130).

1) The condition should be an important health problem

2) An accepted treatment of the disease for patients should be recognised

3) Facilities for diagnosis and treatment should be available

4) There should be a recognisable latent or early symptomatic stage

5) There should be a suitable test for disease detection

6) The test should be acceptable to the public

7) The natural history of the condition, including the development from latent to declared disease, should be adequately understood

8) There should be an agreed policy on who to treat as patients

9) The cost of case-finding should be economically balanced in relation to possible expenditure as a whole

10) Case-finding should be a continuous process

In children with T1D, CD is often asymptomatic or presents vague symptoms (100) with less than 10 % having gastrointestinal/symptomatic disease (120). Although asymptomatic, children with increased anti-tTG have intestinal changes (131). Therefore, since CD fulfils many of the above principles, routine screening for CD in children with T1D is common in many countries and consequently, most cases of CD in children with T1D are detected by screening (100). The recommendations/guidelines for the frequency of screening are not well established, and who and when to screen are poorly studied. Both the International Society for Paediatric and Adolescent Diabetes (ISPAD) and The American Diabetes Association (ADA) recommend screening for CD at diagnosis, and two and five years after T1D diagnosis (89, 132). It is not known whether these screening guidelines and the recommended frequency of screening apply to all children with T1D or whether it is only necessary for certain subgroups. For more than two decades in Sweden, all children and adolescents have been screened for CD at diagnosis of T1D and annually thereafter. Little is known whether the different recommendations are cost-effective.

Complications

There has been discussion about whether or not to identify and treat asymptomatic CD in children with T1D due to the fact that these children frequently exhibit little to no signs of the disease. Also, because there are little or no symptoms it can be difficult to achieve good compliance to a GFD, and in a review article the adherence at 1-year follow-up after starting a GFD varied between 59-100% (133). Those with CD-related symptoms at diagnosis had better adherence to the GFD (134).

There are inconsistent findings regarding the effect of a GFD on glycaemic control, insulin dosage, HbA1c, hypoglycaemic episodes and growth in children with both T1D and CD. A review reported that some studies have showed better glycaemic control and growth while others have showed no differences (120). In the SWEET registry, children with both T1D and CD had a lower BMI-SDS and height-SDS compared to children with T1D only (103), which has been shown by others as well (135). One study reported that children with T1D and diagnosed with CD and on a GFD, increased in weight-SDS and height-SDS (136), but others reported stable

weight, height and BMI z-scores (133). On the other hand, many studies have found no significant differences in height-SDS and BMI-SDS between children with and without CD (133, 137, 138).

Since GFDs often are high in glycaemic index (139), and the recommendation for children with T1D is a diet with a low glycaemic index, it has been thought that T1D children with contemporary CD should have worse metabolic control. However, studies have shown better HbA1c levels in patients with T1D and CD than in those with T1D only (103), others have found no effect on HbA1c (133, 137, 138). The frequency of severe hypoglycaemia and diabetic ketoacidosis have also been compared with those with both T1D and CD and those with T1D only, with no significant differences (133, 137). Some have reported a shorter time to peak blood glucose levels, higher peak and higher 2-hour blood glucose value in those with both T1D and CD, however, it did not affect HbA1c (133).

When taking the adherence to the GFD into account, some have reported worse glycaemic control in those who did not adhere to the GFD (134), while others report no differences in growth or metabolic control between those with good or bad adherence to the diet (137).

In addition, being diagnosed with two chronic diseases which have a significant impact on daily life, does not seem to affect the quality of life when comparing T1D patients with and without CD (133, 134). When comparing patients with both T1D and CD on a GFD, those who did not follow a GFD reported lower quality of life (134).

When it comes to other diabetic long-time complications it has been shown that CD is an independent risk factor for microvascular complications such as retinopathy and nephropathy in patients with T1D (120, 138, 140) and a worse macrovascular risk profile (120).

Aims

The overall aim of this thesis is to create a more individual-based screening recommendation for CD in children and adolescents with T1D and to study whether gluten introduction during infancy influence the risk of receiving T1D and when T1D develops. Finally, I also studied predictive factors for multiple autoimmunity in a subgroup of children diagnosed with T1D, CD and ATD, called triple autoimmunity.

The specific aims of this thesis were as follows:

- To study whether the cumulative incidence of T1D differs between children born during the Swedish CD epidemic compared with children born after it, (Study I).
- The prevalence of confirmed CD in children and adolescents before, at and after the diagnosis of T1D, (Study II).
- Investigate immunological and genetic factors in those diagnosed with CD after T1D diagnosis to find predictive factors at T1D diagnosis for a subsequent diagnosis of CD, (Study II).
- Using the prevalence and predictive factors, improve current screening guidelines for CD in children with T1D, (Study II).
- To study the impact of a CD diagnosis on glycaemic control and BMI in children with T1D, (Study III).
- Investigate the prevalence of both CD and ATD in children and adolescents with T1D, (Study IV).
- In children with T1D, identify predictive factors for receiving a diagnosis of both CD and ATD, (Study IV).
- To compare risk and sex ratio between children diagnosed with T1D, CD and ATD, with age-matched children from the general population diagnosed with CD and ATD, (Study IV).

Material and Methods

The studies included in this thesis are based on Swedish cohorts. In Sweden, all children and adolescents, <18 years of age, with a diabetes diagnosis are diagnosed and treated in one of 42 paediatric clinics. The care at paediatric clinics, both outpatients visit and hospital admissions, as well as prescribed insulin and other drugs and technical devices are free for the patients.

Study Design

Study I

Study I was a population-based study where the cumulative incidence of T1D in children was compared between two cohorts of births from the general population. We chose birth cohort from 1992-1993, that is during the Swedish CD epidemic, and another from 1997-1998, that is after the Swedish CD epidemic. These two cohorts were chosen because we know from the Swedish study ETICS, described below, that the birth cohorts 1993 and 1997 differ in CD prevalence (106), and to gain power we added 1992 and 1998. We also chose these two cohorts because we wanted to have a short time span between the cohorts to avoid confounders.

The cohorts were identified from Statistics Sweden. By merging data from the National Patient Register (NPR) and national diabetes register (NDR)/Swediabkids, information regarding T1D diagnosis prior to the age of 17 was obtained. The data was collected between 1st of January 1992 until 31st of December 2015.

Study II

Study II was a longitudinal cohort study investigating the prevalence of CD before, at and up to 10 years' after the T1D diagnosis in a cohort of children from the Better Diabetes Diagnosis (BDD) study. We used the NPR to validate the T1D diagnosis and to find those diagnosed with CD in the cohort. The study cohort was followed until 18 years of age, diagnosis of CD or end of study follow-up on 31st of December 2016.

The novel design in our study compared to many others was that we divided the study population into groups based on the timing of the CD diagnosis in relation to the T1D diagnosis. We chose this group division to be able to separate individuals

with known CD before T1D, those with a screening-detected CD at T1D diagnosis and those who were screened and developed CD after T1D. The groups were as follows:

- Group 1: Children with known CD *before* T1D diagnosis, assumed to have a clinically symptomatic detected CD before T1D.
- Group 2: Children diagnosed with CD *at* T1D diagnosis. These children have an ICD-code defining CD for the first time at the same time as T1D diagnosis or within one year after T1D diagnosis. This group is supposed to have had an undiagnosed/asymptomatic CD at T1D diagnosis, detected by screening with anti-tTG at the time of T1D diagnosis. Most often anti-tTG is controlled once more after a positive value, and if there is a second positive value, a referral to a paediatric gastroenterologist is made and an intestinal biopsy is undergone. With this background we decided that the group with CD at T1D diagnosis could have developed the disease within a year after the T1D diagnosis.
- Group 3: Children who developed CD *after* the T1D diagnosis. Children with an ICD-code defining CD in the NPR for the first time at least one year after T1D diagnosis and then assumed to have a screening-detected CD after T1D diagnosis.
- Group 4: Children with *no diagnosis* of CD before or during the study follow-up period.

We compared groups 3 and 4 in order to identify predictive factors for a CD diagnosed after T1D, to identify those who benefited from screening after the T1D diagnosis. We chose to study age at T1D diagnosis, sex, HLA genotype and diabetes-related autoantibodies at diabetes diagnosis as potential predictive factors as they already are clinical practice at diabetes diagnosis. The variables are further described below.

Study III

This study was designed as a case-control study to investigate glycaemic control and BMI between children with T1D and CD (cases) with those with T1D only (controls). As in Study II, we used the NPR to validate the T1D diagnosis and to find those diagnosed with CD in the cohort.

We chose to divide the population into the same four groups described in Study II. We did this in order to study whether the timing of a CD diagnosis affects the study outcome, that is differences in glycaemic control and BMI between groups. Follow-up data on HbA1c, height and weight were retrieved from Swediabkids at clinical visits registered 1, 2, 3, 4 and 5 years after T1D diagnosis.

Study IV

Study IV is like Study II, a cohort study with children and adolescents from the BDD study, but we also included information about a concomitant ATD except for only CD as in Study II.

In this cohort we analysed the prevalence of diagnosed CD and ATD during follow-up after T1D diagnosis, that is until the end of the study at December 31, 2016 or at 18 years of age. We divided the cohort into four groups based on concomitant CD (T1D+CD), ATD (T1D+ATD), CD and ATD (triple autoimmunity) or only T1D.

To find predictive factors for triple autoimmunity, we compared sex, age of T1D diagnosis, HLA genotype and diabetes-related autoantibodies at T1D diagnosis between the groups.

Within this study, we also compared the prevalence of being diagnosed with both CD and ATD in children with T1D with age-matched children from the general population. To do this we used a group of children from the ETICS study, screened for both CD and ATD at 12-13 years of age, with age-matched children from the BDD cohort, that is children diagnosed with T1D, CD and ATD before 14 years of age.

The children in ETICS were screened with anti-tTG for CD and with TSH and free T4 for ATD. Children with an increase in TSH serum concentration above the reference range (4.3mIE/L) and a decrease in free T4 serum levels below the reference range (12pmol/L) were diagnosed with overt hypothyroidism (141). In contrast, children with a decrease in TSH serum concentration below the reference range (0.51mIE/L) and increased free T4 serum levels above the reference range (22pmol/L) were diagnosed with overt hyperthyroidism (141).

Study populations

Children and adolescents born between 1987 and 2012 in Sweden were included in the studies. The cohorts were recruited from different Swedish registers, the BDD study and the ETICS study described below.

In Study I we included all children born during the years 1992, 1993, 1997 and 1998. According to Statistic Sweden, 240,844 children were born between 1992-1993 and 179,530 children between 1997-1998. Data regarding T1D diagnosis was collected from NPR and Swediabkids/NDR. Of those in the birth cohort 1992/1993, 1,692 were diagnosed with a diabetes diagnosis <17 years of age. We excluded 50 children who had other diabetes than T1D, leaving 1,642 children with T1D. In the cohort

1997/1998, 1,419 was diagnosed with diabetes. In this group, 39 children were excluded due to another diabetes type than T1D, leaving 1,380 children with T1D.

In Studies II and IV, we used a cohort of 5,451 children and adolescents enrolled in the BDD study between 2005 and 2012. We excluded 151 children because they had no T1D diagnosis in the NPR. These children had either T2D, secondary diabetes, unclassified diabetes or MODY. Another five children were excluded as they were over 18 years old at T1D diagnosis, leaving a study population of 5,295 children, see Figure 6.

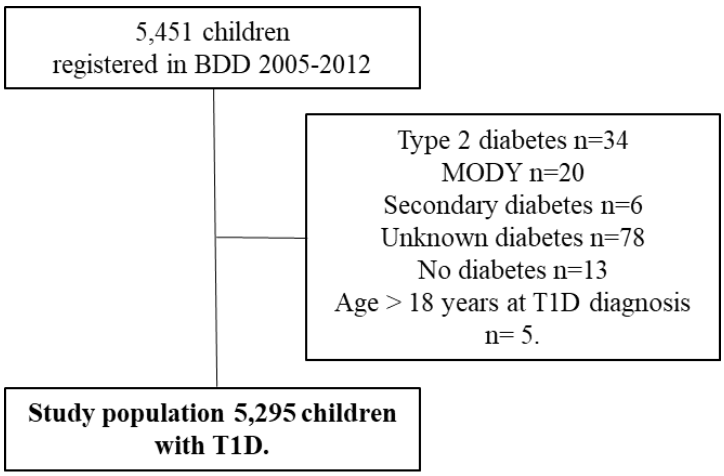

Figure 6: Flowchart over the study cohort and excluded individuals in Studies II and IV.

In Study III, we again used the BDD study, but this time only children enrolled during the years 2005 until the end of 2010 were included. During these years, 3,732 children, of which, 41 were excluded due to the lack of data, and another 79 because T1D were diagnosed before May 2005. Thus, the final sample consisted of 3,612 participants with T1D.

In Study IV, we also used a population of children from the ETICS study. In total, 12,632 children were screened for CD of which 309 had CD and also underwent screening for ATD.

Data Sources

Data from the BDD study, ETICS study, national quality registries, and national health and population registries have been used in the four studies.

There are several quality registries in Sweden, which are organised databases of patient-specific clinical data that are collected to develop and safeguard the care of patients and monitor and improve patient care, ensure that recommendations are followed, and also serve as a source of data for research (142, 143). For both healthcare providers and patients, it is voluntary to participate in a national quality register (142). On the other hand, Sweden has national health registries managed by the National Board of Health and Welfare and national population registries managed by Statistics Sweden. Participation in these registries is required by law for both healthcare providers and patients (142). Since 1947 all permanent residents of Sweden have had a unique personal identity number (144). When reporting to different registers, the personal identity number is used and thereby can be used to link data from different registers for research purposes (144).

The Swedish National Patient Register (NPR)

In 1964, the National Board of Health and Welfare founded the Swedish National Inpatient Register to collect data about Swedish inpatient care (145). Since 1987 the inpatient register has had complete national coverage (145). From 1997, the NPR was extended by surgical day care procedures being reported, and since 2001 all clinics are required to report physician visits for hospital-based outpatients (145). The coverage from the outpatient register is almost 100% from public caregivers (145). Primary care is not covered in the NPR. The Swedish International Classification of Diseases System (ICD) is used by the NPR to code diagnoses (145).

The National Diabetes Register (NDR) and Swediabkids.

The Swedish NDR is one of the national quality registries in Sweden; it was started in 1996. In 2000, a special part for children and adolescents, the Swediabkids, was founded (143). All Swedish paediatric diabetes centres report to the register in conjunction with the patient visiting the clinic, it thereby includes data from diabetes onset and clinical visits during follow-up. HbA1c, weight, height, diabetic ketoacidosis, severe hypoglycaemia etc are recorded in the register at every visit. With a reporting degree of almost 100%, the register has a high degree of accuracy for children and adolescents (143).

Statistics Sweden

Statistics Sweden is a government agency with the responsibility to report information about official population statistics.

The Better Diabetes Diagnosis study (BDD study)

The BDD study is a nationwide prospective study in Sweden. The study started in May 2005 and is still ongoing. All children and adolescents with newly diagnosed diabetes according to the criteria of ADA (3), are offered to participate in the study.

The study has a high participation rate, at its start, 40 of Sweden's 42 paediatric clinics (87%) participated in the study, and since 2011 all of the clinics have been included and more than 99 % of the patients have given their consent to participate (146). This means that the results are representative of all children with T1D in Sweden.

The overall aim of the BDD study is to improve the classification of diabetes and explore the heterogeneity of the patients with T1D to be able to give the best treatment of diabetes to children and adolescents. One of the more specific aims is to investigate predictors for autoimmune comorbidity in children and adolescents with T1D (146).

The BDD study includes blood tests taken at the diagnosis of diabetes, often before insulin is given. The tests are analysed for HLA-DQ genotype, diabetes-related autoantibodies and levels of c-peptide. In the beginning, between 2005 and 2010, the study took place within a research setting, called BDD1. Since the analyses were a reliable way of classifying diabetes and helped distinguish between different forms of diabetes it became a clinical routine in January 2011, called BDD2, and since then divided into a clinical and research part (146).

Exploring the Iceberg of Celiacs in Sweden (ETICS) study

The ETICS study is a cross-sectional school-based screening study of CD in two cohorts of 12-year-old children conducted to study the Swedish epidemic of CD during the years 1984-1996. One cohort, born in 1993, was screened for CD between 2005 and 2006, representing the epidemic cohort, and the other cohort, born in 1997 was screened between 2009 and 2010 representing the post-epidemic cohort (106). The study was designed as a multicentre study including 10% of all 12-year-olds in Sweden during the years in question with paediatric clinics from the whole country (106).

Blood samples from all children, except those with a clinically detected CD before the study, were analysed for anti-tTG. Children with elevated anti-tTG were recommended to undergo an intestinal biopsy and referred to the nearest paediatric clinic. In those with clinically detected CD before the study, the diagnosis was confirmed by reviewing the histology and serological markers at diagnosis from the National Swedish childhood celiac disease register and/or the medical journal. (106)

Variables

Concomitant autoimmune diseases

NPR was used to verify the T1D diagnosis in the BDD study and to find individuals with concomitant CD and/or ATD. We defined T1D, CD and ATD by the ICD

numbers listed in Table 2. The first date with an ICD-code defining T1D, CD or ATD in the NPR was considered as the date of diagnosis for the respective diagnosis.

Table 2: International classification of disease system (ICD) version 9 and 10 defining type 1 diabetes, celiac disae and autoimmune thyroid disease in the National patient register.

	ICD-9	ICD-10
Type 1 diabetes	250 A-X	E10.0-9
Celiac disease	579A	K90.0, K90.0A-B, K90.0X
Autoimmune thyroid disease	240A-X, 242-245A-X	E03.0-9, E05.0-9, E06.0-9

Between 1987 and 2016, the clinical guidelines in Sweden and those of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (147), stated that screening-detected CD in T1D should be confirmed with an intestinal biopsy. We therefore assume that those with a diagnosis of CD had undergone an intestinal biopsy.

Patients with an ICD code defining ATD were divided into two groups, one with a diagnosis of autoimmune hypothyroidism, and one with a diagnosis of autoimmune hyperthyroidism. Some participants received more than one thyroid diagnosis, and we then followed a special protocol and made an individual assessment to determine the most likely diagnosis. In this assessment, the dates of diagnoses were compared to each other, and very uncommon diagnoses were interpreted as being given by mistake if a more common diagnosis was also given. For more details, see Appendix 1 in Study IV.

Age at diabetes diagnosis

In Studies II and IV, we divided the study population into groups based on age at T1D. We chose to have preschool children 0-4.9 years of age, pre-teenage children 5-9.9 years, teenaged children 10-14.9 years, and finally a group of children 15-18 years of age at T1D diagnosis.

HLA genotype

HLA-DQ genotypes were analysed within the BDD study at diabetes diagnosis. They were used to study genetic factors in Studies II and IV. The blood samples in BDD 1 were analysed at the Clinical Research Centre (CRC), Malmö, Skåne's University Hospital and in BDD 2 at the Department of Clinical Chemistry, Skåne's University Hospital, Malmö, Sweden. HLA DQA1-DQB1 genotypes were determined with polymerase chain reaction (PCR). The methods used for HLA-typing differ somewhat between BDD1 and BDD2; for further details see the review by Persson et al. (146). The DQA1 and DQB1 alleles were combined into haplotypes and encoded as DQ types, see Table 3.

In total, 181 (3.4%) of 5295 children were excluded from the analyses of different HLA-DQ types because of missing data.

We found that six patients with HLA DQX/DQX had a diagnosis of CD in the NPR, which was somewhat surprising. We therefore reanalysed the HLA blood tests for these individuals at the Department of Immunology, Oslo University Hospital, with the same DQX/DQX results. We then asked the diabetes teams where the patients were treated whether these individuals had a CD diagnosis. Five patients had been investigated for possible CD (K90.0B or K90.0), but the CD diagnosis could not be confirmed. One patient, however, had a CD diagnosis (K90.0A), and this child also had Downs Syndrome.

Table 3: HLA DQA1-DQB1 genotypes. DQA1 And DQB1 alleles combined into haplotypes and encoded as DQ types. Reprinted with permission from the American Diabetes Association (148).

Haplotypes	DQ type
DQA1*05-DQB1*02	DQ2
DQA1*Z-DQB1*02	DQ2
DQA1*0201-DQB1*02	DQ2.2 = DQ2
DQA1*02-DQB1*02	DQ2.2 = DQ2
DQA1*03-DQB1*0302	DQ8
DQA1*Z-DQB1*0302	DQ8
DQA1*Z-DQB1*0302/0304	DQ8
Anything except alleles already mentioned	X (any number except 2 or 8)

Diabetes-related autoantibodies.

As for HLA-DQ genotypes, diabetes-related autoantibodies were analysed at diabetes diagnosis within the settings for the BDD study. The data were used in Studies II and IV. The analyses were performed at the same laboratory as for HLA. In BDD 1, all children and adolescents were tested for GADA, IA-2A, IAA and ZnT8A. In 2011, when BDD became part of a clinical routine, BDD2, GADA and IA-2A were analysed primarily. If these tests were negative, IAA and ZnT8A analyses were performed. The specific analytic methods used are described in the review carried out by Perssons et al. (146).

Because of the change of protocol in BDD1 and BDD2, only children from BDD1, that is 3,870 children analysed for all four autoantibodies, were included to study associations between autoantibodies at T1D diagnosis and the risk of forthcoming associated autoimmune disease in Studies II and IV.

HbA1c

Data on HbA1c were collected from Swediabkids retrospectively. In Study III, we used HbA1c, often taken venously, at T1D diagnosis and during follow-up when visiting the paediatric diabetic clinics at 1, 2, 3, 4 and 5 years after T1D diagnosis.

During follow-up, the tests are often capillary samples. In Sweden, we use the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method. The blood tests were analysed in Swedish laboratories that were all standardised by External Quality Assurance in Laboratory Medicine (EQUALIS).

Diabetic ketoacidosis

Clinicians registered events of ketoacidosis in the Swediabkids. Diabetic ketoacidosis was defined as pH<7.3.

BMI-SDS

Weight and height are registered in the Swediabkids at diabetes diagnosis and then at every visit to the clinics. We collected data retrospectively on weight and height from diabetes diagnosis and then for every visit 1, 2, 3, 4 and 5 years afterwards. BMI was calculated using the formula kg/m^2, and body mass index standard deviation score (BMI-SDS), age and sex-adjusted BMI, were calculated based on norm data for German children and adolescents as they are almost identical to the Swedish norm data (149). The BMI-SDS was used to compare growth between the groups in Study III.

Statistics

For data handling and statistical analyses, IBM SPSS Statistics Version 25 and 28 were used. For Study I, we also used Excel 2016. In all studies, a p-value <0.05, was considered to be statistically significant.

In Study I, the cumulative incidence was calculated and compared using the chi-square test. Because of the large cohorts investigated, the mean age at T1D diagnosis was used and compared using the Student´s T-test.

The statistics in Study II and IV are alike but differ in how the study population is grouped. In Study II, we calculated the prevalence of CD in the subgroups based on when CD was diagnosed in relation to T1D and then the yearly incidence of CD during follow-up after T1D diagnosis. On the other hand, in study IV, we calculated the prevalence of triple autoimmunity and the cumulative incidence of triple autoimmunity at 18 years of age. Descriptive data for the groups are presented as frequencies and percentages for categorical data and as means and standard deviations (SD) when appropriate. To compare variables between groups the Student's T-test and one-way ANOVA were used for means, crosstabs and chi-square test for categorical variables.

In Study III, we had a total missingness of 11.3% of clinical measurements (HbA1c and BMI). The missingness was analysed with an ordinal regression model showing that older participants had less missingness at baseline and more missingness over time. Therefore, missingness could not be assumed to be completely random and to achieve unbiased estimates missingness was handled by using multiple imputations. We conducted multiple imputations with the R package *mice* and the model was carried out in R studio (version 1.3.959). Ten imputations and ten iterations were used and all variables were imputed with predictive mean matching using all the variables analysed in the study as inputs. To analyse associations between the different CD groups and clinical outcomes, we performed regression models.

When comparing our T1D cohort with a cohort from the general population in Study IV, there were very few individuals diagnosed with both CD and ATD in the general cohort and therefore we calculated and compared the absolute value of the prevalence.

Ethical considerations

The principles of the Declaration of Helsinki were followed in all studies.

Study I was a population-based retrospective study using national quality, health and population registries. Because of the large study cohort, we were not able to contact all individuals to obtain informed consent, but our study was accepted by Lund's University's Ethical Committee. The National board of health and welfare merged the birth cohorts with data from the Swediabkids/NDR and anonymised it before we got the data in order to protect the patients.

Before inclusion in the BDD study, child-friendly information, both oral and written, is provided to the children by the clinicians if deemed mature enough to understand, and to their guardians. All participants included gave their written informed consent to participate in the BDD study. For children not mature enough to understand the information, only their guardians were informed and gave their consent. Study participants can opt out of the study at any time. The results from the blood tests, also during BDD1, were reported back to the patient's diabetic clinic. This means that the children could directly benefit from the study.

To merge data from the BDD study with the National Patient Register and the NDR/Swediabkids we asked for ethical permission from the regional ethical committee of the medical faculty of Lund's University but were not able to get informed consent from the participants due to the large study cohort. Before inclusion in the Swediabkids, the children and parents are informed that the data in the register can be used for research purposes. In Studies II-IV, the information from the National Board of Health and Welfare was not anonymised since we needed to correlate the personal identity number with the BDD data. To protect the integrity of the patients, each participant in the BDD study was given a BDD number that was used after merging the data.

In this thesis, no experiments were conducted and therefore there was no risk of physical harm since all data already was collected for other reasons. All data used in this thesis were known by the participants and already registered. Since the cohorts studied in all four papers are large and population-based and the results are presented at group level, I believe that the integrity of the participants is maintained. None of the children and adolescents included were caused any harm, and hopefully, knowledge was gained for children and adolescents in the future.

Ethical approvals

Study I

The study was approved by the Regional Ethics board at Lund's University, Dnr 2014/476.

Study II-IV

The studies were approved by the Regional Ethics Board at Karolinska Institute, Sweden, Dnr 04-826/1, 2006/1082-32 and 2007/1383-32, and by the regional ethics board at Lund's University, Dnr 2014/476 and 2017/473.

Results

Study I

Cumulative incidence of T1D during and after the Swedish CD epidemic.

Demographic factors for those born 1992-1993, in the epidemic cohort, and those born 1997-1998 in the post epidemic cohort are shown in Table 3. The T1D diagnosis was set in the age span of 0 to 17 years. There were no differences in the sex ratio between the birth cohorts, nor between the subgroup of children with T1D. There was no significant difference in mean age at T1D diagnosis between the cohorts.

Table 3 Demographic characteristics in Study I. Demographic characteristics of the birth cohorts born during the Swedish celiac disease epidemic, the epidemic cohort 1992-1993 and the post epidemic cohort born 1997-1998. Reprinted with permission from Springer Nature (150).

	Epidemic cohort	**Post-epidemic cohort**
Birth cohort	240,844	179,530
Sex (%)		
Girls	117,323 (48.7)	87,079 (48.5)
Boys	123,521 (51.3)	92,451 (51.5)
T1D diagnosed between 0-17 years of age (%)		
Birth cohort	1,642	1,380
Girls	732 (44.6)	628 (45.5)
Boys	910 (55.4)	752 (54.5)
Mean age T1D diagnosis (SD)		
Birth cohort	9.8 years (4.2)	9.5 years (4.2)
Girls	9.3 years (3.9)	9.1 years (4.0)
Boys	10.2 years (4.3)	9.9 years (4.3)

The cumulative incidence of T1D was statistically significantly higher at age 17 years in the post-epidemic cohort, 0.77%, compared with the epidemic cohort 0.68%, $p<0.001$, see Figure 7. The higher cumulative incidence of T1D after the CD epidemic was true both for girls and boys. When dividing those with T1D into groups based on age at T1D diagnosis, the incidence of T1D was statistically significantly higher after the epidemic only in those diagnosed with diabetes between 2-10 years of age.

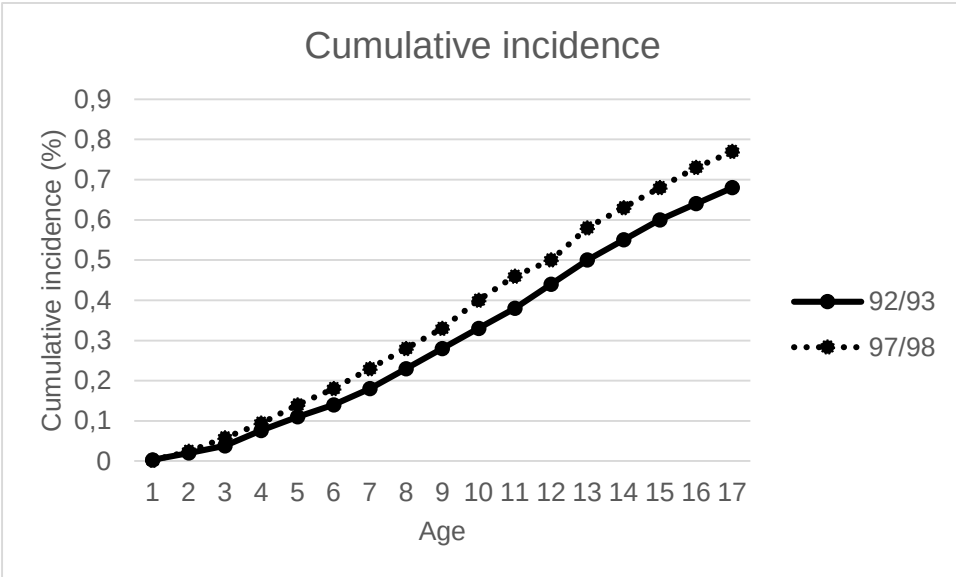

Figure 7: Cumulative incidence of type 1 diabetes in children followed from birth to 17 years of age in the epidemic cohort born 1992/1993 and the post-epidemic cohort born 1997/1998. Reprinted with permission from Springer Nature (150).

Study II

Prevalence of CD in children with T1D

The prevalence of CD in our cohort of 5,295 children with T1D in Study II, was 9.8% (n=521). Of these children, 1.9% (n=99) had a known CD diagnosed before T1D (group 1), 3.9% (n=204) children were diagnosed with CD within a year after T1D diagnosis (group 2), and 4.5% (n=218) were diagnosed after T1D diagnosis (group 3) during up to ten years follow-up, see Figure 8.

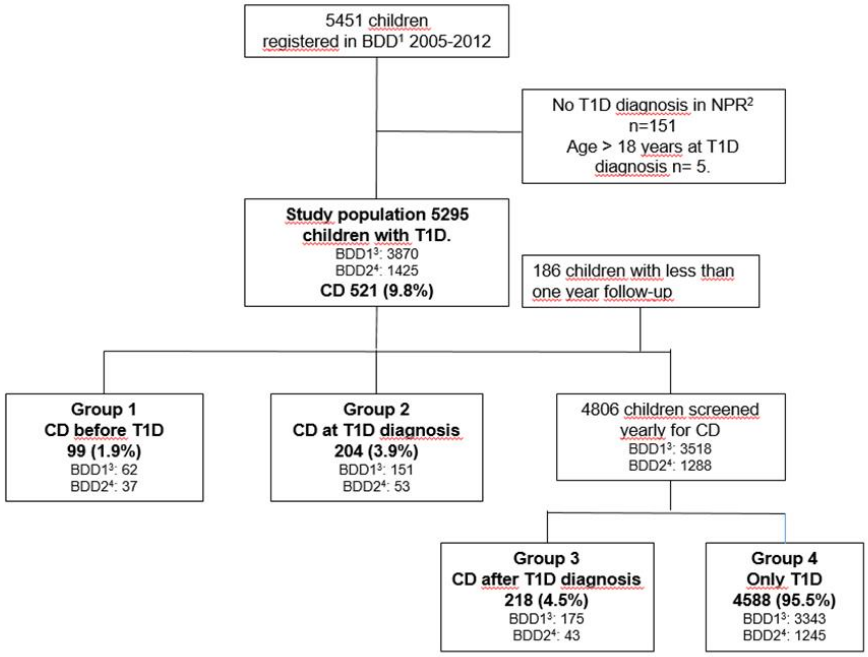

Figure 8: Flowchart of inclusion and exclusion criteria in the study population and the prevalence of celiac disease (CD) in the different groups based on when CD is diagnosed in relation to type 1 diabetes (T1D) diagnosis. [1]BDD=Better Diabetes Diagnosis study. [2]NPR=Swedish National Patient Register. [3]BDD1=children included in BDD between May 2005 to December 2010. [4]BDD2=children included in BDD from January 2011 until December 2012. Reprinted with permission from the American Diabetes Association (148).

Yearly incidence after T1D diagnosis

The yearly incidence of a CD diagnosis in the study cohort is shown in Figure 9. Of those with a double diagnosis, 58.2 % (n=303) had a CD diagnosis before, or within one year after a T1D diagnosis, namely group 1 and group 2.

Of the 218 children diagnosed with CD more than one year after a T1D diagnosis (group 3), 95.9% (n=209) were found within five years after a T1D diagnosis, see Figure 10. Of 2,137 children who were screened for CD more than five years after a T1D diagnosis, only 9 (0.4%) were found to have CD.

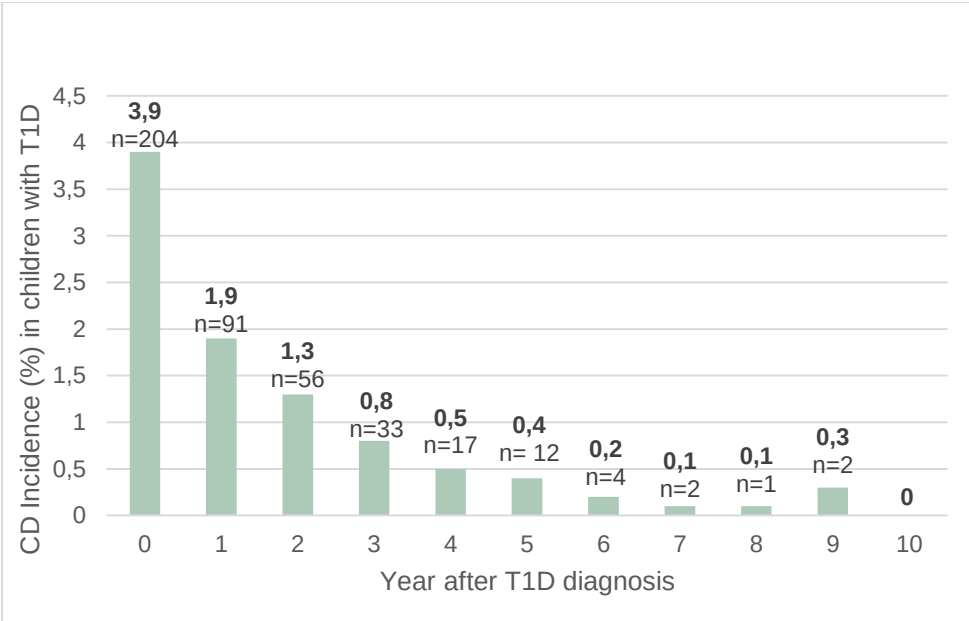

Figure 9: Yearly incidence of Celiac disease (CD) after Type 1 diabetes (T1D) diagnosis. "Year after T1D diagnosis" represents the year screening took place, e.g., year 0 = children screened at T1D diagnosis and CD diagnosed within the first year after T1D diagnosis, and year 1 = children screened 1 year after T1D diagnosis and CD diagnosed between the first and second year after T1D diagnosis etc. Reprinted with permission from the American Diabetes Association (148).

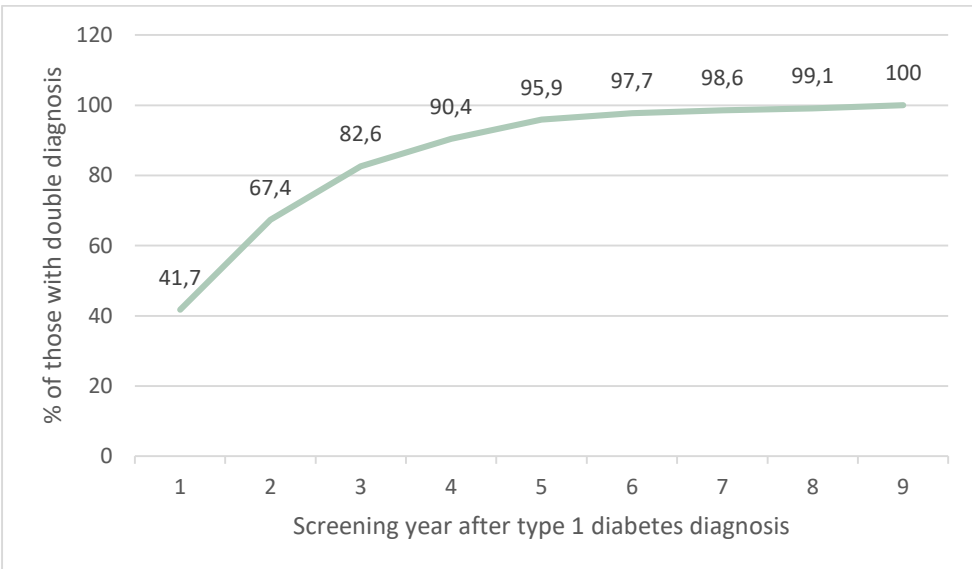

Figure 10: Proportion of those diagnosed with celiac disease (CD/double diagnosed) after the diagnosis of type 1 diabetes (T1D) found during each year of follow-up/screening after the diagnosis of T1D.

Predictive factors for the development of CD after T1D diagnosis.

To find predictive factors at T1D diagnosis for being diagnosed with CD during the yearly screening after the diagnosis of T1D we compared children in group 3 with those in group 4. The factors studied are shown in Table 4.

Table 4: Potential predictive factors at type 1 diabetes (T1D) diagnosis in those diagnosed with celiac disease (CD) one year or more after the diagnosis of T1D and in those with T1D only during follow-up. P-values are for comparsions between group 3 and group 4. Reprinted with permission from the American Diabetes Association (148).

	Group 3 CD after T1D	**Group 4 Only T1D**	**Group 3 vs group 4 P-value**
Age at T1Ddiagnosis (years), mean (SD)	6.6 (4.26)	9.7 (4.29)	**<0.001**
Female, n (%)	109 (50.0)	2,042 (44.5)	0.11
Male, n (%)	109 (50.0)	2,546 (55.5)	
HLA, n (%)			
DQ2/DQ8	80 (36.7)	1,339 (29.2)	**0.036**
DQ2/DQ2	25 (11.5)	212 (4.6)	**<0.001**
DQ2/DQX	37 (17.0)	551 (12.0)	**0.044**
DQ8/DQ8	24 (11.0)	476 (10.4)	0.874
DQ8/DQX	50 (22.9)	1,364 (29.7)	**0.016**
DQX/DQX	0 (0)	478 (10.4)	**<0.001**
Autoantibodies, n(%)			
0	7 (4.0)	249 (7.4)	0.095
1	25 (14.3)	388 (11.6)	0.245
2	51 (29.1)	833 (24.9)	0.161
3	57 (32.6)	1,106 (33.1)	0.995
4	23 (13.1)	589 (17.6)	0.148
GADA n (%)			
Positive	106 (60.6)	2,052 (61.4)	0.80
Negative	69 (39.4)	1,283 (38.4)	
IA2A n (%)			
Positive	121 (69.1)	2,449 (73.3)	0.21
Negative	54 (30.9)	886 (26.5)	
IAA n (%)			
Positive	86 (49.1)	1,375 (41.1)	**0.026**
Negative	82 (46.9)	1,862 (55.7)	
ZnT8A n (%)			
Positive	93 (53.1)	2,075 (62.1)	**0.033**
Negative	71 (40.6)	1,123 (33.6)	

Those diagnosed with CD during follow-up were significantly younger at T1D diagnosis than those with only T1D, 6.6 years compared to 9.7 years (p=<0.001; 95% confidence interval 2.5-3.66). When further dividing the cohort into subgroups based on age at T1D diagnosis, those in the youngest age group, 0-5 years of age at T1D diagnosis, had the highest prevalence of CD (14.9%). They also had the highest risk of being diagnosed after T1D diagnosis, see Table 5 and Figure 11.

Table 5: Total prevalence of celiac disease (CD) and the risk of CD diagnosed after the diagnosis of type 1 diabetes (T1D) in groups based on age at T1D diagnosis.

	Total prevelance of CD	Group 3 CD after T1D
0-4.9 years n=946 **% (n)**	14.9 (141)	10.4 (98)
5-9.9 years n= 1621 **% (n)**	10.5 (170)	3.9 (64)
10-14.9 years n=1934 **% (n)**	8.2 (159)	2.6 (50)
15-18 years n=794 **% (n)**	6.4 (51)	0.8 (6)

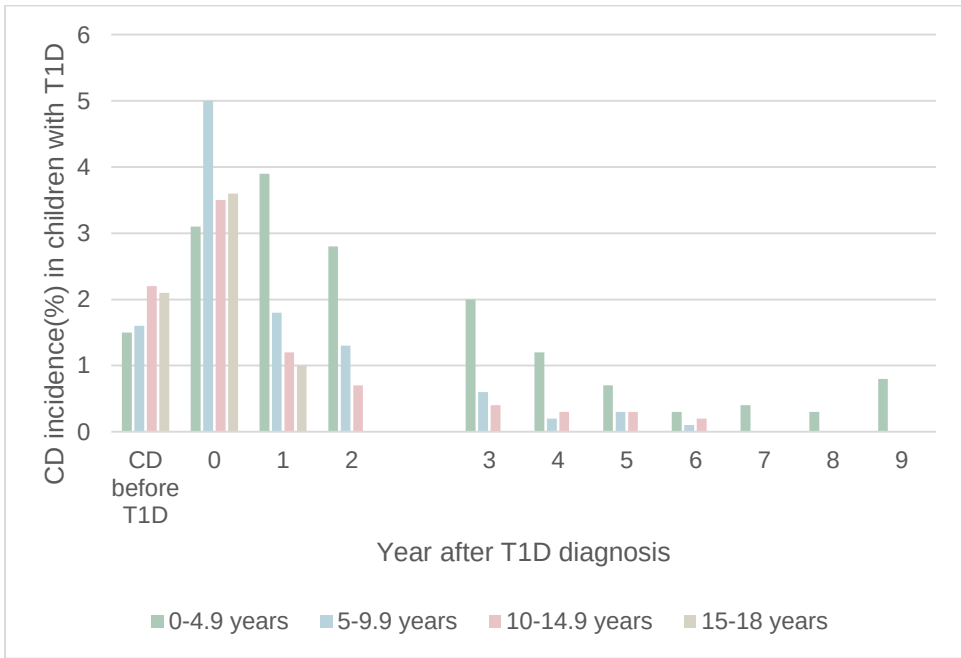

Figure 11: Yearly incidence of Celiac Disease (CD) after type 1 diabetes (T1D) diagnosis with the study population in groups based on age at T1D diagnosis. "Year after T1D diagnosis" represents the year screening took place, e.g., year 0 = children screened at T1D diagnosis and CD diagnosed within the first year after T1D diagnosis, year 1 = children screened 1 year after T1D diagnosis and CD diagnosed between the first and second year after T1D diagnosis, etc. Follow-up time began at T1D diagnosis and ended at CD diagnosis, 18 years of age or study period completion, meaning that the oldest age-groups do not have ten years' follow-up time.

In those children with CD detected by screening after T1D diagnosis, there was no significant difference in the proportion of girls versus boys diagnosed with CD and the sex-ratio was the same as those with T1D only.

Those with HLA DQX/DQX had no risk of being diagnosed with CD after T1D diagnosis. All HLA combinations with at least one copy of DQ2 were significantly more common in those diagnosed with CD during follow-up (group 3) compared to those with T1D only (group 4). The combination DQ8/DQX was less common in those with a double diagnosis (group 3), (p=0.02). The yearly incidence after T1D diagnosis was not affected by the HLA genotype, see Figure 12.

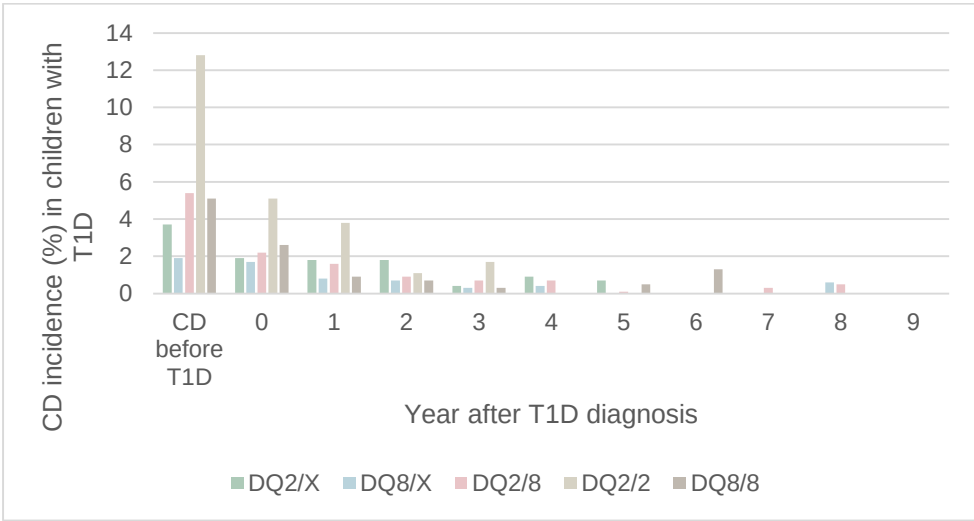

Figure 12: Yearly incidence of celiac disease (CD) after type 1 diabetes (T1D) diagnosis with the study population in groups based on HLA. "Year after T1D diagnosis" represent the year screening took place, e.g. year 0 = children screened at T1D diagnosis and CD diagnosed within the first year after T1D diagnosis, year 1 = children screened 1 year after T1D diagnosis and CD diagnosed between the first and second year after T1D diagnosis etc. Follow-up time began at T1D diagnosis and ended at CD diagnosis, 18 years old or study period completion, meaning that not all have 10 years follow-up time.

The prevalence of CD after T1D diagnosis was highest (10.5%) in individuals who were homozygotes for DQ2, Table 6. Individuals positive for DQ8/X and DQ8/8 were significantly older than those who were DQ2/8 positive, see Table 6 (p= 0.002 resp. p=<0.001), while no significant differences were found between other groups.

Table 6: Prevalence of celiac disease (CD) and mean age at type 1 diabetes (T1D) diagnosis in children with T1D screened for CD after T1D diagnosis based on HLA-DQ combination.

	Prevalence of CD after T1D diagnosis. % (n)	**Mean age at T1D diagnosis (SD)**
DQ2/X (588)	6.2 (37)	9.5 (4.3)
DQ8/X (1414)	3.5 (50)	9.6 (4.3)
DQ2/8 (1419)	5.6 (80)	9.0 (4.4)
DQ2/2 (237)	10.5 (25)	9.4 (4.2)
DQ8/8 (500)	4.8 (24)	10.2 (4.0)

There was no significant difference in the distribution of the number of autoantibodies between those diagnosed with CD after T1D and those with T1D only. Being positive for IAA was significantly more common in those diagnosed with CD after T1D, than in those with T1D only. However, when analysing the percentage of IAA-positive individuals across the four age groups, a significant difference was observed solely among those aged 10-14.9 years and in the opposite direction, IAA was more common in those with T1D only, see Table 7.

Table 7: Proportion positive for IAA in those diagnosed with celiac disease (CD) one year or later after type 1 diabetes (T1D) diagnosis (group 3) and those with only T1D (group 4) divided into age groups.Reprinted with permission from the American Diabetes Association (148).

	Group 3 CD after T1D n (%)	**Group 4 Only T1D n (%)**	**Group 3 vs group 4 p-value**
0-4.9 years			0.074
Positive	58 (74.4)	370 (66.3)	
Negative	15 (19.2)	164 (29.4)	
Missing	5 (6.4)	24 (4.3)	
5-9.9 years			0.539
Positive	20 (39.2)	442 (42.1)	
Negative	31 (60.8)	572 (54.5)	
Missing	0	35 (3.3)	
10-14.9 years			0.020
Positive	7 (16.7)	455 (34.4)	
Negative	33 (78.6)	832 (63.0)	
Missing	2 (4.8)	34 (2.6)	
15-18 years			*
Positive	1 (25.0)	108 (26.0)	
Negative	3 (75.0)	294 (70.8)	
Missing	0	13 (3.1)	

* Not able to calculate due to few individuals.

Study III

The effect of a CD diagnosis on BMI and HbA1c.

The results from the linear regression with multiple imputed datasets showed that at T1D diagnosis, all groups had low BMI scores compared to norm scores (BMI-SDS = -0.5 to -0.37). Those with CD before or at T1D diagnosis had a lower BMI-SDS than those with T1D only, but the differences were not statistically significant. The BMI-SDS score had increased and largely normalised in all four groups (BMI-SDS = +0.1 to +0.4) at the one-year post-diagnosis visit, Figure 13.

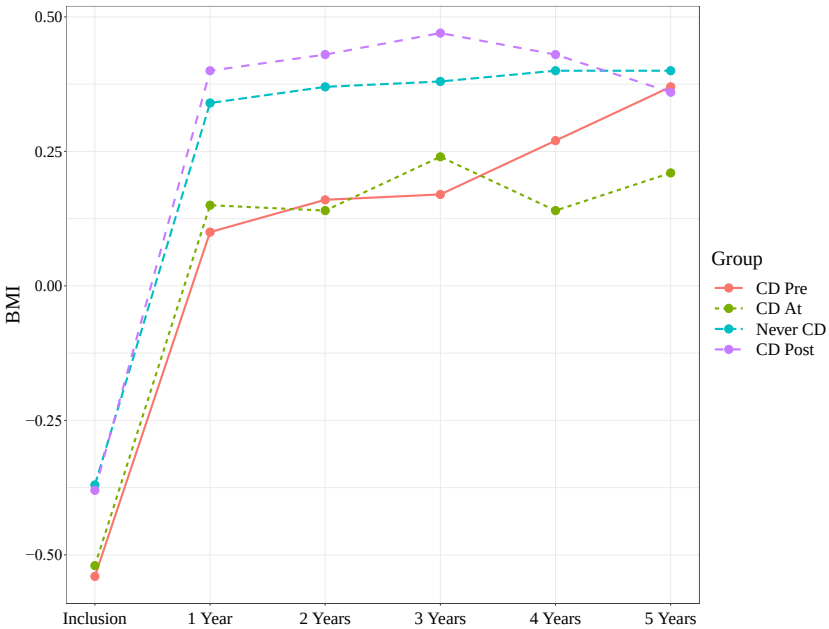

Figure 13: Age- and sex-adjusted BMI (population mean = 0, *SD* = 1) over time across the four groups (non-imputed data).

BMI-SDSs were compared between the four groups using linear regressions. Children diagnosed with CD at T1D diagnosis had a lower BMI-SDS than children with only T1D ($p<0.05$) at all follow-up assessments. Children with a known CD at T1D diagnosis differ from those with only T1D during the first two years after T1D diagnosis when BMI-SDS is significantly lower in those with CD ($p<0.05$), but then there was no significant difference between groups. In those diagnosed with CD after T1D diagnosis, CDpost, there was no significant difference in BMI-SDS compared to those with only T1D.

HbA1c levels at diabetes diagnosis and during follow-up were also compared between the four groups using linear regression. There were no differences between groups at any time point, see Figure 14.

There were no statistically significant differences in the prevalence of diabetic ketoacidosis at T1D diagnosis between the four groups.

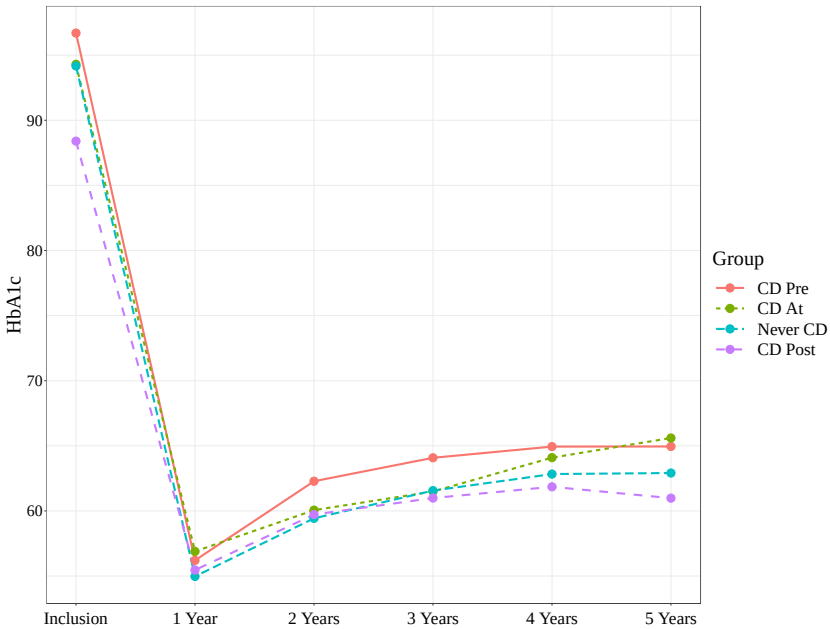

Figure 14: HbA1C over time across the four groups (non-imputed data and values were not adjusted for age and sex)

Study IV

The prevalence of triple autoimmunity in children and adolescents

The study cohort was divided into subgroups based on concomitant autoimmune diseases. Of the 5,295 T1D patients, 14% (746) were diagnosed with CD and/or ATD, whereof 9.0% (n=478) had CD, 4.2% (n=225) had ATD, of which 4.0% (n=210) had hypothyroidism, 0.3% (n=15) hyperthyroidism, and finally 0.8% (n=43) had triple autoimmunity, see Figure 15. In the subgroup followed until 18 years of age (n=2573), 0.6% (n=15) had triple autoimmunity.

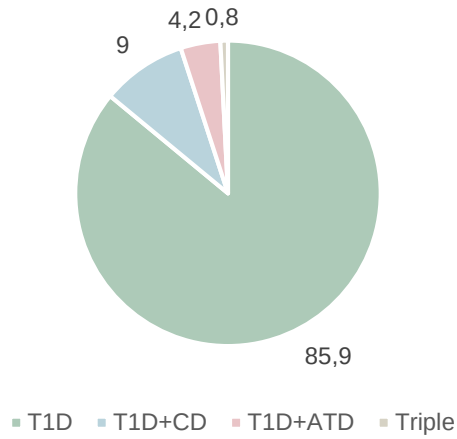

Figure 15: Prevelance (%) of concomittant autoimmune diseases in Study IV.

Since only half, 48.6%, of the study population was followed until 18 years of age we calculated the cumulative incidence of triple autoimmunity at 18 years of age and found it to be 1.7 %, see Figure 16.

When comparing the risk of triple autoimmunity between the sexes, there were no statistically significant differences in the prevalence of triple autoimmunity between girls 1.0% (n=25) and boys 0.6% (n=18), (p=0.09). In addition, in the subgroup of children and adolescents that were followed until they were 18 years of age (n= 2,573), there was no statistically significant difference between girls 0.7% (n=7) and boys 0.5% (n=8), p=0.68.

When dividing the study population into age groups based on age at T1D diagnosis, there were no differences in triple autoimmunity risk.

Predictive factors for triple autoimmunity

In the majority (65.1%) of individuals with triple autoimmunity, T1D was the first to be diagnosed alone or in conjunction with CD and/or ATD. In order to investigate potential predictive factors at T1D diagnosis, we compared the group with triple autoimmunity to the other three groups, see Table 8.

As seen in Table 8, there were no differences in the mean age at T1D diagnosis between those with triple autoimmunity and the other groups. In addition, when comparing sexes there were no statistically significant differences between the groups but there was a strong tendency towards a larger proportion of females in those with triple autoimmunity compared with those with T1D only.

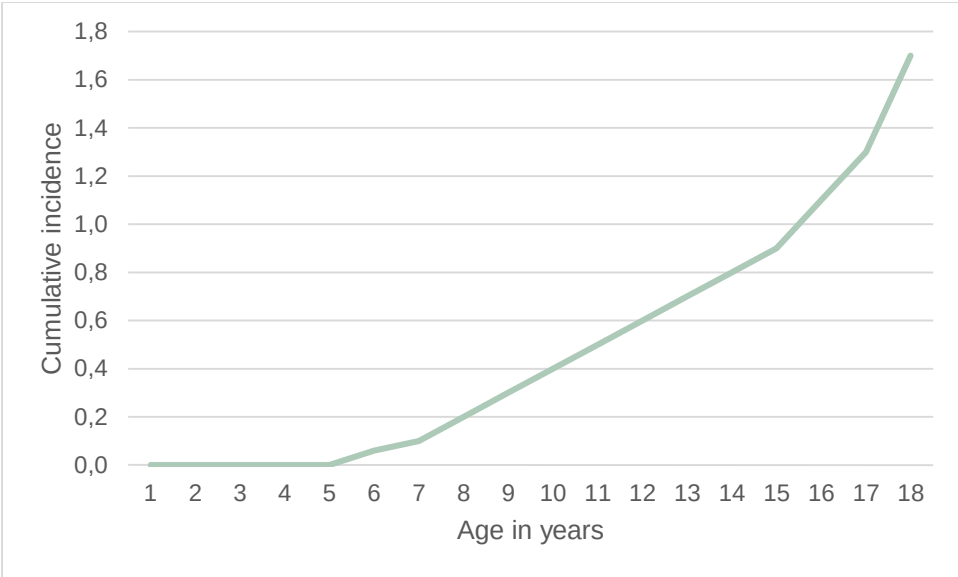

Figure 16: Cumulative incidence of triple autoimmunity (Celiac Disease+Autoimmune Thyroid Disease in children with type 1 diabetes) from 1 to 18 years of age.

The frequency of different HLA types did not differ significantly between those with triple autoimmunity and those with T1D+CD. But when comparing with the T1D only and T1D+ATD group, the HLA DQ2/DQ2 genotype was more common in patients with triple autoimmunity, whereas the HLA DQ8/DQX genotype was less common. None of the patients in the DQX/DQX group was diagnosed with triple autoimmunity.

With regard to diabetes-related autoantibodies, there were no significant differences in the number of autoantibodies or the type of autoantibody, but there was a tendency towards GADA being more often positive in those with triple autoimmunity than in those with only T1D and T1D+CD. There was no significant difference in the proportion of GADA autoantibodies between girls' vs boys' with triple autoimmunity, see Table 9.

Table 9: Proportion GADA positivity in girls vs boys with triple autoimmunity (Children with T1D diagnosed with both CD and ATD).

GADA	Female	Male	P-value
Positive	16 (88.9)	9 (64.3)	0.095
Negative	2 (11.1)	5 (35.7)	

CD+ATD in children with T1D and children from the general population.

As described, we used results from the ETICS study (141) to compare thyroid and celiac autoimmunity in children with T1D, with 12 to 13-year-old children from the general population (without T1D).

In the ETICS study, ATD+CD was found in 3 out of 12,632 children, giving a prevalence of 0.02%, 0% for boys and 0.05% for girls.

Of the children included in the BDD study, 4,120 (77.8%) received T1D before turning 14 years of age. Of these, 32 had triple autoimmunity, rendering a prevalence of 0.8%. Of the girls 20 (1.0%) children had triple autoimmunity and 12 (0.6%) children were boys.

Table 8: Descriptive factors for the four groups in Study IV and comparsions between triple autoimmunity (Triple) and the other groups.

	T1D n=4549	T1D+CD n=478	T1D+ATD n=225	Triple n=43	P-value Triple vs T1D	P-value Triple vs T1D+CD	P-value Triple vs T1D+ATD
Age at T1D diagnosis, mean (SD)	9.96 (4.48)	8.61(4.46)	10.2 (4.04)	8.89 (5.12)	0.12	0.70	0.11
Female, n (%) **Male, n (%)**	1,959 (43.1) 2,590 (56.9)	257(53.8) 221 (46.2)	160 (71.1) 65 (28.9)	25 (58.1) 18 (41.9)	0.05	0.58	0.09
HLA, n (%) *DQ2/DQ8*	1,325 (29.1)	187 (39.1)	58 (25.8)	15 (34.9)	0.41	0.59	0.22
DQ2/DQ2	212 (4.7)	72 (15.1)	9 (4.0)	10 (23.3)	<0.001	0.16	<0.001
DQ2/DQX	551 (12.1)	75 (15.7)	33 (14.7)	8 (18.6)	0.2	0.62	0.51
DQ8/DQ8	483 (10.6)	56 (11.7)	17 (7.6)	4 (9.3)	0.78	0.64	0.70
DQ8/DQX	1,351 (29.7)	81 (16.9)	65 (28.9)	5 (11.6)	0.01	0.37	0.02
DQX/DQX *Missing*	462 (10.2) 165 (3.6)	1 (0.2) 6 (1.3)	34 (15.1) 9 (4.0)	0 (0) 1 (2.3)	0.03	0.76	0.006
Autoantibodies, n (%)							
0	259 (7.8)	15 (4.2)	11 (6.3)	2 (6.3)	0.74	0.59	1.0
1	384 (11.6)	53 (14.9)	18 (10.2)	4 (12.5)	0.88	0.72	0.7
2	831 (25.1)	97 (27.2)	31 (17.6)	9 (28.1)	0.70	0.92	0.17
3	1,089 (32.9)	113 (31.7)	69 (39.2)	11 (34.4)	0.86	0.76	0.61
4	573 (17.3)	57 (16)	34 (19.3)	6 (18.8)	0.83	0.69	0.94
Missing	170 (5.1)	21 (5.9)	13 (7.4)	0 (0)			
GADA n (%)							
Positive	2,015 (60.9)	223 (62.6)	128 (72.7)	25 (78.1)	0.05	0.08	0.59
Negative	1,285 (38.9)	133 (37.4)	46 (26.1)	7 (21.9)			
Missing	6 (0.2)	0 (0)	2 (1.1)	0 (0)			

IA2A n (%) *Positive* *Negative* *Missing*	 2,418 (73.1) 882 (26.7) 6 (0.2)	 251 (70.7) 105 (29.5) 0 (0)	 127 (72.2) 47 (26.7) 2 (1.1)	 12 (37.5) 20 (62.5) 0 (0)	0.17	0.35	0.23
IAA n (%) *Positive* *Negative* *Missing*	 1,335 (40.4) 1,870 (56.6) 101 (3.1)	 151 (42.4) 194 (54.5) 11 (3.1)	 74 (42.0) 94 (53.4) 8 (4.5)	 17 (53.1) 15 (46.9) 0 (0)	0.19	0.31	0.35
ZnT8A n (%) *Positive* *Negative* *Missing*	 2,050 (62.0) 1,118 (33.8) 138 (4.2)	 214 (60.1) 123 (34.6) 19 (5.3)	 110 (62.2) 55 (31.3) 11 (6.3)	 17 (53.1) 15 (46.9) 0 (0)	0.17	0.25	0.14

Discussion

Gluten introduction in infancy and risk of T1D – Study I

As described in the background, there are many uncertainties behind the increasing incidence of T1D worldwide and gluten has been one of the many suspicious triggers. Children with T1D and CD share the same HLA risk alleles, DQ2 and DQ8 (124), and some studies support a connection between gluten and the risk of developing T1D (59, 60, 62). The Swedish CD epidemic has been attributed to the national change in gluten feeding recommendations in infancy and the increased amounts of gluten in the formulas. In recent years, the timing of gluten introduction has been questioned to affect the risk of CD (117, 151, 152). There is, however, some evidence linking the effect of the amount of gluten consumed and the risk of CD (116, 117).

In Study I, we showed that the cumulative incidence of T1D did not increase in the same way as it did for CD during the Swedish CD epidemic. Instead, the cumulative incidence of T1D was higher following the CD epidemic, which, if gluten is a risk factor, should mean that a gradual introduction of gluten at 4 months of age and in smaller amounts increases the risk of T1D in children. However, since most Western countries have had an increased incidence of T1D (12, 13, 153) without experiencing an epidemic-like incidence pattern of CD as Sweden has, it seems unlikely that the differences gluten feeding recommendations and the amounts of gluten explain the increase in incidence seen between the birth cohorts in our study. This indicates that gluten and its timing and amounts when introduced during infancy may not be a risk factor for T1D, at least not in the general population.

Besides being a trigger for T1D, another possibility is that gluten could act as a driver, affecting the progression towards T1D. In Study I, there were no differences in age at T1D diagnosis between the epidemic and post-epidemic cohorts. Differences in gluten introduction did not seem to affect the age at T1D diagnosis and thereby not the progression towards T1D.

An important difference from studies showing that the introduction and amount of gluten may affect the risk of T1D is that the study groups in these studies consisted of children with a high genetic risk of developing T1D (59, 60, 62), but our results were from the general population. Another difference is the study design, where we had a cohort study based on registry data instead of case-control study in many of the mentioned studies. There may be many different triggers in different individuals

depending on the genetic upset, and it could be that gluten may have a role in the risk behind T1D but only in some endotypes.

Except for the risk of CD and T1D, BMI has also been studied in these two birth cohorts. Those born after the epidemic, in 1997, had a higher BMI and increased prevalence of being overweight than those born during the epidemic, in 1993 (154). A rise in BMI and overweight has been proposed to increase the ß-cell stress and trigger autoimmunity and the process towards T1D as described in the background. An increasing number of studies have indicated a relationship between obesity/body size and the risk of T1D (73, 74, 76, 155, 156). I therefore speculate whether the increase in BMI and overweight in those born after the epidemic in 1997, explain the increase in cumulative incidence of T1D as seen in our study.

Prevalence of CD in children with T1D – Study II

In Study II, we found that the prevalence of CD in Swedish children and adolescents was 9.8%, meaning that CD is 10 times more common in Swedish children with T1D compared to peers in the general population. The result with a prevalence of 9.8%, is in line with earlier smaller studies in Sweden and Denmark (121, 122, 136), but higher than the 5-6% reported in studies from many other parts of the world (100, 101). The reasons for the varying prevalence may be differences in follow-up time (101), screening practices and genetic differences in the populations.

Most previous studies have not analysed the prevalence of CD in relation to T1D diagnosis, and many report that CD is to a greater extent diagnosed after T1D diagnosis (100, 121). Therefore, it has been speculated whether T1D causes the diagnosis of CD. In our study, we have studied the prevalence of CD in relation to the diagnosis of T1D and found that in more than half of the children with both T1D and CD, CD diagnosis is known before, or is found at T1D diagnosis.

We have also studied the differences in the prevalence of CD in children with T1D between the same birth cohorts as in Study I. In that study, we showed that the prevalence of CD in children with T1D was the same during and after the epidemic (157) even though the risk of T1D was higher in the cohort born after the epidemic according to the result in Study I. This suggests that CD may not be caused by T1D, but rather that a shared genetic predisposition and perhaps also environmental factors accounts for the higher incidence of CD in children with T1D.

Risk factors at T1D diagnosis for being diagnosed with CD after the diagnosis of T1D – Study II

The time after the diagnosis of T1D is a risk factor for the diagnosis of CD. In Study II we showed that a majority of those who were diagnosed with CD after T1D diagnosis received their CD diagnosis already within 2-3 years, and it is uncommon

that CD is diagnosed 5 years after the diagnosis of T1D. Screening up to 5 years after diagnosis of T1D captured 95.9% of individuals who developed CD in our cohort. A review from 2015 (100), showed that 79% of those who developed CD did so within five years after T1D diabetes diagnosis (100). In addition, a large multi-centre study from Italy that included 4,322 children with T1D and yearly CD screening showed that biopsy-confirmed CD is usually diagnosed within the first year after T1D diagnosis and is rarely found after ten years of diabetes (126).

Another risk factor for CD after T1D in our cohort was age at T1D diagnosis. Children diagnosed with T1D before the age of five had a higher risk and prevalence of CD diagnosed after T1D diagnosis than older children. Similar results, with a higher overall risk of CD in younger children, have been demonstrated in earlier studies (126, 127, 158) and mirrors the general population where CD develops in young children but is not always detected (107).

As in the general population, being positive for HLA DQ2, and above all being a homozygote, confers an increased risk of developing CD after T1D diagnosis. DQ2/DQ2 has also been associated with an earlier onset of CD (113), which could explain the higher risk in young children. Since the HLA genotype DQ2/DQ2 and young age at T1D diagnosis increase the risk for CD, the risk of developing CD could be enclosed in the age-related endotypes mentioned in the background (41).

Interestingly, we found no difference between the sexes regarding the risk of CD after the diagnosis of T1D. This differs from the general population, in which the majority of patients who develop CD are female (97). However, considering the overall prevalence as a whole in our study, CD was more common in girls than in boys, but not in the group that developed CD after T1D diagnosis. This difference may explain why earlier studies have found conflicting results regarding sex ratios (100, 102, 126, 159). Why girls seem to be more prone to develop CD than boys in the general population is not known, but boys seem to have the same risk as girls when they also have T1D.

Little is known about the relationship between diabetes-related autoantibodies at T1D diagnosis and the risk of CD. A Finnish study of 24 children with both CD and T1D reported that individuals with a double diagnosis had a lower number of diabetes-related autoantibodies (128). In our study, Study II, which included a much larger number of individuals with double diagnosis, we concluded that the number or type of antibody at T1D diagnosis was not associated with a risk of developing CD after T1D.

Screening for CD in children and adolescents with T1D – Study II.

The prevalence before, at and after T1D diagnosis affects who will benefit from screening and how many. As the majority of children with both T1D and CD are diagnosed before or at T1D diagnosis, a screening test at the time of T1D diagnosis

is important. In patients diagnosed with CD after T1D diagnosis, the highest risk was within 2-3 years after T1D diagnosis and 5 years after T1D diagnosis, the risk of being diagnosed with CD was very low.

From Study II we also know that the youngest group of children, below 5 years of age, has the highest risk of CD after T1D diagnosis, therefore our screening should focus on this group of children. In addition, children with HLA DQ2 also had an increased risk of developing CD, but HLA did not affect the annual incidence after T1D diagnosis, therefore we did not use this as a factor in the proposed screening algorithm. Neither sex nor diabetes-related autoantibodies need to be considered in screening guidelines since the pattern or number of autoantibodies and the sex do not affect the risk of being diagnosed with CD or the timing after T1D diagnosis.

HLA genotyping has been recommended by some as a first-line screening method in children with T1D since only genetically susceptible patients need further serological testing for CD (147). This has been questioned because a celiac-specific HLA genotype is very common in patients with T1D and no overall cost saving could be expected (160, 161). While it may not be cost-effective to HLA genotype all patients, it can provide valuable information for individuals lacking DQ2 or DQ8 for whom no further screening is usually needed. In our study, 10 % of the patients had neither DQ2 nor DQ8 and could be excluded from further screening after HLA testing.

With these results, we propose the following screening algorithm, see Table 9.

- For children <5 years of age, at diagnosis of T1D and then two and five years later;
- For children between five and ten years of age, at diagnosis of T1D and five years later;
- For children > 10 years of age, only at diagnosis of T1D;
- Final screening could be performed in all adolescents before being transferred to adult care;
- If HLA-typing is clinically routine at T1D diagnosis, and the child, regardless of age, has neither HLA DQ2 nor DQ8, no further CD screening is needed.

Children with symptoms suggestive of CD should be investigated, irrespective of diabetes duration and HLA genotype.

Since results from previous studies are in line with ours when CD is diagnosed in relation to T1D (100, 126), and a higher risk in young children (126, 127, 158), we believe that our results apply to other similar populations.

Table 9: Proposed new screening recommendations for celiac disease (CD) in children with type 1 diabetes (T1D). If HLA-typing is clinically routine at T1D diagnosis, and the child regardless of age, has neither HLA DQ2 nor DQ8, no further CD screening is needed.

Age at T1D diagnosis	T1D diagnosis	Two years after T1D diagnosis	Five years after T1D diagnosis
<5 years*	✖	✖	✖
5-<10 years*	✖		✖
≥10 years*	✖		

*Final screening could be be performed i all adolescents before being transferred to adult care.

Positive screening test, what is the next step?

During the years the study cohort in Study II was included and followed, the clinical routine after a positive screening test was to confirm the CD diagnosis with an intestinal biopsy. In the 2012 guidelines for CD from the ESPGHAN, children with symptoms suggestive of CD and anti-tTG concentration ≥ 10 times the ULN could be diagnosed with CD without a small bowel biopsy (147). Since 2012, an increasing number of studies have shown that this approach of diagnosing CD without a biopsy can also be applied to cases with asymptomatic CD. In the ESPGHAN guidelines for diagnosing CD from 2020 (118), screening-detected anti-tTG concentration ≥10 times the ULN could be diagnosed according to the no-biopsy approach, but T1D was not included due to lack of data.

In 2021, we published an article on data from the BDD study population (2,035 patients) showing that children with anti-tTG ≥10 times above the ULN have biopsy-proven CD (162). Therefore, I think and hope that the new revised ESPGHAN guidelines for diagnosing CD also will include children with T1D in the no-biopsy approach.

Growth and metabolic control in children diagnosed with CD – Study III

In Study III we compared measurements that mirror growth (BMI-SDS) and glycaemic control (HbA1c) with respect to the timing of CD in relation to a T1D diagnosis. We found that children with a known or screening-detected CD at T1D diagnosis had a lower BMI-SDS during follow-up after the T1D diagnosis than those with T1D only. The children diagnosed with CD after T1D diagnosis did not differ in BMI-SDS during follow-up from those with T1D only at any time point during 5 years of follow-up after diagnosis of T1D. Regardless of when CD was diagnosed, it did not affect HbA1c at any time point or the frequency of DKA at T1D diagnosis.

Since the children in this cohort are screened yearly and often asymptomatic when diagnosed, they may be discovered before affecting BMI-SDS and growth. This is interesting in terms of the screening recommendations. In Study II, we suggested a

new screening algorithm in which some, although very few, will probably experience an undiagnosed CD for a longer period. Whether this affects the BMI-SDS score or metabolic control in patients diagnosed with CD after T1D cannot be determined from our results. We know from a prospective study comparing 79 children with and 56 children without markers for CD and the risk of diabetes-related complications that there were no significant differences between groups (163). The same study also showed that in those with positive anti-tTG results, no significant adverse effects were identified in those who delayed the treatment with a GFD for two years (163). Another study showed no differences in long-term metabolic control, acute diabetes complications, or weight loss in children with late confirmation of CD compared to children with early confirmation of CD (164). In another study of biopsy-proven CD detected by screening in both children and adults who were randomised into a GFD or a gluten-containing diet, no differences in HbA1c or growth parameters were observed between the groups after 12 months (165). The only difference was greater postprandial glucose in those on a GFD (165). The results from Study III and other studies indicate that delaying the diagnosis of CD for some years if asymptomatic, does not affect growth or metabolic control.

In the other two groups in Study III, those diagnosed with CD before or at T1D diagnosis, there were differences in BMI-SDS when compared with the group with T1D only. Children with known CD at T1D diagnosis had a lower BMI-SDS score than those with T1D only during the first 2 years after T1D diagnosis, and those diagnosed with CD at T1D diagnosis had a lower BMI-SDS score during the entire follow-up period. Therefore, it seems that CD diagnosed before or at T1D diagnosis has a negative effect on the BMI-SDS, although no low BMI.

CD is, above all, a disease affecting the intestinal mucosa, that can lead to malabsorption and nutritional deficits, causing decreased growth and other side effects. This could explain the decrease in BMI-SDS seen in those with a concomitant CD at T1D diagnosis. The healing process of the mucosa is a process lasting for approximately one year after starting the GFD treatment (166), and it has been shown that in children with only CD, most catch-up growth is expected during the first 6 months after a GFD has been initiated but can continue for 2-3 years (167, 168). In patients with both T1D and CD, a previous study showed that the intestinal mucosa healed substantially slower than in children with CD only (166). Why this process takes longer in children with both T1D and CD is not known. One explanation could be poorer compliance to the GFD in those with two diseases affecting everyday life. Although we don't have any information on compliance in our cohort, it would be interesting to know. However, another Swedish study reported that around 70% of Swedish children with CD and T1D comply with a GFD (169), whereas a 90% compliance rate has been shown in the general population of Swedish children with CD (170, 171).

Poorer compliance could be attributed to the fact that CD is often asymptomatic in children with T1D. It can be speculated that those diagnosed with CD at T1D diagnosis, which is most likely having an asymptomatic screening-detected CD, adhere less well to the GFD than those with a symptomatic detected CD before T1D, explaining the lower BMI-SDS score during the whole follow-up period. The Swedish study mentioned (169) did not provide any support for this theory; instead it supported poorer compliance to poorer metabolic control, which was significant in teenagers, not when CD was diagnosed.

In terms of the effect on metabolic control, HbA1c in Study III, we could not find any differences between the groups at any point during follow-up. This is in line with several other studies (102, 135, 136, 172, 173), including two recent reviews (120, 133). In a study comparing the effect on compliance to the GFD, measured as anti-tTG negative or positive three years after CD diagnosis, it was found that those with positive anti-tTG had worse glycemic control (174). Whether this was due to stricter adherence to both gluten and insulin treatment in those anti-tTG negative, or an effect of not adhering to the GFD nor good insulin treatment is not known (174).

Multiple autoimmunity in children and adolescents with T1D, and children from the general population – Study IV.

In Study IV we show that the risk of being diagnosed with both CD and ATD during childhood (before 18 years of age) when having T1D is very low, with a prevalence in our cohort of only 0.8%. Few studies have examined the prevalence of CD and ATD in children with T1D, and to our knowledge, none has related the risk of triple autoimmunity to variables such as sex, HLA and islet cell autoimmunity. Further, no studies have compared the prevalence to an age-matched population screened both for thyroid disease and CD. Studies including both children and adults and also many different autoimmune diseases, have reported that 2-5 % of individuals with T1D are diagnosed with two more autoimmune diseases (90, 92). The large difference in prevalence, is most probably due to differences in follow-up. We restricted our study to only include associated autoimmune diseases diagnosed before 18 years of age. If we had followed our cohort beyond childhood, that is after 18 years of age, the prevalence of triple autoimmunity would probably have increased, since the risk of being diagnosed with ATD and/or multiple autoimmune diseases, but not CD, increases with age (90, 92). This is supported by a study showing that in patients with T1D, the median age at ATD diagnosis was 25 years and the highest risk for ATD was ten years after the diagnosis of CD (175).

Although a very low risk, children with T1D were found to have a much higher risk of developing both CD and ATD than age-matched children without T1D, 0.6% compared with 0.02% in the general population.

Predictive factors for being diagnosed with both CD and ATD in children with T1D – Study IV

Considering the low number of children with triple autoimmunity, our results regarding predictive factors are uncertain although there were some interesting and also some significant differences.

Those with triple autoimmunity had the genotype DQ2/DQ2 more often than those with T1D only. DQ2/DQ2 is a strong risk factor for CD in T1D, as well as in the general population (148), therefore we think this HLA genotype is related to the CD risk in these children. If the clinical routine is HLA genotyping at T1D diagnosis as in children in Sweden, clinicians should be extra aware of associated CD and ATD in children with DQ2/DQ2 and maybe a more individualised screening routine could be considered in these few children.

When it comes to autoantibodies, those with triple autoimmunity were more similar to the group with T1D+ATD, in that GADA was more common. GADA at diagnosis of T1D has previously been found to predict a future ATD (176).

There was no significant difference in the prevalence of triple autoimmunity between boys and girls, as described in the next section.

Sex and risk of autoimmune comorbidities – Study IV

In Study II, we found that boys had the same risk as girls for being diagnosed with CD after the diagnosis of T1D. This result was somewhat surprising, since it has been found that females with T1D are more likely than males to have more than one additional autoimmune disease (90). Therefore, we went on to Study IV to see if the same was true in children when it came to being diagnosed with T1D, CD and ATD.

In Study IV, we found that there was no significant difference in the prevalence of triple autoimmunity between girls and boys. Given the small size of the triple autoimmunity group of children, it is possible that we did not have enough power to show a significant difference between the groups. However, it is also possible that in children and adolescents with T1D, there are no sex differences in the risk of associated autoimmune disease after the onset of T1D. If this is true, this would mean that the sex difference in autoimmune diseases seems to be less pronounced in children with T1D, which has been shown in the adult population previously (93).

When we compared the prevalence of autoimmunity with age-matched children, screened for both CD and ATD, the risk was higher in girls than boys in this population. However, since only 3 cases of concomitant CD and ATD were found, (all girls), we did not do any further statistical analyses, but we can conclude that both girls and boys had a higher risk of being diagnosed with other autoimmune diseases when having T1D.

A Finnish study by Turtinen et al. studied sex differences at T1D diagnosis (32), and found that HLA-DQ2/DQ2 was more frequent in boys and also showed a trend towards the HLA-DQ2 haplotype being more common in boys, while HLA-DQ8 was more common in girls (32). When HLA typing 666 children and adolescents in Italy with CD, DQ2/DQ2 was more frequent in males than females although CD was more frequent in females (114). In addition, an earlier study with data from the BDD study showed that in some age groups, some high-risk HLA alleles including HLA DQ2/DQ2 were more common in boys than girls (31). This would mean that more boys with T1D had an increased risk of developing CD which could be one reason for the lost dominance for girls.

When it comes to autoantibodies, boys more often tend to test positive for IAA, IA-2A and ZnT8A while girls more often test positive for GADA (31, 32). On the other hand, HLA-DQ2 is associated with GADA, and HLA-DQ8 with IAA (26, 29, 30). More research is needed to clarify the relationship between genetic, immunological factors and sex. Could it be that HLA is an important factor for the association between T1D and CD while for ATD other immunological factors are more important for the association?

Strength and limitations

In all four studies, we have used large nationwide Swedish study populations. In Study I we included the whole birth cohorts and in Studies II-IV from the BDD study in which 40 of Sweden's 42 paediatric clinics participated from the start 2005 and since 2011, when some parts of the BDD study became clinical routine, all clinics were included and almost 99% of patients chose to participate (146). Therefore, the study population in Study II-IV covers almost all children with T1D during the years that were included making the study population-based when it comes to children who have been diagnosed with diabetes and reducing the risk of selection bias. Also for Study I, I am fairly certain that we have covered almost all children with T1D during the years studied since almost all children in Sweden are treated with inpatient care at diagnosis and thus registered in the NPR.

The strength of Study I, is the unique situations with birth cohorts that differ in feeding recommendations and amount of ingested gluten during gluten introduction which is very thoroughly studied according to the true prevalence of CD, both screening and not screening detected. We chose to analyse two birth cohorts with different feeding recommendations but only 4-6 years apart, to limit other changes in the environment that could affect our results.

Another strength is the recommendations in Sweden with annual screening for CD and T1D in children with T1D, meaning that I am relatively sure about not missing any cases of CD or ATD during follow-up. Also the long follow-up time, for some up to 10 years is a strength. Although the recommendation in Sweden is annual screening for CD and ATD, there are still local recommendations for screening at different hospitals, which may have influenced the outcome and yearly incidence.

Validating the T1D diagnosis in Studies II and IV with NPR and in Study I with SWEDIABKIDS also gives strength to these studies.

In Study IV we used the ETICS study as an age-match control group from the general population. The strength of this control group is that they are screened for both CD and ATD as the children with T1D in the BDD study. This is extra important though most individuals who have CD are undiagnosed due to atypical or no symptoms also in the general population.

Studies with large cohorts linked to different registers also have their limitations. The information in the register is recorded by clinicians at health-care visits and in-

patient care. Since some of the ICD codes are very similar, there are potential risks for misclassification and sometimes clinicians fail to report diagnoses. However, for CD we have a small study performed locally in Sweden, using patient's hospital files (121), and a larger cohort study, including 2,035 children from this study cohort, also based on patient's hospital files (122), reporting CD prevalence in line with our 9.8% from the register, which means that for CD the misclassifications from the registers are low.

Missing data in the BDD study in Studies II and IV were not included in the analyses. We assumed that the missing data occurred at random. There is a possibility that it was not random giving us skewed data in the comparisons and giving rise to bias. In Study III, we had a larger degree of missingness from the SWEDIABKIDS when it comes to data about BMI and HbA1c during follow-up and to minimise the risk of bias, we analysed the missingness and used multiple imputations as described in the section about statistical analyses.

In Study I, we assume that the parents of the children followed the national recommendations on how to introduce gluten in infancy and gave them a larger amount of gluten during the epidemic, but we do not have individual infant feeding data, which of course is a limitation. We know from the ETICS that children born in 1993 had a larger intake of gluten from formulas than children born in 1997 and that 60-70 % of parents followed the recommendations(106, 177). The fact that there was a change in the risk of CD must mean that something in the environment, such as the difference with in abrupt introduction and a higher amount of gluten affected the children differently during these years.

A limitation of Study III was that we did not have data on compliance with the GFD, so we could not tell whether our results were affected by compliance to GFD or not.

Clinical implications

In the preface I described the background for Study II, all these normal anti-tTG tests that came back after meeting children with T1D at the diabetic out-patient ward. Hopefully, the proposed screening recommendations in Study II, where age at T1D diagnosis has to be considered when and how to screen for CD, will be accepted by the paediatric clinics in Sweden and also outside of Sweden and implemented in the care of children and adolescents with T1D. This will lead to a more individual-based and, although not investigated, cost-effective screening of children with T1D.

In addition, the results from study IV, provide information about the small risk of developing triple autoimmunity in children with T1D, which will be valuable information for patients and their families, but also provide insights on how to screen for both diseases. The risk of developing thyroid disease is very low in children below ten years of age, but we are still screening annually for the youngest. Should we individualise screening according to this risk? I do not know. It is a rare disease in the youngest population; however, screening with TSH and T4, is cheap, and detection of clinical thyroid dysfunction early is difficult in children. The symptoms may be vague and can be first detected when growth is impaired.

In Study III, having two diagnoses, T1D and CD, was not associated with worse metabolic control compared to T1D alone, but an affected growth. Therefore, extra attention on growth during follow-up in those with concomitant CD is important.

During the work with this thesis, I have taken part of several studies supporting overweight and obesity as a cause of the increased incidence of T1D in children and adolescents. Because the birth cohort in Study I with the highest cumulative incidence of T1D also has a higher prevalence of overweight and obesity at 12 years of age (154), it is tempting to speculate that this may affect the increase in cumulative incidence. If true, we need to do more to prevent children from developing overweight and obesity, not only to treat children that already have overweight or obesity because then the process towards T1D may have already been started and cannot be stopped.

Thesis conclusion

The changes in national feeding recommendations and the increased amount of gluten in the diet during infancy did not affect the cumulative incidence of T1D in the same way as it did for CD during the epidemic of CD in Sweden. I argue that the differences in feeding during infancy did not affect the incidence and gluten is not part of the pathogenesis behind T1D in the general population.

One in ten children and adolescents with T1D in Sweden have CD. I propose updated screening guidelines in light of the fact that few new cases are found during annual screening, the risk is dependent upon age at T1D diagnosis, and the benefit of an earlier diagnosis is minimal. The new recommendations are based on age at T1D diagnosis and time after the diagnosis of T1D since we have shown that these are risk factors for the development of CD in children and adolescents with T1D. To have both diseases does not seem to affect metabolic control in children with T1D.

Being diagnosed with both CD and ATD is uncommon in children and adolescents with T1D but much more common than in the general population without T1D. There does not seem to be any sex differences in developing another autoimmune disease in children when diagnosed with T1D.

Future work

The work with the studies in this thesis has answered some questions but also generated new questions to be answered along with ideas for future work.

- I would like to further study the associations between increased BMI and the risk of developing T1D. If this is a true risk factor, primary prevention for T1D is possible. This could be done by studying BMI in early childhood by using data from our BVC (child health care) centres.
- Should we screen for CD at all or let the patients/families choose if they want the screening? CD is often asymptomatic and we cannot show that a concomitant CD has any big effects on growth and metabolic control. The best would of course be to set up a randomised study where those with an asymptomatic disease were randomised to a gluten-free or gluten-containing diet and then followed for five to maybe ten years. I am not sure that a study design like that would be given ethical approval. Instead, the assessment of anti-tTG as a measurement of compliance to a GFD should be interesting. Except for metabolic control and growth, it would be interesting to follow quality of life and DEXA measurements. Should we let the patients decide for themselves? I think information about the pros and cons is of course always valuable. The most crucial thing could be to screen the youngest patients who are at a high risk of developing CD, with many years ahead of growing and could experience harsher side effects if their symptoms go untreated. Is it not always good to know, then you can choose yourself if you benefit from a GFD? Further studies on this question would be valuable.
- Is it possible with further genetic testing at T1D diagnosis to further refine the screening guidelines to become more individual-based and cost-effective with a genetic risk score? If in the future, ways are found to cure or even prevent CD, this will become even more relevant.
- The incidence of T1D is rising in countries with low T1D risk and migration from an area with low risk to an area with high risk also increases the risk. What about the risk of CD in these children? Most studies on associated autoimmune diseases are from populations in the Western world who are mainly white Caucasians. How about the risk in other ethnic groups? Should we screen them in another way?

- What is the prevalence of CD in adults screened for CD during childhood? CD has been regarded as a disease affecting children, but over the past few years, more and more adults have been diagnosed. It would be interesting to monitor our cohort of T1D children who have undergone CD screening in order to see whether any of them go on to acquire CD as adults or if we have identified all of them through screening in childhood.
- It would also be interesting to further investigate the immunological differences between the sexes that can explain the differences in risk of associated autoimmune diseases.

Acknowledgements

First of all, a big thank you to all the children who participate in research studies such as BDD and quality registers, so that we can develop and improve care for both you and others who end up in the same situation. Special thanks to the children and their families that I met at the diabetic clinic at Vrinnevisjukhuset, for everything you share that inspires me to want to know more.

Annelie, I am so glad that you answered the email I sent to you during term 10 at medical school and became my supervisor for the Master's project. You have inspired me to do my research with your enthusiasm and curiosity. You are always there to provide me with sound advices. At times when the research has felt tough, you have encouraged me to continue but also allowed me to have breaks when needed.

Lars Stenhammar, without really knowing what I was getting myself into, I went with you and Annelie to an ETICS meeting in Umeå. As your travel companion, I got to share your wisdom and over a "waffle" the first ideas for this thesis were born.

Anna, Fredrik and Ulf, my co-supervisors. Thank you for all the advice along the way. You have taught me a lot and guided me through all the statistics and epidemiological considerations.

Hanna and Elsa, thanks for your cooperation with studies I and III.

Elenor, Anna and David thank you for your excellent work with the data and your Master's project that inspired me and brought new input.

Thank you also to Johnny, Martina, Helena, Gun and Karin, co-authors in the BDD study, who read and gave feedback on my scripts so that they developed and improved.

Quefsere, thanks for keeping all the data in order.

My dear colleagues at the Department of Paediatrics at Vrinnevisjukhuset in Norrköping. Thank you for all the encouragement, curious questions and cheers during the years. Extra thanks to Magdalena who guided me through my training to become a specialist in paediatrics, encouraging me to continue with this thesis and for all the advice I received from you. And Maria, thanks for always letting me bother you with my questions and if you don't have the answer, although very

seldom, always having an article to pick up that provide the answer. You have taught me to always question what I hear and read and to think for myself.

Mamma, Pappa, Roger, Ronny and Anna, thanks for always being there. Carina, for always knowing when to show up in one way or another, without me needing to say anything. To all my friends, you are the best.

Johan, jag är så tacksam för att jag får dela mitt liv med dig och att du står ut med alla mina knasigheter. Älskar dig.

Astrid, Hedda och Tage, ni är de finaste jag vet och jag älskar att vara er mamma.

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

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FACULTY OF MEDICINE

Pediatrics
Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:125
ISBN 978-91-8021-622-7
ISSN 1652-8220