

Epidemiological studies of childhood diabetes

and important health complications to the disease

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To my family and our future

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Abstract

Background and aims: Both type-1 diabetes (T1D), principally associated to autoimmunity, and type-2 diabetes (T2D) with its stronger link to lifestyle factors such as overweight and obesity, are increasing worldwide. In Sweden childhood onset T1D has increased steadily since the beginning of incidence registration in 1977 and we now have one of the world's highest incidence rates. In the light of increasing childhood obesity, also childhood onset T2D is a rising concern in many countries. There is however, little known on the prevalence of T2D among Swedish children. The two first studies included in this thesis aimed to describe and analyze the cumulative incidence of childhood onset T1D in Sweden, and to assess the occurrence of undetected T2D in Swedish children. Since T1D may lead to long term complications, such as renal failure, we wanted to assess the cumulative risk for end-stage renal disease (ESRD) in Swedish T1D patients. Onset of T1D at young age has been associated with lower risk for ESRD. The aim with our third study was to describe the cumulative incidence of ESRD, and to analyze how ESRD risk differs with age at-onset and sex. Patients with T1D still have an excess mortality in Sweden, partly due to long term complications of disease. It is also well known that socioeconomic factors associate with health and mortality in the general population. The aim of the fourth study was to show how parental socioeconomic status (SES) affects all cause mortality in Swedish patients with childhood onset T1D.

Study populations: The foundation for the studies on T1D was data from the Swedish Childhood Diabetes Registry (SCDR). The study on T2D was a population-based screening study where BMI was measured in 5528 school-children and hemoglobin A1c (HbA1c) was measured in children with overweight according to international age and sex specific BMI cut-offs. To study ESRD and mortality, we linked the SCDR to various nationwide registers, i.e. the Diabetes Incidence Study in Sweden (DISS), the Swedish Renal Registry, Longitudinal integration database for health insurance and labor market studies (LISA) and the Swedish Cause of Death Register (CDR).

Results: We found that the incidence rates of childhood onset T1D has continued to increase in Sweden 1977–2007. Age- and sex-specific incidence rates varied from 21.6 (95% CI 19.4–23.9) during 1978–1980 to 43.9 (95% CI 40.7– 47.3) during 2005–2007. Cumulative incidence by birth-cohorts has shifted to a younger age at-onset over the first 22 years of incidence registration. From the year 2000 there was a significant reverse in this trend ($p < 0.01$). In contrast to the increase of T1D, we found no evidence of undetected T2D among Swedish school children. Despite a relatively high

incidence in T1D in Sweden there is low cumulative incidence of ESRD, 3.3% at maximum 30 years of duration. We found difference between the sexes regarding long-term risk of developing ESRD that was dependent on the age at onset of T1D. There is still an excess mortality among patients with T1D in Sweden. In our cohort the mortality was doubled compared to the general population. When analyzing how socioeconomic status affects mortality in different age at death groups, we found that having parents that received income support increased mortality up to three times in those who died after 18 years of age.

Conclusion: The incidence of childhood onset T1D continued to increase in Sweden 1978-2007. Between the years 1978-1999 there was a shift to a younger age at-onset, but from the year 2000 there is a change in this shift indicating a possible trend break. The prevalence of T2D among Swedish children up to 12 years of age is probably very low. There is still a low cumulative incidence of T1D associated ESRD in Sweden. The risk of developing ESRD depends on age at-onset of T1D, and there is a clear difference in risk between men and woman. Excess mortality among subjects with childhood onset T1D still exists, and low parental socioeconomic status additionally increased mortality in this group.

Populärvetenskaplig sammanfattning

Under de senaste 30 åren har ökningen av barn- och ungdomsdiabetes (typ-1 diabetes) accelererat i Sverige. Idag har Sverige den näst högsta förekomsten av typ-1 diabetes bland barn i världen. Orsakerna till detta är inte klarlagda. Förutom ärftlighet har även ett antal miljöfaktorer identifierats som risker för att få sjukdomen. Bland dessa riskfaktorer ingår bland annat virusinfektioner och kosthållning.

Under samma period har barnfetman ökat, både globalt och i Sverige. Typ-2 diabetes är kopplat till fetma och i vissa länder har typ 2-diabetes hos barn ökat. Detta har väckt farhågor att även svenska barn ska drabbas av denna sjukdom. Kännedomen om förekomsten av typ-2 diabetes hos barn är låg i Sverige.

De två första studierna i den här avhandlingen syftar till att beskriva och analysera insjuknandefrekvensen i typ-1 diabetes, samt utforska om typ-2 diabetes förekommer hos barn och ungdomar, och hur vanligt det i sådana fall är.

Eftersom typ-1 diabetes kan leda till följsjukdomar som till exempel njursvikt, ville vi i den tredje studien undersöka förekomsten av njursvikt hos svenska typ-1 diabetespatienter. Eftersom det är känt att ålder och kön påverkar insjuknandefrekvensen ville vi även titta på dessa aspekter.

I den fjärde studien undersökte vi hur dödlighet hos personer med typ-1 diabetes är kopplad till socioekonomi. Det är sedan tidigare känt att personer med typ-1 diabetes har en ökad risk att dö i förtid, delvis beroende på följsjukdomar av diabetes. Det är också känt att patienter med låg socioekonomisk status, som låg utbildningsnivå eller fattigdom, riskerar att dö i förtid. Syftet med den fjärde studien var att undersöka om det finns något samband mellan dödligheten hos personer som insjuknat i typ-1 diabetes som barn och föräldrarnas socioekonomi.

Grunden för studierna på typ-1 diabetespatienterna var data från Det Svenska Barndiabetesregistret. Studien på typ-2 diabetes var en screeningstudie där vi mätte BMI hos ett antal svenska barn i årskurs 6 för att identifiera riskgrupper för typ-2 diabetes. De barn som hade ett BMI som klassificeras som övervikt undersöktes vidare med ett blodprov som kan visa om typ-2 diabetes föreligger eller ej (HbA_{1c}). I studierna där vi tittade på njursvikt respektive dödlighet kopplade vi svenska barndiabetesregistret till olika nationella register med uppgifter om dödlighet, socioekonomi och förekomst av terminal njursjukdom.

Gällande typ-1 diabetes hos barn och ungdomar i Sverige kunde vi konstatera att insjuknandefrekvensen har fortsatt att öka. Incidensen har ökat från 21,6/ 100 000 barn per år till 43,9/100 000 barn per år mellan 1977 och 2007. Insjuknandet i olika åldersgrupper skilde sig från varandra, särskilt de sista fem åren som studerades. I studien kunde vi konstatera en avtagande trend i åldern 0-4 år. I motsats till ökningen av typ-1 diabetes kunde vi i vår screening-studie inte hitta något barn med typ-2 diabetes.

Trots en relativt hög och stigande insjuknandefrekvens i typ-1 diabetes hos barn i Sverige sedan 1970-talet så har vi en relativt låg förekomst av njursvikt orsakat av typ-1 diabetes. Studien visade en skillnad mellan könen beträffande insjuknandefrekvens i njursvikt.

Det är fortfarande en ökad risk att dö i förtid hos patienter som fått typ-1 diabetes i barndomen. När vi undersökte hur socioekonomisk statusytterligare påverkade dödligheten såg vi att låg socioekonomisk status hos föräldrar gav en ytterligare ökad risk att dö i förtid inom gruppen som hade fått typ-1 diabetes som barn, men bara bland de som dog i vuxen ålder. Vi kunde inte konstatera att föräldrarnas socioekonomi hade påverkan på dödligheten i åldrarna 0-17 år.

Original Papers

This thesis is based on the following articles and manuscripts, which in the text will be referred to by their Roman numerals (I-IV). The papers included in this thesis have been reprinted with permission by the publishers.

- I. **Berhan Y**, Waernbaum I, Lind T, Möllsten A, Dahlquist G. *Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden*. Diabetes. 2011 Feb; 60(2):577-81.
- II. **Berhan Y**, Möllsten A, Carlsson A, Högberg L, Ivarsson A, Dahlquist G. *Screening for undiagnosed type-2 diabetes in Swedish 6th grade school children*. (Under revision)
- III. Möllsten A, Svensson M, Waernbaum I, **Berhan Y**, Schön S, Nyström L, Arnqvist HJ, Dahlquist G. *Cumulative risk, age at-onset, and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes: a nationwide population-based cohort study*. Diabetes. 2010 Jul; 59(7):1803-8.
- IV. **Berhan Y**, Eliasson M, Waernbaum I, Möllsten A, Dahlquist G. *Impact of parental socioeconomic status on excess mortality in subjects with childhood onset type-1 diabetes*. (Submitted)

Introduction

Diabetes mellitus is a metabolic disorder, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. The defects of insulin action lead to hyperglycemia together with disturbances of carbohydrate, fat and protein metabolism. Among the characteristic clinical presentations are thirst, polyuria, weight loss, fatigue and blurry vision. Type-1 diabetes (insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production. Type-2 diabetes (non-insulin dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. Diabetes is a disease of multiple etiologies and this will be discussed in the coming sections.

Historical overview

Patients with diabetic symptoms have been described since antiquity. The first written report on diabetes may be an Egyptian papyrus dating from around 1550 BC describing a condition of polyuria and weight loss that was inevitable fatal. Around 500 BC, Indian physicians described (by tasting) the sweetness of diabetic urine that attracted ants and flies, and that the disease was most prevalent in those who were overweight and those who consumed sweet and fatty food. The Indian physicians also suspected a difference between two types of the disease, observing that thin individuals developed diabetes at a younger age in contrast to heavier individuals, who had a later onset and lived longer period of time after the diagnosis¹.

The term “diabetes” was first used in writing by the ancient Greek physician Aretus of Cappodia (1st century AD) and stems from the Greek for “to pass through”, relating to the excessive thirst and continuous urination a diabetic patient suffer from. Aretus of Cappodia is recognized for his great accuracy in the detail of symptoms and in seizing the diagnostic character of the disease²:

“Diabetes is a dreadful affliction, nor very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; their viscera seems scorched up, the patients are affected by nausea, restlessness and burning thirst, and within short time they expire”

The adjective “mellitus”, from the sweet honey tasting urine, was added in the late 18th century. In the first half of 19th century it was clear that it was glucose that was present and elevated both in urine and blood. By the end of

the 19th century the role of pancreas was discovered by showing that pancreatectomy caused diabetes in dogs and that pancreatic islets produced an internal secretion that regulated glucose metabolism, later to be named insulin. During the same period the disease was subdivided by the French physician Lanceraux into *diabète maigre* (lean subjects) and *diabète gras* (obese). This was an early archetype to the current etiological classification of diabetes type-1 (T1D) and type-2 (T2D) respectively².

During the first part of the 20th century, prior the discovery of insulin, diabetes treatment mostly consisted of starvation diets. Most of the early descriptions of diabetic complications were on acute conditions, such as diabetic ketoacidosis, leading to coma and death. Eventually, long term complications also were described, most likely in patients with T2D that could survive for a longer time on the type of treatment that was offered during the pre insulin era. The finding of retinopathy in patients with long standing diabetes was the first description of a long term complication to diabetes, made by Henry Noyes in 1869, and has since then been an important marker for the microvascular complications of the disease¹.

In 1921 the hormone “insulin” was finally isolated and for the first time used by two Canadian physicians, Fredric Banting and Charles Best, as a “pancreatic extract” that was injected in dogs with induced diabetes; that was the starting point for clinical trials with insulin and current treatment of diabetes. The first clinical trial with refined insulin took place soon thereafter (January 11 1922) on a 14-year old boy who had been on a starvation therapy since 1919².

During the 100 years that have elapsed from the first clinical trial with insulin until now, the knowledge of diabetes has increased considerably. Among the landmarks are; classifying the role and structure of insulin, the ability to synthesize insulin though recombinant DNA technology, knowledge about the impact of metabolic control on long term complications to the disease, improvement of treatment regimens, better facilities to monitor the disease and the identification of several risk factors for both T1D and T2D. Although diabetes treatment has improved and we partly understand how to prevent T2D and long term effects of hyperglycemia, we seem to be far from finding a cure for diabetes or preventive measures for T1D¹.

Today diabetes is a growing global public health challenge. Both T1D, principally associated to autoimmunity, and T2D with its stronger link to life-style factors such as overweight and physical inactivity, is increasing worldwide. According to estimates made by the WHO and the International

Diabetes Federation (IDF), the global prevalence of diabetes among adults (20-79 years) was 8.3% in 2011 (366 million persons) and projections for 2030 show an increase of the prevalence to 5.6% (552 million persons)³. The large numbers are mainly attributed to T2D in adults, but quite a few of them will be due to a cumulative effect of those with onset of diabetes in childhood.

Criteria for diagnosis of diabetes

Diabetes in childhood is classified in three main categories:

- 1, Type-1 diabetes (T1D)
- 2, Type-2 diabetes (T2D)
- 3, Monogenic diabetes (genetic defects in insulin action or secretion)

There are also a couple of pre-diabetic states referred to as Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycemia (IFG).

Type-1 diabetes is characterized by a lack of sufficient insulin production. Type-2 diabetes is caused by the body's ineffective use of insulin and hampered insulin secretion from the pancreas. The diagnosis of diabetes mellitus is established according to international guidelines⁴ by blood tests measuring casual plasma glucose, fasting plasma glucose or measuring 2 hour post-load glucose (OGTT). To receive a diabetes diagnosis, step 1 or step 2 or step 3 should be fulfilled (Table 1). The same criteria are valid for both T1D and T2D but the range of symptoms are generally very different. Hemoglobin A1c (HbA1c) is also included in the international criteria since 2011 but is not used alone in diagnosing diabetes.

-
- 1. Symptoms + casual plasma glucose concentration ≥ 11.1 mmol/l**
(Asymptomatic children with high risk for T2D and a screening casual plasma glucose level ≥ 5.6 mmol/l and < 11.1 mmol/l, should have a repeated screening test before further testing according to step 3.)
Casual is defined as any time of day without regard to time since last meal.
-
- or**
-
- 2. Fasting plasma glucose ≥ 7.0 mmol/l**
Fasting is defined as no caloric intake for at least 8 hours.
-
- or**
-
- 3. 2 hour post-load glucose ≥ 11.1 mmol/l during an OGTT**
The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g
-
- 4. HbA1c $\geq 6.5\%$ (48 mmol/mol)**
Difficulties with assay standardization and individual variation in the relationship between blood glucose and HbA1c may outweigh the convenience of this test.
-

Table 1. Criteria for the diagnosis of diabetes mellitus in childhood and adolescence according to international guidelines by International Diabetes Federation (IDF) and International Society for Pediatric and Adolescent diabetes (ISPAD)^{4,5}.

Background to this thesis

Type 1-diabetes in childhood

Childhood onset diabetes is primarily T1D and is now one of the most common endocrine and metabolic disorders among children worldwide. In 2011, according to estimations by the IDF, about 490 000 children (aged 0-14 years) had T1D. The estimated number of new cases in the world were 78000 annually⁶.

There are large variations in the incidence rates of childhood T1D worldwide. In 2006, an international collaboration (DIAMOND/WHO project group) examined global incidence and trends of childhood T1D for the period 1990–1999 and reported rates from 0.1 per 100000/year in China and Venezuela to 40.9 per 100000/year in Finland⁷. In that report the annual increase in incidence was seen in all continents, with 2.8% increase globally and 3.2% increase in Europe. These figures are rather aged but illustrate the vast geographic differences in incidence and also that T1D is increasing globally.

Recent studies from Europe (EURODIAB), for the years 1999-2008, have confirmed that the incidence rate of childhood T1D continues to rise across Europe by an average of approximately 3-4% per year⁸.

Next to Finland, Sweden has the highest reported nationwide incidence of T1D in the world^{6,7}. (Figure 1)

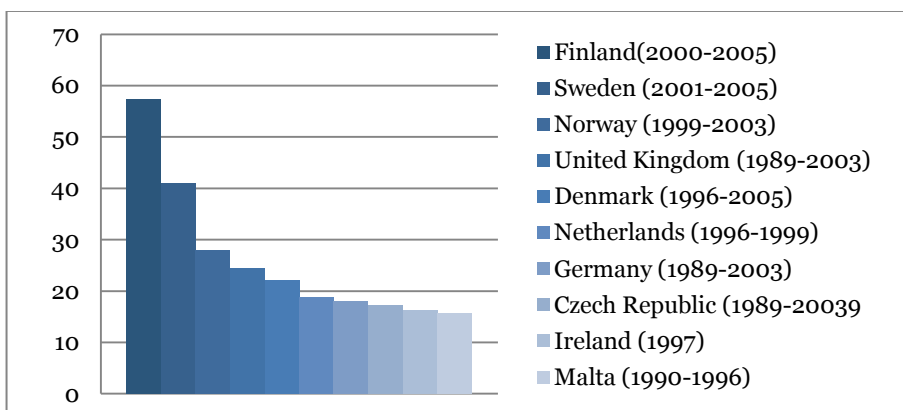


Figure 1. Childhood onset T1D (0-14 years). Estimated *age-specific* incidence rates /100000 children per year. Top 10 European countries 2010. Data source: International Diabetes Federation, IDF 2013. Microsoft Excel tables for making the graph were downloaded from: <http://www.idf.org/node/23640>

Over a 20 year period, 1st January 1978 to 31st December 1997, the incidence of T1D among children 0-14 years of age was almost doubled in Sweden⁹. According to data from the Swedish Childhood Diabetes Registry (SCDR), the largest increase during that period was seen among children 0-5 years old; a trend that also recently has been described in many European countries¹⁰.

Although 20-year follow up in Sweden had shown an accelerating increase of T1D there was a transient leveling off in the increase during 1985-1990⁹. Similar transient changes have also been reported from Norway¹¹. When I started my PhD project in 2009, data illustrated by 3 year moving averages indicated a leveling off in the increasing trend from around 2003. (Figure 2) Given these indications, I thought it would be interesting to further study the cumulative incidence and the time trend of childhood onset T1D in Sweden.

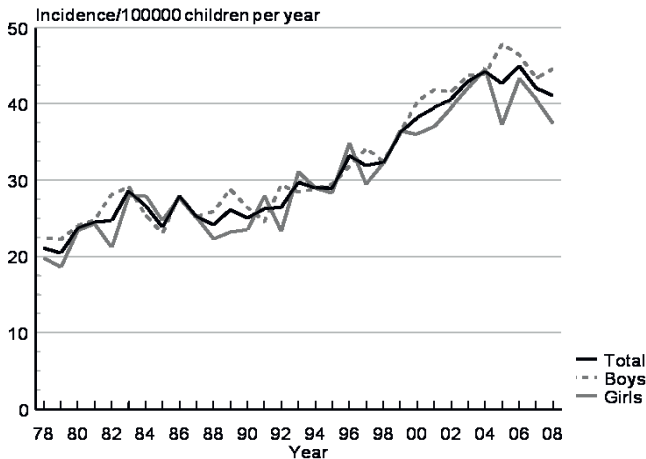


Figure 2. Incidence of T1D 1978-2008 in Sweden, three years moving averages. Data from the Swedish Childhood Diabetes Registry (SCDR) 2008

Etiology

The etiology of T1D is not known, but influence of both genetic and environmental factors is evident. The pathogenesis of the disease is essentially autoimmune. In the majority of cases, T1D is caused by a T-cell mediated autoimmune destruction of the insulin producing β -cells in the pancreatic islets². Autoantibodies are found in up to 90% of T1D cases. The autoantibodies are not thought to cause the disease but may reflect an ongoing attack towards the β -cells¹².

Genetic predisposition

The strongest genetic association to T1D is found in human leukocyte antigen (HLA) genes, particularly the HLA DR3-DQ2 and DR4-DQ8. A combination of these two HLA genes give a high risk of developing T1D while those who carry one of them have moderately increased risk^{13, 2}. On the other hand it has also been shown that only 10% of genetically susceptible individuals progress to clinical disease¹⁴ and only around 30% of monozygotic twin pairs both develop T1D¹⁵. Furthermore, migration studies have pointed out that an increased incidence is seen in population groups who have moved from low-incidence to high-incidence regions¹⁴. This together with the rapid increase in incidence of T1D within genetically stable and homogenous populations (such as Sweden and Finland) implies that genetic susceptibility is important but not sufficient for developing T1D.

Environmental risk factors

A large number of environmental risk factors have been identified in case-control studies, mainly from the Scandinavian countries. Some of the risk factors have been interpreted as important for the initiation of autoimmunity towards the β -cells, e.g. viruses^{16, 17}, diet¹⁸ and early perinatal factors^{19, 20}. The autoimmune process may start in early life and continue for many years before the clinical onset of disease (Figure 3a).

Other risk factors have been held responsible for accelerating β -cell destruction towards clinical disease and diagnosis. Those risk factors are proposed to work as accelerators through the so called “overload effect”²¹ or according to “the accelerator hypothesis”²². These theories imply that factors increasing the need for insulin and causing an overload of the β -cell also leads to β -cell stress and increases the amount of β -cell antigens. These processes would thereby accelerate an already ongoing autoimmune process, leading to enhanced β -cell destruction and cell death²³. Such risk factors might be high energy diet²⁰, an increased weight-height development in childhood^{24, 25} as well as infectious diseases²⁶ and psychological stress²⁷, all increasing the insulin need and sensitizing the β -cells to immune damage, ultimately leading to clinical onset of diabetes (Figure 3a and 3b).

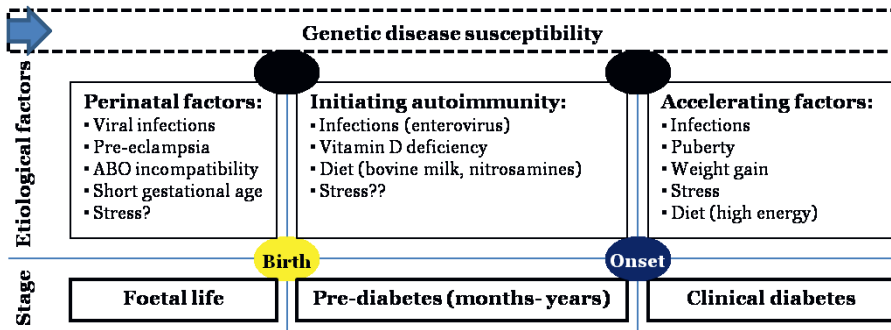


Figure 3a.

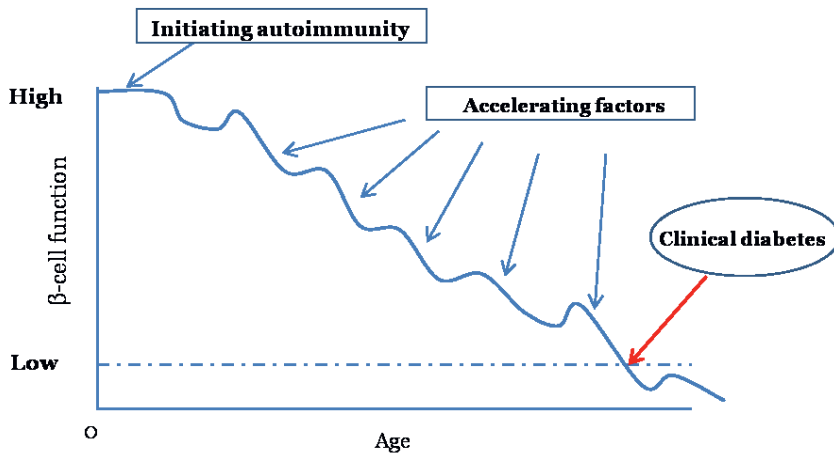


Figure 3b.

Figure 3a and 3b. Schematic presentation of natural history of T1D and possible etiological factors according to the “accelerator hypothesis” and “the over load hypothesis”. Figure 3a modified from Holt et.al Textbook of diabetes²; 3b modified from Knip, M et.al *Diabetes* (2005)¹⁴

In summary, childhood onset T1D has doubled in Sweden since the beginning of incidence registration in 1977. Environmental risk factors are important in the etiology of T1D and may play a part both in the autoimmune initiation of the disease and in the acceleration of the progress^{19, 14}. The accelerating factors are considered to be responsible for the recent increasing time trend according to the “the accelerator hypothesis” and “the overload hypothesis”.

Type-2 diabetes in childhood

When I started my PhD project in 2009, the IDF had reported that T2D in children and adolescents was increasing in some countries, most likely due to a change in lifestyle patterns and an increasing incidence of childhood obesity²⁸. Compared to adults there was little information on T2D incidence and prevalence in the young. Even today, clinic-based surveys or case series make up the largest group of studies on T2D in children and adolescents²⁹.

A few population-based studies have been performed, mainly in North America and Japan^{30, 31}, reporting increasing T2D among children and young people. Variations in study design and variable size of studies is making it difficult to compare the results. Among children and adolescents, T2D is thought to account for 2-3% of all cases of diabetes worldwide. There are vast regional and ethnic differences, with the highest rates being reported in Japan and certain ethnic groups in USA²⁸.

Compared to T2D in adults, the natural history and etiology of childhood onset T2D is sparsely described. Apart from age, heredity and ethnicity; the risk factors in adults are central abdominal obesity², physical inactivity and cigarette smoking^{32, 33}. The suggested risk factors for T2D in children and adolescents are, as expected, similar to those seen in adults, with obesity being almost always present and linked to changing patterns in diet and physical activity³⁴. Also within the young population, ethnicity is an important risk factor in T2D development, with higher incidence in Asians, Hispanics, African Americans and indigenous people²⁸. Many studies regarding risk factors for T2D have been performed in groups with already high genetic susceptibility for the disease. Apart from ethnicity they present possible risk factors including obesity and diet³⁰, insulin resistance that frequently occurs in adolescents during puberty^{35, 36}, family history with T2D and intrauterine environment (i.e. being exposed to gestational diabetes as a fetus) ³⁷.

The ongoing epidemic of childhood obesity in most developed countries is now an established public health problem³⁸. In a Swedish cross-sectional study comparing two cohorts of 10-years old school children examined in 1984 and 2000, a twofold increase in the prevalence of overweight and a fourfold increase in obesity was observed³⁹. In an more recent follow up from the same authors in children examined in 2004/2005 the obesity epidemic was confirmed, although a reversed trend was indicated among girls⁴⁰.

In conjunction with writing the research plan for my PhD studies, I carried out a MEDLINE search and found one contemporary study from 2008 based

on blood samples of all newly diagnosed diabetes patients in a Swedish county (Kronoberg) during three years. The pediatric population in this study was rather small, but as much as 4/53 of new cases were diagnosed as T2D, leading to an estimated incidence of 3.1/100 000 children per year (0-19 years of age) according to the authors⁴¹. Another not peer reviewed study, based on case reports from Swedish pediatric clinics, estimated that approximately 0.5% of the diabetic children have T2D ⁴².

Since child and youth obesity also has increased in Sweden, there is a concern for rising incidence of T2D in young Swedes. There was little known on the epidemiology of T2D in Swedish children in 2009, and reliable population-based data on T2D epidemiology in children and adolescents was and still is sparse worldwide. Both the IDF and the WHO have declared that more information about T2D in the young is needed.

Diabetes related health complications

People with diabetes have an increased risk of developing a number of serious health problems, and also an increased risk of mortality. Chronic elevation of blood glucose will eventually lead to tissue damage in many organ systems; most significantly in the kidneys (nephropathy), eyes (retinopathy), peripheral nerves and vascular tree.

While T1D patients often are diagnosed early after disease onset and thus presumably monitored for long term complications before they occur, it is well known that T2D in adults often is undiagnosed for long periods of time due to a more “quiet” onset of disease. It has been estimated in adults that T2D may have its onset up to 12 years before its clinical diagnosis⁴³ and many cases of T2D show signs of long-term complications, e.g. nephropathy and retinopathy, already at diagnosis⁴⁴.

Recent studies assessing the risk of complications in youth with T2D (1-18 years) have reported an earlier diagnosis of renal and neurological complications T2D patients compared T1D patients, manifesting within 5 years of diagnosis^{45, 46}. Earlier age at onset of T2D was shown to increase the risk for these complications⁴⁵.

The negative effects of long term hyperglycemia have been demonstrated numerous times in both animal models and epidemiological studies, and duration of the disease is shown to be an implicit risk factor for developing macro- and microvascular complications of diabetes². In addition to that the explicit benefits of good self-management with intensive insulin treatment and good metabolic control (near to normal glucose levels) has been shown

to limit the progression of diabetic complications in several reports from the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS)⁴⁷⁻⁵⁰. These findings have subsequently been confirmed and the beneficial effect of intensive treatment in delaying the progression to diabetic complications, i.e. diabetic nephropathy, has also been shown to persist over long time in follow-up studies^{51, 52}.

Renal disease in T1D patients

Diabetic nephropathy (DN) is one of the most serious complications of T1D. It's a chronic condition developing over many years and is characterized by persistent and gradually increasing albumin excretion in urine (proteinuria or albuminuria)². This complication not only leads to renal failure, but also leads to rising blood pressure and a ten times increased risk of cardiovascular disease⁵³. DN, starting with microalbuminuria before progressing to persistent proteinuria, is therefore a marker for an increased risk of coronary heart disease, stroke and death⁵⁴.

DN is the cause of at least 25% of all cases of end-stage renal disease (ESRD) in Sweden⁵⁵. Patients with ESRD are those who require active uremia treatment (dialysis and/or renal transplantation). Several studies have shown that mortality among dialysis patients with diabetes mellitus is higher than in non-diabetic dialysis patients. It has also been suggested that mortality is higher in dialysis patients with DN than in those with diabetes and renal failure as co-morbidity⁵⁶. This indicates that renal failure as a complication to diabetes may be more serious than having diabetes and a renal failure that is not caused by diabetes.

About 50% of the patients with T1D develop microalbuminuria at some point². In approximately one third of these patients the disease will progress to DN, while one third will stay microalbuminuric and one third will regress to normal albumin excretion⁵⁷. Once DN is present, with persistent proteinuria, the progression to ESRD is usually inevitable². (Figure 3)

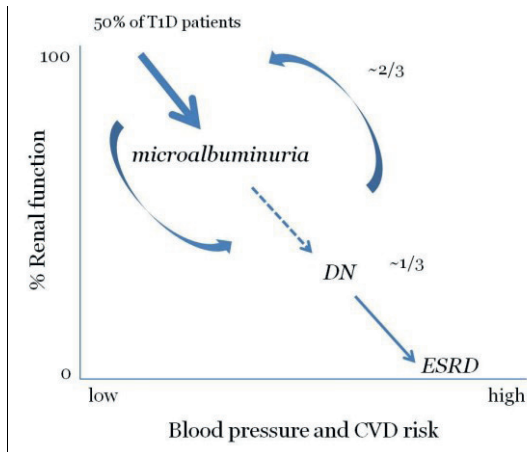


Figure 3. The progression of renal disease in T1D patients. Data from Marshal, S. et al *Br Med J* (2006)

Early epidemiological studies from Denmark (1983) have suggested that the cumulative incidence of DN was around 40% after 40 years of T1D duration⁵⁸. Over the last decades, however, Scandinavian studies have reported that cumulative incidence of DN has declined to around 10-14% after 20-25 years duration^{59, 60} and large Finnish population-based study from 2005 reported a cumulative incidence of ESRD of 7.8% after 30 years of diabetes duration⁶¹

This change in ESRD occurrence may be attributed to prevention through more aggressive therapy of dyslipidemia, hypertension and intensified diabetes treatment (intensive treatment with frequently monitored blood glucose levels and at least three daily insulin injections, implemented from around year 1990)⁶². In a follow-up of the DCCT-cohort it was reported that intensive treated T1D patients showed a cumulative incidence of nephropathy of 9% at 30 years of diabetes duration compared with 25% in the conventionally treated group⁶³.

The incidence of DN has been shown to peak after 20-25 years of diabetes duration and thereafter level off, suggesting that only a subset of individuals will ever develop DN⁵⁸. This observation, in addition to familial clustering of DN^{64, 65}, strongly indicates that genetic factors are necessary but not sufficient for this complication to occur. Apart from diabetes duration, the non genetic risk factors identified are suboptimal glycaemic control, presence of retinopathy, smoking, dyslipidemia, hypertension and male sex⁶⁶.

In childhood onset T1D, young age at diagnosis (0-5 years) is reported to lengthen the time span to development of microalbuminuria⁶⁷. Another

report on subjects with childhood onset T1D in Sweden showed that less than 1% had developed ESRD after a diabetes duration >15 years and a maximum follow up of 27 years⁶⁸. In that study, a pre pubertal onset of T1D seemed to prolong the time to development of ESRD compared to onset during the pubertal years, and no patient with T1D onset before 5 years of age had developed ESRD.

Despite the encouraging reports suggesting a declining incidence of ESRD among T1D patients, the rapidly increasing incidence of childhood onset T1D, with a clear trend to younger age at-onset, will most likely result in an increasing number of young individuals with DN and ESRD. This may lead to an increase in T1D related cardiovascular diseases and mortality. Longitudinal studies to follow up T1D cases for a long-term complication such as ESRD are important, and may contribute with new and significant knowledge that could become a basis for better preventive strategies.

Mortality in T1D patients

Reviews from a number of countries have shown significantly elevated mortality rates in both T1D and T2D patients, with consistently higher standard mortality ratios (SMR) compared to their respective general populations⁶⁹⁻⁷¹. Global estimates show that up to 50% of persons within the entire diabetes population die of cardiovascular disease (CVD), and 10-20% die from renal failure⁶. It is complex, however, to study causes of death and perform comparison between countries due to variations in certification practices and coding procedures for the underlying causes of death⁷².

Despite marked improvements in diabetes care and a decrease in diabetes related mortality, T1D is still associated with excess mortality in all ages^{71, 73-76}. While most studies show that long term mortality in T1D patients is attributed to renal complications and cardiovascular disease, early mortality has been related to acute complications such as diabetic ketoacidosis^{71, 74, 75, 77, 78}.

An European multi-centre study from 2007 on early mortality in patients with childhood onset T1D, showed that the number of deaths among the diabetic patients were twice as many as would have been expected from the general age/sex specific mortality rates in each country. The overall SMR, defined as the ratio of observed deaths to expected deaths, was doubled (2.0) and varied from <1-4.7 between the 12 countries; with a significantly higher overall SMR in female (2.7) than in men (1.8)⁷⁶. The same study revealed that as many as 35% of early deaths were due to acute diabetic complications, with another 53% due to non-diabetes complications (infections, accidents or violent deaths). A parallel Norwegian study,

assessing cause-specific mortality in individuals with childhood onset T1D, also found that acute complications was the leading cause of death before the age of 30 years, while CVD was the leading cause of mortality after long standing disease.

In a recent study on cause-specific mortality after long standing childhood onset T1D (more than 20 years of disease duration); the excess mortality seen was almost entirely related to long term complications of the disease, with no evidence of excess mortality for instance in cancer or accidents/violent deaths among the diabetic patients⁷⁷. Also in that study CVD and renal disease were the major contributors to the excess mortality, and an important finding was that renal disease significantly contributed to onset of CVD along with the increasing disease duration.

Many risk-factor studies on long term complications and mortality in T1D patients focus directly on metabolic control and treatment regimens. Socioeconomic status (SES), however, is frequently shown to associate with health and mortality in the general population. While it is an established fact that time to diabetes complications and mortality in T1D patients is dependent on metabolic control, it is also suggested that low individual SES may hamper self-management of the disease and further increase morbidity and mortality in this group^{79, 80}.

A number of reports have also shown that individuals exposed to low SES during childhood, i.e. having parents or caregivers with low SES, have increased morbidity and all-cause mortality in all ages⁸¹⁻⁸⁵. Furthermore it is also suggested that low parental SES, mirrored by low parental educational level and low economic resources, negatively affects disease care and metabolic control in the diabetic child^{86, 87}. Although recent epidemiological studies have suggested that all-cause mortality in T1D patients increases with lower SES in the individuals themselves, the association between *parental* SES and mortality among patients with childhood onset T1D seems not to have been reported before.

There has been a declining but persistent and well documented excess mortality among subjects with childhood onset T1D and the role of diabetic complications is well studied. Since it is an established fact that low SES increases morbidity and mortality in the general population, it also important to assess if- and how SES additionally affects mortality among individuals with onset of T1D during childhood.

Aim

The overall aim of this thesis was to increase knowledge regarding the occurrence of childhood onset T1D and T2D and in relation to that describe and elucidate important aspects on two grave complications to diabetes; ESRD and mortality.

The specific aims for the papers were:

- To describe and analyze the current time trend of childhood onset T1D in Sweden by sex, age at-onset and birth cohorts. (Paper I)
- To assess the occurrence of undetected T2D in Swedish 10-13 year old school children. (Paper II)
- To study the effects of sex and age at-onset of T1D on the cumulative incidence and long-term risk of ESRD. (Paper III)
- To assess if parental and individual SES affects excess mortality in subjects with childhood onset T1D. (Paper IV)

Study populations

This section starts with a short summary of the study populations and the different nationwide registers that were used in the papers and manuscripts included in this thesis. The summary is then followed by a section with separate descriptions for each study population and each register.

Summary of study populations and registers

The studies on T1D (Paper I, III, IV) were based on a dynamic cohort of childhood onset T1D patients recorded in the Swedish Childhood Diabetes Registry (SCDR). In Paper III the Diabetes Incidence Study in Sweden (DISS), with incident cases of adult onset T1D, was also included to broaden the age at-onset study population. In Paper II, for the assessment T2D occurrence in children, the study population was enrolled in cooperation with a cross-sectional celiac disease screening study on Swedish school children in 6th grade (Exploring the Iceberg of Celiac Disease in Sweden, ETICS).

To meet up with the specific aims in Paper III the SCDR was merged with the DISS cohort, and linked to the Swedish Renal Registry (SRR) and the Cause of Death Register (CDR).

To meet up with the specific aims in Paper IV the SCDR was linked to the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) and the Cause of Death Register (CDR).

The SCDR, DISS and the nationwide registers included in this thesis all use the unique Swedish national personal identification number (PIN, in Swedish *personnummer*) of the person for whom information is collected, hence information on the individual level was retrieved.

Description of the study populations and the nationwide registers

The Swedish Childhood Diabetes Registry (SCDR)

The starting point of the studies on T1D (Paper I, III and IV) is data from the Swedish Childhood Diabetes Registry (SCDR). All children with newly diagnosed T1D in Sweden are initially treated at pediatric clinics in a hospital setting. After informed consent from the parents, the clinics report their T1D cases to the SCDR with date of diagnosis, birth date and each patient's unique PIN. Date of diagnosis is set to the date of the first insulin injection.

The SCDR has recorded incident cases of childhood onset T1D (0–14 years) since 1st July 1977 with a high level of coverage (96–99% of cases) ascertained by internal revisions and yearly matching to official population databases^{9, 88}. Accordingly data from more than 30 years of prospective registration of childhood onset diabetes T1D can now be analyzed.

Similar methods of data collection and verification have been used since the start of the register. Misclassifications are rare since diabetes in children chiefly is T1D, and clinical classification is fairly easy due to a normally abrupt onset of disease. During two years (1999 and 2000), three pediatric hospitals did not deliver data prospectively, however this has been adjusted afterward. To ensure the quality of data, the SCDR has since 2003 introduced a continuous validation alliance with the Swedish Quality Assessment Register, which covers age-groups 0–18 years. In addition to that, the SCDR is now on the way to establishing validation through the Swedish National Drug Register, kept by the National Board of Health and Welfare since 2005, from where individual data on pharmaceutical drugs (insulin) dispensed through Swedish pharmacies can be retrieved.

Due to a high degree of coverage together with the relatively long follow up time, the registry today allows studies from a large set of good data with approximately 17000 childhood onset cases of diabetes.

The population screened for T2D

The screening study on T2D (Paper II) was conducted in collaboration with a study on the prevalence of celiac disease in Swedish school children (ETICS). ETICS is a cross sectional, multicenter screening study focusing on time trends of celiac disease in Sweden^{89, 90}. The study took place in five study sites and was conducted in two phases (years 2005–2006 and 2009–2010). The children enrolled in the second phase were the basis for our screening study on T2D.

Each study site (Umeå, Norrtälje, Norrköping, Växjö and Lund/Malmö) invited all school children attending the 6th grade (aged 11–13 years) in the town and the municipalities including the surrounding suburbs and countryside. The geographic locations of the study sites were distributed from northern to southern Sweden. A total of 8284 children were invited to participate in the ETICS study, 5712 (69%) approved to participate in our study and there were marginal differences in participation rate between the study sites (66–70%). (Figure 1, Paper II)

There was an equal distribution of male and female subjects in our population, with a male/female ratio of 1.03, corresponding to that of the general Swedish population. In the year 2009, 29% of children in Sweden were of non-Swedish origin (either born abroad or at least one parent born

abroad)⁹¹. In our study population 24% of the children were of non-Swedish origin according to the same definition. The general population in the study sites had aggregated health parameters (consumption of health related social welfare per capita) and unemployment rates similar to the national population⁹². Our general population study sites could therefore be considered to fairly mirror the health status, socioeconomic context and ethnicity as in the general Swedish population.

The Diabetes Incidence Study in Sweden (DISS)

The specific aim in Paper III was to study the cumulative incidence of ESRD and its association to sex and age onset of T1D. Since it is shown that pre-pubertal onset of T1D may increase time to onset of ESRD compared to onset during puberty, a cohort of subjects with adult (post pubertal) onset T1D patients were required for the completeness of the study design.

The DISS register has prospectively recorded incident cases of diabetes (T1D, T2D and unclassified) in Swedish adults (15–34 years) since 1st January 1983. Clinical criteria are used to determine if the patient has T1D, T2D or unclassified diabetes. During 1983–1991, the WHO criteria were used, and since 1992 the ADA classification criteria were used. A validation study with biological markers for T1D has shown that < 10% of the patients is misclassified (having T2D or unclassified diabetes) in the DISS register⁹³. The coverage of the DISS register has varied between 82–91%, depending on the source of ascertainment⁹⁴ with no significant sex difference.

The Cause of Death Register (CDR)

Mortality data from the CDR was linked to the incidence registers in Paper III and IV. The CDR is maintained by the National Board of Health and provides official statistics on mortality and causes of death in Sweden. The register data is also regularly used for research purposes. The CDR includes all deceased individuals registered as Swedish citizens at the time of death, whether they died domestically or abroad. The CDR contains data from 1961 and is yearly updated. The validity regarding the information on the underlying causes of death has been questioned⁹⁵, but the CDR is considered to be a reliable source for retrieving population data on all-cause mortality.

The Swedish Renal Registry (SRR)

In Paper III, data on ESRD from the Swedish Renal Registry (SRR) was used. The SRR has since 1991 prospectively collected data on all Swedish patients with ESRD who start dialysis treatment or receive a kidney transplant. A validation study in 2004 has shown that >95% of the patients who started treatment for ESRD in Sweden had been reported to the SRR⁹⁶.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

To meet up with the specific aims in Paper IV, data on parental SES and the adult patients own SES was retrieved from the LISA database. The LISA database is maintained by Statistics Sweden and contains individual- as well as household level data. The database integrates existing data from the labor market, educational and social sectors and thus accumulates data on demographics, education, employment and income, including that from salaries and various benefits (e.g. sick leave compensation, unemployment benefits, pensions and social support). Data is updated yearly since 1990 and includes all Swedish citizens 16 years of age and older as of December 31.

Ethical considerations

All studies were approved by the regional research ethics committee in Umeå, according to the Swedish law on research ethics and in line with the principles of the Helsinki Declaration and the European convention on human rights and biomedicine.

The nationwide diabetes incidence registers (SCDR and DISS) were approved by the Swedish Data Inspection Board and the regional research ethics committees (Karolinska Institute, Stockholm and Umeå University, respectively). Parents or patients gave individual informed consent to be registered in the incidence registers.

The study in Paper IV was also approved by the ethics committees at the National Board of Health and Statistics Sweden respectively. Linkage to national register data was performed at Statistics Sweden and only coded data were delivered to the researchers. According to current Swedish regulation, the use of national register data does not require informed consent.

For the study on T2D (Paper II) a separate application concerning this sub-study was approved in addition to the original decision on the main study on screening for celiac disease. Patients /parents had an opportunity to opt out of this separate sub-study.

Methods

The methods are described for each paper. At the end of this chapter a concise description of the statistical methods used in all studies is presented.

Time trend of childhood onset type-1 diabetes (Paper I)

In Paper I the aim was to describe and analyze the current time trend of childhood onset T1D in Sweden by sex, age at-onset and birth cohorts. This study was based on 14721 incident cases of childhood-onset T1D occurring from 1st January 1978 - 31st December 2007, recorded in the SCDR. Patients recorded 1st July 1977 - 31st December 1977 were excluded because it was not a full year's contribution of cases. Incidence data recorded after 31st December 2007 was not yet validated, and therefore not used. Yearly incidence rates were extracted from the SCDR and relevant population data⁹⁷ from Statistics Sweden. Mean annual incidence rates were calculated and described for the whole study population and stratified by sex and age-groups (0–4, 5–9, and 10–14 years).

Generalized additive models

The idea behind generalized additive models (GAMs) is to "plot" the value of the dependent variable along a single independent variable and then to calculate a smooth curve that goes through the data as well as possible. Using linear models for describing time trends of diabetes incidence is possible but not the most favorable, as the relationship between the dependent variables (incidence) and the covariates (e.g. age at-onset) are non linear. The strength of GAMs, compared to linear models, is their ability to deal with non-linear relationships between the response and the set of explanatory variables (covariates)⁹⁸. For that reason, the more flexible generalized additive models (GAM) were used.

GAMs are fitted for the Poisson family of distributions with the log link function. Smoothing terms are allowed in GAMs that permit flexible, nonlinear modeling of selected covariates. In the model, the impact of each calendar year at onset, age-group (0–4, 5–9, and 10–14 years), sex, and interaction terms were tested.

A nonparametric smoothing function for the time trend (year) is used by a penalized regression spline approach, with an automatic smoothness selection in the statistical software. This means that the curve is stepwise fitted in intervals by a limited number of years rather than over the entire

follow up time, and that a penalty term is added to the function to reduce “over fitting” in each limited time interval.

Because the response variable (incidence) is a rate rather than a count, as custom for the Poisson model, we included the population size in the respective age–sex group as an offset for each of the models.

Cohort analyses

We used cohort analysis to study if there were differences in cumulative incidence between different birth cohorts across the investigated time span. To analyze possible trend shifts, we fitted a linear regression curve with the cumulative incidence as a dependent variable and age at-onset as a predictor. The analysis was performed for the entire follow up time by yearly cohorts and grouped by five year periods.

We also investigated and compared two periods by yearly cohorts; the not yet completed birth cohorts 2000-2006 for which a possible decreasing time trend was indicated, and the completed birth cohorts 1978-1987 for which there was a transient decrease in mean incidence between 1985 and 1990. For the study on the early cohorts (1978-1987) the children born in 1978 served as the reference cohort, and the children born in the year 2000 served as the reference cohort for the study on the cohorts born 2000-2006.

Type-2 diabetes in children (Paper II)

Screening for children with increased risk of T2D

In Paper II the aim was to assess the occurrence of undetected T2D in Swedish 10-13 year old, overweight school children. A total of 8284 children were invited and out of them 5712 (69%) approved to participate in our study. All children underwent height and weight measurements and blood sampling in the initial phase of the screening. The parents also responded to a questionnaire including questions on the child’s health. In the questionnaires, 22 (0.38%) were reported to have a diabetes diagnosis prior to the study. Due to the potential uncertainty in this reported information they were not excluded at this stage.

Overweight and obesity was defined by international age-sex specific BMI cut-offs, corresponding to adult BMI cut-offs of 25 and 30 kg/m² respectively at 18 years of age (ISO-BMI \geq 25 and ISO-BMI \geq 30). ISO-BMI \geq 25 in our cohort corresponded to a measured BMI \geq 21.2 kg/m² for boys and \geq 21.7 kg/m² for girls⁹⁹. BMI was missing in 184 (3.2%) of the children who initially agreed to participate, consequently they were excluded from the study.

Screening for undetected T2D

After a repeated informed consent, with an opt-out procedure, hemoglobin A1c (HbA1c) was analyzed in all children with ISO-BMI ≥ 25 . In our study the cut-off point for inclusion was HbA1c $\geq 6.1\%$ (43 mmol/mol) corresponding to DCCT-aligned HbA1c values.

All children with HbA1c equal to or above the cut-off were informed by a pediatrician and at the same time offered additional HbA1c tests. If the second HbA1c also was $\geq 6.1\%$, the investigation continued with an oral glucose tolerance test (OGTT) performed according to WHO/IDF standards. If HbA1c $< 6.1\%$ in the second test, a third blood sample was analyzed. Accordingly, if the 1st and 3rd HbA1c was $\geq 6.1\%$, the study subjects were recommended to undergo an OGTT as above.

We analyzed all the primary HbA1c in our research lab at Umeå University (Afinion instrument, EQUALIS standard). Some of the subsequent tests including the OGTTs were analyzed in other laboratories (EQUALIS standard) at the pediatric clinics in the different study sites.

ESRD in young patients with type-1 diabetes (Paper III)

In Paper III the aim was to study the effects of sex and age at-onset of T1D on the cumulative incidence and long-term risk of ESRD. This study was performed by linking a merger of SCDR (launched in 1977) and the Diabetes Incidence Study in Sweden (DISS – launched in 1983) to the Swedish Renal Registry (SRR – launched in 1991) and the Cause of Death Register (CDR). The study covered cases of ESRD with T1D duration of 13 years or longer during 1991–2007. Patients with 13 years duration (i.e., diabetes onset 1st July 1977 to 31st December 1995 for the SCDR and 1st January 1983 to 31st December 1995 for the DISS) would have equal chance of entering the SRR, starting in 1991.

Mortality dates were obtained by linking the diabetes registers to the CDR. When the specified type of diabetes differed between the diabetes incidence registries and the SRR; the type of diabetes reported to the SRR was used since there the diagnosis is established after a long clinical follow-up.

Assessing the effects of sex and age at-onset of T1D on the cumulative incidence and long-term risk of ESRD

The age at-onset of T1D was divided into three groups, aged 0–9, 10–19, and 20–34. The age groups were chosen to capture the pre-pubertal, pubertal and post-pubertal years respectively.

All included patients had at least 13 years of T1D duration, and they were stratified in groups by numbers of years at risk (duration) in 6 years intervals (13-18, 19-24 and 25-30 years of T1D). Incidence rates of ESRD were calculated as number of cases divided by number of years at risk within each 6-year interval of duration (13–18, 19–24, and 25–30 years).

Survival analysis was used to describe and calculate the cumulative incidence and to estimate the hazard ratio (HR) of developing ESRD within each group. We also analyzed the cumulative incidence when taking into account death as an event that implies a competing risk. Hazard ratios were compared by age at-onset groups and sex, and adjusted for the potential confounding variables age at follow-up and sex. In these analyses, the time at risk was calculated from onset of diabetes until ESRD (i.e., date of first treatment with renal replacement therapy), death, or 31st December 2007.

Basic concepts of competing risks in survival analysis

Survival analysis (the Kaplan-Meier estimator) was used when we estimated the cumulative incidence of ESRD. In our scenario, the T1D patients with at least 13 years of age were followed from onset of T1D until they were diagnosed with ESRD or by 31st December 2007. Those who died were censored in the same way as those censored for other reasons. However, the censoring due to mortality can be considered as informative, since these patients were censored due to the occurrence of an event (death) that was intervening with the possibility to get ESRD.

Given that death eliminates both the possibilities of *acquiring ESRD*, or *not acquiring ESRD*, we also computed the cumulative incidence when taking into account death as a competing risk event. This method is considered to be a more accurate estimate of the risk¹⁰⁰.

Mortality and impact of socioeconomic status (Paper IV)

In Paper IV the aim was to assess if parental and individual socioeconomic status (SES) additionally affects excess mortality in subjects with childhood onset T1D. For the desired analyses the SCDR database was linked to the cause of death register (CDR) for mortality data and the LISA database to obtain data on SES. Linkage was done at Statistics Sweden using the study subjects unique PIN, but the individual data was anonymously retrieved.

The SES measures used in this study were 1) highest completed educational level by the year 2010 and 2) the requirement of income support through the Swedish social welfare system (in Swedish *försörjningsstöd*) for the years 1990-2010. Since we were interested in how SES during childhood and how

SES in the adult T1D patient affects mortality, data was retrieved for both the parents and the patients. From the CDR we retrieved data on all-cause mortality only, avoiding the validity problems that may occur due to misclassification when analyzing cause-specific mortality rates.

Definition of the SES measures

The Swedish educational system has 9 years of compulsory schooling followed by 3 years of voluntary high school. After high school, graduates can proceed to college and university. Low education level was defined as no more than 9 years of school.

In the Swedish social welfare system an income support is provided for those who totally lack financial resources of their own and are not entitled to unemployment pay/activity grant or sick pay/sickness benefit. Income support is means-tested and granted by the social services after an individual assessment to people over 18 years of age. Low parental income was defined as any family member ever having received income support (any/none) from 1st January 1990 – 31st December 2010.

Assessing the effect of parental and individual SES on mortality

All patients recorded in the SCDR from 1st January 1978-31 December 2007 were followed until death or 31st December 2010. Patients recorded 1st July, 1977 to 31st December 1977 were excluded because it was not a complete year's contribution of cases. Incidence data recorded after 31st December 2007 was not yet validated when the linkage was performed, and therefore not used. The level of missing data for each parental socioeconomic variable was < 6.5% for the whole cohort. However, among the group who died during follow up 10.9% had missing values on income support to parents. Mortality data were recorded as of 31st December 2010. Age and sex standardized mortality ratio (SMR) was calculated based on population data from Statistics Sweden.

The cohort was subjected to crude analyses and stratified analyses by sex and age at follow-up groups (0-17, 18-24 and \geq 25 years). The age at follow-up groups were chosen to make a distinction in the cohort by the different causes of death that is known to prevail at young age and later on. In this stratification, each subject contributes with different time at risk within the different age at follow-up strata. (Figure 4) Since mortality is higher among men in the general population as well as in ESRD patients, the stratification by sex was also justified in the analysis.

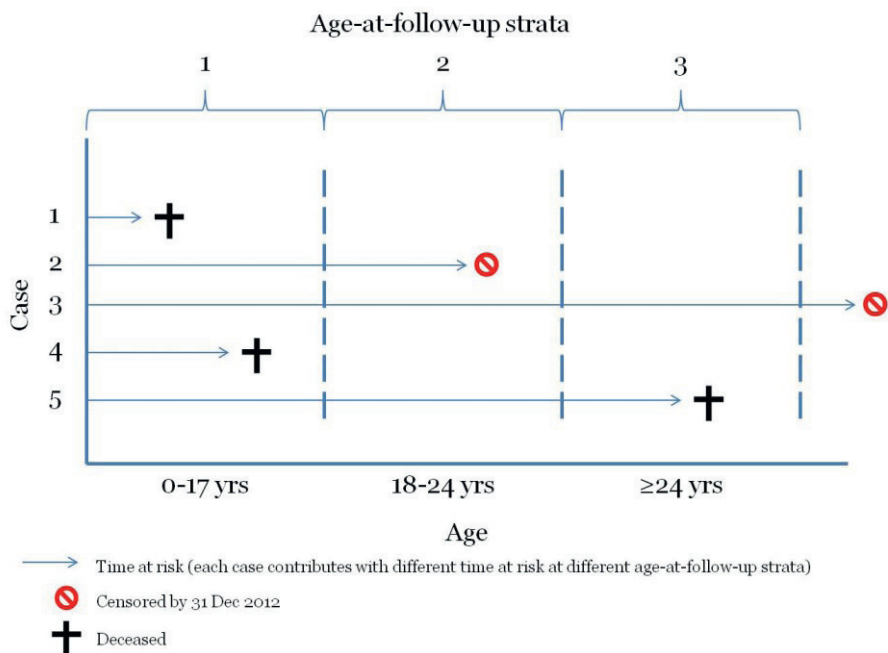


Figure 4. The study design for the survival analysis in Paper IV, schematic presentation of the stratification principles

Time at risk was calculated from date of birth until death or 31st December 2010. Survival analyses were performed to compare the effect of low maternal educational level, low paternal educational level and the effect of parental requirement for income support respectively. Hazard ratios (HR) were used to estimate and describe the impact of the socioeconomic variables in a model, and to adjust for the potential confounding variables age at-onset and sex. For those who died ≥ 18 years of age, the patient's own low economic resources (i.e. requirement of income support) was included in the model as a potential independent risk factor.

Statistical analysis

SPSS for Windows 18.0-20.0 (SPSS Inc, Chicago, IL, USA) and the statistical software “R” (R-foundation for statistical computing, version 2.5.1 and 2.10.1, <http://www.R-project.org/>) were used for the statistical analyses reported in this thesis. The analysis of the GAM in Paper I was performed in “R” with the functions “gam.” and “anova.gam” from the package “mgcv.”

The Student’s t-test was used to test differences in slopes between the different birth cohorts in Paper I.

When comparing continuous variables between groups as described in Paper II, the Mann-Whitney test was used since the tested variables (BMI and HbA1C) were not normally distributed in the population.

In the studies described in Paper III and IV, Kaplan-Meier with log rank tests and Cox-regression analyses were used for describing and analyzing cumulative incidence of ESDR, mortality and to estimate hazard ratios for related factors.

In Paper III, for the calculations of cumulative incidence with death as a competing risk event, the “R” statistical software was used with function “cuminc” from the “cmprsk” package. A 95% confidence interval (CI) was used in all studies, thus a p -value <0.05 was considered statistically significant.

Major findings

Time trend of childhood onset type-1 diabetes (Paper I)

In Paper I the aim was to describe and analyze the current time trend of childhood onset T1D by sex, age at-onset and birth cohorts. A total of 14721 children (7769 boys and 6952 girls) from the SCDR were included in this study. Stratified by three age at-onset groups (0–4, 5–9, and 10–14 years), the mean age-specific annual incidence rates over the full observation period were 20.5, 33.9, and 37.6/100000 respectively. When studying the incidence in 3-year periods for the whole cohort it was evident that T1D incidence has continued to increase in Sweden. The increase in incidence rate was highest between the periods 1999–2001 and 2002–2004, while the increase seems to level off during 2005–2007 (Table 2).

Time period	Mean incidence	
1978-1980	21.6	(18.4 – 24.0)
1981-1983	25.8	(21.1 – 29.1)
1984-1986	26.2	(23.1 – 28.0)
1987-1989	25.6	(22.7 – 29.6)
1990-1992	26.9	(24.0 – 30.6)
1993-1995	29.9	(28.5 – 32.1)
1996-1998	32.7	(29.4 – 35.2)
1999-2001	35.4	(32.3 – 41.8)
2002-2004	42.5	(39.4 – 44.9)
2005-2007	43.9	(37.6 – 48.1)

Table 2. Rates of T1D in Sweden 1978–2007: mean incidence per 100,000 children /year by 3-year periods (CI).

Describing the time-trend

We used a generalized additive model (GAM) to describe and analyze the time trend for the whole cohort. This method allowed us to compute a smooth curve, with a high “goodness-of-fit”, running through the data accurately and visualizing the time trend in a comprehensive manner. In the GAM, the impact of each year (calendar year at-onset), age (age at-onset group), sex, and interaction terms were tested. The best fit model explained 91% of the variation over time and contained year + age + sex, and the

interaction terms year*age and age*sex (Table 2 in Paper I, model 7). The curve based on that model, however, "wiggled" significantly and rather displayed the recorded cases for each year than a clear trend.

A model containing year + age + sex was sufficient for explaining 71% of the variation over time (Table 2, Paper I, model 4). With that model the time trend was described with a smooth curve showing that two periods of decreasing incidence was evident, 1986-1990 and around 2003-2007. We could also see that the incidence was doubled 1978-2007. (Figure 6)

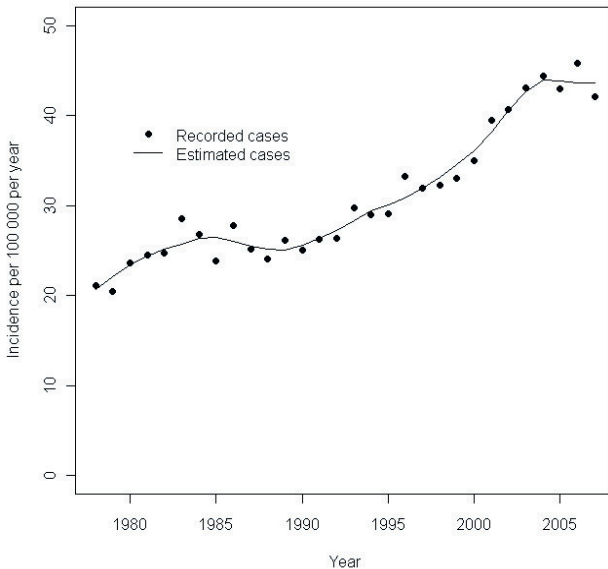


Figure 6. Incidence of childhood onset T1D (0-14.9 years) by calendar-year. Observed and estimated data. GAM; model : Year+Age+Sex ($R^2=0.71$)

Analyzing the cumulative incidence

To analyze the cumulative incidence by birth cohorts we fitted a linear regression curve with the cumulative incidence as a dependent variable and age at-onset as a predictor.

We studied birth cohorts by 5 calendar-year groups and could see a clear trend towards an increasing cumulative incidence for almost every consecutive birth-year cohort group. This was in accordance with the increasing cumulative incidence and the younger age at-onset that has previously been described in this thesis, reported from Swedish and

international studies. The increasing cumulative incidence with the younger age at-onset of T1D was evident until the birth year cohorts 1998-2002, when a shift to older age at-onset was indicated. That shift was even more pronounced in the children born 2003-2006. (Figure 2a, Paper I)

To analyze the apparent shift in age at-onset, we studied each birth year cohort separately for the years 2000-2006. In that analysis we found a pattern showing successive declining slopes, with each consecutive year having a lower cumulative incidence than the year before, indicating an increasing age at-onset during this time period. (Figure 7) When tested statistically, each year differed significantly from year 2000 ($p=0.01$). A similar analysis of the birth cohorts 1978–1987 showed no clear shift in age at-onset that could explain the transient decrease in mean incidence seen in the years 1985-1990. These data indicated a reversed pattern with a shift to older age at-onset of T1D among those born after the year 2000.

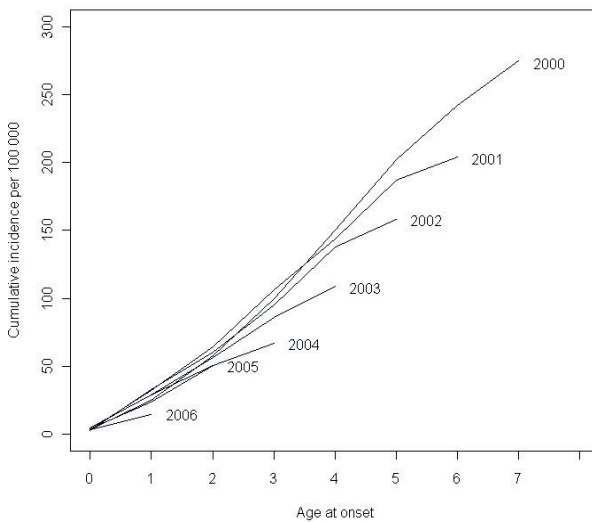


Figure 7. Cumulative incidence of childhood T1D for yearly birth cohorts 2000–2006. Berhan Y. et al, *Diabetes*. (2011) Feb; 60(2):577-81

Type-2 diabetes in children (Paper II)

In paper II the aim was to assess the occurrence of undetected T2D by a screening study in Swedish 10-13 year old school children. The screening procedure was performed in two steps as previously described in the methods section. In the first step 1275 children with overweight or obesity (ISO-BMI ≥ 25) were identified. Among them, 230 (18%) were categorized as obese (ISO-BMI ≥ 30) and 15 (1.2%) as severely obese (ISO-BMI ≥ 35).

In the next step HbA1c was analyzed in 1126 eligible study subjects who were identified with an ISO-BMI ≥ 25 . At this step 146 patients were lost to follow up, and six patients excluded due to a T1D diagnosis. We found no significant differences in sex specific median BMI between the children who completed the study and those who were lost to follow up at this stage. The cut-off for additional testing was HbA1c $\geq 6.1\%$, and we found 24 children with an HbA1c level at or above cut-off.

To eventually establish the diagnosis with OGTT, we required HbA1c $\geq 6.1\%$ on two out of three possible occasions. In the whole cohort of 1126 eligible children only 3 were identified with two HbA1c values at or above the cut-off. These three children were further tested with OGTT according to the study protocol; none of them showed reduced glucose tolerance. No child with undetected T2D was found. An overview of the study design and results is presented below (Figure 8).

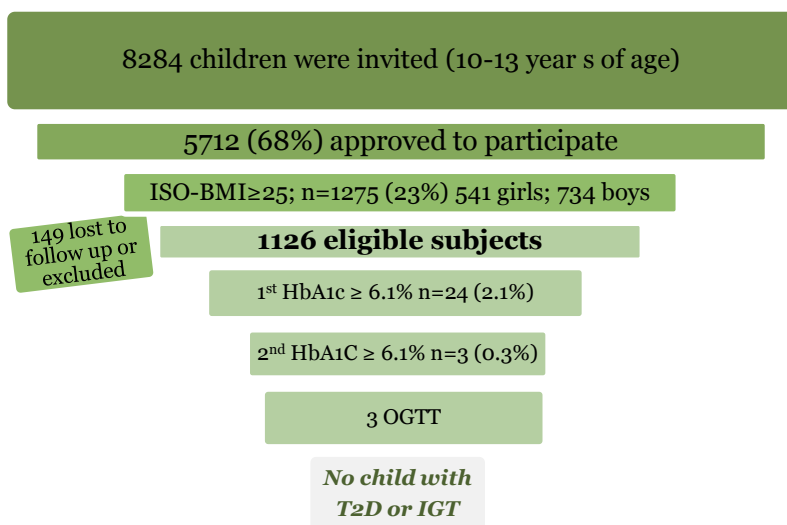


Figure 8. Study design and results in Paper II.

ESRD in young patients with type-1 diabetes (Paper III)

In Paper III the aim was to study the effects of sex and age at-onset of T1D on the cumulative incidence and long-term risk of ESRD. The study consisted of 6789 patients with childhood onset T1D recorded in the SCDR and 4892 patients with adult onset T1D recorded in the DISS. In total, 127 patients (81 men; 46 women) had developed ESRD due to T1D. The cumulative incidence of ESRD was 3.3% at 30 years of duration (men 4.1%; women 2.4%). (Table 4, Paper IV)

We analyzed the cumulative incidence of ESRD stratified by sex in three groups with onset of T1D in different ages (0-9, 10-19 and 20-34). In these analysis we found that male subjects who were aged 20–34 years when diagnosed with T1D had twice as high risk of ESRD (HR=2.3; CI 1.0-5.3) as female subjects at duration of T1D ≥ 20 years. (Figure 9) Those with T1D debut at 0-9 years had the lowest risk of developing ESRD, and there was no difference between men and woman with T1D onset before the age of 20 years.

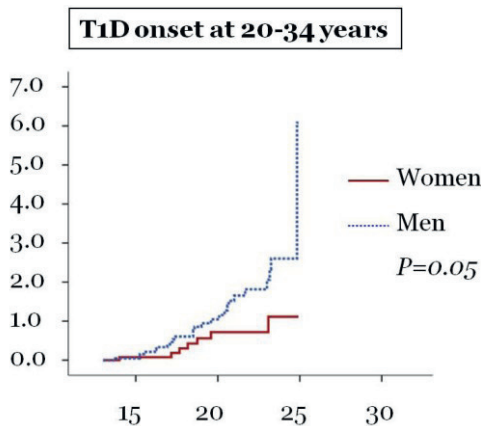


Figure 9. Cumulative incidence of ESRD in T1D patients with onset at 20-34 years, stratified by sex. (Möllsten A et al, *Diabetes*. (2010) Jul; 59(7):1803-8

We also analyzed the cumulative incidence of ESRD stratified by the three T1D age at-onset groups in men and women respectively. Among male patients, the risk of developing ESRD was significantly increased in those who acquired T1D at 20–34 years of age (HR 3.0 [CI 1.5–5.7]) as well as at

10–19 years of age (HR 2.6 [CI 1.5– 4.7]), compared with the youngest age at-onset group (0–9 years). In woman, there was no difference in the risk of developing ESRD among those who acquired T1D at ages 20–34 years compared with the youngest age group with onset of T1D before 10 years of age, (HR 1.4 [CI 0.5–3.6]). (Figure 10) The highest risk for ESRD in women was observed among those diagnosed with T1D at 10–19 years (HR 2.8 [CI 1.4–5.5]).

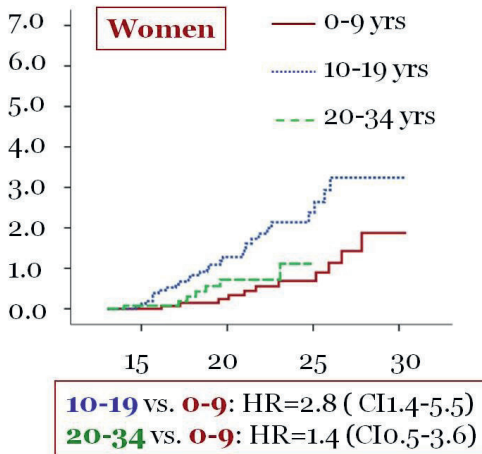


Figure 10. Cumulative incidence of ESRD in women, stratified by age at-onset of T1D. Möllsten A et al, *Diabetes*. (2010) Jul; 59(7):1803-8

Mortality and impact of socioeconomic status (Paper IV)

In Paper IV we wanted to assess if- and how parental and individual SES affects mortality in subjects with childhood onset T1D. Since the patient's own SES in adulthood may affect the outcome, this was also taken into consideration. For this purpose, we linked the SCDR to LISA for information on SES measures and the CDR for mortality data.

The study included 14409 patients with childhood onset T1D. A total of 238 deaths (male/female; 154/84) occurred in a total of 354567 person-years at risk. The overall SMR up to the age of 48 years was 2.3 (CI 1.35 – 3.63).

In crude analysis on how the SES measures affected mortality, we found that low maternal education increased mortality for male T1D cases (HR 1.43 [CI 1.01 – 2.04]; $p=0.048$), but not significantly for female cases (HR 1.21 [CI

0.722-2.018]; $p=0.472$). The father’s educational level had no significant effect on mortality in either men or women. Parental income support (any/none to any of the parents during follow up) was associated with an increased risk of death in both male and female subjects with childhood onset T1D (HR 1.89 [CI 1.36 – 2.64, $p<0.001$] and HR 2.30 [CI 1.43 – 3.67, $p=0.001$] respectively).

We stratified the cohort in age at follow-up groups (0-17, 18-24 and ≥ 25 years) to assess how paternal SES affects mortality in different ages at death. Cox model including maternal education level together with parental income support, adjusting for age at-onset and sex, showed that having parents who required income support predicted mortality in the two oldest age at death groups (HR 3.16, [CI 1.87-5.32], $p<0.001$ and HR 1.93 [CI 1.31-2.83], $p=0.001$). We found no significant impact of parental SES among those who died at 0-17 years of age. (Table 2) Among the T1D patients who died after the age of 25 years, their own need of income support was a stronger predictor for mortality than their parental SES. (Table 4, Paper IV)

	Age at death					
	0-17 yrs		18-24 yrs		≥ 25 yrs	
	HR	(CI)	HR	(CI)	HR	(CI)
Male sex	1.61	(0.86-3.02)	1.61	(0.94-2.74)	1.96	(1.30-2.94)
Low age at onset	0.68	(0.46-1.01)	0.96	(0.67-1.38)	0.89	(0.64-1.24)
Low maternal education	1.61	(0.78-3.30)	1.09	(0.60-2.0)	1.26	(0.84-1.88)
Parental income support	1.01	(0.53-1.93)	3.16	(1.87-5.32)	1.93	(1.31-2.83)

Table 3. Effect of parental socioeconomic resources on mortality. Cox model, adjusted for age at-onset and sex; stratified by age at death/follow up groups.

Discussion of major findings

The overall aim of this thesis was to increase knowledge regarding the occurrence of childhood onset T1D and T2D; and in relation to that describe and elucidate important aspects on two grave complications to diabetes, ESRD and mortality. In this section I discuss the major findings for each paper followed by discussion on strengths and limitations of the studies.

Time trend of childhood onset type-1 diabetes (Paper I)

T1D incidence among Swedish children is higher than ever

In Paper I, the specific aims were to describe and analyze the current time trend of childhood onset T1D in Sweden by sex, age at-onset and birth cohorts. In that study it was shown that the incidence in Sweden has more than doubled since registration started in 1977 until 2007, from 20-46/100000 children per year. In a systematic literature review from 1999¹⁰¹, the authors made rather gloomy forecasts and predicted that the incidence would be 32.2/100000 per year in Sweden by the year 2010. Unfortunately, they were wrong. The increase over the past decades has also been confirmed in a large number of studies covering many parts of the world.

An accelerating increase of T1D in the light of childhood obesity

Simultaneously with the accelerating incidence of childhood T1D, also childhood obesity has increased worldwide. A twofold increase in the prevalence of overweight and a fourfold increase in obesity among Swedish 10-years old school children was reported between the years 1984 and 2000³⁹.

Ecological studies have pointed at life style factors as driving forces for the rapid changes in T1D in children, with a positive association between risk and estimates of national prosperity (such as low infant mortality and high gross national product¹⁰² and meat consumption¹⁰³). Ecological studies may only generate hypotheses on causality and may clearly be misleading unless they are confirmed by individual-based studies. In the case of childhood diabetes, population-based case-control studies confirm that high calorie intake^{104, 105} as well as rapid growth and weight development during infancy are risk markers for childhood onset diabetes^{24, 106-108}. In the light of the “overload hypotheses” and “accelerator hypothesis” (as described in the introduction), the same life style factors that drive the increasing prevalence

of childhood obesity may well be explanatory in finding the factor(s) behind the accelerating incidence of T1D during the past decade.

A shift to younger age at-onset due to life style factors?

In most countries the increasing incidence of childhood onset T1D has been highest among the youngest children^{9, 10}. In Paper I, when studying the cumulative incidence by birth cohorts, we found an increasing cumulative incidence with a younger age at-onset until around the year 2000.

The shift to younger age at-onset and the accelerating increase of T1D coincided with the increasing prevalence of obesity among Swedish children, as previously mentioned. A number of reports preceding ours have described a stable or even decreasing incidence rate in young adults during the same period¹⁰⁹⁻¹¹¹. These findings have also been confirmed by a recent Swedish study that reported a clear shift to younger age at onset rather than a uniform increase in incidence rates across all age-groups¹¹². The main drive behind the increasing T1D incidence among children may thus be explained by a regrouping between ages, with environmental factors leading to an earlier onset, rather than actual increase in the entire population.

Given that that the life styles factors that are causing childhood obesity also may be the same accelerating risk factors explaining the increasing T1D incidence, it's possible that these same factors may also explain the younger age at-onset in T1D^{21, 113}.

A reversed trend

In the years 2000-2007, our study found an apparent leveling off in the increasing incidence, and that was illustrated for the whole cohort in the curve fitted by a GAM. (Figure 6, results) In our analysis on the birth cohorts during this period, we found a shift with a reversed trend towards an increasing age at-onset. This indicated that the increasing incidence among the youngest children is slowing down. Although it was too early to appreciate a decreasing cumulative incidence, due the incomplete birth cohorts of the children born 2000-2007, these data at least indicated a reversed pattern with a shift to older age at-onset of T1D among those born after the year 2000.

A reversed trend due to life style changes?

The possible role of obesogenic life style factors behind the shift to *younger* age at-onset and the accelerating incidence of T1D were discussed above. During the past decade, however, efforts have been made to decrease child obesity in Sweden through preventive health care programs. This has been carried out at child health care centers and at schools by national guidelines from the Swedish National Institute of Public Health¹¹⁴. Studies after the implementation of these guidelines have shown a declining prevalence of

overweight and obesity among 4-years old Swedish children¹¹⁵. Although the association could not be studied, the possible reduction of these obesogenic life style factors was parallel with our finding that the accelerating incidence of T1D among the youngest age groups (0-4 years) is slowing down.

While the increasing incidence of T1D may have leveled-off in Sweden, rates of newly diagnosed T1D have continued to rise in other European countries^{116, 10}. A large study on childhood onset T1D in Finland (also using GAMs for describing the time trend) showed an ongoing accelerating time trend by the year 2005, with the largest increase among the youngest children (0-4 years). In a recent study, however, the same group reported that the incidence in Finnish children younger than 15 years had ceased to increase in the years 2006-2011¹¹⁷. The authors could not draw a parallel to decreasing childhood obesity in Finland as we did in Sweden. The Finnish authors rather speculated that fortification of dairy products with vitamin D after 2003 may have contributed to the leveling off of T1D incidence. A

To the best of my knowledge, apart from the study mentioned above, no other study has followed up or confirmed a declining incidence of obesity among the youngest Swedes. Considering that the current findings in Finland had no parallel to decreasing childhood obesity, the risk factors within the concept of “acceleration” or “overload”, and their possible association to the findings in our study on T1D incidence, should therefore be considered as one possible contributory factor among many. It is yet to be seen if the seemingly declining cumulative incidence of childhood onset T1D in Sweden and Finland is of a transient nature.

Type-2 diabetes in children (Paper II)

Should we worry about T2D in Swedish children?

Although there may be a declining prevalence in obesity among 0-4 year old children as discussed above, childhood obesity is with no doubt an established public health problem in Sweden. The specific aim with the study in Paper II was to assess the occurrence of undetected T2D in a population-based screening study on overweight and obese Swedish 10-13 year old school children.

Given the public health challenge of childhood overweight and obesity and the likely parallel increase in T2D globally, the rationale of this study was strong. In children it may be difficult to always be certain it is T2D. Although T2D is characterized by a silent onset, with many years between onset and clinical presentation, children with T2D can also have a rather abrupt presentation of the disease (resembling T1D). In some populations

approximately 5% of patients with type 2 diabetes have DKA at the time of diagnosis¹¹⁸. In addition to that children with *T1D* can be overweight. Therefore the population-based approach, in contrast to the more frequent clinical-based studies, was a good choice.

We expected to find few, and we actually found none with undetected T2D. Hence it was a “negative” but encouraging result. The prevalence of T2D in Swedish children is probably very low, but certainly not zero. A very large population of children is most likely needed in order to find a stable estimate of the prevalence. A reason to our results could be that the enrolled children were too few and were only 11-13 years old, many of them still pre-adolescents. Furthermore, of the 5712 enrolled children, 1275 were categorized as overweight and only 230 were categorized as obese (ISO-BMI \geq 30). Increasing age and BMI has several times been reported to increase the risk of developing T2D ¹¹⁹⁻¹²². Hence our population may have been too young, and consist of too few obese children to find undetected cases of T2D. But since the proportion of overweight and obese children in our cohort corresponded well to previous prevalence estimations in Sweden, our result should be regarded as meaningful. My conclusion is that we do not have to be anxious for undetected T2D among Swedish children in the pre pubertal ages. This study confirms that the prevalence of T2D in Swedish children is low.

Should we worry about T2D in Swedish adolescents?

A recent Swedish/German study on impaired fasting glycemia (IFG, referred to as “pre-T2D”) among obese children and adolescents reported that an increased degree of obesity and increasing age was associated with a higher risk for developing IFG (the highest risk for IFG was shown to be in the age of 13–15.9 years compared with children under 9 years)¹²³.

In the same study it was also shown that obese Swedish children and adolescents had more than three times higher risk to develop the pre-diabetic stage, IFG, than children in Germany. Although the cause for this large difference between two similar European countries is unknown, the authors speculated that a difference in early dietary patterns, physical activity, levels of vitamin-D or viral infections could be linked to the difference in IFG between the studied populations.

Recalling that the incidence of *T1D* is more than two times higher in Sweden than in Germany (Figure 1) and that similar risk factors may explain the high incidence of T1D in Sweden as well as the higher risk for IFG in obese children; it’s not farfetched to (again) consider the concept of the “acceleration” as an attractive way to partly explain both the increasing time trend of T1D in Sweden, and the finding that Swedish adolescents have an

increased risk for IFG. Perhaps Sweden, along with Finland, has unfavorable socio-environmental risk factors that in some respect differ from the other European countries?

We did not find any *children* with T2D or IFG in our study. But knowing that increasing age and BMI also increase the risk of developing IFG in Swedish children, and accounting for the indications that specific socio-environmental risk factors for diabetes may exist in Sweden; my conclusion is that we need to be vigilant regarding emerging T2D among obese adolescents, and that population-based studies on T2D in Swedish adolescents are highly desirable.

ESRD in young patients with type-1 diabetes (Paper III)

The aims of the study in Paper III were to estimate and describe the cumulative risk of developing ESRD, due to T1D, in a large nationwide population-based prospective cohort. Given that 1) the rapidly increasing incidence of childhood onset T1D will most likely result in an increasing number of young individuals with ESRD and 2) a clear trend to younger age at-onset of T1D has been evident and 3) the pre-pubertal onset of T1D seems to lengthen time to ESRD compared to onset at puberty and 4) men are at higher risk for ESRD due to T1D than women; the specific aims were to study the effects of sex and age at-onset of T1D on the cumulative incidence and long-term risk of ESRD after 30 years with intensive insulin treatment.

Diabetic nephropathy, “then and now”

As mentioned in the introduction, an early epidemiological study from Denmark (1983) reported that the cumulative incidence of diabetic nephropathy (DN, a precursor to ESRD) was 41% after 40 years of T1D duration⁵⁸. In that same study, the highest prevalence of diabetic nephropathy was 21% after 20-25 years of T1D duration, followed by a decline to 10% after 40 years. Men were at significantly higher risk of developing DN. The prognosis for these patients was poor, within 7 years of the onset of persistent proteinuria, 49% had died. Compared to the patients in the Danish study, T1D patients today are under improved medical treatment. Today we have better means to monitor microalbuminuria and use an aggressive treatment of hypertension with reno-protective drugs. Coupled with the intensive treatment of T1D that has been implemented over the past decades, the rationale for our study was strong.

The age and sex specific differences

In Paper III we reported that the cumulative incidence of ESRD in Swedish T1D patients was 3.3% at 30 years of diabetes duration. An earlier but comparable Finnish study from 2005 reported that the cumulative incidence of ESRD was 7.8% after 30 years of T1D duration⁶¹. Thus, in our study the cumulative incidence was found to be substantially lower than in Finland.

One explanation to this discrepancy could have been that the oldest patients in our cohort had onset of T1D in 1977, while the Finnish cohort had included T1D patients with onset starting from 1965. In our study we presumed that all included patients had been treated according to modern regimens, both for metabolic control and renal protection. Regarding the discrepancy between Sweden and Finland, we hypothesized that early inferior treatment regimens may have had a negative effect on the Finnish patients with T1D onset from 1965. A birth cohort effect was seen among the Finnish patients, with a declining cumulative incidence of ESRD over time (1965-1999) that could not be found in our study. And this disparity supported our hypothesis.

Our study also showed that those with T1D onset before puberty (0-9 years) had the lowest risk of developing ESRD, and that there was no difference in ESRD risk between men and woman with T1D onset before the age of 20 years. Similar findings had previously been described in several studies^{61, 66, 68}.⁶⁸ In Paper III, we speculated that the reasons for this age at-onset effect could be genetic, endocrine, or health care related (i.e. that children and families who become used to insulin treatment at an early age might adhere better to treatment and diet than those that are diagnose with diabetes at an older age-especially during puberty).

Among those with T1D onset at 20–34 years of age we found a difference between the sexes, although borderline significant, with a higher risk of developing ESRD in men than in women. In accordance with our findings in the youngest age at-onset group, a current Finnish study over 40 years of T1D duration reported no sex-related differences in cumulative incidence of ESRD in patients diagnosed with T1D between 0-9 years. In that same Finnish study, however, the risk started to diverge earlier than in ours, and showed that the sex difference in cumulative incidence of ESRD occurred in patients with T1D onset at as early as 10 years; with a significantly higher in risk in men than in women.

Our study reported cumulative incidence over no more than 30 years of diabetes, while in the Finnish study the sex related differences in the T1D patients with younger age at-onset did not become significant until 40 years

of diabetes duration. It should be noted, however, that at 30 years of T1D duration we could see a tendency of diverging cumulative incidence between men and women with T1D onset at 10-19 years of age, (Figure 1, Paper III), and at 40 years of duration this difference may be significant also in Sweden.

The age at-onset specific difference between men and women

We found a striking sex difference in cumulative incidence of ESRD when we analyzed the age at-onset effects in men and in women respectively. Since we found the lowest risk for ESRD among those with T1D onset at 0-9 years, this group served as a base line. While men had a significantly increased risk of developing ESRD among those who acquired T1D at 20-34 years of age *as well as* at 10-19 years of age, the higher risk for ESRD in women was observed among those diagnosed with T1D at 10-19 years only. (Figure 10, results) The reason(s) to this age at-onset specific difference between men and women is unknown. But again genetic, endocrine or health care related reasons were suggested as potential explanatory factors. Especially the role of sex hormones was highlighted in our discussion.

In addition to this, I would also like to underscore the possible role of health care related reasons, such as health-care seeking behavior or adherence to medical advice that may differ between men and women. Another possible explanation may be the intensive monitoring and support to optimize metabolic control that women with T1D in Sweden are offered during pregnancy. Although it may be argued that pregnancy constitutes an increased risk of renal failure in T1D patients^{124, 125}, controversy exists regarding the effect of pregnancy on the development and course of diabetic nephropathy^{126, 127}. In a study that included women with T1D and normal renal function or mild DN in the conception, no adverse effect of pregnancy on initiation as well as on the progression of DN was reported. And the authors concluded that good glycaemic control may have contributed to their results¹²⁷.

It would certainly be interesting to challenge my hypothesis in the future, and it is fairly achievable with the information that is accessible through the incidence registers and databases that were previously described in this thesis.

Our results together with the findings in the recent Finnish study suggest that the difference between the sexes as regards to long-term risk of developing ESRD is dependent on the age at onset of T1D. We have also shown that pre-pubertal age at onset of diabetes seems to protect against ESRD development, and the same may be true for post-pubertal onset in female subjects. The onset of ESRD due to T1D at least has been delayed and that the outlook certainly has improved since the 1980s.

Mortality and impact of socioeconomic status (Paper IV)

In Paper IV, we analyzed the possible impact of parental socioeconomic status (SES) on all cause mortality adjusted for age at onset and sex in within the SCDR cohort. Since the patient's own socioeconomic status in adulthood may affect time to death, this was also taken into consideration.

Socioeconomic status and mortality

Socioeconomic inequalities in overall and cause-specific mortality have previously been reported from several western European countries including Sweden^{128, 129}. Low SES has been shown to associate with a higher mortality with various SES measures used (e.g. occupation, educational level, income or a combination of these factors)¹³⁰.

In view of *parental* SES, numbers of reports have shown that individuals with lower SES during childhood have increased morbidity and all-cause mortality in all ages⁸¹⁻⁸⁵. Furthermore, parental SES, mirrored by parental educational level and economic resources, is shown to affect disease care and metabolic control in the diabetic child^{86, 87}. To the best of my knowledge, no other studies have assessed the impact of *parental* SES on mortality in patients with T1D. Accordingly, the rationale for our study was strong.

The Swedish health care system is supposed to be equal and accessible for all children with T1D, regardless of parental SES. Children with T1D are cared for in pediatric clinics with high coherence to national guidelines, and the outcome is monitored by a national quality register today including 100% of the pediatric clinics. This monitoring and regimentation in Swedish pediatric diabetes care offers a good opportunity to evaluate the specific effects of social and economical adversity in childhood.

Impact of parental SES on mortality

Despite a well-developed health care system in Sweden, we found that overall mortality up to the age of 48 years is doubled in both men and women with childhood onset T1D. These results were unsatisfactory, but in accordance with previous Swedish studies and reports from other comparable countries^{71, 73, 74, 76}

In stratified analysis, adjusted for sex and duration of T1D (age at-onset); we found that low parental SES, mirrored by low income, additionally increases mortality in patients with childhood onset T1D. When we stratified our cohort by age at death groups, however, we found a striking difference. Low parental SES, mirrored by parental need of income support, appeared to increase mortality in those who died after 18 years of age only; while none of

our SES measured seemed to predict mortality in those who died at young age (0-18 years).

A couple of large population-based studies from the Nordic countries have recently reported and underlined the important association between low parental SES (mirrored by low educational level) and increased all-cause mortality among children and adolescents in the general population^{131, 132}. In these studies the negative effect of low parental education was strong even in the youngest age groups. In light of the studies mentioned above, our results were a bit surprising.

Why did we find different mortality risk in different ages at death?

None of our SES measures seemed to predict mortality in the ages 0-17 years, which might be explained by low power. The number of deaths increases with age hence the youngest age group had fewer events than the older (Table 1, Paper IV). On the other hand, the effect of low maternal education was not even border line significant in the youngest age at-death group (HR 1.61 [CI 0.78-3.30]) and as regards to low parental income, there was not even a tendency (HR 1.01 [CI 0.53-1.93]).

There could, however, be a true age specific difference in impact of parental SES on mortality in our cohort. Compared to the general population, and adult diabetic patients, the pediatric diabetes patients (up to 18 years of age) are normally seen at least every 3-4 months by a pediatrician and a specialized nurse, and there is normally a high alertness if compliance is insufficient among families with diabetic children. In addition to this, health care providers are required by law to inform the Social Services if they fear that the family is neglecting the child's needs. Furthermore, families applying for income support have to establish contact with the Social Services where the means testing is done. A hypothesis may be that Swedish standards of pediatric diabetes care, together with the mandatory engagement of Social Services when child neglect is suspected by health care providers or a family applies for income support, to some extent could be protective for the diabetic patient younger than 18 year of age living in families with low SES in Sweden.

In conclusion, we have shown that having parents with low SES is associated to additional excess mortality among young adults with childhood onset T1D in Sweden, but this effect could not be seen in those who died before 18 years of age. These findings are important and show that we need more research that focuses on how socioeconomic health inequalities in children and young adults can be explained and tackled in Sweden.

Strengths and limitations of the studies

A major strength in the studies on T1D is that we used nationwide registers (SCDR and DISS) that has prospectively recorded incident cases T1D over a long time and with a high level of coverage. Especially the SCDR, that covers almost 100% of all childhood onset T1D cases in Sweden since 1978.

In Paper I, we used a flexible model approach (GAM) that increased the accuracy of the statistical analysis of the time trend. A limitation in the cohort-analysis, when we analyzed cumulative incidences in children born after 1993, was that the birth year cohorts were not followed for the full age span. Thus, an unknown number of potential new cases may change the future picture.

In Paper II, to assess prevalence of T2D, the major strengths of the cross-sectional study were its rather large population size and that the prevalence of T2D among children was virtually unknown in Sweden. To perform mass screening in healthy children is expensive, and also a delicate task ethically, thus an additional strength was that we were able to collaborate with an ongoing screening study for another disease. However, it's important to acknowledge that our study could be suffering from selection bias since we studied T2D, associated to overweight. Some of the 10-13 year old children in the risk group may have declined to participate due to the possible stigma a T2D diagnosis might imply. Furthermore, the cut-off point of HbA1c at 6.1% could have been too high, especially when it needed to be found on two separate occasions. An additional possible limitation is that the screening method with HbA1c had not been validated for children.

In the study on ESRD (Paper III), apart from the merger of the nationwide T1D incidence registers that also provided patients with adult onset T1D, an additional strength was the high level of ascertainment in the renal register SRR. While the choice of ESRD as marker for DN was robust, a weakness in these registers was that we did not have individual data on possible confounders such as Hb1Ac or smoking habits, two known risk factors for ESRD.

In Paper IV, we used government databases that were linked to the SCDR. Since the whole population is included in these databases they comply no/or limited selection bias. These registers provide SES data on the individual level with a high completeness. A possible limitation in using income support in a dichotomized way as we did may be that it did not distinguish the most extreme cases of poverty with high and longstanding need for income support from those who required income support episodically.

Conclusions

- Childhood onset T1D incidence has accelerated and increased dramatically in Sweden 1977-2007, with a shift to a younger age at onset during first 22 years of incidence registration. From the year 2000 a reversed trend, with an apparent leveling off in acceleration seen among the youngest children. This shift may indicate a change in socio-environmental risk factors affecting especially young children.
- The prevalence of T2D is probably very low among pre-pubertal children in Sweden. Further Screening studies including adolescents are required.
- The onset of ESRD due to T1D has been delayed, and the cumulative incidence may have declined. There is an unexplained difference between the sexes on long-term risk of developing ESRD that is dependent on the age at onset of T1D, and that needs to be further studied.
- Parental SES, mirrored by low parental income, additionally increases excess mortality among young adults with childhood onset T1D. Parental SES does not seem to contribute to additional excess childhood mortality in this group.

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References

1. Poretsky L. Principles of diabetes mellitus. 2nd ed. New York: Springer; 2009.
2. Holt RIG. Textbook of diabetes. 4th ed. Chichester, West Sussex ; Hoboken, NJ: Wiley-Blackwell; 2010.
3. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; **94**: 311-21.
4. IDF. International Diabetes Federation, The Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence. 2011.
5. IDF. International Diabetes Federation, Global Guideline for Type 2 Diabetes. 2012.
6. IDF. International Diabetes Federation, IDF. Diabetes Atlas, 5th edition. Brussels, Belgium; 2011.
7. DIAMOND. DIAMOND project group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabet Med* 2006; **23**: 857-66.
8. Patterson CC, Gyurus E, Rosenbauer J, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. *Diabetologia*; **55**: 2142-7.
9. Dahlquist G, Mustonen L. Analysis of 20 years of prospective registration of childhood onset diabetes time trends and birth cohort effects. Swedish Childhood Diabetes Study Group. *Acta Paediatr* 2000; **89**: 1231-7.
10. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 2009; **373**: 2027-33.
11. Aamodt G, Stene LC, Njolstad PR, Sovik O, Joner G. Spatiotemporal trends and age-period-cohort modeling of the incidence of type 1 diabetes among children aged <15 years in Norway 1973-1982 and 1989-2003. *Diabetes Care* 2007; **30**: 884-9.
12. Eisenbarth GS. Update in type 1 diabetes. *J Clin Endocrinol Metab* 2007; **92**: 2403-7.
13. Notkins AL, Lernmark A. Autoimmune type 1 diabetes: resolved and unresolved issues. *J Clin Invest* 2001; **108**: 1247-52.

14. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. *Diabetes* 2005; **54 Suppl 2**: S125-36.
15. Kumar D, Gemayel NS, Deapen D, et al. North-American twins with IDDM. Genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. *Diabetes* 1993; **42**: 1351-63.
16. Hyöty H. Environmental causes: viral causes. *Endocrinol Metab Clin North Am* 2004; **33**: 27-44, viii.
17. Honeyman M. How robust is the evidence for viruses in the induction of type 1 diabetes? *Curr Opin Immunol* 2005; **17**: 616-23.
18. Gerstein HC, VanderMeulen J. The relationship between cow's milk exposure and type 1 diabetes. *Diabet Med* 1996; **13**: 23-9.
19. Dahlquist G. Viruses and other perinatal exposures as initiating events for beta-cell destruction. *Ann Med* 1997; **29**: 413-7.
20. Dahlquist G, Bennich SS, Kallen B. Intrauterine growth pattern and risk of childhood onset insulin dependent (type I) diabetes: population based case-control study. *BMJ* 1996; **313**: 1174-7.
21. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* 2006; **49**: 20-4.
22. Wilkin TJ. Changing perspectives in diabetes: their impact on its classification. *Diabetologia* 2007; **50**: 1587-92.
23. Eizirik DL, Darville MI. beta-cell apoptosis and defense mechanisms: lessons from type 1 diabetes. *Diabetes* 2001; **50 Suppl 1**: S64-9.
24. Blom L, Persson LA, Dahlquist G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 1992; **35**: 528-33.
25. EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. *Diabetes Care* 2002; **25**: 1755-60.
26. Blom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study. Vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia* 1991; **34**: 176-81.
27. Hägglöf B, Blom L, Dahlquist G, Lonnberg G, Sahlin B. The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood. *Diabetologia* 1991; **34**: 579-83.

28. IDF. Type 2 diabetes in the young. *DIABETES ATLAS*; 2006. p. 193-207.
29. Fazeli Farsani S, van der Aa MP, van der Vorst MM, Knibbe CA, de Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. *Diabetologia* 2013; **56**: 1471-88.
30. Kitagawa T, Owada M, Urakami T, Yamauchi K. Increased incidence of non-insulin dependent diabetes mellitus among Japanese schoolchildren correlates with an increased intake of animal protein and fat. *Clin Pediatr (Phila)* 1998; **37**: 111-5.
31. Urakami T, Kubota S, Nitadori Y, Harada K, Owada M, Kitagawa T. Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. *Diabetes Care* 2005; **28**: 1876-81.
32. Weinstein AR, Sesso HD, Lee IM, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. *Jama* 2004; **292**: 1188-94.
33. Eliasson M, Asplund K, Nasic S, Rodu B. Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. *J Intern Med* 2004; **256**: 101-10.
34. Pinhas-Hamiel O, Zeitler P. "Who is the wise man?--The one who foresees consequences:". Childhood obesity, new associated comorbidity and prevention. *Prev Med* 2000; **31**: 702-5.
35. Wilkin TJ. Diabetes: 1 and 2, or one and the same? Progress with the accelerator hypothesis. *Pediatr Diabetes* 2008; **9**: 23-32.
36. Morrison JA, Glueck CJ, Horn PS, Schreiber GB, Wang P. Pre-teen insulin resistance predicts weight gain, impaired fasting glucose, and type 2 diabetes at age 18-19 y: a 10-y prospective study of black and white girls. *Am J Clin Nutr* 2008; **88**: 778-88.
37. Shaw J. Epidemiology of childhood type 2 diabetes and obesity. *Pediatr Diabetes* 2007; **8 Suppl 9**: 7-15.
38. James WP. The challenge of childhood obesity. *Int J Pediatr Obes* 2006; **1**: 7-10.
39. Marild S, Bondestam M, Bergstrom R, Ehnberg S, Hollsing A, Albertsson-Wikland K. Prevalence trends of obesity and overweight among 10-year-old children in western Sweden and relationship with parental body mass index. *Acta Paediatr* 2004; **93**: 1588-95.
40. Sjoberg A, Lissner L, Albertsson-Wikland K, Marild S. Recent anthropometric trends among Swedish school children: evidence for decreasing prevalence of overweight in girls. *Acta Paediatr* 2008; **97**: 118-23.

41. Thunander M, Petersson C, Jonzon K, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Res Clin Pract* 2008; **82**: 247-55.
42. Zachrisson I. Epidemin av typ 2 diabetes bland barn och ungdomar i Sverige - fiktion eller realitet? *Diabeologinytt* 2003; 2-3.
43. Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992; **15**: 815-9.
44. Spijkerman AM, Dekker JM, Nijpels G, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the hoorn screening study. *Diabetes Care* 2003; **26**: 2604-8.
45. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. *Diabetes Care*.
46. Dart AB, Sellers EA, Martens PJ, Rigatto C, Brownell MD, Dean HJ. High burden of kidney disease in youth-onset type 2 diabetes. *Diabetes Care*; **35**: 1265-71.
47. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**: 977-86.
48. DCCT. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr* 1994; **125**: 177-88.
49. DCCT. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 1995; **47**: 1703-20.
50. UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-53.
51. EDIC. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Jama* 2003; **290**: 2159-67.

52. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**: 580-91.
53. Tuomilehto J, Borch-Johnsen K, Molarius A, et al. Incidence of cardiovascular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia* 1998; **41**: 784-90
54. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1985; **28**: 590-6.
55. SRAU. SRAU report 2000. 2000.
56. Schroijen MA, van de Luitgaarden MW, Noordzij M, et al. Survival in dialysis patients is different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. *Diabetologia* 2013; **56**: 1949-57.
57. Marshall SM, Flyvbjerg A. Prevention and early detection of vascular complications of diabetes. *BMJ* 2006; **333**: 475-80.
58. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in Type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia* 1983; **25**: 496-501.
59. Hovind P, Tarnow L, Rossing K, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. *Diabetes Care* 2003; **26**: 1258-64.
60. Marshall SM. Diabetic nephropathy in type 1 diabetes: has the outlook improved since the 1980s? *Diabetologia* 2012; **55**: 2301-6.
61. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. *Jama* 2005; **294**: 1782-7.
62. Rossing K, Jacobsen P, Pietraszek L, Parving HH. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomized double-blind crossover trial. *Diabetes Care* 2003; **26**: 2268-74.
63. Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med* 2009; **169**: 1307-16.

64. Borch-Johnsen K, Norgaard K, Hommel E, et al. Is diabetic nephropathy an inherited complication? *Kidney Int* 1992; **41**: 719-22.
65. Harjutsalo V, Katoh S, Sarti C, Tajima N, Tuomilehto J. Population-based assessment of familial clustering of diabetic nephropathy in type 1 diabetes. *Diabetes* 2004; **53**: 2449-54.
66. Raile K, Galler A, Hofer S, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. *Diabetes Care* 2007; **30**: 2523-8.
67. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. *Diabetes Care* 2004; **27**: 955-62.
68. Svensson M, Nystrom L, Schon S, Dahlquist G. Age at onset of childhood-onset type 1 diabetes and the development of end-stage renal disease: a nationwide population-based study. *Diabetes Care* 2006; **29**: 538-42.
69. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001; **44 Suppl 2**: S14-21.
70. Secrest AM, Becker DJ, Kelsey SF, LaPorte RE, Orchard TJ. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry. *Diabetes Care* 2010; **33**: 2573-9.
71. Skriverhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia* 2006; **49**: 298-305.
72. Jouglu E, Papoz L, Balkau B, Maguin P, Hatton F. Death certificate coding practices related to diabetes in European countries--the 'EURODIAB Subarea C' Study. *Int J Epidemiol* 1992; **21**: 343-51.
73. Harjutsalo V, Forsblom C, Groop PH. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *BMJ* 2011; **343**: d5364.
74. Dahlquist G, Kallen B. Mortality in childhood-onset type 1 diabetes: a population-based study. *Diabetes Care* 2005; **28**: 2384-7.
75. Waernbaum I, Blohme G, Ostman J, et al. Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. *Diabetologia* 2006; **49**: 653-9.

76. Patterson CC, Dahlquist G, Harjutsalo V, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 2007; **50**: 2439-42.
77. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes* 2010; **59**: 3216-22.
78. Hamman RF. Mortality risk in long-standing type 1 diabetes: hope and concern. *Diabetes* 2010; **59**: 2997-8.
79. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Associations between socioeconomic status and major complications in type 1 diabetes: the Pittsburgh epidemiology of diabetes complication (EDC) Study. *Ann Epidemiol* 2011; **21**: 374-81.
80. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Association of socioeconomic status with mortality in type 1 diabetes: the Pittsburgh epidemiology of diabetes complications study. *Ann Epidemiol* 2011; **21**: 367-73.
81. Turrell G, Lynch JW, Leite C, Raghunathan T, Kaplan GA. Socioeconomic disadvantage in childhood and across the life course and all-cause mortality and physical function in adulthood: evidence from the Alameda County Study. *J Epidemiol Community Health* 2007; **61**: 723-30.
82. Poulton R, Caspi A, Milne BJ, et al. Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. *Lancet* 2002; **360**: 1640-5.
83. Hjern A. Chapter 7: children's and young people's health. *Scand J Public Health Suppl* 2006; **67**: 165-83.
84. Vagero D, Ostberg V. Mortality among children and young persons in Sweden in relation to childhood socioeconomic group. *J Epidemiol Community Health* 1989; **43**: 280-4.
85. Ostberg V. Social class differences in child mortality, Sweden 1981-1986. *J Epidemiol Community Health* 1992; **46**: 480-4.
86. Hassan K, Loar R, Anderson BJ, Heptulla RA. The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus. *J Pediatr* 2006; **149**: 526-31.
87. Araujo MB, Mazza CS. Assessment of risk factors of poor metabolic control in type 1 diabetic children assisted in a public hospital in Argentina. *Pediatr Diabetes* 2008; **9**: 480-7.
88. Dahlquist G, Mustonen L. Childhood onset diabetes--time trends and climatological factors. *Int J Epidemiol* 1994; **23**: 1234-41.

89. Ivarsson A, Myélus A, Norström F, et al. Reduced Prevalence of Childhood Celiac Disease: an effect of changes in infant feeding? . *Under revision* 2012.
90. Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr* 2009; **49**: 170-6.
91. SCB. Antal personer med utländsk eller svensk bakgrund (fin indelning) efter region, ålder i tioårsklasser och kön. År 2002-2012. <http://www.ssd.scb.se/databaser/makro/MainTable.asp?yp=tansss&xu=C9233001&omradekod=BE&omradetext=Befolkning&lang=1> (Accessed May 2010). SCB, STATISTICS SWEDEN.
92. SCB. Statistik med inriktning mot ohälsotalet. Fördelning efter kommun och kön. År 1997-2011. http://www.ssd.scb.se/bjssd/sok_link.asp?sokord1=efter+kommun&xu=c5587001&yp=duwird&lang=1 (Accessed Nov 2011). SCB, STATISTICS SWEDEN.
93. Borg H, Arnqvist HJ, Bjork E, et al. Evaluation of the new ADA and WHO criteria for classification of diabetes mellitus in young adult people (15-34 yrs) in the Diabetes Incidence Study in Sweden (DISS). *Diabetologia* 2003; **46**: 173-81.
94. Ostman J, Lonnberg G, Arnqvist HJ, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. *J Intern Med* 2008; **263**: 386-94.
95. Appelros P, Terent A. Validation of the Swedish inpatient and cause-of-death registers in the context of stroke. *Acta Neurol Scand*; **123**: 289-93.
96. Schon S, Ekberg H, Wikstrom B, Oden A, Ahlmen J. Renal replacement therapy in Sweden. *Scand J Urol Nephrol* 2004; **38**: 332-9.
97. SCB. Swedish Population (in one-year groups) 1860-2008. <http://www.scb.se/Statistik/BE/BE0101/2008A01/Be01010Folkm%c3%a4ngd1860-2008eng.xls> (Accessed 22 Jan, 2010). SCB, STATISTICS SWEDEN.
98. Gusian A. Generalized linear and generalized additive models in studies of species distributions: setting the scene. *Ecological Modelling* 2002: 89-100.
99. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; **320**: 1240-3.

100. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer* 2004; **91**: 1229-35.
101. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. *Diabetologia* 1999; **42**: 1395-403.
102. Patterson CC, Dahlquist G, Soltesz G, Green A. Is childhood-onset type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia* 2001; **44 Suppl 3**: B9-16.
103. Muntoni S. Epidemiological association between some dietary habits and the increasing incidence of type 1 diabetes worldwide. *Ann Nutr Metab* 2006; **50**: 11-9.
104. Dahlquist GG, Blom LG, Persson LA, Sandstrom AI, Wall SG. Dietary factors and the risk of developing insulin dependent diabetes in childhood. *BMJ* 1990; **300**: 1302-6.
105. Pundziute-Lycka A, Persson LA, Cedermark G, et al. Diet, growth, and the risk for type 1 diabetes in childhood: a matched case-referent study. *Diabetes Care* 2004; **27**: 2784-9.
106. Hyponen E, Virtanen SM, Kenward MG, Knip M, Akerblom HK. Obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes Care* 2000; **23**: 1755-60.
107. Patterson C DG, Soltesz G for the EURODIAB substudy 2 study group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. *Diabetes Care* 2002; **25**: 1755-60.
108. Lamb MM, Yin X, Zerbe GO, et al. Height growth velocity, islet autoimmunity and type 1 diabetes development: the Diabetes Autoimmunity Study in the Young. *Diabetologia* 2009; **52**: 2064-71.
109. Pundziute-Lycka A, Dahlquist G, Nystrom L, et al. The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0-34 years group in Sweden 1983-1998. *Diabetologia* 2002; **45**: 783-91.
110. Weets I, De Leeuw IH, Du Caju MV, et al. The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation. *Diabetes Care* 2002; **25**: 840-6.
111. Feltbower RG, McKinney PA, Parslow RC, Stephenson CR, Bodansky HJ. Type 1 diabetes in Yorkshire, UK: time trends in 0-14 and 15-29-year-olds, age at onset and age-period-cohort modelling. *Diabet Med* 2003; **20**: 437-41.

112. Dahlquist GG, Nystrom L, Patterson CC. Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends. *Diabetes Care* 2011; **34**: 1754-9.
113. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* 2001; **44**: 914-22.
114. The Swedish National Institute of Public Health. Eating habits and foods. <http://www.fhi.se/en/About-FHI/Public-health-policy/10-Eating-habits-and-foods/> (accessed 25 Jan, 2010)
115. Bergstrom E, Blomquist HK. Is the prevalence of overweight and obesity declining among 4-year-old Swedish children? *Acta Paediatr* 2009; **98**: 1956-8.
116. Imkampe AK, Gulliford MC. Trends in Type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. *Diabet Med* 2011; **28**: 811-4.
117. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. *Jama*; **310**: 427-8.
118. Sugihara S, Sasaki N, Kohno H. Survey of Current Medical Treatments for Childhood-Onset Type 2 Diabetes Mellitus in Japan. *Clinical Pediatric Endocrinology* 2005; **Vol. 14**: 65-75
119. Type 2 diabetes in children and adolescents. American Diabetes Association. *Diabetes Care* 2000; **23**: 381-9.
120. Aylin P, Williams S, Bottle A. Obesity and type 2 diabetes in children, 1996-7 to 2003-4. *BMJ* 2005; **331**: 1167.
121. Baranowski T, Cooper DM, Harrell J, et al. Presence of diabetes risk factors in a large U.S. eighth-grade cohort. *Diabetes Care* 2006; **29**: 212-7.
122. Colagiuri S, Hussain Z, Zimmet P, Cameron A, Shaw J. Screening for type 2 diabetes and impaired glucose metabolism: the Australian experience. *Diabetes Care* 2004; **27**: 367-71.
123. Hagman E, Reinehr T, Kowalski J, Ekblom A, Marcus C, Holl RW. Impaired fasting glucose prevalence in two nationwide cohorts of obese children and adolescents. *Int J Obes (Lond)* 2013.
124. Biesenbach G, Stoger H, Zazgornik J. Influence of pregnancy on progression of diabetic nephropathy and subsequent requirement of renal replacement therapy in female type I diabetic patients with impaired renal function. *Nephrol Dial Transplant* 1992; **7**: 105-9.
125. Purdy LP, Hantsch CE, Molitch ME, et al. Effect of pregnancy on renal function in patients with moderate-to-severe diabetic renal insufficiency. *Diabetes Care* 1996; **19**: 1067-74.

126. Rossing K, Jacobsen P, Hommel E, et al. Pregnancy and progression of diabetic nephropathy. *Diabetologia* 2002; **45**: 36-41.
127. Young EC, Pires ML, Marques LP, de Oliveira JE, Zajdenverg L. Effects of pregnancy on the onset and progression of diabetic nephropathy and of diabetic nephropathy on pregnancy outcomes. *Diabetes Metab Syndr* 2011; **5**: 137-42.
128. Mackenbach JP, Bos V, Andersen O, et al. Widening socioeconomic inequalities in mortality in six Western European countries. *Int J Epidemiol* 2003; **32**: 830-7.
129. Weires M, Bermejo JL, Sundquist K, Sundquist J, Hemminki K. Socio-economic status and overall and cause-specific mortality in Sweden. *BMC Public Health* 2008; **8**: 340.
130. Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc* 2007; **99**: 1013-23.
131. Gissler M, Rahkonen O, Mortensen L, et al. Sex differences in child and adolescent mortality by parental education in the Nordic countries. *J Epidemiol Community Health* 2010; **66**: 57-63.
132. Remes H, Martikainen P, Valkonen T. Mortality inequalities by parental education among children and young adults in Finland 1990-2004. *J Epidemiol Community Health* 2009; **64**: 136-41.