Physical, psychological and socioeconomic effects of childhood-onset diabetes in Sweden – longitudinal, register-based studies

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Purpose and Aims

The overarching purpose of the suggested research is to investigate the incidence and risk factors as well as long-term complications and consequences of childhood-onset type 1 diabetes (T1D), with an emphasis on understanding the multifactorial aetiology, socioeconomic disparities and gender differences associated with the disease. Through a population-based approach, this research aims to provide evidence for more effective prevention, management, and long-term care strategies for individuals with T1D, while at the same time advancing research methodologies for this and similar chronic conditions. We focus on five main research areas with the following specific aims:

1. Time trends in childhood-onset type 1 diabetes:

- To examine time, age and cohort effects on the incidence of childhood-onset T1D in Sweden.
- To identify environmental and lifestyle-related risk factors contributing to the increasing incidence of T1D.
- To assess the potential impact of early-life exposures, including pre- and perinatal factors and early childhood infections, on the development of islet autoimmunity and T1D.

2. Diabetic nephropathy and end-stage renal disease:

- To investigate the incidence, survival and associated risk factors for diabetic nephropathy and end-stage renal disease (ESRD) among individuals with childhood-onset T1D.
- To explore the impact of diabetes management improvements on the declining incidence of ESRD.
- To evaluate sex-specific differences and the influence of pregnancy on the progression of microvascular complications in women with T1D.

3. Socioeconomic circumstances and health outcomes:

- To examine the impact of familial socioeconomic stress on metabolic control and risk of complications.
- To investigate the long-term health and social outcomes of siblings of individuals with T1D compared to matched controls

4. Health economics and type 1 diabetes:

- To estimate risk-equations for T1D-related complications and outcomes adapted for use in health-economic models for children, young adults and middle-aged people.
- To analyse consequences of T1D onset in a child on socioeconomic and health-related outcomes for parents.

5. Target trial emulation, case-control studies and time-zero implementation:

- To develop statistical methods for cohort and case-control designs for setting of “time zero” in target trial emulation for the purpose of assessing causal structures using T1D and various complications as empiric models.

Survey of the Field

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Time Trends in Childhood-onset Type 1 Diabetes

The aetiology of childhood-onset type 1 diabetes (T1D) is multifactorial, arising from a complex interaction between genetic predisposition and environmental risk factors (1,2). In contrast to other autoimmune diseases, T1D predominantly affects younger populations (3). Between 1978 and 2008, the incidence of T1D among children below 15 years in Sweden more than doubled (4). Consequently, alongside asthma, T1D has become one of the most prevalent chronic diseases among children in Sweden. Similar upward trends in incidence have been documented in numerous other countries (5). Over the past decade, the incidence has remained high but stable (Figure 1) (6).

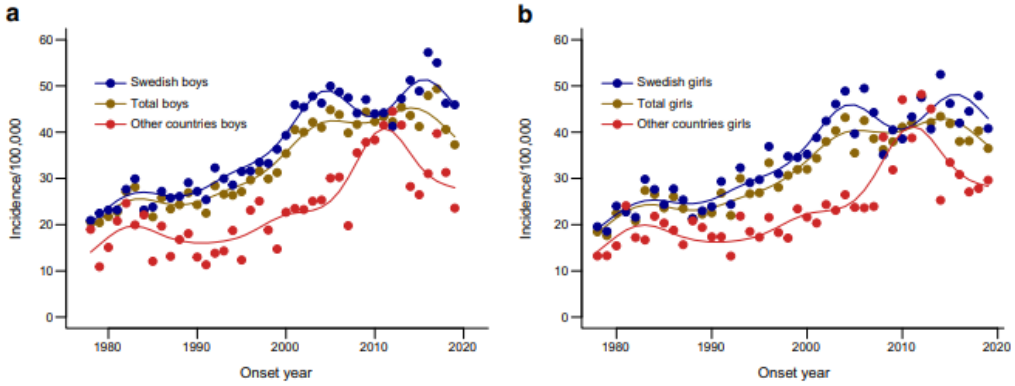

Figure 1: The incidence childhood-onset type 1 diabetes in Swedish, foreign and total population 0-15 years divided on boys (a) and girls (b), dots being incidence and lines being predicted incidence from a general additive model (GAM) for Poisson response (6).

The rapid increase in the incidence of childhood-onset T1D can only be attributed to a rise in non-genetic, lifestyle-related risk factors (7). The peak incidence of autoimmunity against insulin-producing β-cells occurs in the second year of life (8), suggesting that environmental triggers likely operate very early, either in utero or during early childhood. A wide range of environmental risk factors have been investigated (2), with several pre- and perinatal factors consistently associated with T1D risk, including maternal obesity, preterm birth, and postnatal growth (9,10). Infections, particularly viral infections, have also been implicated in T1D pathogenesis (11), although their population-level impact is harder to study due to the frequent lack of diagnosis or aetiological identification of childhood infections. Some prospective studies have found associations between respiratory infections and islet autoimmunity (12), whereas others have not (13). During the COVID-19 pandemic, reports indicated an initial rise in T1D incidence followed by a subsequent decline, a trend less pronounced in younger children (14,15). Preliminary data from Sweden suggest similar patterns, though these observations require confirmation through extended follow-up and analysis. A whole-population study in Denmark (16) found no association between SARS-CoV-2 infection and subsequent T1D risk in children, whereas a preliminary report from Norway described a 60% risk increase (17).

Significance and Scientific Novelty

Given the chronic nature of T1D, its severe long-term complications, and the necessity for life-long healthcare, the disease demands increased attention. Continued surveillance of T1D incidence trends is crucial for generating hypotheses on disease aetiology and providing a foundation for future diabetes care and research planning. To better understand the drivers of changing incidence rates, it is essential to link individual-level microdata to population-based variables that could accelerate the pre-existing autoimmune process of T1D. Such variables may be maternal weight, gestational age and postnatal growth.

Diabetic Nephropathy and End-Stage Renal Disease

Diabetic nephropathy is the most severe long-term complication of T1D, leading to glomerulosclerosis, progressive glomerular dysfunction, and ultimately ESRD. This life-threatening condition necessitates renal replacement therapy (RRT) via dialysis or transplantation. Diabetic nephropathy is also a key contributor to premature mortality in T1D, driving both renal failure and cardiovascular disease risk (18). A meta-analysis demonstrated increased cardiovascular and all-cause mortality in diabetes patients, although mortality risk among those with chronic kidney disease was comparable irrespective of diabetes status (24), which emphasizes the importance of renal disease. Our research group previously reported that T1D accounted for 10% of ESRD cases, later decreasing to 5.6%, potentially reflecting improved diabetes management, hypertension, and dyslipidaemia control (19,20). Finnish data also indicated a declining ESRD incidence, with onset typically 15 years post-T1D diagnosis, peaking at 25 years before plateauing (21). However, it remains unclear whether current interventions genuinely reduce risk or merely delay nephropathy progression.

Epidemiological studies show varying nephropathy incidence across populations (22), disproportionately affecting socioeconomically disadvantaged individuals (23,24). Survival after RRT onset depends on treatment modality and socioeconomic status, highlighting disparities in healthcare access and outcomes (25).

Sex differences in nephropathy risk remain inconsistent. While men appear at higher risk than premenopausal women, postmenopausal women show increased susceptibility. Age at diabetes onset may further influence this risk (26). Among women with T1D, pregnancy outcomes are closely linked to glycaemic control, with poor metabolic control increasing maternal and foetal morbidity and mortality; however, the long-term impact of pregnancy on complications such as nephropathy progression remains understudied, despite that evidence-based guidance could have a significant impact on pregnancy strategies for all T1D women (27).

Significance and Scientific Novelty

Continuous monitoring of ESRD trends concerning socioeconomic factors, comorbidities, and RRT modalities is vital to understanding this serious complication. Exploring pregnancy as a novel risk factor for diabetic nephropathy will enhance knowledge of gender differences in T1D outcomes.

Socioeconomic Circumstances and Health Outcomes

Type 1 diabetes management requires strict adherence to insulin therapy and blood glucose monitoring (28). Socioeconomic stress, particularly in families with low income or parental edu-

cation, has been linked to increased risks of long-term complications, including nephropathy and premature mortality in adulthood (29,30). Socioeconomically disadvantaged children with T1D also exhibit poorer metabolic control (31); however, whether this persists into adulthood remains debated, as systematic reviews report conflicting results (32).

A T1D diagnosis affects the entire family, inducing distress in parents and siblings (33). While siblings develop coping mechanisms, their emotional needs may be underestimated, leading to increased rates of depression and anxiety (34). Previous research has primarily examined the immediate post-diagnosis period, often with small sample sizes and short follow-up durations (35). Our prior findings indicate that brothers of individuals with T1D, but not sisters, have lower annual earnings compared to their peers (36), yet the long-term health consequences for siblings are largely unexplored.

Significance and Scientific Novelty

Understanding T1D in a life course perspective requires examining the relationship between childhood socioeconomic status and long-term glycaemic control. Further research into mortality, hospitalisations, and mental health outcomes among T1D siblings compared to matched controls is essential for comprehensively addressing the broader impacts of T1D on affected families.

Health Economics and Type 1 Diabetes

Health-economic evaluation models in diabetes, typically microsimulations or Markov models (37), rely on risk equations that capture short- and long-term outcomes influenced by interventions such as improved diagnostics and treatment (38–40). These models link health outcomes to costs and patient benefits, aiding healthcare decision-making and guideline optimisation. Traditionally, models for T1D have been based on the American Diabetes Control and Complications Trial (DCCT) (41), and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42), alongside frameworks borrowed from Type 2 Diabetes, despite fundamental differences in aetiology, onset and risk factors.

There is a growing need to refine models for T1D evaluation (39,40), including the integration of risk equations derived from more recent patient cohorts, such as Swedish observational data (40). Existing health-economic models predominantly focus on adult populations and long-term vascular complications, with limited data available on children and adolescents. Additionally, mental health effects (43) and other non-vascular complications remain underrepresented. While international research on T1D complications is expanding, it tends to be clinically focused and lacks straightforward applicability to health-economic models.

Understanding the short- and long-term consequences of T1D across the lifespan is increasingly important due to advances in early risk identification, interventions to reduce incidence (44) (GPPAD-POInT at ClinicalTrials.gov IDNCT03364868), and discussions on newborn screening. In this context, health-economic models will support decision-makers in assessing the value of delaying T1D onset in terms of patient outcomes and cost savings.

Significance and Scientific Novelty

There is a critical need for updated risk estimates of T1D complications that can be integrated into health-economic simulation models. Such models are essential for researchers to assess

new interventions and for organisations that evaluate treatments and diagnostics, including Health-Technology Assessment agencies and the life sciences industry. While existing models primarily address micro- and macrovascular complications that typically arise after age 50, future models should incorporate risk estimates for T1D-related outcomes affecting children, adolescents, and younger adults, as well as the caregiving burden on parents of children with T1D.

Target Trial Emulation, Case-Control Studies and Time-zero Implementation

Observational studies are increasingly designed to emulate randomised controlled trials (RCTs) to strengthen causal inference, a concept known as Target Trial Emulation (TTE) (45). RCTs remain the gold standard for causal effect estimation due to their ability to eliminate confounding and simplify analyses. However, well-structured observational studies can provide valuable insights by incorporating key RCT elements such as eligibility criteria, treatment assignment, randomisation, and clearly defined "time zero" for follow-up. In Hernán et al. (46) four examples are given of failures to emulate a target trial using observational data (Figure 2).

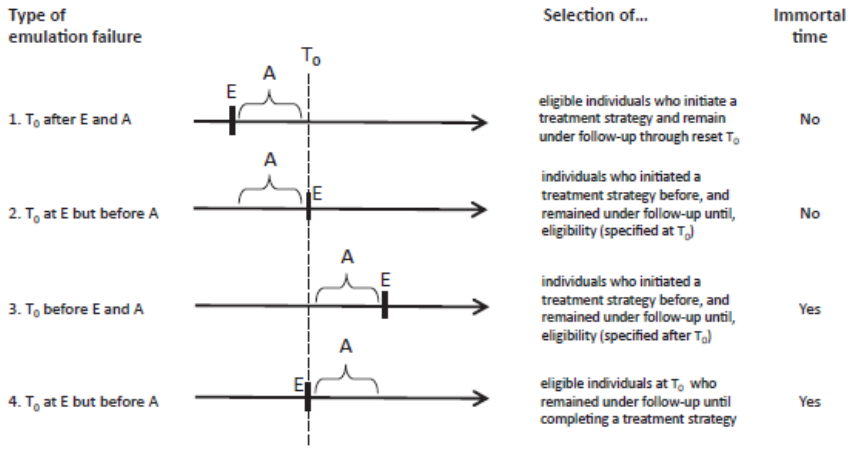

Figure 2. Four examples of failures of emulation of a target trial using observational data. Here, T0, is time zero, E is eligibility, and A is a period under which treatments are assigned (46).

Significance and Scientific Novelty

The significance of TTE continues to grow within epidemiological and statistical research. Advancing this framework necessitates new case-control study designs that can be practically applied by data analysts. Further methodological development is required to refine observational study designs to more closely resemble RCTs.

Preliminary and Previous Results

Time Trends in Childhood-onset Type 1 Diabetes

The research group has followed childhood-onset T1D incidence since the early 1980s (47). More recently, we have considered trends for a levelling off of the incidence (4) and the impact of demographic dynamics on the incidence trends (6). We have also explored various aetiological risk factors, showing among other things that higher birthweight, moderate prematurity and maternal obesity are independent risk factors for T1D (10).

Diabetic Nephropathy and End-Stage Renal Disease

The group has published extensively on various aspects of diabetic nephropathy and ESRD (19,20,29,48,49). Recently, we have investigated the risk of renal failure and death in individuals with parental T1D, i.e., having parents with the same disease, finding slightly higher mean glycated haemoglobin and a higher risk of renal failure. Also, women with parental T1D, but not men had higher risk of premature death (50).

Socioeconomic Circumstances and Health Outcomes

We have researched socioeconomic disparities between individuals with and without T1D both in aetiological and prognostic studies, see (29,30,49,51,52) for some examples. Most recently, we have investigated socioeconomic exposure during childhood and impact on glycaemic control in the individual as an adult. Preliminary data show that HbA1c is higher if the individual lived in household that received income support (effect size 0.45 SD), unemployment benefits (effect size 0.19 SD) or if the parents had less than 12 years of education (effect size 0.46 SD).

Health Economics and Type 1 Diabetes

Research from our group and its collaborators has demonstrated positive trends in T1D complications, including a decline in ESRD incidence (20,49), Additionally, we have explored the socioeconomic consequences of T1D (52,53), developed risk equations for Type 2 Diabetes (54) and validated health-economic models (55). Ongoing work at the Swedish Institute for Health Economics (secondary affiliation of co-applicant Steen-Carlsson) includes the development of a health-economic model for T1D, initially focusing on adults (40) but with plans to incorporate childhood and adolescent risks for a full lifespan perspective. Preliminary data indicate that T1D in children has lasting effects on parental labour-market outcomes, suggesting a need to integrate a family impact module into health-economic models.

Case-Control and Cohort Registers as a Part of Statistical Method Development

Our group has extensive experience in developing statistical methods for observational studies. Since 2009, our team has advanced theoretical frameworks related to causal inference in disease incidence data, see (49,56–59) for some examples. Research has alternated between applied and theoretical studies, with particular focus on the design and methodologies used in the SCDR.

Equipment

The Swedish Childhood Diabetes Register (SCDR) started for research purposes and records virtually all incident cases of childhood-onset T1D (0-14 years) since 1 July 1977 (47). The SCDR includes more than 24 000 cases and for each case there are four controls matched for age and municipality at the time of T1D diagnosis. In 2008, the SCDR was linked to several national registers to create a comprehensive database. These registers include the Swedish Renal Register (SRR), the Medical Birth Register (MBR), the National Patient Register (NPR), the Cause of Death Register (CDR), the Prescribed Drug Register (PDR), the Cancer Register (CR), the Integrated Database for Labour Market Research (Swedish acronym LISA) and the Multiple Generation Register (MGR). The SCDR is also collaborating with the National Diabetes Register (NDR). For this project, particularly hypothesis 1, we will link SCDR to the Child Health Services Register (CHS).

The SCDR database has been updated with longitudinal data several times, most recently in 2023. It is stored and administered at the Umeå University SIMSAM-laboratory.

Project Description

The SCDR, initially established through collaboration with all Swedish paediatric diabetes clinics, collected clinical data until 2010 (4). Since then, the National Board of Health and Welfare has provided incident data via the Prescribed Drug Register (PDR) (6). An interdisciplinary team has long been engaged in SCDR research, encompassing expertise in paediatric diabetes medicine, general medicine, molecular biology, endocrinology, nephrology, statistics, and health economics. PhD students from multiple institutions contribute to this work. The SCDR research project is registered at ClinicalTrials.gov with identifier NCT06883318.

Hypothesis 1: The incidence of childhood-onset type 1 diabetes will peak in Sweden during the early 2020s.

To deepen our knowledge on incidence trends and understand more of age-period and cohort effects in T1D incidence trends, we will make use of hierarchical Age-Period-Cohort (APC) analysis with covariates, see e.g. (60) for a comprehensive overview. Incident cases come from the PDR and covariates will come from the MBR concerning early pregnancy weight and gestational age and from the CHS regarding child growth (61). We will expand our previous analysis using non-linear semiparametric generalized additive models for count data (4,6). The time related changes we study are age effects (A), period effects (P) and shared life events for a set of individuals, i.e., cohort effects (C). The fitted APC models can be evaluated with model diagnostics and give (i) the magnitude of the individual APC effects. For example, the minimum and maximum values of the marginal APC effects and the overall size of each effect, (ii) an assessment of one-dimensional covariate smooth effects, for example for child weight or mother's weight respectively, and (iii) a table with full model results. Either a list of several models or for a single model, here both linear coefficients and all nonlinear estimates are returned. The work will resume during the latter part of the period, with IW and TL leading.

Hypothesis 2: The incidence of ESRD, caused by T1D, will stabilize at a low level but we will see a delayed peek incidence in ESRD, with pregnancy as a significant risk factor in women.

Both socioeconomic background and sex are important mediators of risk to develop ESRD and can also be important for survival in RRT. Another important determinant of survival in RRT is the mode of treatment, where early renal transplantation is associated with increased survival (25). The SCDR is regularly linked to the SRR, allowing analyses of ESRD incidence by duration of diabetes, age and gender. In the coming years, part of our population will have reached post-menopausal age, and we have the possibility to follow-up on renal failure and ESRD with respect to differences between men and women in different ages. Linkage to LISA allows further analyses on socioeconomic risk determinants and region of living, linkage to the PDR will allow us to study effects of antihypertensive medication and linkage to the MBR with give data on pregnancy circumstances. We will use conventional life table and Cox regression but also more recent proposals from causal survival analysis. These studies will be performed in collaboration with Ce-

cilia Toppe and Staffan Schön at SRR, Jönköping. In 2024, the most recent SRR data was added to the SCDR. Analytic work can commence in early 2026.

Hypothesis 3: Glycaemic control is on the causal pathway linking socioeconomic status during childhood and long-term complications in adults with childhood-onset T1D. Family health shocks such as a child with T1D negatively affects the health of siblings.

In these cohort studies, we identify parents and siblings through the MGR. Exposure data on parents' educational level, income, well-fare support and other socioeconomic circumstances come from LISA. Outcome data on glycaemic control and other clinical parameters (blood pressure, weight, urine-albumin, etc.), come from the NDR; we take data on pharmacologic treatment from the PDR and data on long-term complications from the NPR and the SRR. To account for repeated measures of glycaemic control and also perform variable selection, we will use a penalized generalized linear mixed model approach (62,63).

In the analysis on the siblings, we use pharmacological information from the PDR, specifically data on antidepressants and compare them to non-related controls. We will retrieve health data from the NPR and the CDR and use LISA for socioeconomic variables. We will apply a non-parametric approach, focusing on population effects with analyses based on Persson et al (58). Both these studies will involve PhD-student Marie Fredriksson.

Hypothesis 4: Health-economic evaluation models require risk equations tailored for integration into Markov and microsimulation models. These equations must capture T1D-related complications and outcomes from childhood through middle age, reflecting current diabetes management practices.

Modern T1D management has improved outcomes for individuals diagnosed in childhood, as well as their parents. We will use NPR data to develop a comprehensive set of risk equations predicting a wide range of T1D-related outcomes, including micro- and macrovascular complications such as myocardial infarction, stroke, heart failure, peripheral vascular disease, hypoglycaemia, hyperglycaemia, amputation, end-stage renal disease, and retinopathy. These analyses will incorporate time-to-event methods and assess excess risks for additional comorbidities, including psychiatric conditions and all-cause hospitalisations. Mortality risk estimates will also be included.

Risk factors such as age, diabetes duration, and clinical variables (e.g., HbA1c) will be considered. Sensitivity analyses will evaluate changes in risk estimates over time in response to evolving treatment recommendations. Additionally, the impact of T1D onset on parents will be examined using hospitalisation data (NPR) and employment-related records (LISA). We will compare T1D parents to control parents, adjusting for confounders such as sibling number, age, employment, and education using panel-data regression methods. This work, led by Steen-Carlsson, will involve a PhD student based at Lund University with proximity to modelling expertise at the Swedish Institute for Health Economics (https://ihe.se/).

Hypothesis 5: Target trial protocols can be specified for research questions lacking a predefined time zero, allowing for both cohort and case-control study designs in the SCDR. For research questions related to disease-free controls, a case-control sample analogue can be given.

This project will address methodological challenges in defining time zero when emulating a target trial. Key challenges include specifying eligibility criteria, treatment strategies, and treatment assignment while ensuring appropriate follow-up. We will define causal contrasts (intention-to-treat and per-protocol effects) and outline statistical analyses suited to target trial, cohort, and case-control studies.

We will follow the TTE framework (46) and focus on Emulation Failure 1 (Figure 2). Statistical methodology will be developed using standard inference, causal inference, and epidemiological methods adapted for TTE applications. Research will progress in three phases: First, analytical methods will be developed. Second, these methods will be integrated into computer software, followed by testing with simulated data. Finally, the methods will be applied to the SCDR data. In the final phase, interdisciplinary collaboration will extend beyond epidemiology and statistics to incorporate expertise from education and health sciences, addressing real-world challenges. The project will involve IW and EP in phases one and two, with TL and AM contributing to the final phase to contextualise the empirical findings.

International and National Collaboration

The research group itself is a nation-wide collaboration working on data from national registers.

Since 2015, IW is part of an international initiative for experts on observational data analysis, Strengthening Analytical Thinking for Observational Studies (STRATOS), (http://www.stratos-initiative.org). IW is co-chair of the STRATOS Topic Group 7: Causal Inference.

Since 2009, KSC is part of the Swedish Institute for Health Economics, an institute that during more than two decades has developed health-economic models for the evaluation of diabetes interventions (https://ihe.se/). The institute is a driving contributor to the Mount Hood Diabetes Challenge Network (www.mthooddiabeteschallenge.com), an international collaboration with regular conferences focusing on comparing and exploring validations of health-economic simulation models in diabetes.

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