Risk Factors for Diabetic Ketoacidosis in Children

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I am a firm believer in the theory that you can do or be anything that you wish in this world, within reason, if you are prepared to make the sacrifices, think, and work hard enough and long enough.

Sir Frederick Banting (1928)

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes. It is preventable if timely administration of sufficient amounts of insulin is initiated. A large proportion of children are affected by DKA annually, especially at onset of type 1 diabetes (T1D). Mortality is relatively rare in developed countries but high in developing parts of the world and is mostly related to cerebral edema. Although severe, permanent cerebral injury is uncommon in the majority of children with DKA, there may be a risk of cognitive impairment, both in the mid- and long-term setting. Moreover, it has been shown that acute kidney injury is common during DKA. The long-term consequences of this are yet to be investigated. Acute renal impairment resolves uneventfully in most children after DKA, but there is concern that tubular injury in the acute may increase the risk of chronic kidney disease in children with diabetes. Since DKA is preventable, it is important to investigate factors that may be associated with increased risk of this condition.

Aims: The main aims of this thesis were 1) to describe the extent of delayed referral among children admitted to hospital for new-onset T1D and DKA, and to analyze the effect of delayed treatment on the severity of DKA; 2) to investigate if continuous subcutaneous insulin infusion (abbreviated CSII, commonly known as insulin pumps) are associated with increased risk of DKA in children, compared with multiple daily injections (abbreviated MDI, commonly known as “insulin pens”); 3) to estimate the effect of an internationally standardized measurement of low economic standard on the risk of DKA at onset of T1D, and 4) to analyze the effect of DKA at onset of T1D on the risk of a first-recorded recurrent DKA episode. Secondary aims

were to assess the effects of age at diagnosis, parental level of education and family income on the risk of another episode of DKA.

Methods: Study I and II were prospective, national population-based studies. Questionnaires were designed to collect survey data from all patients admitted to hospital in Sweden for DKA, from February 1, 2015, to January 31, 2017. The pediatric part of the Swedish National Diabetes Register (NDR) was used to assess the extent of missing data compared with the register, and to complete data when possible. Medical records were checked by the children's attending physicians in some cases. Two questionnaires were used for data collection and presented to participating caregivers and children at the time of hospital admission. One questionnaire was filled out by the caregivers (together with children if older than 15 years) and used for pre-admission data and assess for coherency with register data. Another questionnaire was filled out by attending pediatricians (and specialized nurses in some cases) primarily for in-hospital data and for coherency with the caregivers' questionnaires and the register. Study III and IV were register-based, retrospective national population studies. Individual data from the pediatric part of the NDR and from Statistics Sweden (a public, national statistical agency) were merged. For socioeconomic variables, the longitudinal integrated database for health insurance and labor market studies (LISA) provided by Statistics Sweden was used and study-specific variables derived from LISA. For the main exposure variable in study III, relative low economic standard as defined by the European Union's statistical agency and Statistics Sweden was used. By this definition, an individual is at persistent risk of poverty if disposable income, weighted for household composition, is below 60% of the population median. For study IV, Cox regression models were built to estimate the effect of DKA, age of the child, parental level of education and disposable income quartile at diagnosis of T1D, on the risk of a later episode of DKA during established T1D. Censoring was set to five years after diagnosis to limit the extent of uncontrolled confounding.

Results: Delayed referral to hospital was common in Sweden during the study period in study I. It was estimated that delay occurred in 43% of the cases, and delay was associated with significantly more severe ketoacidosis at hospital admission. Parental suspicion of diabetes was associated with milder ketoacidosis. The most common misdiagnosis was gastroenteritis. Treatment with CSII was associated with significantly higher risk for DKA than MDI in study II. However, the increased risk with CSII was only seen in cases of mild DKA (pH 7.29 – pH 7.20) but not in children hospitalized for moderate to

severe DKA (pH<7.20). Children with MDI had significantly higher mean HbA1c levels (102.7 mmol/mol, SD 23.3 mmol/mol) compared with children with CSII (73.9 mmol/mol, SD 18.1 mmol/mol). In both children with CSII and MDI, the use of sensor-based continuous glucose monitoring was lower than the national average, but it was higher among children with CSII (56%) than in children with MDI (28%). Persistent low economic standard was significantly associated with 42% higher risk of DKA at onset of T1D (RR 1.42, C.I. 1.13 - 1.79, p = 0.003). There was no evidence that DKA at onset of T1D in children was associated with another episode of DKA during established diabetes (hazard ratio 0.78, C.I. 0.39 - 1.6, p=0.47). There was a higher risk of DKA during established T1D for primary level of education compared to tertiary level (hazard ratio 5.8, p=0.001), and for secondary level of education compared to tertiary level (hazard ratio 1.8, p=0.031). There was also significant association between higher risk of DKA for children from the lowest household income quartile compared to the highest income quartile (hazard ratio 0.30, p=0.011).

Conclusions: Delayed referral is common in children with new-onset T1D who present with DKA. Delayed referral leads to worse outcome measured as pH at hospital admission. CSII is associated with increased risk of mild DKA, but not with moderate or severe DKA. Persistent low economic standard is associated with increased rates of DKA at new-onset T1D in children, even in a high-income country with completely reimbursed public healthcare like Sweden. There is no evidence that DKA at new-onset T1D is associated with a later episode of DKA and the risk factors for DKA at onset of T1D and during established T1D may be partially different. However, parental education level and low household disposable income are risk factors of DKA, both at onset of T1D and during established T1D.

Keywords: Diabetic ketoacidosis, type 1 diabetes, continuous subcutaneous insulin infusion, multiple daily injections, cerebral edema, acute kidney injury, socioeconomic status, low economic standard, level of education.

SAMMANFATTNING PÅ SVENSKA

Diabetisk ketoacidos är en livshotande komplikation till diabetes. Denna komplikation uppstår till följd av absolut eller relativ insulinbrist. Med absolut brist avses total, eller nästan total avsaknad av insulin. Med relativ insulinbrist menas att effekten av andra hormoner, som till stor del har motsatt verkan jämfört med insulin, blir för kraftig i förhållande till insulintillgången.

En person som inte har typ 1 diabetes har hela tiden en viss nivå av insulin som insöndras i blodet via bukspottkörtelns betaceller. När personen äter stiger glukosnivån i blodet och bukspottkörteln stimuleras av detta, och insöndrar insulin som håller glukosnivån på en jämn nivå och låter glukos komma in i cellerna för att där lagras som energi. Under fasta stimuleras inte bukspottkörteln celler lika mycket, men kontinuerlig insöndring av insulin sker ändå för det grundläggande behovet och för att behålla jämvikten i kroppen.

Insulin är att så kallat anabolt (”uppbyggande”) hormon. Med detta avses exempelvis att insulin bidrar till att glukos kommer in i celler och där kan lagras som ett förråd tills ökat behov av glukos uppstår. Insulin hämmar också nedbrytningen av fetter i kroppen, samt bidrar till att bygga upp proteiner och bevara proteiner från att brytas ned. När absolut eller relativ insulinbrist uppstår sker det motsatta. Glukos kan inte längre komma in i cellerna och stannar kvar i blodet, och orsakar gradvis ökande urinmängder innehållande glukos. Symtom som frekventa urintömningar och stark törst ökar i omfattning. Kroppen börjar torka ut. Eftersom insulinbristen hindrar glukos från att komma in i cellerna uppstår också trötthet och viktnedgång, som förvärras av att protein börjar brytas ned. Nedbrytning av fett i kroppen ökar, vilket leder till höga halter av fettsyror, och av sura ämnen skapade av dessa. Om denna process går för långt utan att insulin tillförs töms förr eller senare kroppens egna kompensationsmekanismer, och symtom på surhet i blodet uppstår. Den sjuke börjar då andas allt kraftigare för att få ut kolsyra (genom att andas ut koldioxid), mår illa, och börjar kräkas av den sura miljön i kroppen. I detta läge har symtom på diabetisk ketoacidos uppstått. Allt starkare trötthet och efterhand medvetslöshet tillkommer. Om behandling med insulin inte inleds kommer sjukdomsprocessen till sist att leda till döden i samtliga fall.

Hos barn ses ofta diabetisk ketoacidos vid insjuknande i typ 1 diabetes. Sedan många år har ungefär en femtedel till en fjärdedel av alla barn i Sverige redan diabetisk ketoacidos när de får diagnosen typ 1 diabetes på sjukhus. Utomlands är andelen oftast större.

Hos barn som har känd diabetes sedan tidigare är diabetisk ketoacidos inte lika vanligt, varken i Sverige eller utomlands. I Sverige registreras årligen 70–80 fall hos barn med känd diabetes. Det är en låg siffra vid internationell jämförelse.

Eftersom insulin i blodet bryts ner mycket snabbt, måste insulinbehandling utanför sjukhus alltid ske via tillförsel i underhuden. Det sker via två olika sätt. I båda fallen är tanken att efterlikna kroppens normala, egna insulintillförsel. Det ena sättet är dagliga injektioner en eller två gånger per dag med en långverkande typ av insulin, för kroppens grundbehov. Utöver detta ges injektioner med kortverkande insulintyper, med snabbt insättande och snabbt avtagande effekt, inför måltider eller vid alltför höga blodsockernivåer. De sprutor som använda kallas ofta för ”insulinpennor”. Det andra sättet är via kontinuerlig införsel av insulin via en insulinpump för grundbehovet, och extra doser via pumpen vid måltider eller högt blodsocker. Både vid behandling med insulinpenna eller insulinpump kan övervakning av blodsockret, som traditionellt skett via blodsockermätningar med stick i fingret, kompletteras med en sensor som fästs i huden och kontinuerligt mäter blodsockret under ett par veckor. De mest moderna insulinpumparna tar emot trådlös information av sådana sensorer, och kan sedan automatiskt minska eller öka insulintillförseln beroende på det aktuella eller förväntade blodsockervärdet.

Den första och den tredje studien i denna avhandling handlar om barn som nyinsjuknat med typ 1 diabetes, och riskfaktorer för att få diabetisk ketoacidos hos dessa barn. Den andra och den fjärde studien handlar om barn som redan har haft diabetes ett tag, och riskfaktorer för diabetisk ketoacidos hos dessa barn.

I den första studien undersöktes förekomst av försenad remittering av barn från primärvård (till exempel vårdcentraler eller sjukvårdsupplysning) till akutmottagning på sjukhus, och huruvida försenad remittering kan relateras till allvarlighetsgraden av diabetisk ketoacidos. Denna studie fann att en stor del av barn som lägg in för nyupptäckt diabetes med diabetisk ketoacidos hade haft primärvårdkontakter för diabetesrelaterade symtom inom fyra veckor före inläggningen, men att dessa kontakter inte hade lett till kontakt med sjukhus samma dag. I många fall hade även blodsockret testats och var högt, men utan att detta ledde till inläggning på sjukhus samma dag. Barn som hade fått en försenad handläggning hade svårare ketoacidos än de som kommit till sjukhus samma dag som primärvårdskontakten. I de fall föräldrar hade misstänkt

diabetes innan någon kontakt med sjukvården, hade barnen lättare former av diabetisk ketoacidos.

I den andra studien undersöktes om diabetisk ketoacidos var vanligare bland barn med insulinpump jämfört med insulinpenna. I denna studie jämfördes andelen barn med insulinpump som fått ketoacidos under två år, med andelen barn som behandlades med insulinpump i hela Sverige under samma tidsperiod. Studien fann ett samband mellan behandling med insulinpump och diabetisk ketoacidos, dvs att risken för ketoacidos verkade något högra bland barn med insulinpump. Detta samband sågs dock bara för lättare fall av ketoacidos. Vid svårare former sågs ingen skillnad mellan insulinpump och insulinpenna. Däremot fanns tecken till att barn med insulinpenna hade högre nivåer i blodet veckorna eller månaderna innan de fick ketoacidos, jämfört med de som fick ketoacidos med insulinpump.

I den tredje studien undersöktes om risken för DKA vid insjuknandet i T1D var ökad för barn boendes i hushåll med låg ekonomisk standard. I studien användes en standardiserad definition av låg ekonomisk standard som används av både Statistiska Centralbyrån och den Europeiska unionens statistikbyrå. Enligt denna definition har en individ relativ låg ekonomisk standard om den disponibla inkomsten understiger 60% av medianvärdet för den disponibla inkomsten i ett land. Studien visade ett starkt samband mellan låg ekonomisk standard och risk för DKA.

I den fjärde studien undersöktes om det fanns ett samband mellan diabetisk ketoacidos vid diagnos av typ 1 diabetes och risk för framtida episoder av diabetisk ketoacidos. Ett samband kunde inte påvisas. Däremot sågs ett samband mellan låg disponibel inkomst (den fjärdedelen av familjerna med lägst inkomst) och/eller låg utbildning i familjen (utbildningsnivå maximal grundskola) vid diagnos av typ 1 diabetes, och inläggning på sjukhus för diabetisk ketoacidos under en senare tidpunkt.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Wersäll JH., Adolfsson P., Forsander G., Ricksten SE., Hanas R. *Delayed referral is common even when new-onset diabetes is suspected in children. A Swedish prospective observational study of diabetic ketoacidosis at onset of type 1 diabetes*. Pediatr Diabetes. 2021; 22(6): 900-908

II. Wersäll JH., Adolfsson P., Forsander G., Hanas R. *Insulin pump therapy is associated with higher rates of mild diabetic ketoacidosis compared to injection therapy: A 2-year Swedish national survey of children and adolescents with type 1 diabetes*. Pediatr. Diabetes. 2022; 23:1038–1044

III. Wersäll JH, Ekelund J., Åkesson K. Hanas R., Adolfsson P., Ricksten SE., Forsander G. *Relative poverty is associated with increased risk of diabetic ketoacidosis at onset of type 1 diabetes in children. A Swedish national population-based study from 2014 to 2019.*

Submitted

IV. Wersäll JH, Ekelund J., Forsander G., Adolfsson P., Ricksten SE., Hanas R. *Is diabetic ketoacidosis at onset of type 1 diabetes associated with recurrent episodes of ketoacidosis? A nationwide longitudinal study of Swedish children 2012–2019.*

In manuscript

CONTENTS

ABBREVIATIONS

AID	Automated Insulin Delivery
CGM	Continuous Glucose Monitoring
CNS	Central Nervous System
CSII	Continuous Subcutaneous Insulin Infusion therapy
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic KetoAcidosis
HLA	Human Leucocyte Antigen
HR	Hazard Ratio
ISCED	International Standard Classification of Education
ISPAD	International Society for Pediatric and Adolescent Diabetes
MAR	Missing At Random
MCAR	Missing Completely At Random
MDI	Multiple Daily Injections therapy
MNAR	Missing Not At Random
OECD	Organization for Economic Cooperation and Development
RR	Relative Risk
SES	SocioEconomic Status

1 INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening acute complication to diabetes. The biochemical criteria for DKA are hyperglycemia, hyperketonemia, and metabolic acidosis. Thirst, vomiting, and polyuria are examples of typical symptoms, but not all children show these symptoms at presentation for DKA. In principle, delayed treatment is the reason for all cases of DKA to occur, as timely initiation of insulin treatment will prevent metabolic acidosis from developing. It is thus an entirely preventable condition. DKA is seen in a relatively large portion of children with new-onset type 1 diabetes (T1D) and to a lesser extent in children with known, established diabetes.

1.1 HISTORICAL BACKGROUND

Diabetes mellitus (from the classical Greek word diabetes, meaning “to pass through” and the Latin word mellitus, meaning “honey-sweetened”) has been known since ancient times. (1) Ancient texts probably describe what is known today as T1D with DKA, and it was understood that this condition ultimately led to death. (1) Detailed, clinical descriptions of the symptoms of DKA appeared in medical literature in the nineteenth century, and before the turn of that century it was also discovered that the later stages of diabetes were characterized by acidosis and urine excretion of ketone bodies. (2)

Before the discovery of insulin, T1D was invariably fatal, and DKA was an unavoidable end-stage manifestation. Although insulin (from the Latin word insula, referring to the islets of Langerhans) had already been proposed as a hypothetical pancreatic hormone that could be involved in glucose homeostasis, it was the research work of Frederick Banting, with the help of laboratory assistant Charles Best, that led to the first treatment with insulin. (3) In January 1922, a 14-year-old Canadian boy named Leonard Thompson became the first patient with diabetes to be successfully treated, and the same year several other children went on to start treatment. Banting and the head of his research department, John MacLeod, were awarded the Nobel Prize in 2023

for the discovery of insulin (both decided to share the prize sum with their assistants).

The rate of insulin production soon accelerated, and treatment for T1D eventually became available on a larger scale. At the time, insulin was made from bovine pancreatic tissue and associated with several immunologic side effects with sometimes serious reactions. However, the availability of a treatment changed T1D from a palliative condition to a chronic disease. Since the early days of insulin treatment, physiological understanding, pharmacological progress, and technical innovations have advanced enormously.

Research on the importance of glycemic control, and particularly the landmark Diabetes Control and Complications Trial (DCCT) during the end of the last century, changed insulin treatment regimes. (4-6) The DCCT study established the paramount importance of intensive glycemic control by longitudinal measurements of glycated hemoglobin (HbA1c) and showed that efforts to keep HbA1c low were effective in preventing neurological and vascular long-term injury. (7, 8)

Insulin was made from bovine or porcine pancreatic tissue for many decades, but since the end of the last century, recombinant DNA techniques allow for industrial mass production of insulin that is identical to naturally secreted human insulin. (9) Thus, it can avoid the relatively common problems with immunological reactions encountered when animal insulins were used. Moreover, insulin is now available in various formulae, with long-acting, medium-acting, and short- or ultrashort-acting types depending on the type of individual treatment regime. (10)

During the last three decades, several technical advances have been made regarding insulin delivery mechanisms and daily monitoring of glucose control and metabolic status. Many children with T1D are currently offered advanced types of treatment devices, such as continuous subcutaneous insulin infusion systems (CSII systems, commonly known as insulin pumps) and continuous glucose monitoring systems (CGM systems, subcutaneous sensors that provide continuous information on glucose levels), with the possibility of alerting the child and caregivers if blood glucose levels become too high or too low.

Nonetheless, even to date, lack of insulin is the leading cause of death among children with T1D. (11) Children still die or become seriously injured from

DKA in cases of delayed treatment at the onset of disease, or due to scarcity of resources or mismanagement during established disease. (12-14) Moreover, DKA also carries high public costs in monetary terms. Most hospitals routinely admit children with DKA to an intensive care unit according to guidelines, and even when intermediary care can be adequately provided, the public cost remains high. (15-19)

1.2 PATHOPHYSIOLOGY

Insulin is an anabolic hormone that exerts a wide range of effects in the human body. The metabolism of glucose, fat and proteins is affected by the actions of insulin. It facilitates glucose uptake in most cells of the body (with some exceptions, such as neurons, pancreatic beta-cells, erythrocytes, and intestinal mucosa, which do not need insulin for this transport). Moreover, it both induces the synthesis and inhibits the breakdown of glycogen. It is thus a vital component in the process of replenishing and storing energy depots within cells and in regulating blood glucose levels. Insulin is also a major component in lipid metabolism. It reduces lipolysis by inhibiting the action of lipase, increases the conversion of free fatty acids to triglycerides, and facilitates the synthesis of triglycerides from glucose. Adding to the anabolic and regulatory effects are increased cellular intake of amino acids and decreased gluconeogenesis.

To maintain homeostasis, other hormones exert counterregulatory effects, which directly or indirectly oppose the actions of insulin. The most important of these are catecholamines, glucagon, cortisol, and human growth hormone. Catecholamines and glucagon have immediate effects and rapidly increase glucose availability. Cortisol and human growth hormone have less rapid (but more lasting) counterregulatory effects, with onset and effect durations ranging within hours.

DKA is caused by insufficient blood levels of insulin. This can be understood in absolute terms, when insulin depots are effectively depleted, or in relative terms, when insulin levels may not be depleted but are insufficient to balance the increased relative effect of counterregulatory hormones (Figure 1). In both cases, an uninhibited catabolic state eventually appears with an unregulated

breakdown of glycogen and triglycerides, increased gluconeogenesis, and severely impaired cellular intake of glucose. Rising levels of blood glucose and free fatty acids lead to osmotic diuresis with dehydration, loss of electrolytes, and metabolic acidosis. Metabolic acidosis primarily results from the accumulation of ketone bodies but may be aggravated by lactic acidosis due to impaired tissue perfusion from severe dehydration. A depiction of these pathophysiological process is shown in Figure 1 below:

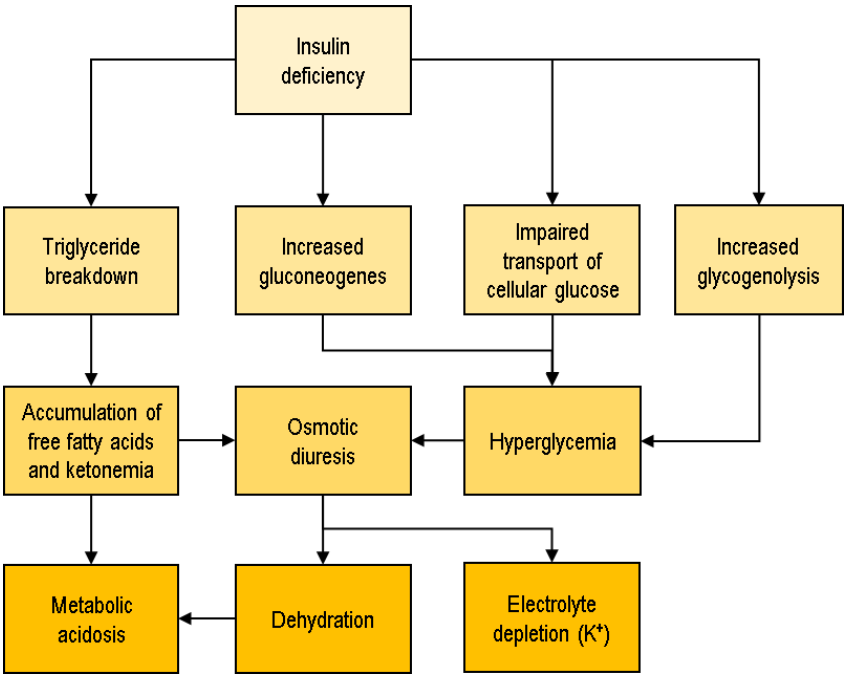

Figure 1. Pathophysiological process of diabetic ketoacidosis.

1.3 STAGES OF DEVELOPMENT OF T1D

There is a genetic susceptibility to develop T1D. A child whose biological sibling or parent has T1D has a substantially increased risk of developing T1D. On average, one out of twenty children with at least one first-degree biological relative with T1D will also develop clinical T1D sometime in life. (20-22)

The importance of genetic risk factors has also been shown in various studies where associations between certain genes and HLA groups and risk of clinical T1D are demonstrated. (23-25) On the other hand, most children who are diagnosed with T1D do not have known close relatives with this type of diabetes, so the contribution of environmental factors seems to have a major role at the population level. It is not clear which types of environmental exposures are involved, and many different factors have been proposed, ranging from early exposure to cereals, bovine dairy products, enteroviruses, among many others. (26, 27)

There is evidence that genetic susceptibility and environmental factors can initiate an autoimmune response in some individuals, with the production of autoantibodies to pancreatic endocrine islets and beta-cell destruction, and eventual progression to clinical symptoms. (26) A model for this process has been proposed and divided in three stages. (28) The link between these stages is the finding of multiple beta-cell autoantibodies during all three stages. In stage 1, two or more islet autoantibodies can be detected in blood samples, but there are no clinical symptoms, and there is normoglycemia both during fasting and after meals. (29) In stage 2, multiple antibodies can be detected in blood and abnormal glucose levels can be seen, but no clinical symptoms of diabetes have yet appeared. In stage 3, there are multiple antibodies, blood glucose levels have reached above the threshold for diabetes, and clinical symptoms typical of diabetes have started to appear in many individuals, although not in everyone. At this stage, a formal diagnosis of clinical T1D can be made. (30, 31)

1.4 SYMPTOMS OF T1D AND DKA

Some symptoms, or rather combinations of symptoms, are more specific for new-onset T1D than others. In a primary healthcare setting where a previously healthy child presents with polyuria and thirst, new-onset diabetes should be a typical differential diagnosis, and a blood glucose test should be made. Other symptoms, such as tiredness, weight loss, and stomach pains, are less specific and may not lead to immediate suspicion of diabetes. Unintended weight loss is always a serious symptom, especially in children. Nonetheless, this symptom, as well as tiredness and stomach pains may be attributed to other, less acute albeit serious conditions or circumstances. A blood glucose test in this setting could reveal the real nature of these symptoms, and blood glucose tests should be performed liberally in all children presenting with unexplained symptoms. If symptoms that may be attributable to diabetes are present and blood glucose levels ≥11.1 mmol/L (200 mg/dl), or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl), then a diagnosis of can be made, and the child should be referred the same day to a hospital with pediatric emergency capabilities.

In addition to specific or less specific symptoms of diabetes, alarm symptoms signaling progressive disruption of homeostatic buffer mechanisms eventually appear in all children with new-onset diabetes, with tachypnoea, (characterized by large tidal volumes, so-called Kussmaul breathing), vomiting, pronounced nausea, stupor, and finally coma, which are all signs of DKA and worsening metabolic acidosis.

In rare cases (0.5-1% of DKA), clinically manifest cerebral edema ensues which carries high mortality and risk of severe morbidity even when prompt treatment is initiated. Clinical signs of cerebral edema in children with DKA were described by Muir et al. who presented a scoring system that is still in use in clinical practice. (32)

1.5 TREATMENT OF DKA

The initial treatment of T1D with DKA is in principle the same as treatment of T1D without DKA. The main physiological derangements, dehydration, electrolyte loss and metabolic acidosis, should be addressed in that order. This means that rehydration should first be initiated and continued for 1-2 hours, until signs of improved tissue perfusion are found. However, there are a few caveats to evaluation of the degree of dehydration in children with DKA. First, sodium measurements can be misleading as a guide for rehydration regimes, since pseudohyponatremia often occur due to high blood glucose concentrations. (33, 34) Corrected sodium levels should be calculated (the expected sodium level, given that blood glucose would have been in the normal range) and used as a complement during rehydration and treatment, until normal glucose levels and normal pH are reached. (34, 35) Second, evaluation of the degree of dehydration based on clinical signs is not reliable in children and especially not in children with DKA, as has been shown in several publications. (36-39) It is therefore recommended to rehydrate with volumes corresponding to between 5-10% of the child's weight, depending on the level of acidosis.

Metabolic acidosis result in potassium efflux from cells, and this can result in laboratory values of potassium that may appear to be within normal ranges or slightly elevated. (34) However, potassium is always depleted in absolute terms, and parenteral potassium must be administered before or at the time of start of insulin treatment. Even in severe DKA, administration of bicarbonate buffer solutions should be avoided whenever possible since it generally does not improve outcome, can lead to rapid hypokalemia, and has been associated with increased risk of cerebral edema. (40-43)

Insulin treatment should be started as a continuous infusion. Bolus doses of insulin should not be given, since they cause rapid intracellular shift of potassium and risk of hypokalemia, may increase intravascular volume depletion due to rapid intracellular flux of glucose and water, and have not been shown to shorten the time until resolution of acidosis. (44)

1.6 POTENTIAL ACUTE AND CHRONIC COMPLICATIONS OF DKA

The leading cause of death in children with DKA is cerebral edema. Clinically manifest cerebral edema is relatively rare in developed countries (0.5% - 0.9% of children with DKA) but is likely much more common in developing countries. (45-47) Mortality rates in children with clinically apparent cerebral edema is 20% - 30%, making it a dreaded complication with frequent long-term and permanent sequelae in survivors. (48, 49). The pathophysiology of cerebral edema in children with DKA is not fully understood, but recent research points towards subacute neurovascular inflammation and impaired cerebral autoregulation as potential contributing mechanisms. (50, 51) Risk factors for cerebral edema during DKA have been described in several publications. (52, 53)

Subclinical edema may be present in a considerable proportion of children with DKA. (54-56) The long-term implications of this are not fully established, but a growing number of publications have shown a relationship between signs of acute injury to the central nervous system (CNS) in children with DKA and impaired cognitive function at mid- to long-term follow-up. (57-60)

In addition to potentially adverse CNS consequences, acute renal injury is present in many children admitted to hospital for DKA.(61, 62) Although only a small minority need dialysis in the acute setting and kidney function normalizes in the majority of cases, acute kidney injury is a matter of concern in a population already at risk of chronic kidney disease.(63, 64) The best treatment protocols to prevent or alleviate acute kidney injury in children with DKA needs further research. (65)

1.7 EPIDEMIOLOGY OF T1D AND DKA

T1D is one of the most common chronic childhood diseases in the world, and it is particularly common in Sweden where 1 in 200 children has T1D, making it the second most common chronic childhood disease after asthma. (66, 67) Only Finland has a higher annual incidence of T1D than Sweden among

children worldwide. (68) There seem to be an inverse relationship between the prevalence of T1D in a country and the incidence of DKA. (69)

In Sweden, the annual DKA rates among children have been stable for decades, yet there is a tendency for an increase in DKA at diabetes onset since the last seven to eight years. Between one-fourth to one-fifth of all children with new-onset T1D, and less than 1% of all children with established T1D are admitted to hospital for DKA each year. There is considerable age variation, with children < 2 years having the highest frequency of DKA at diagnosis and children 2-4 years the lowest frequency. (70)

Internationally, DKA rates at onset of T1D show great variation from one country to another but are generally higher than in Sweden. In Europe and the United States, relative frequencies of DKA at onset of T1D vary between 15-70%. (71). In children with established diabetes, the annual rates of DKA show great variation depending on which country is surveyed but is generally higher than in Sweden. (72-74)

1.8 INSULIN DELIVERY TYPES

In children with T1D, a goal of the therapy is to mimic the normal pancreatic function as much as possible. The normal endocrine pancreas continuously secrete insulin to maintain basal homeostasis, and automatically up- or downregulates this secretion in accordance with the physiologic needs. During meals, a secretion spike occurs when rising blood glucose triggers beta cells to secrete large amounts of insulin, and during fasting, lower blood glucose levels inhibit insulin secretion and the effects of counter-regulatory mechanisms may increase. With these feedback mechanisms, blood glucose levels are kept within a tight range under normal physiologic circumstances.

In T1D, these normal physiologic fluctuations of insulin levels are mimicked by employing a so-called basal-bolus treatment regime, to ensure continuous delivery of a basal insulin level, and bolus doses to ensure “spikes” in insulin levels during meals. Since insulin only has a half-life of a few minutes in blood, delivery of insulin must be made subcutaneously in children with T1D. To achieve this, there are two types of insulin delivery modes for children with T1D.

One is Continuous Subcutaneous Insulin Infusion therapy (CSII), or more commonly known in society as insulin pump therapy. With CSII, a continuous basal insulin infusion is given through a catheter, which is attached to a subcutaneous cannula in one end and a pump in the other end. During meals or to correct hyperglycemia, bolus doses are given through the same catheter. In CSII, only short- or ultrashort-acting types of insulins are used. The technological progress has been rapid in this field. As for the time of writing, several CSII systems communicate with subcutaneously attached sensors for continuous glucose monitoring and permit automatic tuning of basal insulin infusion rate, and in certain systems automatic bolus infusions in case of hyperglycemia. These systems have shown promising results in several studies in maintaining metabolic control, including both lower DKA rates and lower HbA1c levels compared with older systems. (75-77) The use of Continuous subcutaneous insulin infusion (CSII) has gradually increased and has become the commonest type of insulin delivery for children with T1D in many high-income countries. Since 2015, most children in Sweden with T1D use CSII, and this proportion is steadily increasing in the national population. (70)

The other type of insulin delivery is via Multiple Daily Injection therapy (MDI), during which subcutaneous injections of long-acting insulin types are given once or twice daily for basal requirements, and bolus doses with short-acting insulin types are given during meals, or to correct hyperglycemia. MDI is substantially cheaper than CSII, which has implications for children in societies without publicly reimbursed healthcare, or where political decisions or public finances do not allow for CSII, the financial situation in a family may be decisive for the type of treatment that can be allowed. This is important to consider when comparing CSII with MDI, since various types of selection biases may influence results, depending on which population is studied.

1.9 CAUSES OF DKA

1.9.1 SOCIOECONOMIC FACTORS

Socioeconomic status has been reported to be associated with DKA in children in many studies. Socioeconomic status is an umbrella term for various aspects

of societal coping resources which include, but are not limited to, education level, economic capacity, occupational status, perceived “social status”, to name a few.

Of the various aspects of socioeconomic status, parental education level and parental income level have been discussed and included in many studies and reviews of risk factors for DKA in children. (78-81) Indeed, education level and income are factors that are associated with health outcomes on a general population level and not just in children with diabetes, as has been shown in several publications. However, when studying and discussing parental education level and income as risk factors for acute complications in children with T1D, it is important to point out that political, economic, and social differences between countries mandate careful interpretation of education and income as exposure factors. Income level in a country without publicly financed healthcare for children means something else than it does in a country where all pediatric care is paid for by the public healthcare system. Moreover, assumptions of cause and effect are important both in the design and interpretation of study results based on education and income. For example, it may seem intuitive that income, generally, should rather be an effect caused by education level and mediates the effects of parental education. (82)

1.9.2 AGE OF THE CHILD

Age at onset T1D is a known risk factor for DKA. This has been consequently shown in various publications where the youngest children consequently have highest rates of DKA. (71) In Sweden, data from the NDR show a clear association between age and DKA, with the youngest children (<2 years) having DKA rates more than double the rates of children 2-17 years, according to reports from the last decade. (70) Children <2 years have DKA in half or almost half of the cases with new-onset T1D at admission to hospital. The rate of DKA is lowest in children 2-4 years of age and increases in comparison during adolescence.

1.9.3 DELAYED ADMISSION TO HOSPITAL

Delayed initiation of insulin treatment is, in terms of principle, always the reason for DKA to develop. This can be caused by either the so-called "patient's delay", or the "doctor's delay", or a combination of both. In patient's delay (when parents seek healthcare evaluation at a late stage in diabetes development), many factors may play at hand.

Lack of awareness to diabetic symptoms, cases of child neglect, or language barriers can all cause parents or caregivers to seek medical evaluation at later stages than would have been preferable. Also in doctor's delay, (when healthcare personnel fail to refer a child with new-onset diabetes to the nearest hospital with pediatric emergency capabilities) several factors also may influence the failure to perform prompt referral to hospital. Unfamiliarity with management and diagnostical procedures for suspected T1D could be important in a primary healthcare setting, where type 2 diabetes is often much more common. This may cause underestimation of the urgency of the condition if procedures for suspected type 2 diabetes are followed. Language barriers may also play a role, creating risks of misunderstandings between the caregiver and the parents/caregivers or the child regarding the symptoms, and the temporal evolution of those symptoms. Moreover, ignorance regarding T1D can have had a role in certain cases, where diabetic symptoms were present and blood glucose tests showed high levels, yet were attributed to stress, or other causes than diabetes. (83) Delayed referral has been shown to be relatively common in several publications, also when countries with different types of healthcare infrastructure are compared. (84, 85)

1.9.4 INSULIN DELIVERY MODE

Insulin delivery mode (CSII or MDI) as a risk factor for DKA has been studied in several publications in which some have shown increased risk with CSII while others the opposite, and yet others have not shown evidence for significant differences between CSII and MDI with respect to the risk of DKA. (86-91) A plausible assumption of an inherent higher risk of DKA with CSII lies in the nature of the treatment, since only short-acting insulin types are used with this type of insulin delivery mode. If continuous delivery of insulins with

short half-lives is interrupted, for example because of accidental dislocation of the infusion set, there is rapid depletion of insulin depots, which leads to earlier ketosis than is the case with long-acting insulins used in MDI. If an accidental dislocation of the infusion set occurs before bedtime, interrupted infusion may go undetected for a long time, until routine glucose monitoring at morning hours reveal the problem. However, modern CSII systems come with subcutaneous continuous glucose monitoring sensors, which are designed to alert the child or caregiver about worsening hyperglycemia. (92, 93)

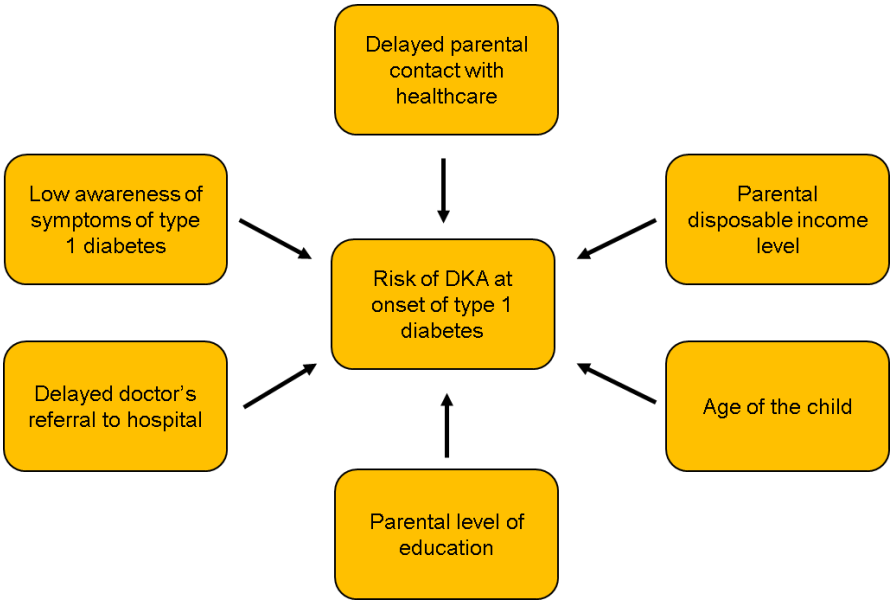

Figure 2. Risk factors for diabetic ketoacidosis at onset of type 1 diabetes.

1.10 DKA PREVENTION

1.10.1 AWARENESS CAMPAIGNS

Several interventional attempts to decrease DKA at onset of T1D have been made across various populations. (94) One notable example is an intervention to increase population awareness by Vanelli et al. in two Italian regions. (95) In this study, posters, oral information, and plastic memo cards were used to raise awareness of typical symptoms of diabetes. The campaign was directed to healthcare workers, parents and children, and school employees, and was so successful that DKA rates were brought down to 0% during one period. The positive effects of this campaign were followed up and has been estimated to last for many years. (96) Apart from this very ambitious interventional study, other interventions have proven effective, moderately effective, or inconclusive depending on the study protocol and the population. (97) What can be learnt at a general level from these campaigns is that awareness of symptoms typically attributed to diabetes indeed contribute to decrease DKA at new-onset type 1 diabetes. (94)

1.10.2 SCREENING FOR T1D

A recent and promising approach to improving care and preventing DKA is screening for diabetes, either in high-risk groups of children or in the general population of children in certain ages. (98) In an ongoing, prospective intervention study initiated in 2015 in Bavaria, Germany (the Fr1da study), it has been shown that a group of children screened and tested positive for islet autoantibodies had remarkably low rates of DKA (2.5%) at diagnosis of symptomatic diabetes. (99) Within the framework of this and other studies, screening for T1D is becoming a clinical reality internationally. (100, 101) First-degree relatives of patients with T1D are now offered clinical tests for islet autoantibodies in the United States, and in Italy a law was passed in October 2023 which mandates national screening of all children 0-17 years at risk of T1D, with one of the explicit aims being to decrease the rate of DKA at new onset diabetes. (102) It remains to see the effects of screening programs

in the future and the feasibility of such programs in different countries and regions worldwide.

1.10.3 PREVENTION OF DKA IN CHILDREN WITH ESTABLISHED T1D

In children with established diabetes who develop moderate to severe DKA, technical mismanagement, child neglect, skipped doses, or gastroenteritis have often been found to be involved. (103) In cases with skipped doses, social problems should be suspected, if not already known. In general terms, prevention of DKA in this group should be focused on a multi-dimensional team-based approach, frequent follow ups, and re-evaluation of the type of insulin delivery (CSII or MDI) that may be the best option for the individual child. (104, 105) However, it is also important to consider the severity of the DKA episode and whether the child has suffered recurrent episodes of DKA since diagnosis of T1D.

In first-time cases with only mild DKA and good long-term HbA1c levels, penetration of the triggering mechanism may be sufficient to conclude that a misfortune happened and that more information should likely prevent further events from happening. (105) On the other hand, in children with established T1D who suffer moderate or severe DKA events, or recurrent events, a deeper problem should be assumed, especially if occurring against a background problematic of HbA1c levels. (106) In these children, multidisciplinary healthcare efforts, with possible involvement of school personnel and sometimes contacts with the public social assistance services could be required to improve the situation. (104, 106)

2 AIMS

OVERALL AIMS

The overall aim of this dissertation is to investigate risk factors DKA in children with T1D.

STUDY I

The primary aim of this prospective observational study was to characterize children whose caregivers had suspected new-onset diabetes before contacting healthcare services with delayed referral to hospital after contacts with the primary healthcare system. The secondary aims were to analyze the effects of parental suspicion of diabetes and delayed referral on pH levels at hospital admission for DKA.

STUDY II

The primary objective was to compare the distributions of CSII and MDI in the national pediatric T1D population with the population admitted to hospital for DKA. Secondary objectives were to analyze the effect of CSII and MDI on the level of acidosis at hospital admission for DKA and to compare HbA1c levels between CSII and MDI in DKA.

STUDY III

The aim of this study was to estimate the effect of an international, standardized measurement of low household economic standard on the risk of DKA among children with new-onset T1D.

STUDY IV

The primary aim of this study was to analyze if DKA at onset of T1D in children is associated with an increased risk of a recurrent DKA episode. Secondary aims were to assess the effects of parental education and family income on the risk of DKA during established T1D.

3 METHODS

3.1 DATA SOURCES

3.1.1 THE SWEDISH NATIONAL DIABETES REGISTER

The National Diabetes Register (NDR) was founded in 1996 and has since then become one of the largest national population-based diabetes registers in the world. (107) The Swedish Society for Diabetology created the NDR and still maintains it. It includes a pediatric part formerly known as Swediabkids which was merged with the NDR in 2018 and publishes open-access annual reports. It is expected to cover a large part of the pediatric population with diabetes and is widely used for research. (108) The register has a longitudinal structure, covering a large number of variables for each individual, from initial admission to hospital and diagnosis through regular follow-ups.

3.1.2 THE LONGITUDINAL INTEGRATED DATABASE FOR HEALTH INSURANCE AND LABOR MARKET STUDIES (LISA)

Statistics Sweden is a public agency responsible for official statistics, and for coordination of statistics from other governmental agencies, including a wide range of socioeconomic data from the national population level to the individual level. Statistics Sweden initiated the LISA database in 2003, to a large extent for health research purposes. This database includes many socioeconomic variables created from Statistics Sweden's own data as well as from several other governmental agencies and is updated annually. (109) Examples of socioeconomic variables in LISA are level of education, income, country of birth, marital status, and occupational status. In many cases, the classification of data in LISA is similar or identical to international standards, such as level of education, which is based on the International Standard Classification of Education (110, 111).

3.1.3 QUESTIONNAIRES

Questionnaires were used for data collection in study I and II. These questionnaires were filled out online via a digital questionnaire, constructed with the help of a web survey program (SurveyMonkey®, SVMK Inc., Palo Alto, CA) or printed out and compiled in paper format. The questionnaires were anonymous and for each patient a code was used as identifier. The code keys are kept at each clinic, and the identity of individual children were accessible only to the researchers and to the health staff in charge of the child's care. The digital questionnaires were equipped with "smart jumping" features, so that questions that were irrelevant to the responder were never shown. For example, when the respondent was asked "did your child see a primary healthcare provider within four weeks before admission to this hospital for diabetes?", other questions regarding primary healthcare contacts were not visible if the answer was "no". For the paper respondents, all questions including those that were irrelevant, were visible. One questionnaire was for parents/caregivers (or children if > 15 years of age and fully capable of participating) and collected data on healthcare events within the four weeks before diagnosis of diabetes at hospital admission. The other questionnaire was for healthcare personnel (the attending pediatrician, or in some cases the nurse in charge of the child). This questionnaire mainly collected data on in-house events and measurements, such as laboratory values, clinical signs of brain edema, intensive care support, etcetera. For study II, a few questions were identical both in the questionnaire for healthcare personnel and for parents/caregivers, such as use of CSII or MDI, use of CGM, and access to ketone meters at home.

3.2 METHODS STUDY I - IV

STUDY I was an observational study of children with DKA at the onset of diabetes and included all cases from February 1, 2015, to January 31, 2017. All health care contacts within 4 weeks before admission were registered and the respondents were asked for data on the type of healthcare provider, the date of the contact with that healthcare provider, and if an emergency referral to hospital was arranged for the same day as the contact was made with the provider. Two separate questionnaires were used, one for the legal custodians/caregivers and another for the attending physician or nurse. The questionnaire for custodians/caregivers was used for preadmission data and the questionnaire for physicians for data during and after hospital admission.

The main purpose of the study was to characterize delay in referral. To this aim, delay was defined as 1) primary healthcare contacts for any or a combination of the classic diabetes symptoms described in table X within 1–28 days before admission for DKA without referral to a pediatric emergency ward the same day, 2) primary healthcare contacts the same day as hospital admission on the initiative of the caregiver without referral to a pediatric emergency ward, and/or 3) identification of hyperglycemia in a primary healthcare setting without referral to a pediatric emergency ward. The type of primary health care contacts included were person-to-person contacts with a physician or nurse; telephone contact with a medical professional from the Swedish National Healthcare Service; contacts with a school nurse or contacts with an operator from the national emergency telephone line. If several types of primary healthcare providers were contacted before hospital admission, then the first provider was considered the exposure in the study.

STUDY II included all children with established T1D who presented with DKA in a Swedish hospital during the time from February 1, 2015, to January 31, 2017. All hospitals with pediatric emergency capacity participated. As in Study I, data were collected through a questionnaire for the caregivers/legal custodians and another questionnaire for the physician or nurse in charge of the child's diabetes care. Both caregivers and healthcare personnel filled out data on the type of insulin delivery that was used at the time of admission for DKA, and for how long it had been used. Moreover, data on access to home ketone meters (so-called point-of-care ketone meters) and CGM was recorded

from both questionnaires. Laboratory and physiological measurements during and after admission were filled out by the physician or nurse.

STUDY III included all children registered in NDR from January 1, 2014, to December 31, 2019. The reason for the end date of the period was the beginning of CoViD-19 pandemic starting in early 2020, so that confounding effects from mass infections with SARS-CoV-2 would be avoided. The start period was chosen because Statistics Sweden utilizes different weights for calculation of equivalized disposable income from the year 2011, and since the exposure variable was based upon three consecutive years preceding the event (DKA). A binomial regression model with a log link was built to analyze if exposure to persistent relative risk of poverty was associated with the risk of DKA at the time of hospital admission for new-onset T1D. The statistical method was used under the assumption of a binomial distribution, and for calculation of relative risks. Assumptions of causal relationships between the exposure variables and the outcome variable were made, based on prior literature, tabulation of the main exposure variable across the hypothetical confounders, and tabulation of the outcome variable across the main exposure variable and other explanatory variables. A causal diagram was drawn from which the statistical model was built.

STUDY IV included all children registered in NDR from January 1, 2012, to December 31, 2019. The reason for the end of the period was the same as in Study III, namely, to avoid confounding from the CoViD-19 pandemic. The starting period also had to do with Statistics Sweden's newly changed weights for equivalized disposable income from 2011. However, in Study IV, the equivalized disposable income during the year before diagnosis of diabetes was divided into income quartiles. As in study III, assumptions were made regarding associations and causality between the main exposure variable (DKA at diagnosis of T1D) and the other explanatory variables and the outcome variable (the first recorded occurrence of a DKA episode within five years after the date of T1D diagnosis). For the Cox regression model, it was assumed that a registered DKA episode, having occurred sometime before the follow-up outpatient visit that recorded it, likely would have occurred temporally very close to that visit. Assumptions for the validity of both univariate and multivariable analyses were performed using Schoenfeld's test

and by visual assessment using log-log plots. Models for multivariable analyses are shown in figures 3-6.

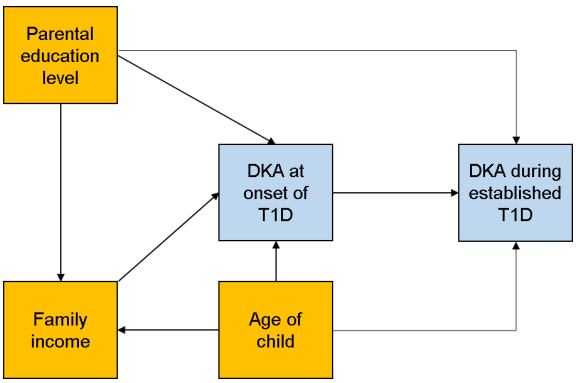

Figure 3. Assumed causal diagram for total effects of DKA at onset of T1D on the risk of DKA during established type 1 diabetes in children.

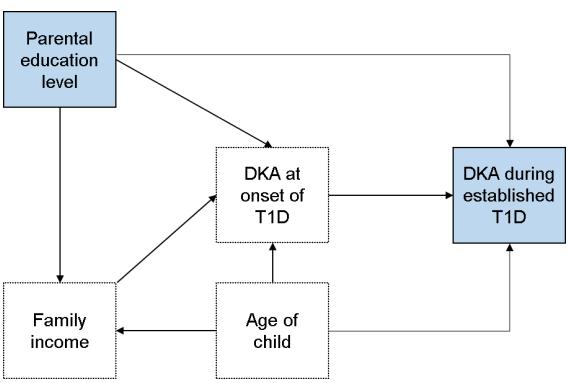

Figure 4. Assumed causal diagram for total effects of parental level of education at onset of T1D on the risk of DKA during established type 1 diabetes in children.

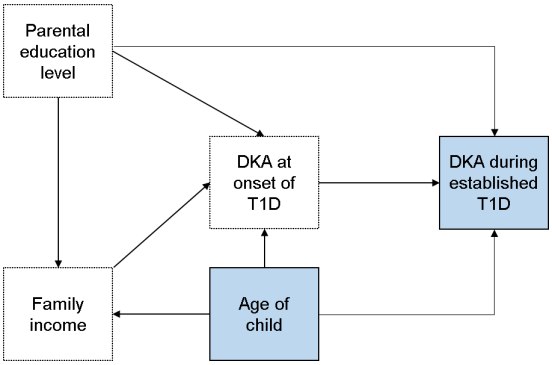

Figure 5. Assumed causal diagram for total effects of age of the child at onset of T1D on the risk of DKA during established type 1 diabetes.

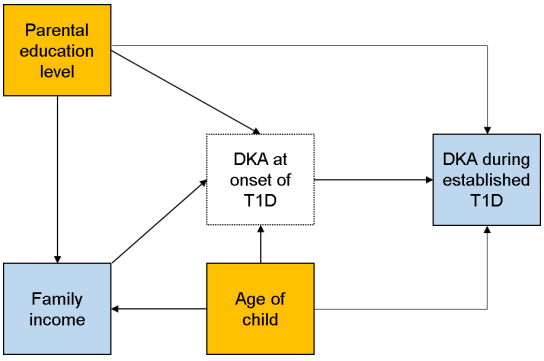

Figure 6. Assumed causal diagram for total effects of family income at onset of T1D on the risk of DKA during established type 1 diabetes in children.

3.3 ETHICAL APPROVALS

STUDY I

Permission for conduct of the study granted by Regional Ethical Review Board in Gothenburg, Sweden. (No. 748-14)

STUDY II

Permission for conduct of the study granted by Regional Ethical Review Board in Gothenburg, Sweden. (No. 748-14).

STUDY III

Permission for conduct of the study granted by the Swedish Ethical Review Authority (No. 2019-03600).

STUDY IV

Permission for conduct of the study granted by the Swedish Ethical Review Authority (No. 2019-03600).

4 RESULTS

4.1 STUDY I

There were 237 children with DKA included in the study, of whom 22 were not found in the NDR. With a total of 299 recorded children with DKA in the NDR, and an additional 22 patients from the study, the national coverage of the study was expected to be 74% (237/321) with the NDR as reference point.

In 39% of the cases, caregivers/custodians reported having had suspicions of new-onset diabetes before contacting the healthcare system. In 215/237 cases, data on the type of healthcare contact was available. In 59% of those cases, there were reports of primary healthcare contacts within four weeks before hospital admission for DKA. Whether delay or not had occurred, according to the study definition, could be clarified in 112 children. In this group, there were 48 children (43%) who did not receive an acute referral to hospital the same day as having contact with the healthcare provider. In all cases, symptoms that could be attributed to diabetes were reported to be present at the time of contact with the primary healthcare provider. Blood or urine glucose test were performed in 27% of the children who had seen a physician at a primary healthcare center.

Children with DKA at new-onset T1D had less metabolic derangement at hospital admission if there were reports of parental suspicion of diabetes before healthcare contacts were taken. Parental suspicion of diabetes before any healthcare contacts were taken predicted higher pH at hospital admission, both in univariate analysis ($p < 0.001$, 95% C.I. 0.053-0.13) and adjusted for sex and age in multivariable analysis ($p < 0.001$, 95% C.I. 0.058-0.129).

Children with delayed referral to hospital had significantly lower pH values than children who were admitted to hospital the same day as contacts with a primary healthcare provider (pH 7.15 vs 7.20, Figure 7). The difference in pH between these groups was statistically significant ($p=0.018$, Mann-Whitney U Test). Hodge-Lehmann's test to estimate median difference was -0.04 (95% C.I. -0.080 to – 0.010).

The distribution of different symptoms was similar in children with and without delayed treatment for T1D with DKA (Figure 8).

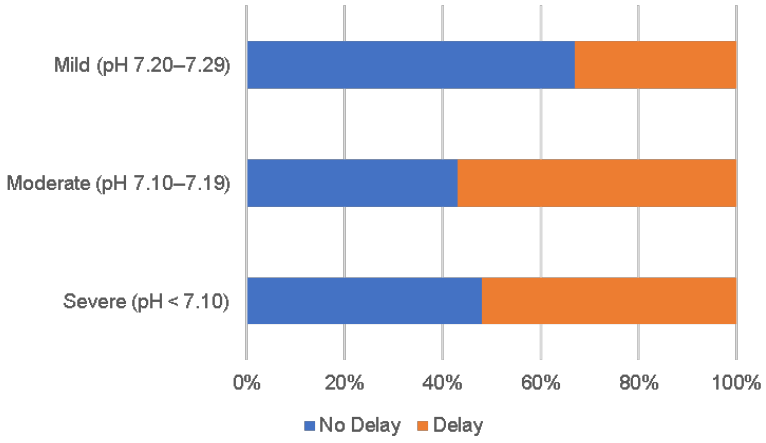

Figure 7. Diabetic ketoacidosis in children with or without delayed referral for new-onset type 1 diabetes in Sweden, divided into severity grades at hospital admission during the period February 1, 2015, to January 31, 2017 (Study I).

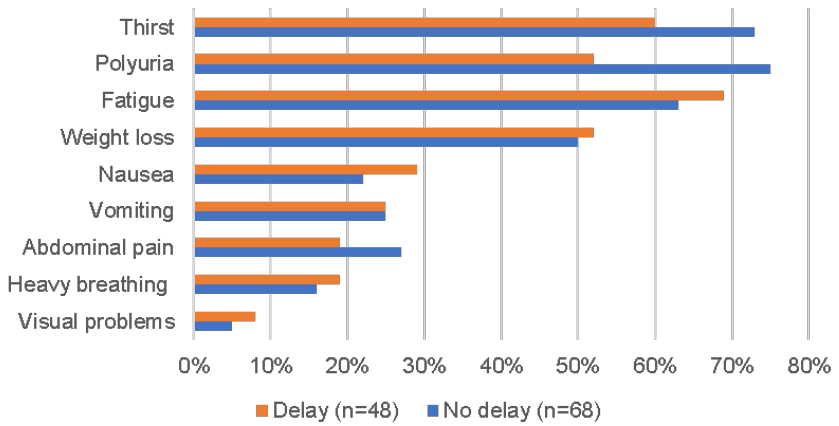

Figure 8. Distribution of reported symptoms at primary healthcare contacts among children with or without delayed referral for new-onset diabetes type 1 in Sweden during the period February 1, 2015, to January 31, 2017 (Study I)

4.2 STUDY II

The inclusion rate in the study was 84% compared with background data from the NDR (99 cases with DKA in the study and 118 cases registered in NDR). DKA episodes not recorded in the study were assumed to be missing at random.

The use of CSII was more common than expected among children admitted for DKA when compared to the total use of CSII during the study period. In total, CSII was used 60% of the time by the whole national pediatric population with T1D, and this was the proportion of children expected to use CSII at admission for DKA. However, 75% of the children used CSII at admission for DKA. This difference was significant ($p=0.002$), and the null hypothesis of this difference having occurred by chance was rejected.

This difference between total use of CSII in children with T1D and its use at the time of admission for DKA was only significant for children with mild metabolic derangement (pH 7.29 - 7.20). In this group, 85% used CSII at admission for DKA ($p<0.001$). Children with moderate/severe metabolic derangement (pH < 7.19) used CSII in a similar proportion to the total use during the study period (62% vs 60%, Figure 9). Multivariable regression analysis of exposure to either insulin delivery mode (CSII or MDI) on pH, adjusted for sex, age, and access to ketone meters and CGM (yes/no) showed higher mean pH for CSII ($p=0.028$) without significant interactions.

Mean HbA1c levels were substantially higher in children with MDI compared with CSII (Figure 10).

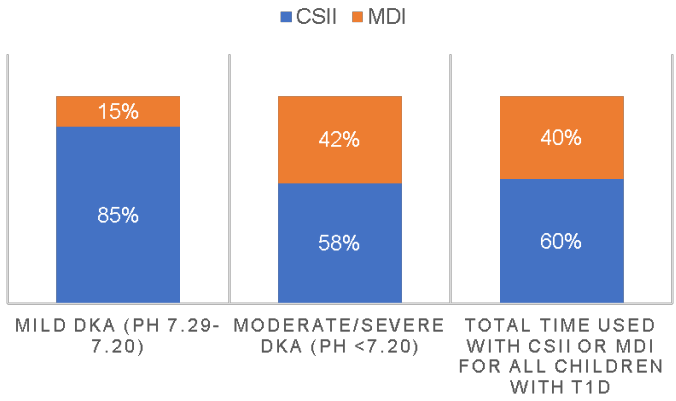

Figure 9. Distribution of CSII and MDI among children with established type 1 diabetes admitted to hospital for diabetic ketoacidosis, compared with the use of CSII in the national population during the period February 1, 2015, to January 31, 2017

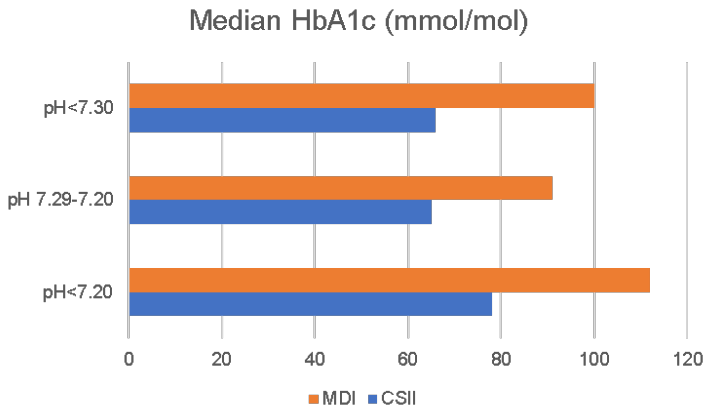

Figure 10. Median HbA1c levels among children with established type 1 diabetes admitted to hospital for diabetic ketoacidosis. CSII and MDI are compared for the period February 1, 2015, to January 31, 2017

4.3 STUDY III

In descriptive terms, DKA was more common in children from households exposed to persistent risk of poverty than in the rest of the population with new-onset T1D (30% vs 21%). There was strong evidence of an association between exposure to persistent risk of poverty and DKA at diagnosis of T1D under the significance level of 0.05. In univariate analysis, the risk of DKA was 44% higher among households with persistent risk of poverty (95% confidence interval 1.20 - 1.72, $p < 0.001$). In multivariable analysis adjusted for confounding from parental education level, parental cohabitation, and age at admission, the risk of DKA was 42% higher for children from households with persistent risk of poverty (95% confidence interval 1.13 - 1.79, $p=0.003$), without a significant interaction term between education level and the main exposure variable ($p=0.49$).

Sub-analyses of the effect of persistent risk of poverty on DKA, divided in severity grades, were performed for moderate/severe DKA (pH < 7.20) and severe DKA (pH < 7.10). These showed an increased risk of 76% for moderate/severe DKA (95% CI 1.31 - 2.37, $p = 0.001$), and 210% for severe DKA (95% CI 1.35 - 3.25, $p = 0.001$).

Univariate analyses were performed for sex, age, parental cohabitation, and parental education level. Sex and parental education level were not significantly associated with DKA. There was evidence that non-cohabiting parents entailed a 20% increased risk of DKA in univariate analysis (95% CI 1.02 – 1.41, $p=0.02$). As is known a priori from the annual reports from the NDR, age of the child at diagnosis of T1D was strongly associated with higher risk of DKA at diabetes onset in the study data, confirming data from the annual reports where children 2-4 years have the lowest proportion of DKA. Using the age group 2-4 years as reference point, the youngest children (9 months – 24 months) had 3.9 times higher risk of DKA, children 5-9 years 1.5 times higher risk, children 10-14 years 2.6 times higher risk, and children 15-17 years 2.3 times higher risk.

4.4 STUDY IV

Multivariable Cox proportional hazards models for the main exposure (DKA at onset of T1D) was built which included adjustments for age, parental education level, and income quartiles with the event-time equaling the time of the nearest follow-up with a record of a prior DKA episode. Three other models for age, parental level of education, and household disposable income were built according to assumptions described in Methods Study IV.

There was no evidence that DKA at onset of T1D in children was associated with another episode of DKA during established diabetes (hazard ratio 0.78, C.I. 0.39 - 1.6, p=0.47). There was a higher risk of DKA during established T1D for primary level of education compared to tertiary level (hazard ratio 5.8, p=0.001), and for secondary level of education compared to tertiary level (hazard ratio 1.8, p=0.031). There was also significant association between higher risk of DKA for children from the lowest household income quartile compared to the highest income quartile (hazard ratio 0.30, p=0.011).

5 DISCUSSION

5.1 CHILDREN WITH DKA AT ONSET OF TYPE 1 DIABETES

The findings in study I is in line with findings from other countries, which have also shown that delayed admission to hospital at onset of T1D might be a common problem. (83, 84, 112) The children included in Study I were not exposed to SARS-CoV-2 and the direct and indirect adverse public health effects of the CoViD-19 pandemic, and delayed diagnosis and treatment for diabetes was likely accentuated during the height of the pandemic. Global lockdowns, public reluctancy to seek medical evaluation, logistic problems in physical contacts with healthcare providers all contributed negatively, and the proportion of children with DKA at onset of diabetes increased in many countries. (113-117).

It has been shown that the more common T1D is in a population, the less common is DKA at onset of T1D. (69) This is likely due to early recognition of symptoms of diabetes in a population where awareness of typical symptoms is high. Sweden, being one of the countries with the highest prevalence of T1D in the world, has relatively few children with DKA at disease onset. Nonetheless, Study I showed that more than half of the children who presented with DKA had at least one primary healthcare contact for symptoms that could be attributed to T1D within four weeks before diagnosis of T1D, and many of these children were not immediately referred to hospital, which in turn seemed to carry a risk of worse metabolic derangement. On the other hand, children whose parents had suspected diabetes before contacting healthcare services had milder DKA at hospital admission. It may be that awareness of symptoms typical of T1D is indeed high in the general population and acts as a protective factor, while primary healthcare staff is less aware of T1D and more used to diagnosis and management of type 2 diabetes in the adult and the elderly population. If so, the urgency of the situation may not be apparent even if diabetes is on the list of differential diagnoses. However, misdiagnosis was also a reason of delay in some cases. From the study results there seem to be a need for awareness and education not only in the general population but also among healthcare practitioners.

Study I focused on delayed referral and did not include adjustment for socioeconomic background factors in multivariable analyses. Socioeconomic status (SES) is often used as an umbrella term for such factors. SES is a construct that encompasses many different (but not necessarily independent) variables, which can be thought of as an individual's societal coping resources. Such resources may have a protective role against both development of disease and complications of existing disease.

Maintaining HbA1c levels within recommended ranges is paramount in the pediatric age. A recent study found that poor metabolic control with high HbA1c levels in childhood predict increased mortality in adults <30 years, and the causal relationship between HbA1c levels and chronic diabetes complications is well established. (118-120) There are many recent studies that have found an association between DKA at onset of T1D and high HbA1c levels that may persist over long time. (121-124) The findings in these well-performed observational studies are important and not disputable as such and should raise concern. However, causal inference is not necessarily evident regarding the proposed physiological impact of DKA on long-term metabolic control in these children. Some of these studies discuss the hypothesis that DKA enhances beta-cell injury in children with clinical T1D, which in turn may contribute to impaired metabolic control and higher HbA1c levels compared with children without DKA at admission for new-onset diabetes. This may be an explanation of the findings, but DKA at onset of diabetes may also be an effect of more aggressive beta-cell destruction rather than a cause of beta-cell destruction. In other words, DKA could mediate the effect of rapid and severe beta-cell dysfunction on long-term metabolic control. Indeed, fulminant, rapid development of T1D has been discussed in relation to risk of DKA in recent publications. (125)

When discussing possible reasons for associations between low income and DKA, it is important to emphasize national differences. Countries may not be comparable in terms of the consequences of certain household disposable income level. Low income may indeed lead to increased risk of DKA generally, but for different reasons depending on the country in which the child is living. (126) Often, low income, level of education, occupational status, and in some countries private insurance status are expressed as a whole, in terms of SES when investigating exposures that may be related to certain health outcomes such as complications to T1D. In a country with highly accessible, publicly reimbursed healthcare services it may appear reasonable to assume that income per se does not affect utilization of healthcare but is rather a

mediator to other risk factors, such as level of education (assuming that the higher the level of education, the higher the income, and the higher the level of education, the better the health). In fact, high education has often been shown to be associated with better health. However, in Study III it was not apparent that the parents' level of education confounded the effect of low economic standard on the risk of DKA at T1D onset.

Rather than being too focused on causal inference, it may be more fruitful to investigate direct effects of certain exposures. It is yet to be analyzed in larger international surveys, that should include comparable countries, whether the association of a standardized measurement of low economic standard used by the OECD and Eurostat and DKA at onset of T1D can be externally validated.

5.2 CHILDREN WITH DKA DURING ESTABLISHED TYPE 1 DIABETES

From what was found in study II and IV evidence emerged that CSII, disposable income, and parental education level were associated with increased risk for DKA among children with established, known T1D. There are several other reports from different countries that also show increased of DKA among children with CSII, just as there are a number of studies that show the opposite. (86, 87, 89, 90, 127)

One of the challenges in comparing CSII with MDI are the ethical and practical difficulties that would arise in randomized-controlled designs (RCT). There have been attempts to conduct small RCTs (in which DKA was not the primary endpoint) but most studies are observational, and without any possibility to conduct RCTs with blinded, long-term longitudinal designs, interpretation and generalization of study results are challenging. (90) Moreover, as CSII technology is evolving fast, even relatively recent studies can rapidly become historical. Nonetheless, individualized treatment should be guiding care of children with T1D, also when choosing the insulin delivery type for a particular child. A comprehensive review of diabetes care by Cameron and Wherrett discusses CSII and MDI in a wider setting and emphasize the importance of individualized care, while also underlining the rapid, ongoing technological advances in CSII treatment. (128)

From the vast body of published literature and expert recommendations on the subject, technological advances and access to these advances are regarded as key parts of successful diabetes management. That is likely true for many children with T1D. However, in some large-population data, for example in Sweden, there has not been indications of neither statistically nor clinically significant differences in HbA1c levels between children with CSII and MDI. (129) There are instead data that support a higher risk of DKA with CSII in some populations, as demonstrated in Study II. However, for methodological reasons as mentioned above, it is not possible to draw the conclusion from the register alone that either one treatment is the "better" treatment for all children, or that they are equally effective for everyone. Again, individualized treatment and multi-dimensional views are paramount. In a recent publication, the authors discuss the problem with excessively technology-oriented views and put it eloquently: "the blame paradigm eschews that in suboptimal outcome situations the technology, the patient or the outcome measure are the things that 'need to change.' This paradigm though, has demonstratively not been successful at universally improving clinical outcomes after many years of experience." (130)

Therefore, when presenting the finding in study II that CSII was associated with higher risk of DKA, it would be oversimplified to simply state that DKA is more common among children with CSII without deepen the discussion of possible reasons for this. It is important to stress a few observations particular to the study. The first observation is that the higher risk for this insulin delivery type only was seen in children presenting with mild DKA, and that HbA1c levels among children with CSII and DKA were close to the population average. The second is that children with MDI at admission for DKA had considerably higher HbA1c levels. These distinctions are important, as hospital admission for mild DKA without alarming HbA1c levels indeed calls for closer follow-ups but does not necessarily warrant deeper concerns regarding the metabolic control of the child if the medical history points toward good maintenance of the disease. In fact, ketosis develops rapidly in case of interrupted insulin delivery from CSII, as only short-acting insulins are used with this type of insulin delivery type. A full night without insulin infusion may suffice to provoke symptoms of ketosis in this group of children. This can happen if the subcutaneous needle become dislocated or detached, or in any case when the continuous infusion stops, such as in an anecdotal example of a boy with excellent metabolic control whose cat chewed on the plastic infusion set at night, and who woke up with early symptoms of ketosis but was rapidly treated with oral water and insulin at home. With MDI, long-acting insulins

are administered, and considerably longer time spans are expected before DKA develops. With current recommendations of daily glucose tests during wake hours and high prevalence of CGM, DKA among children with MDI and high HbA1c vales instead points towards the possibility of skipped insulin doses by the child or the caregiver and/or misuse of the CGM system. The concomitant finding of high HbA1c levels adds to this concern and should warrant more thorough follow-up.

In addition to CSII, other technological features of daily diabetes care, such as ketone meters for home use and continuous glucose monitoring sensors (CGM) have been linked to lower rates of DKA. (87, 131-132) CGM is standard equipment for Swedish children and permits the user to check glucose levels at any time and may lower rates of DKA although evidence for this is not conclusive. (87, 133, 134) In Study II, it was found that CGM was used to a considerably lower extent among the study participants than in the general population with T1D. This possibly indicates that children who developed DKA did not use their advanced monitoring devices since CGM was used by 58% of the children with CSII and only 29% of the children with MDI compared with 80-90% in the national population during the study period. Use of diabetes technology can be assumed to be associated with the type of public funding program utilized in various countries. Regardless of conflicting results in publications comparing MDI and CSII with respect to the risk of DKA, it has been shown in various recent studies that the use of CSII correlates with better metabolic control. In fact, for this and many other reasons, ISPAD now strongly recommend the use of CSII instead of MDI whenever possible in its recent publication of clinical guidelines. (135) An interesting aspect of the use of monitoring devices is that lower socioeconomic status (which was not accounted for in Study II) has been shown to be associated with lower use of CGM and CSII in Swiss publications. (136) Access to blood ketone meters for use at home has been linked to decreased risk of DKA in various studies. In study II, most children (98%) with CSII had access to such meters but only 68% of children with MDI, which is concerning, although the multivariable regression analysis did not indicate access to ketone meters as an important confounder.

There are several studies from other countries than Sweden with opposite results, showing significantly lower rates of DKA in children treated with CSII compared with MDI. This may reflect the fact that countries differ regarding healthcare infrastructure and access to healthcare, socioeconomic population

factors, and that selection bias may cause different outcomes depending on the population studied, to name a few possible explanations.

There was not enough evidence to support the hypothesis that DKA at onset of T1D was associated with higher risk of DKA during established disease. Other studies have shown such an association but may not be comparable to a Swedish setting, and do not assume causality. (137, 138) There are several possible reasons for the inconclusive main result in Study IV. First, power is likely not large with only 63 events, and therefore significance test may not appropriately evaluate such an association. Second, the complex relationships between observed covariates and non-observed potential confounders may not be accurately reflected by the model for this study; for example, insulin delivery mode (CSII or MDI) was not included, and neither was CGM. Thirdly, there may not exist an association at all, although the lack of evidence in the study cannot be taken as evidence of lack. Fourth, it could be hypothesized that children with DKA at admission for new-onset T1D may even be at lower risk of another DKA episode, due to a greater awareness after an unpleasant and potentially life-threatening experience during the first admission to hospital at the time of diagnosis. All these speculations must be seen in light of their speculative nature and further research on larger populations may be needed to explore this question further.

There have been many publications that show associations between adverse social determinants of health and the risk of recurrent DKA. This is in line with the findings in Study IV, where low parental education level and low parental disposable income were associated with DKA in children with established diabetes. It is plausible to assume that there is indeed an association between DKA and socioeconomic factors, specifically defined as parental education level and family income in Study III and IV. Under this assumption, DKA at onset of diabetes mediates the effect of socioeconomic factors on the risk of DKA during established diabetes. The negative main result in study IV does not contradict this assumption, although a positive result would have strengthened it.

5.3 GENERAL REMARKS

DKA continues to inflict human suffering, public financial expenditure, risk of collateral injury, and strains healthcare resources. This condition is avoidable in principle and has been shown to be entirely preventable in at least one large-population intervention. One of the challenges is to achieve sustainability of large preventive campaigns aimed at raising awareness in whole populations including healthcare workers. It is inspiring that the positive effects in reducing DKA lasted for a remarkably long time in one awareness campaign. (95) The magnitude if this campaign has not been repeated in any other setting, to the knowledge of this writer. With the economic burden of many developing countries in mind, awareness-raising campaigns of this extent may be cost-effective and, from a logistical perspective, less challenging compared with the promising screening programs offered in high-income countries.

One group of children with T1D that warrants special consideration are those with immigrant backgrounds. In study I and II, these were not treated separately, and in study III and IV they were excluded from analyses to avoid bias, due to expected heterogeneity and a large proportion of missing data on the outcome variable for this group. Nonetheless, it is known from various studies that children from immigrant backgrounds may have higher risk of DKA, both at admission for new-onset diabetes and afterwards. (71, 139, 140) In study III, DKA was present in 33% of the children with foreign background at new onset T1D, which was higher than in the non-immigrant population. To address possible reasons for DKA, and to characterize socioeconomic characteristics and the extent of delayed referral in this group of children, it may be necessary to conduct future studies based on questionnaires since both Statistics Sweden and the NDR provide insufficiently precise data on people with foreign background. It is plausible to suspect that several factors have a role in adverse outcomes in this group. This may have to do with language difficulties, lower socioeconomic status, and lower prevalence of T1D in the country of origin leading to decreased awareness of diabetes symptoms in children. Indeed, the success of the awareness campaign by Vanelli et al. (95, 96) can perhaps be partly attributed to the fact that the poster information was written not only in Italian, but also in other languages.

5.4 METHODOLOGICAL CONSIDERATIONS

5.4.1 TOTAL STUDIES VS. SAMPLES

In a study that includes every individual in a finite population, or every event in a finite total of events, hypothesis tests may not be meaningful. For example: if the pH of all individuals in a national population is known, and if that population is assumed to be non-comparable to any other population, then a small difference of just 0.01 between males (mean pH 7.30) and females (mean pH 7.29) is a difference, full stop. This finding could perhaps warrant a discussion of clinical significance, but not of statistical significance. However, if the same national population were regarded as hypothetical sample of an "infinite" superpopulation, then hypothesis tests could indeed have meanings. This may be the case if a national population is studied during a certain time interval and the boundaries of that time interval are regarded as sample boundaries, on the condition that information that lies before and after the time interval is assumed to be comparable to the sample. Another hypothetical superpopulation is a hypothetical entity of "all possible individuals" including individuals from all other national populations.

5.4.2 CAUSAL DIAGRAMS

Causal diagrams are excellent tools to graphically illustrate assumptions in multivariable study designs, and to build statistical models at the same time. (141) Causal assumptions in models are based on sensible hypotheses, on prior knowledge, and sometimes on necessity. By necessity, we mean for example that the country of birth of an individual cannot be caused by that individual's income level or level of education, yet the opposite may (or may not) be true. By prior knowledge, we mean for example that there may be ample scientific evidence that country of birth is associated with income level in adulthood. By sensible hypotheses, we mean for example that income in adulthood (our outcome variable that we want to investigate), which is assumed to be associated with country of birth, may also be associated with level of education based on scientific reports. Since neither someone's level of education nor

income level can cause that person to go back in time to be born somewhere else, country of birth can only influence income and education level, not vice versa. So, put together; if the research question is whether level of education has effect on income level, and if country of birth has effects on both education and income, then country of birth potentially confounds the estimate of the total effect of education on income, and must be included in the multivariable analysis. If the research question instead would be if country of birth has a significant total effect on income, things become different. In this case, level of education should NOT be included in the analyses since it is a mediator and not a confounder of the effect of country of birth on income level.

5.4.3 QUESTIONNAIRES

Questionnaires are cost-effective and permit standardized question formulae that are identical for all participants (as opposed to interviews). This makes them useful for studies in which existing register data alone would not be sufficient to answer specific research questions. As an example, Statistics Sweden used questionnaires to estimate the proportion of children with "shared parenting" (children who stay equal amounts of time in each parent's home if the parents are separated, which is common in Sweden). This would not have been possible to estimate from register data from LISA database alone. Naturally, it can be the other way around, in that register data can instead be of importance as a complement to data from questionnaires, for example as they were used in study I and II in this dissertation, where the number of respondents (the number of children with DKA) from the questionnaires were compared with the number of children with DKA from the register, to estimate total inclusion rate from the national population. The design of questionnaires is a difficult matter. Recall bias has been extensively discussed and is of concern in every study design in which questionnaires have been used for data collection. (142-146) In Study I and II, the respondent knew that the child had DKA at the time of completing the questionnaire, and the respondent also knew about the study since oral and written information was given before consent to participation was granted.

Another limitation with questionnaires is that missing data are relatively common. Because of this, assumptions should be made about the mechanism of missingness. Unless the nature of missing data is addressed and assumptions

of the reasons of missingness are made, study results may be taken for granted without consideration of possible selection bias that may distort the results in unpredictable ways. (145)

5.4.4 INTERVAL-CENSORED DATA

In some data, such as medical records and patient registers, the time span from an exposure to an event may not always be precisely recorded. Such is the case with DKA in children with established diabetes in the NDR. During an outpatient visit, it is just recorded that a DKA episode has happened some time since the last visit. Such data are interval-censored. In populations with unevenly recorded time intervals, and with different interval lengths from one individual to another, this can cause bias, and special difficulties in model building can appear if time-dependent covariates, that may themselves be interval-censored, are included to adjust for confounding.

5.4.5 ASSUMPTIONS FOR THE COX PROPORTIONAL HAZARDS MODEL

As the name implies, the cox model requires the hazard ratio to be proportional (or constant) over time. It means that the relative risk of an event, or β in a regression model, is constant over time. If we do not have proportional hazards the assumption is not met, and the estimate may be biased. There are a few diagnostical approaches that can (and should) be used to help in evaluating the assumption of proportional hazards in a Cox model. One is an hypothesis test, often called Schoenfeld's test after its inventor, who also gave name to the Schoenfeld residuals used in the test. (147, 148) The mathematical explanations and proofs are complex, and for practical purposes it may suffice to know that a significant test is evidence against the null hypothesis of proportional hazards and is an argument against using a Cox model. Other ways to assess proportionality of the hazard ratio is graphical assessment of the assumption of proportional hazards. This can be done using log-log plots or Kaplan-Meier curves to visually check that the curves do not cross or show increasing deviation from each other over the time variable. These are

subjective but accepted assessments for validity of the assumption of the Cox model.

5.4.6 MECHANISMS OF MISSING DATA

In many studies, missing data are assumed to be a random subset of the studied population. This may not always be the case. If no assumption of the mechanism of missingness is made and the possibility of non-random selection of missing data is ignored, then a serious risk of biased results may be overlooked.

Rubin identified three principal mechanisms: missing completely at random (MCAR); missing at random (MAR); not missing at random (MNAR). (149) At a first glance, the difference between MNAR and the rest may seem obvious while the difference between MCAR and MAR may appear less evident.

MNAR occurs if the values of the outcome variable are themselves causing the missingness. This may be the case, for example, if participation in a non-anonymous drug screening would be offered by an employer who wishes to analyze factors associated with sick leave. In this setting, it is quite rational to assume that employees who are taking drugs will be less likely to participate, leading to bias and probably misleading results with heavy underestimation of the true extent of drug use. It is important to point out that MNAR cannot be entirely excluded in any dataset. There is always the possibility that the missing values are missing because of their actual value, had they been known.

In MCAR, which is probably the commonest assumptions in research articles, missing outcome data are simply assumed to be a completely random sample from the population. As such, excluding them from further consideration does not make a difference in terms of bias if this assumption holds true.

In MAR, some of the outcome data themselves are randomly missing, but one or more of the observed exposure variables are not randomly missing. A hypothetical example would be if a random sample of laboratory data went missing, and data on foreign backgrounds of the test persons also went missing, simply because data for many persons with foreign background were systematically left out. If the research question was how foreign background

influenced the laboratory outcome, the results would be biased, not because of the randomly missing laboratory data, but for the missing foreign background.

6 CONCLUSIONS

Delayed referral to hospital from primary healthcare providers is common and is associated with adverse outcome in children with new-onset T1D.

There is some evidence that use of CSII may increase the risk of DKA compared with MDI. A higher risk with CSII was seen only for mild DKA.

Even in a high-income country with universal access to publicly reimbursed healthcare, children from families with low economic standard have increased risk of DKA at onset of T1D.

There is no evidence that DKA at onset of T1D is associated with increased risk of recurrent DKA. The exposures that increase the risk of DKA at onset and during established T1D may be only partly overlapping. There is evidence that the child's age at diagnosis of T1D, low parental level of education, and low economic standard are associated with DKA after diagnosis, during established T1D.

Children with foreign background are likely a socially and economically vulnerably group as a whole, and therefore likely to be at higher risk of DKA. More research on this group is warranted in Sweden and elsewhere.

7 FUTURE PERSPECTIVES

Further development of new techniques, especially closed-loop systems (CLS) and automated insulin delivery (AID) systems have shown promising results in recent studies. (150) Interestingly, chronic complications of T1D seem to be less frequent with sensor-augmented insulin delivery systems regardless of similar HbA1c values when compared to MDI systems within the same population. Whether acute hyperglycemic complications, particularly DKA, are now less frequent with CSII compared to MDI in Sweden remains an open question. The technological advances are rapid in the field of CSII, and the data behind Paper II in this dissertation do not necessarily reflect the current situation in Sweden regarding the distribution of acute complications between CSII and MDI. However, all future insulin delivery systems that aim to mimic the normal pancreas are developments of insulin pumps with continuous insulin infusion. The availability of such systems, and the necessary infrastructure surrounding them, will depend on public and private financial resources in the countries where children with diabetes live.

Patient registers warrant continuous coordinated international cooperation and development. It will be of importance that national registers continue to develop, both for benchmarking and for research.

Screening for diabetes will likely be a very important tool to initiate timely treatment of type 1 diabetes before acute complications develop. Whether this can and should be done only in high-risk groups, or generally in all children at certain ages, remains to be investigated in future analyses.

Awareness campaigns have proven to be effective in the past, sometimes to point of reducing DKA to undetectable levels. Further spread and availability of information technology and social media could offer cost-effective means to increase awareness of symptoms of diabetes. In developing and low-income countries, who have vastly higher mortality rates from DKA and T1D than high-income countries, awareness campaigns may offer opportunities to reduce acute complications at onset of T1D.

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REFERENCES

1. Principles of Diabetes Mellitus. 3 ed: Springer Cham; 2017. 1066 p.

2. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes care. 2014;37(11):3124-31.

3. Fletcher AA. Early clinical experiences with insulin. Can Med Assoc J. 1962;87(20):1052-5.

4. Nathan DM. Realising the long-term promise of insulin therapy: the DCCT/EDIC study. Diabetologia. 2021;64(5):1049-58.

5. Hanssen KF, Bangstad HJ, Brinchmann-Hansen O, Dahl-Jørgensen K. Blood glucose control and diabetic microvascular complications: long-term effects of near-normoglycaemia. Diabet Med. 1992;9(8):697-705.

6. Hanssen KF, Dahl-Jørgensen K, Lauritzen T, Feldt-Rasmussen B, Brinchmann-Hansen O, Deckert T. Diabetic control and microvascular complications: the near-normoglycaemic experience. Diabetologia. 1986;29(10):677-84.

7. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

8. Group DCaCTR. 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. The Journal of pediatrics. 1994;125(2):177-88.

9. Johnson IS. Human insulin from recombinant DNA technology. Science. 1983;219(4585):632-7.

10. Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nat Rev Endocrinol. 2017;13(7):385-99.

11. Beran D, Lazo-Porras M, Mba CM, Mbanya JC. A global perspective on the issue of access to insulin. Diabetologia. 2021;64(5):954-62.

12. Edge JA, Nunney I, Dhatariya KK. Diabetic ketoacidosis in an adolescent and young adult population in the UK in 2014: a national survey comparison of management in paediatric and adult settings. Diabet Med. 2016;33(10):1352-9.

13. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2018;67(12):362-5.

14. Poovazhagi V. Risk factors for mortality in children with diabetic keto acidosis from developing countries. World J Diabetes. 2014;5(6):932-8.

15. Virdi N, Poon Y, Abaniel R, Bergenstal RM. Prevalence, Cost, and Burden of Diabetic Ketoacidosis. Diabetes Technol Ther. 2023;25(S3):S75-s84.

16. Dhatariya KK, Skedgel C, Fordham R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. Diabet Med. 2017;34(10):1361-6.

17. Dhatariya KK, Parsekar K, Skedgel C, Datta V, Hill P, Fordham R. The cost of treating diabetic ketoacidosis in an adolescent population in the UK: a national survey of hospital resource use. Diabet Med. 2019;36(8):982-7.

18. Tieder JS, McLeod L, Keren R, Luan X, Localio R, Mahant S, et al. Variation in resource use and readmission for diabetic ketoacidosis in children's hospitals. Pediatrics. 2013;132(2):229-36.

19. Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health Care Utilization and Burden of Diabetic Ketoacidosis in the U.S. Over the Past Decade: A Nationwide Analysis. Diabetes care. 2018;41(8):1631-8.

20. Allen C, Palta M, D'Alessio DJ. Risk of diabetes in siblings and other relatives of IDDM subjects. Diabetes. 1991;40(7):831-6.

21. Dahlquist G, Blom L, Holmgren G, Hägglöf B, Larsson Y, Sterky G, et al. The epidemiology of diabetes in Swedish children 0-14 years--a six-year prospective study. Diabetologia. 1985;28(11):802-8.

22. Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J, Knip M. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes care. 2013;36(2):348-54.

23. Erlich H, Valdes AM, Noble J, Carlson JA, Varney M, Concannon P, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes. 2008;57(4):1084-92.

24. Hippich M, Beyerlein A, Hagopian WA, Krischer JP, Vehik K, Knoop J, et al. Genetic Contribution to the Divergence in Type 1 Diabetes Risk Between Children From the General Population and Children From Affected Families. Diabetes. 2019;68(4):847-57.

25. Jacobsen LM, Vehik K, Veijola R, Warncke K, Toppari J, Steck AK, et al. Heterogeneity of DKA Incidence and Age-Specific Clinical Characteristics in Children Diagnosed With Type 1 Diabetes in the TEDDY Study. Diabetes care. 2022;45(3):624-33.

26. Isaacs SR, Roy A, Dance B, Ward EJ, Foskett DB, Maxwell AJ, et al. Enteroviruses and risk of islet autoimmunity or type 1 diabetes: systematic review and meta-analysis of controlled observational studies detecting viral nucleic acids and proteins. Lancet Diabetes Endocrinol. 2023;11(8):578-92.

27. Rewers M, Hyöty H, Lernmark Å, Hagopian W, She JX, Schatz D, et al. The Environmental Determinants of Diabetes in the Young (TEDDY) Study: 2018 Update. Curr Diab Rep. 2018;18(12):136.

28. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the

Endocrine Society, and the American Diabetes Association. Diabetes care. 2015;38(10):1964-74.

29. Frohnert BI, Ghalwash M, Li Y, Ng K, Dunne JL, Lundgren M, et al. Refining the Definition of Stage 1 Type 1 Diabetes: An Ontology-Driven Analysis of the Heterogeneity of Multiple Islet Autoimmunity. Diabetes care. 2023;46(10):1753-61.

30. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes care. 2022;45(Suppl 1):S17-s38.

31. Libman I, Haynes A, Lyons S, Pradeep P, Rwagasor E, Tung JY, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatric diabetes. 2022;23(8):1160-74.

32. Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. Diabetes care. 2004;27(7):1541-6.

33. Katz MA. Hyperglycemia-induced hyponatremia--calculation of expected serum sodium depression. N Engl J Med. 1973;289(16):843-4.

34. Palmer BF, Clegg DJ. Electrolyte and Acid-Base Disturbances in Patients with Diabetes Mellitus. N Engl J Med. 2015;373(6):548-59.

35. Oh G, Anderson S, Tancredi D, Kuppermann N, Glaser N. Hyponatremia in pediatric diabetic ketoacidosis: reevaluating the correction factor for hyperglycemia. Arch Pediatr Adolesc Med. 2009;163(8):771-2.

36. Ugale J, Mata A, Meert KL, Sarnaik AP. Measured degree of dehydration in children and adolescents with type 1 diabetic ketoacidosis. Pediatr Crit Care Med. 2012;13(2):e103-7.

37. Sottosanti M, Morrison GC, Singh RN, Sharma AP, Fraser DD, Alawi K, et al. Dehydration in children with diabetic ketoacidosis: a prospective study. Arch Dis Child. 2012;97(2):96-100.

38. Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? Jama. 2004;291(22):2746-54.

39. Koves IH, Neutze J, Donath S, Lee W, Werther GA, Barnett P, et al. The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. Diabetes care. 2004;27(10):2485-7.

40. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med. 2001;344(4):264-9.

41. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. J Clin Endocrinol Metab. 1996;81(1):314-20.

42. Green SM, Rothrock SG, Ho JD, Gallant RD, Borger R, Thomas TL, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. Ann Emerg Med. 1998;31(1):41-8.

43. Viallon A, Zeni F, Lafond P, Venet C, Tardy B, Page Y, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med. 1999;27(12):2690-3.

44. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AQ. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes care. 1980;3(1):15-20.

45. Tiwari LK, Jayashree M, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country: role of fluid refractory shock. Pediatr Crit Care Med. 2012;13(2):e91-6.

46. Jayashree M, Singhi S. Diabetic ketoacidosis: predictors of outcome in a pediatric intensive care unit of a developing country. Pediatr Crit Care Med. 2004;5(5):427-33.

47. Jawaid A, Sohaila A, Mohammad N, Rabbani U. Frequency, clinical characteristics, biochemical findings and outcomes of DKA at the onset of type-1 DM in young children and adolescents living in a developing country - an experience from a pediatric emergency department. J Pediatr Endocrinol Metab. 2019;32(2):115-9.

48. Marcin JP, Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. The Journal of pediatrics. 2002;141(6):793-7.

49. Azova S, Rapaport R, Wolfsdorf J. Brain injury in children with diabetic ketoacidosis: Review of the literature and a proposed pathophysiologic pathway for the development of cerebral edema. Pediatric diabetes. 2021;22(2):148-60.

50. Ma L, Roberts JS, Pihoker C, Richards TL, Shaw DW, Marro KI, et al. Transcranial Doppler-based assessment of cerebral autoregulation in critically ill children during diabetic ketoacidosis treatment. Pediatr Crit Care Med. 2014;15(8):742-9.

51. Roberts JS, Vavilala MS, Schenkman KA, Shaw D, Martin LD, Lam AM. Cerebral hyperemia and impaired cerebral autoregulation associated with diabetic ketoacidosis in critically ill children. Crit Care Med. 2006;34(8):2217-23.

52. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child. 2001;85(1):16-22.

53. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. The Journal of pediatrics. 2005;146(5):688-92.

54. Glaser NS, Marcin JP, Wootton-Gorges SL, Buonocore MH, Rewers A, Strain J, et al. Correlation of clinical and biochemical findings with diabetic ketoacidosis-related cerebral edema in children using magnetic resonance diffusion-weighted imaging. The Journal of pediatrics. 2008;153(4):541-6.

55. Glaser NS, Wootton-Gorges SL, Buonocore MH, Marcin JP, Rewers A, Strain J, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. Pediatric diabetes. 2006;7(2):75-80.

56. Glaser NS, Wootton-Gorges SL, Buonocore MH, Tancredi DJ, Marcin JP, Caltagirone R, et al. Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols. Pediatrics. 2013;131(1):e73-80.

57. Aye T, Mazaika PK, Mauras N, Marzelli MJ, Shen H, Hershey T, et al. Impact of Early Diabetic Ketoacidosis on the Developing Brain. Diabetes care. 2019;42(3):443-9.

58. Ghetti S, Kuppermann N, Rewers A, Myers SR, Schunk JE, Stoner MJ, et al. Cognitive Function Following Diabetic Ketoacidosis in Children With New-Onset or Previously Diagnosed Type 1 Diabetes. Diabetes care. 2020;43(11):2768-75.

59. Ghetti S, Kuppermann N, Rewers A, Myers SR, Schunk JE, Stoner MJ, et al. Cognitive function following diabetic ketoacidosis in young children with type 1 diabetes. Endocrinol Diabetes Metab. 2023;6(3):e412.

60. Cameron FJ, Scratch SE, Nadebaum C, Northam EA, Koves I, Jennings J, et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes care. 2014;37(6):1554-62.

61. Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C. Acute Kidney Injury in Children With Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis. JAMA Pediatrics. 2017;171(5):e170020-e.

62. Marzuillo P, Iafusco D, Zanfardino A, Guarino S, Piscopo A, Casaburo F, et al. Acute Kidney Injury and Renal Tubular Damage in Children With Type 1 Diabetes Mellitus Onset. J Clin Endocrinol Metab. 2021;106(7):e2720-e37.

63. Huang JX, Casper TC, Pitts C, Myers S, Loomba L, Ramesh J, et al. Association of Acute Kidney Injury During Diabetic Ketoacidosis With Risk of Microalbuminuria in Children With Type 1 Diabetes. JAMA Pediatrics. 2022;176(2):169-75.

64. Meena J, Yadav J, Kumar J, Dawman L, Tiewosh K, Mittal A, et al. Incidence, predictors, and short-term outcomes of acute kidney injury in children with diabetic ketoacidosis: a systematic review. Pediatr Nephrol. 2023;38(7):2023-31.

65. Hay RE, Parsons SJ, Wade AW. The effect of dehydration, hyperchloremia and volume of fluid resuscitation on acute kidney injury in children admitted to hospital with diabetic ketoacidosis. Pediatr Nephrol. 2023.

66. Shah AS, Nadeau KJ. The changing face of paediatric diabetes. Diabetologia. 2020;63(4):683-91.

67. Stanescu DE, Lord K, Lipman TH. The epidemiology of type 1 diabetes in children. Endocrinol Metab Clin North Am. 2012;41(4):679-94.

68. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. Jama. 2013;310(4):427-8.

69. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia. 2012;55(11):2878-94.

70. NDR. Annual report of the Swedish National Diabetes Register. 2020.

71. Cherubini V, Grimsmann JM, Åkesson K, Birkebæk NH, Cinek O, Dovč K, et al. Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. Diabetologia. 2020;63(8):1530-41.

72. Maahs DM, Hermann JM, Holman N, Foster NC, Kapellen TM, Allgrove J, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes care. 2015;38(10):1876-82.

73. Cengiz E, Xing D, Wong JC, Wolfsdorf JI, Haymond MW, Rewers A, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatric diabetes. 2013;14(6):447-54.

74. Smith CP, Firth D, Bennett S, Howard C, Chisholm P. Ketoacidosis occurring in newly diagnosed and established diabetic children. Acta Paediatr. 1998;87(5):537-41.

75. Ware J, Allen JM, Boughton CK, Wilinska ME, Hartnell S, Thankamony A, et al. Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes. N Engl J Med. 2022;386(3):209-19.

76. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. 2018;392(10155):1321-9.

77. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5(7):501-12.

78. Morone JF, Cronholm PF, Teitelman AM, Hawkes CP, Lipman TH. Underrepresented Voices: Impacts of Social Determinants of Health on Type 1 Diabetes Family Management in Single-Parent, Black Families. Can J Diabetes. 2022;46(6):602-10.e1.

79. Gesuita R, Maffeis C, Bonfanti R, Cardella F, Citriniti F, D'Annunzio G, et al. Socioeconomic Inequalities Increase the Probability of Ketoacidosis at Diagnosis of Type 1 Diabetes: A 2014-2016 Nationwide Study of 2,679 Italian Children. Frontiers in pediatrics. 2020;8:575020.

80. Hershey JA, Morone J, Lipman TH, Hawkes CP. Social Determinants of Health, Goals and Outcomes in High-Risk Children With Type 1 Diabetes. Can J Diabetes. 2021;45(5):444-50.e1.

81. Limenis E, Shulman R, Daneman D. Is the frequency of ketoacidosis at onset of type 1 diabetes a child health indicator that is related to income inequality? Diabetes care. 2012;35(2):e5.

82. Klingensmith GJ, Tamborlane WV, Wood J, Haller MJ, Silverstein J, Cengiz E, et al. Diabetic ketoacidosis at diabetes onset: still an all too common threat in youth. The Journal of pediatrics. 2013;162(2):330-4.e1.

83. Tas E, Wooley K, Tas V, Wang YA. Delayed Management of Insulin-Dependent Diabetes Mellitus in Children. J Pediatr Health Care. 2023;37(1):56-62.

84. Gunn ER, Albert BB, Hofman PL, Cutfield WS, Gunn AJ, Jefferies CA. Pathways to reduce diabetic ketoacidosis with new onset type 1 diabetes: Evidence from a regional pediatric diabetes center: Auckland, New Zealand, 2010 to 2014. Pediatric diabetes. 2017;18(7):553-8.

85. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. Bmj. 2011;343:d4092.

86. Karges B, Schwandt A, Heidtmann B, Kordonouri O, Binder E, Schierloh U, et al. Association of Insulin Pump Therapy vs Insulin Injection Therapy With Severe Hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes. Jama. 2017;318(14):1358-66.

87. Cardona-Hernandez R, Schwandt A, Alkandari H, Bratke H, Chobot A, Coles N, et al. Glycemic Outcome Associated With Insulin Pump and Glucose Sensor Use in Children and Adolescents With Type 1 Diabetes. Data From the International Pediatric Registry SWEET. Diabetes care. 2021;44(5):1176-84.

88. Brorsson AL, Viklund G, Örtqvist E, Lindholm Olinder A. Does treatment with an insulin pump improve glycaemic control in children and adolescents with type 1 diabetes? A retrospective case-control study. Pediatric diabetes. 2015;16(7):546-53.

89. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. Pediatric diabetes. 2009;10(1):33-7.

90. Blair JC, McKay A, Ridyard C, Thornborough K, Bedson E, Peak M, et al. Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomised controlled trial and economic evaluation. Bmj. 2019;365:l1226.

91. Bratke H, Margeirsdottir HD, Assmus J, Njølstad PR, Skrivarhaug T. Does Current Diabetes Technology Improve Metabolic Control? A Cross-Sectional Study on the Use of Insulin Pumps and Continuous Glucose Monitoring Devices in a Nationwide Pediatric Population. Diabetes Ther. 2021;12(9):2571-83.

92. Boughton CK, Hovorka R. New closed-loop insulin systems. Diabetologia. 2021;64(5):1007-15.

93. Tauschmann M, Hermann JM, Freiberg C, Papsch M, Thon A, Heidtmann B, et al. Reduction in Diabetic Ketoacidosis and Severe Hypoglycemia in Pediatric Type 1 Diabetes During the First Year of Continuous Glucose Monitoring: A Multicenter Analysis of 3,553 Subjects From the DPV Registry. Diabetes care. 2020;43(3):e40-e2.

94. Cherubini V, Marino M, Carle F, Zagaroli L, Bowers R, Gesuita R. Effectiveness of ketoacidosis prevention campaigns at diagnosis of type 1 diabetes in children: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2021;175:108838.

95. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes care. 1999;22(1):7-9.

96. Vanelli M, Chiari G, Lacava S, Iovane B. Campaign for Diabetic Ketoacidosis Prevention Still Effective 8 Years Later. Diabetes care. 2007;30(4):e12-e.

97. Choleau C, Maitre J, Elie C, Barat P, Bertrand AM, de Kerdanet M, et al. [Ketoacidosis at time of diagnosis of type 1 diabetes in children and adolescents: effect of a national prevention campaign]. Arch Pediatr. 2015;22(4):343-51.

98. Sims EK, Besser REJ, Dayan C, Geno Rasmussen C, Greenbaum C, Griffin KJ, et al. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. Diabetes. 2022;71(4):610-23.

99. Hummel S, Carl J, Friedl N, Winkler C, Kick K, Stock J, et al. Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation. Diabetologia. 2023;66(9):1633-42.

100. Weiss A, Zapardiel-Gonzalo J, Voss F, Jolink M, Stock J, Haupt F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia. 2022;65(12):2121-31.

101. McQueen RB, Geno Rasmussen C, Waugh K, Frohnert BI, Steck AK, Yu L, et al. Cost and Cost-effectiveness of Large-scale Screening for Type 1 Diabetes in Colorado. Diabetes care. 2020;43(7):1496-503.

102. Cherubini V, Chiarelli F. Autoantibody test for type 1 diabetes in children: are there reasons to implement a screening program in the general population? A statement endorsed by the Italian Society for Paediatric Endocrinology and Diabetes (SIEDP-ISPED) and the Italian Society of Paediatrics (SIP). Ital J Pediatr. 2023;49(1):87.

103. Ehrmann D, Kulzer B, Roos T, Haak T, Al-Khatib M, Hermanns N. Risk factors and prevention strategies for diabetic ketoacidosis in people with established type 1 diabetes. Lancet Diabetes Endocrinol. 2020;8(5):436-46.

104. Golden MP, Herrold AJ, Orr DP. An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. The Journal of pediatrics. 1985;107(2):195-200.

105. Jefferies CA, Nakhla M, Derraik JG, Gunn AJ, Daneman D, Cutfield WS. Preventing Diabetic Ketoacidosis. Pediatr Clin North Am. 2015;62(4):857-71.

106. White K, Kolman ML, Wexler P, Polin G, Winter RJ. Unstable diabetes and unstable families: a psychosocial evaluation of diabetic children with recurrent ketoacidosis. Pediatrics. 1984;73(6):749-55.

107. Hallgren Elfgren IM, Grodzinsky E, Törnvall E. Swedish Diabetes Register, a tool for quality development in primary health care. Prim Health Care Res Dev. 2013;14(3):250-7.

108. Charalampopoulos D, Hermann JM, Svensson J, Skrivarhaug T, Maahs DM, Akesson K, et al. Exploring Variation in Glycemic Control Across and Within Eight High-Income Countries: A Cross-sectional Analysis of 64,666 Children and Adolescents With Type 1 Diabetes. Diabetes care. 2018;41(6):1180-7.

109. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. European journal of epidemiology. 2019;34(4):423-37.

110. UNESCO. International Standard Classification of Education ISCED 2011. Montréal2012.

111. International Standard Classification of Education, ISCED 1997. In: Hoffmeyer-Zlotnik JHP, Wolf C, editors. Advances in Cross-National Comparison: A European Working Book for Demographic and Socio-Economic Variables. Boston, MA: Springer US; 2003. p. 195-220.

112. Baldelli L, Flitter B, Pyle L, Maahs DM, Klingensmith G, Slover R, et al. A survey of youth with new onset type 1 diabetes: Opportunities to reduce diabetic ketoacidosis. Pediatric diabetes. 2017;18(7):547-52.

113. Lawrence C, Seckold R, Smart C, King BR, Howley P, Feltrin R, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary centre during the COVID-19 pandemic. Diabet Med. 2021;38(1):e14417.

114. McGlacken-Byrne SM, Drew SEV, Turner K, Peters C, Amin R. The SARS-CoV-2 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes mellitus: A multi-centre study of the first COVID-19 wave. Diabet Med. 2021;38(9):e14640.

115. Goldman S, Pinhas-Hamiel O, Weinberg A, Auerbach A, German A, Haim A, et al. Alarming increase in ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the first wave of the COVID-19 pandemic in Israel. Pediatric diabetes. 2022;23(1):10-8.

116. Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J, et al. Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. Jama. 2020;324(8):801-4.

117. Hawkes CP, Willi SM. A trend towards an early increase in ketoacidosis at presentation of paediatric type 1 diabetes during the coronavirus-2019 pandemic. Diabet Med. 2021;38(4):e14461.

118. Samuelsson J, Samuelsson U, Hanberger L, Bladh M, Åkesson K. Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age-A population-based cohort study. Pediatric diabetes. 2020;21(3):479-85.

119. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood--a pilot study using two nation-wide population based quality registries. Pediatric diabetes. 2014;15(3):229-35.

120. Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;2014(2):Cd009122.

121. Clapin HF, Earnest A, Colman PG, Davis EA, Jefferies C, Anderson K, et al. Diabetic Ketoacidosis at Onset of Type 1 Diabetes and Long-term HbA1c in 7,961 Children and Young Adults in the Australasian Diabetes Data Network. Diabetes care. 2022;45(12):2918-25.

122. Duca LM, Wang B, Rewers M, Rewers A. Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Diabetes care. 2017;40(9):1249-55.

123. Fredheim S, Johannesen J, Johansen A, Lyngsøe L, Rida H, Andersen ML, et al. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia. 2013;56(5):995-1003.

124. Shalitin S, Fisher S, Yackbovitch-Gavan M, de Vries L, Lazar L, Lebenthal Y, et al. Ketoacidosis at onset of type 1 diabetes is a predictor of long-term glycemic control. Pediatric diabetes. 2018;19(2):320-8.

125. Luo S, Ma X, Li X, Xie Z, Zhou Z. Fulminant type 1 diabetes: A comprehensive review of an autoimmune condition. Diabetes Metab Res Rev. 2020;36(6):e3317.

126. Matthews S, Coates MM, Bukhman A, Trujillo C, Ferrari G, Dagnaw WW, et al. Health system capacity to manage diabetic ketoacidosis in nine low-income and lower-middle income countries: A cross-sectional analysis of nationally representative survey data. EClinicalMedicine. 2023;55:101759.

127. Pala L, Dicembrini I, Mannucci E. Continuous subcutaneous insulin infusion vs modern multiple injection regimens in type 1 diabetes: an updated meta-analysis of randomized clinical trials. Acta Diabetol. 2019;56(9):973-80.

128. Cameron FJ, Wherrett DK. Care of diabetes in children and adolescents: controversies, changes, and consensus. Lancet. 2015;385(9982):2096-106..

129. Fureman AL, Lilja M, Lind T, Särnblad S, Bladh M, Samuelsson U. Comparing continuous subcutaneous insulin infusion and multiple daily injections in children with Type 1 diabetes in Sweden from 2011 to 2016-A longitudinal study from the Swedish National Quality Register. Pediatric diabetes. 2021;22(5):766-75.

130. Cameron FJ, Arnold M, Gregory JW. Adolescent ambivalence about diabetes technology-The Janus faces of automated care. Pediatric diabetes. 2022;23(8):1717-24.

131. Vanelli M, Mastrorilli C, Fainardi V, Iovane B, Scarabello C, Veronese P, et al. Clinical utility of beta-hydroxybutyrate measurement in the management of physiological ketosis at home in children under 5. Acta Biomed. 2019;90(2):215-20.

132. Klocker AA, Phelan H, Twigg SM, Craig ME. Blood β-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in Type 1 diabetes: a systematic review. Diabet Med. 2013;30(7):818-24.

133. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. Diabetologia. 2022;65(4):604-19.

134. Laffel LM, Kanapka LG, Beck RW, Bergamo K, Clements MA, Criego A, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. Jama. 2020;323(23):2388-96.

135. Sherr JL, Schoelwer M, Dos Santos TJ, Reddy L, Biester T, Galderisi A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. Pediatric diabetes. 2022;23(8):1406-31.

136. Lomax KE, Taplin CE, Abraham MB, Smith GJ, Haynes A, Zomer E, et al. Socioeconomic status and diabetes technology use in youth with type 1 diabetes: a comparison of two funding models. Front Endocrinol (Lausanne). 2023;14:1178958.

137. Ampt A, van Gemert T, Craig ME, Donaghue KC, Lain SB, Nassar N. Using population data to understand the epidemiology and risk factors for diabetic ketoacidosis in Australian children with type 1 diabetes. Pediatric diabetes. 2019;20(7):901-8.

138. Karges B, Prinz N, Placzek K, Datz N, Papsch M, Strier U, et al. A Comparison of Familial and Sporadic Type 1 Diabetes Among Young Patients. Diabetes care. 2021;44(5):1116-24.

139. Cadario F, Cerutti F, Savastio S, Rabbone I, Tumini S, Bruno G. Increasing burden, younger age at onset and worst metabolic control in migrant than in Italian children with type 1 diabetes: an emerging problem in pediatric clinics. Acta Diabetol. 2014;51(2):263-7.

140. Hammersen J, Tittel SR, Warncke K, Fritsch M, Placzek K, Pacaud D, et al. Previous diabetic ketoacidosis as a risk factor for recurrence in a large prospective contemporary pediatric cohort: Results from the DPV initiative. Pediatric diabetes. 2021;22(3):455-62.

141. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.

142. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990;43(1):87-91.

143. Vrijheid M, Deltour I, Krewski D, Sanchez M, Cardis E. The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J Expo Sci Environ Epidemiol. 2006;16(4):371-84.

144. Jager KJ, Tripepi G, Chesnaye NC, Dekker FW, Zoccali C, Stel VS. Where to look for the most frequent biases? Nephrology (Carlton). 2020;25(6):435-41.

145. Eekhout I, de Boer RM, Twisk JW, de Vet HC, Heymans MW. Missing data: a systematic review of how they are reported and handled. Epidemiology. 2012;23(5):729-32.

146. Dalziel K, Li J, Scott A, Clarke P. Accuracy of patient recall for self-reported doctor visits: Is shorter recall better? Health Econ. 2018;27(11):1684-98.

147. SCHOENFELD D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika. 1980;67(1):145-53.

148. SCHOENFELD D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69(1):239-41.

149. Rubin DB. Inference and Missing Data. Biometrika. 1976;63(3):581-92.

150. Kariyawasam D, Morin C, Casteels K, Le Tallec C, Sfez A, Godot C, et al. Hybrid closed-loop insulin delivery versus sensor-augmented pump therapy in children aged 6-12 years: a randomised, controlled, cross-over, non-inferiority trial. Lancet Digit Health. 2022;4(3):e158-e68.

APPENDIX

STUDY I - IV