



Poor Metabolic Control in Children and Adolescents With Type 1 Diabetes and Psychiatric Comorbidity

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Stine M. Sildorf,¹ Nina Breinegaard,² Emilie B. Lindkvist,¹ Janne S. Tolstrup,³ Kirsten A. Boisen,⁴ Grete K. Teilmann,^{5,6} Anne Mette Skovgaard,^{3,7} and Jannet Svensson^{1,6}

OBJECTIVE

Type 1 diabetes is associated with an increased risk of psychiatric morbidities. We investigated predictors and diabetes outcomes in a pediatric population with and without psychiatric comorbidities.

RESEARCH DESIGN AND METHODS

Data from the Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids) and National Patient Register were collected (1996–2015) for this population-based study. We used Kaplan-Meier plots to investigate whether age at type 1 diabetes onset and average glycated hemoglobin (HbA_{1c}) levels during the first 2 years after onset of type 1 diabetes (excluding HbA_{1c} at debut) were associated with the risk of being diagnosed with a psychiatric disorder. Mixed-effects linear and logistic regression models were used to analyze HbA_{1c}, BMI, severe hypoglycemia (SH), or ketoacidosis as outcomes, with psychiatric comorbidities as explanatory factor.

RESULTS

Among 4,725 children and adolescents with type 1 diabetes identified in both registers, 1,035 were diagnosed with at least one psychiatric disorder. High average HbA_{1c} levels during the first 2 years predicted higher risk of psychiatric diagnoses. Patients with psychiatric comorbidity had higher HbA_{1c} levels (0.22% [95% CI 0.15; 0.29]; 2.40 mmol/mol [1.62; 3.18]; $P < 0.001$) and an increased risk of hospitalization with diabetic ketoacidosis (1.80 [1.18; 2.76]; $P = 0.006$). We found no associations with BMI or SH.

CONCLUSIONS

High average HbA_{1c} levels during the first 2 years after onset of type 1 diabetes might indicate later psychiatric comorbidities. Psychiatric comorbidity in children and adolescents with type 1 diabetes increases the risk of poor metabolic outcomes. Early focus on the disease burden might improve outcomes.

Type 1 diabetes in childhood has been found to be associated with an increased risk of psychiatric comorbidities (1–3), which might intensify the burden of disease and accelerate metabolic deterioration (4–6), subsequently increasing the risk of mortality and long-term complications such as retinopathy, nephropathy, and neuropathy (7–9).

Metabolic dysregulation is closely linked to age and diabetes duration, showing a peak in adolescence and early adulthood (10,11). Early adolescence is also

¹Department of Pediatrics and Adolescent Medicine, Herlev Hospital, Herlev, Denmark

²Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

³National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

⁴Center of Adolescent Medicine, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

⁵Department of Pediatrics and Adolescent Medicine, Nordsjællands Hospital, Hillerød, Denmark

⁶Institute of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

⁷Institute of Public Health, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Corresponding author: Jannet Svensson, jannet.svensson@regionh.dk.

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A.M.S. and J.S. contributed equally to this work.

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characterized as a time of psychological vulnerability (12), in which the incidence of major psychiatric disorders increases (13). A diagnosis of type 1 diabetes in early adolescence seems to increase psychological distress (1,2), and three large population-based studies have shown higher rates of psychiatric disorders in children and adolescents with type 1 diabetes compared with the general population (1–3). In particular, increased risk was seen for depression, anxiety, and eating disorders, where the pathogenesis is considered to involve reactive mechanisms and imbalances in the diathesis-stress system (1–3,14). One of these population-based studies, based on the Danish National Patient Register (NPR), found the highest risk of psychiatric comorbidity among children diagnosed with type 1 diabetes at age 10–14 years and among children with diabetes duration >5 years (2).

Another population-based study found increased glycated hemoglobin (HbA_{1c}) levels before diagnosis of a psychiatric disorder (3). However, a small longitudinal study failed to confirm this (15). It is unclear how soon before the diagnosis of psychiatric comorbidity that elevated HbA_{1c} levels can be detected.

Several clinical studies (16–20) and a few population-based studies (4–6) on children and adolescents with type 1 diabetes have detected high HbA_{1c} levels after the diagnosis of a psychiatric comorbidity. The German/Austrian diabetes register study group investigated HbA_{1c} levels and other diabetes-related outcomes in patients with psychiatric comorbidities, including depression, eating disorders, and psychosis. They obtained mixed results regarding BMI but observed that overall diabetes outcomes were poorer and characterized by higher HbA_{1c} levels, more episodes of severe hypoglycemia (SH) and diabetic ketoacidosis (DKA), and longer, more frequent hospitalizations (4–6).

Despite clinical and research evidence that a child with type 1 diabetes often receives more than one psychiatric diagnosis (1,3), most studies evaluate one disorder at a time (4–6,16–20).

Motivated by findings that Danish children and adolescents with type 1 diabetes have a higher risk of developing

a psychiatric disorder compared with the background population (2), we performed two studies based on the NPR and the Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids). First, we investigated age at diabetes onset and metabolic control within the first 2 years of type 1 diabetes as predictors of psychiatric comorbidity, including all psychiatric disorders (study A). Second, we investigated the association of psychiatric comorbidities with a broader range of diabetes-related outcomes in children and adolescents (study B).

RESEARCH DESIGN AND METHODS

Study Design and Population

This population-based study used personal identification numbers to merge data from national registries within Denmark. All Danish citizens have a unique civil personal registration (CPR) number (21). The CPR number can be used to accurately merge data from different national registers to generate comprehensive patient records (21). Danish citizens have free access to health care services, and almost all contact that children and adolescents have with hospitals, including psychiatric inpatient and outpatient settings, is with public hospitals. All children and adolescents with type 1 diabetes are monitored in public hospitals.

The NPR contains psychiatric and somatic diagnoses from all inpatient admissions to Danish public hospitals since 1977. From 1995 and onwards, the register includes inpatient, outpatient, and emergency details. The register has used the ICD-10 since 1994 (22,23). Data on registration of psychiatric and type 1 diabetes diagnoses were collected from the NPR, covering 1996 to April 2015.

DanDiabKids collects information on all children and adolescents diagnosed with type 1 diabetes before the age of 15 years and monitors them until they are transferred to adult clinics at ~18 years of age. All public hospital pediatric units must supply annual data on all patients with diabetes to DanDiabKids. The classification of type 1 diabetes is based on the guidelines drafted by the International Society for Pediatric and Adolescent Diabetes (ISPAD). DanDiabKids contains annual data on all registered patients since 1996, including information on quality indicators,

demographic variables, associated conditions, diabetes classification, diabetes family history, growth, self-management, and treatment variables. DanDiabKids now covers 99% of all Danish children and adolescents diagnosed with type 1 diabetes before the age of 15 years. However, the coverage of clinical data included in the register differs from year to year and ranges between 80% and 95% (24). Clinical data on all patients included in this study was collected from DanDiabKids for the years 1996–2015.

Our study population was generated by merging data from DanDiabKids and the NPR. The inclusion criteria were registration with type 1 diabetes in DanDiabKids, age at onset <15 years, year of onset 1995–2014, and year of birth after 1980. Clinical data were included until 30 April 2015, with visits until the age of 18 years. Data on registration of a psychiatric diagnosis were included for all patients during the entire observational period (1996–April 2015) (e.g., before onset of type 1 diabetes, while in pediatric care, and after referral to adult care).

Measures of Psychiatric Morbidity

In Denmark, the majority of children and adolescents in need of psychiatric assessment and treatment are referred to public hospitals. In these settings, patients are examined and diagnosed according to the clinical and diagnostic guidelines described by ICD-10 (13,23). Thereafter, records of the diagnoses are kept in the NPR.

The ICD-10 diagnoses included in this study as “any psychiatric disorder” were all diagnoses on mental and behavioral disorders from the F section, F00–99, and diagnoses from the X section, X60–84. The diagnoses are listed in Tables 1 and 2 (2,13).

Further, we grouped the included ICD-10 diagnoses in the following two groups: 1) neurodevelopmental/constitutional disorders and 2) potentially reactive disorders, as shown in Table 2. These subdivisions are based on the literature (14), previous research findings (1–3), and current classification schemes (23). We made the a priori assumption that disorders of early developmental and, hereby, constitutional origin (mental retardation, specific learning disorders, autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD),

Table 1—Frequencies of psychiatric diagnoses

ICD-10 diagnoses	Number
F0–9: Organic, including symptomatic, mental disorders	14
F10–19: Mental and behavioral disorders due to psychoactive substance use	190
F20–29: Schizophrenia, schizotypal and delusional disorders	55
F30–39: Mood (affective) disorders	205
F40–48: Neurotic, stress-related, and somatoform disorders, including anxiety disorder	492
F50: Eating disorders	75
F51–59: Behavioral syndromes associated with physiological disturbances and physical factors	12
F60–69: Disorders of adult personality and behavior	104
F70–79: Mental retardation	56
F80–83: Specific developmental disorders	72
F84: Pervasive developmental disorders, including autism spectrum disorders	114
F88–89: Other disorders of psychological development	14
F90, F98.8: Hyperkinetic disorder (ADHD) and ADD	172
F91–95, F98.0–98.6: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (excluding F90 and F98.8)	310
X60–X84: Intentional self-harm, including suicide attempts	27
Total number of diagnoses	1,912

Total number of diagnoses registered in the NPR for the 1,035 patients with both type 1 diabetes and a psychiatric comorbidity.

and other neurobehavioral and personality disorders) would show a different pattern of risk associations, compared with disorders that are considered more stress dependent and reactive in nature (emotional and affective disorders, eating disorders, disorders of substance abuse, self-harm, and suicide attempts).

Diabetes Outcome Variables and Covariates

Clinical data on all patients registered in DanDiabKids and the NPR were collected

from the DanDiabKids register for the period 1996 to April 2015. The variables and covariates included were as follows.

HbA_{1c}

HbA_{1c} levels were measured centrally using a high-pressure liquid chromatography method (Tosoh Bioscience, South San Francisco, CA) with a normal range of 4.3–5.8% (23.5–40 mmol/mol). HbA_{1c} levels were categorized as optimal control (HbA_{1c} <7.5% [<58 mmol/mol]),

intermediate control (7.5–8.5% [58–70 mmol/mol]), and high HbA_{1c} (HbA_{1c} >8.5% [>70 mmol/mol]).

SH

SH was defined according to the ISPAD guidelines as an event associated with severe neuroglycopenia resulting in coma or seizure and requiring glucagon or intravenous glucose (25).

DKA

DKA was defined by ISPAD guidelines as blood glucose >11 mmol/L, venous pH <7.3 or bicarbonate <15 mmol/L, and ketonemia and ketonuria (26).

BMI

BMI was calculated as height (cm)/weight (kg)² and converted to a BMI SD score (BMI-SDS) using national reference material (27).

Background Variables

The background variables were sex, age, diabetes duration (divided into three classes: 0–2, >2–4, and >4 years), and ethnicity (defined as Danish when at least one parent was of Danish origin, or immigrants and offspring of immigrants).

Treatment

Individuals self-monitoring blood glucose (SMBG) or using a continuous glucose monitoring sensor (CGMS) were categorized as SMBG (<3, 3–5, 6–9, or >10 times daily) or using a CGMS for a minimum of 6 days/month. Insulin treatment was categorized according to the basal type of insulin used and the injection method: Mixtard insulin, NPH insulin, or analog or pump treatment. The number of injections/boluses over a given period was included as a continuous variable.

Statistics

Descriptive Data

Data were described by suitable summary statistics: mean (SD) or number (n [%]). Time-dependent variables were summarized across all visits. Descriptive data for all children included mean age at type 1 diabetes diagnosis and mean diabetes duration at last visit. Frequencies were calculated for sex and ethnicity and minimum and maximum for birth year. HbA_{1c} levels, treatment (insulin type and dose), and self-management (insulin bolus injection and SMBG or use of CGMS) were summarized by the mean of all visits or sum over all visits. Observations were

Table 2—Categorization of psychiatric disorders

Disorders of neurodevelopment and constitutional origin	
F20–29	Schizophrenia, schizotypal and delusional disorders
F60–69	Disorders of adult personality and behavior
F70–79	Mental retardation
F80–83	Specific developmental disorders
F84	Pervasive developmental disorders, including autism spectrum disorders
F88–89	Other disorders of psychological development
F90, F98.8	Hyperkinetic disorder (ADHD) and ADD
F94	Disorders of early social functioning
F95	Tic disorders
Disorders of potentially reactive origin	
F10–19	Mental and behavioral disorders due to psychoactive substance use
F30–39	Mood (affective) disorders
F40–48	Neurotic, stress-related, and somatoform disorders, including anxiety disorders
F50, F98.2	Eating disorders
F91–93, F98.0–98.6	Behavioral and emotional disorders with onset in childhood and adolescence, excluding F98.2
X60–X84	Intentional self-harm, including suicide attempts
Uncategorized	
F0–9	Organic, including symptomatic, mental disorders
F51–59	Behavioral syndromes associated with physiological disturbances and physical factors, excluding eating disorders

presented for all children together and divided into two categories: with a psychiatric disorder or with type 1 diabetes only. For each child, visits prior to the first registered diagnosis of any psychiatric disorder were included in the category with diabetes only, whereas visits after this date were included in the category with any psychiatric disorder.

Study A: Predictors of Psychiatric Comorbidity

To investigate associations between psychiatric comorbidities and age at type 1 diabetes onset or mean HbA_{1c} within the first 2 years of type 1 diabetes onset, we estimated the cumulative incidence of psychiatric diagnoses using Proc Lifetest in SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC). Age at type 1 diabetes onset was grouped (0–5, 5–10, and 10–15 years old). Children with a psychiatric disorder before onset of type 1 diabetes were excluded. Mean HbA_{1c} levels were based on recordings made within 2 years after type 1 diabetes onset, excluding values measured at onset. The 2-year limit was chosen because DanDiabKids data are only collected once a year around the birthday of the child; therefore many children could still be in remission if only the first HbA_{1c} value registered in DanDiabKids was used to categorize HbA_{1c} groups. Mean duration of type 1 diabetes for the included HbA_{1c} levels was 1.26 years (range 0.5–2 years). In the analyses of the association between HbA_{1c} and the risk of psychiatric comorbidity, children diagnosed with a psychiatric disorder before type 1 diabetes onset or during the first 2 years were excluded. Unadjusted group comparisons were made using a log-rank test comparing the cumulative incidence between groups.

Study B: Outcome Measurements and Psychiatric Comorbidity

To compare HbA_{1c} levels between groups with or without psychiatric comorbidity, we used mixed-effects linear models for repeated measurements, with a random effect at the person-level, and an autoregressive residual correlation structure (SAS Proc Mixed). The first model with HbA_{1c} as outcome and psychiatric disorder as explanatory variable was adjusted for age (cubic), sex, diabetes duration (<2 years, 2–4 years, or >4 years), ethnicity, and visit year (5-year

intervals). In model 2, we added SMBG measurements and treatment as explanatory variables. All visits prior to a psychiatric diagnosis were categorized as time with no psychiatric disorder, whereas all subsequent visits were categorized as time with a psychiatric disorder. The linear models were repeated with psychiatric diagnoses divided into two main groups of psychiatric disorders (neurodevelopmental/constitutional disorders and potentially reactive disorders, as shown in Table 2) and a third group of children and adolescents diagnosed with a combination of neurodevelopmental/constitutional and potentially reactive disorders. All visits were coded according to the diagnoses the patient had at the time of the visit.

To test for differences in BMI-SDS between psychiatric groups, mixed-effects linear models were used. A mixed-effects logistic regression model (SAS Proc Glimmix) was used to compare the odds of SH events or DKA between the psychiatric groups. The models for BMI, SH events, and DKA were all adjusted for HbA_{1c} levels in addition to the covariates included in model 2.

Ethical Approval

The study was approved by the Danish Data Protection Agency. DanDiabKids was approved by ethics committee number KA 95139M. In Denmark, further ethical approval is unnecessary for studies that use only registry data.

RESULTS

Basic Characteristics

After merging DanDiabKids with the NPR, 4,725 children and adolescents with type 1 diabetes were identified; 259 with a diagnosis of type 1 diabetes were missing from the NPR and therefore excluded. The missing case subjects were evenly distributed through the years 1996–2014. Characteristics for the included subjects were as follows: mean age at onset of diabetes was 8.98 years (SD 3.81), birth year ranged from 1980 to 2013, mean age at last visit was 14.6 years (3.7), 2,462 (52.1%) were boys, mean duration of diabetes at last visit was 5.65 years (3.7), 4,434 (93.8%) were of Danish origin, 254 (5.4%) were immigrants or offspring of immigrants, and 36 (0.8%) had unknown ethnicity. Treatment and self-management characteristics can be found in Table 3.

The observed number of SH and DKA events per 100 person-years was respectively 10.7 (SH) and 3.2 (DKA) in patients with neurodevelopmental/constitutional psychiatric disorder, 12.1 (SH) and 3.7 (DKA) in patients with potentially reactive psychiatric disorder, 12.3 (SH) and 6.4 (DKA) in patients with both types of psychiatric disorders, and 8.1 (SH) and 1.8 (DKA) in patients without psychiatric disorder.

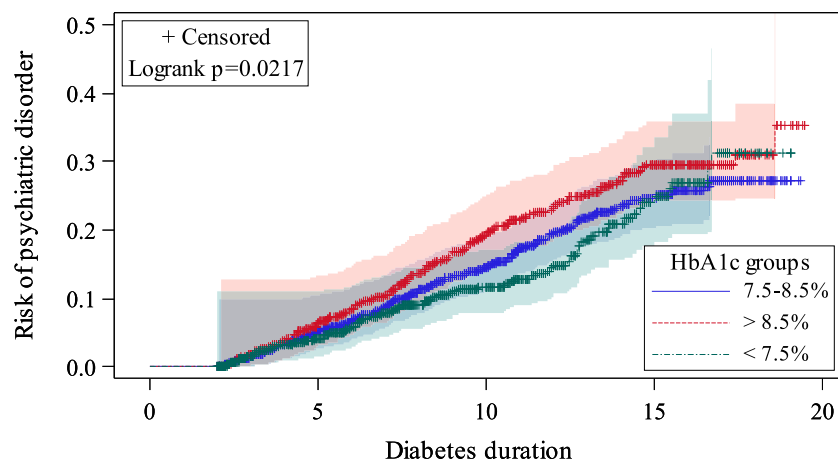
Incident Psychiatric Comorbidity

Among the 4,725 children and adolescents included in the study, 1,035 were diagnosed with at least one psychiatric disorder at some point. Of these, a total of 175 received their first psychiatric diagnosis before the onset of type 1 diabetes, 575 during pediatric care, and 285 were diagnosed after referral to adult care.

Psychiatric diagnoses among the 1,035 patients with psychiatric comorbidity are shown in Table 1. Anxiety disorders were the most common ($n = 492$), followed by “behavioral and emotional disorders” ($n = 310$), mood disorders ($n = 205$), psychoactive substance misuse disorders ($n = 190$), and disorders of inattention and hyperactivity (ADHD/attention-deficit disorder [ADD]) ($n = 172$). Of the 1,035 patients, 46% were diagnosed with two or more psychiatric disorders and 22.8% were diagnosed with three or more psychiatric disorders. The occurrence of diagnoses is presented in Supplementary Table 1.

Study A: Predictors of Psychiatric Comorbidity

The cumulative incidence of psychiatric disorders differed among age-groups ($P = 0.001$) (Fig. 1). Shortly after type 1 diabetes diagnosis, a higher estimated risk of psychiatric disorders was evident among patients who were 10–15 years old at onset of type 1 diabetes. However, after 15–20 years with diabetes, the differences among the groups leveled out at a risk of ~30% (Fig. 1). The cumulative incidence of psychiatric disorders also differed significantly among HbA_{1c} groups ($P = 0.02$) (Fig. 2). Children with high mean HbA_{1c} levels (>8.5% [>70 mmol/mol]) during the first 2 years showed the highest estimated risk of developing a psychiatric disorder, although these differences also appear to level out after 15–20 years with type 1 diabetes.



7.5-8.5%	1232	943	512	166	0
> 8.5%	825	675	388	154	0
< 7.5%	1089	731	329	84	0

Figure 2—Risk of psychiatric diagnosis as a function of diabetes duration (from onset of type 1 diabetes until end of the observational period in the NPR [30 April 2015]) in children and adolescents divided into three groups according to average HbA_{1c} values during the first 2 years after type 1 diabetes onset (excluding values measured at onset). Good metabolic control (<7.5% [<58 mmol/mol]), green line; intermediate metabolic control (7.5–8.5% [58 – 70 mmol/mol]), blue line; poor metabolic control (>8.5% [>70 mmol/mol]), red line.

in early adolescence for young people facing type 1 diabetes (12–14).

Few studies have examined HbA_{1c} levels prior to the diagnosis of a psychiatric disorder. The higher rate of psychiatric disorders in children with high average HbA_{1c} levels early after onset of type 1 diabetes is consistent with results obtained by Cooper et al. (3), who found a hazard ratio for any psychiatric disorder of 1.31, associated with a 1% (10 mmol/mol) increase in mean HbA_{1c} level, across all clinic visits between the diagnosis of type 1 diabetes and the psychiatric disorder. Many factors may affect metabolic control and the disease burden. These include the severity of the disease, socioeconomic status of the family, and the patient's ability to cope with a severe chronic condition. Problems associated with mental health (diagnosed or undiagnosed disorders) and cognitive capabilities (known or unknown disabilities) may also be exacerbated in the child and/or parents due to the many pressures and tasks required to control diabetes. Even though this register-based study does not explain the cause-effect relationship between HbA_{1c} levels and psychiatric comorbidities, poor metabolic control seen during the early years after onset of type 1 diabetes may be a marker of psychological burden.

Our finding that having a psychiatric disorder is associated with compromised treatment outcomes is consistent with previous clinical (16–20) and population-based studies (4–6) in pediatric populations; although previous studies have investigated individual disorders and none included the entire range of psychiatric disorders.

Our categorization of psychiatric disorders into overarching groups seems justified because nearly half of the patients had co-occurring psychiatric diagnoses. We found that having a psychiatric diagnosis from the potentially reactive disorder group or a combination of both types of disorder was associated with higher HbA_{1c} levels. In comparison, the German/Austrian diabetes register study generally found greater differences in metabolic outcome (0.3–0.8% [3.5 – 9 mmol/mol]) when they investigated individual diagnoses (4–6).

In the current study, no increased risk of higher HbA_{1c} levels was found in children with neurodevelopmental/constitutional disorders. Our finding may reflect the influences of health care on children with neurodevelopmental disorders in Denmark, possibly including the support of parents to follow the diabetes guidelines. Still, for the young people themselves, neurodevelopmental problems and associated

impairments in executive functioning may also result in poor adherence to diabetes treatments and a deterioration in metabolic control (19,20).

There were few events of SH or DKA in our population, indicating effective prevention of severe acute complications. However, we confirmed a link established by earlier studies (4–6) between psychiatric comorbidity and hospitalization due to DKA. We observed no effect of psychiatric comorbidity on BMI. This might be due to bidirectional effects on BMI caused by the particular groupings.

The greater differences in HbA_{1c} values and higher rates of acute complications in the German/Austrian studies compared with our results might be due to methodological differences. In the German/Austrian studies, registration depended on the diabetes team being aware of the psychiatric comorbidity and/or medication, whereas we used registrations from the NPR that were independent of diabetes treatment. When registration depends on the diabetes team, patients with high HbA_{1c} levels or more obvious psychiatric symptoms may be more likely to be registered. Additionally, the German/Austrian studies only included data from visits close to the observed diagnosis, whereas we included all subsequent visits.

Implications

Individual variance of HbA_{1c} trajectories in patients with childhood type 1 diabetes over time suggests that deterioration of metabolic control is not an inexorable condition of adolescents but a preventable complication (28). Our results point to an increased risk from disorders with a suggested diathesis-stress imbalance (14). The psychological burden raises the levels of counterregulatory hormones, increasing glucose production (29). This can amplify the demands/difficulties in adjusting insulin dosing in children and adolescents with type 1 diabetes and might influence cognitive function, increase family conflicts, affect school performance, and deteriorate health-related quality of life (30–32).

Reactive psychiatric disorders might be prevented if preliminary symptoms are targeted early and if patients are supported in their everyday life to

normalize life with diabetes (33,34). Psychological and problem-solving interventions have provided some success in improving metabolic control and psychosocial function (35–38).

Strengths and Limitations

The primary strength of this study is its nationwide scope, achieved by using a database that includes the vast majority of children and adolescents with type 1 diabetes. All psychiatric diagnoses were confirmed by a medical doctor and registered in the NPR with 100% coverage (13).

One limitation is that patients with psychiatric disorders diagnosed prior to 1995 in an outpatient public clinic and patients diagnosed by a private psychiatrist were not registered in the NPR. We do not have data on the number of patients treated outside of public hospitals but suspect this is uncommon for children (2). Additionally, the number of patients diagnosed prior to 1995 would be limited because only patients with diabetes onset after 1996 were included. As we do not have dates of remission or recovery for potentially reversible psychiatric disorders, all patients were registered with a psychiatric disorder from the time of diagnosis, and this disorder was used in all subsequent visits in the analysis of diabetes treatment outcomes. This is a potential limitation regarding reactive disorders, but taking into account the risk of recurrence or persistency of these disorders in youngsters facing chronic stressful experiences (12), we believe that our approach is acceptable. We did not have information on the treatment of psychiatric disorders, diabetes-related family stress, quality of life, or socioeconomic factors, all of which might influence diabetes outcomes and the burden of the disease (4,5,32,39,40).

Summary

The estimated risk of developing a psychiatric disorder during the 15–20 years after type 1 diabetes diagnosis is high. The most vulnerable period appeared to be adolescence. Patients with poorly regulated diabetes shortly after onset had a higher estimated risk of developing psychiatric comorbidities. Young patients diagnosed with a psychiatric disorder had more episodes of DKA, and those diagnosed within the reactive

spectrum had higher HbA_{1c} levels. Children and adolescents with type 1 diabetes, and in particular those who fail to reach treatment goals, should be systematically evaluated regarding psychological vulnerabilities.

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Author Contributions. S.M.S. conceived the idea for the study, designed the study, interpreted the results, participated in the discussion, wrote the first draft of the manuscript, and revised the manuscript and approved the final version. N.B. performed the statistical analyses, interpreted the results, participated in the discussion, and revised the manuscript and approved the final version. E.B.L., J.S.T., and K.A.B. interpreted the results, participated in the discussion, and revised the manuscript and approved the final version. G.K.T. conceived the idea for the study, interpreted the results, participated in the discussion, and revised the manuscript and approved the final version. A.M.S. designed the study, interpreted the results, participated in the discussion, and revised the manuscript and approved the final version. J.S. conceived the idea for the study, designed the study, performed statistical analyses, interpreted the results, participated in the discussion, wrote the first draft of the manuscript, and revised the manuscript and approved the final version. J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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