Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes : a population-based cohort study

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Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes: A population-based cohort study.

Running Title: Psychiatric disorders in children with diabetes.

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Abstract

Objective To assess the risk of psychiatric disorders and suicide attempts in children with type 1 diabetes and their healthy siblings.

Research Design and Methods We performed a population-based case cohort study of individuals born in Sweden between 1973 and 2009. Children with type 1 diabetes (*n*=17,122) and their healthy siblings (*n*=18,847) were identified and followed until their 18th birthday. Their risk of psychiatric disorders was compared with matched controls.

Results The risk of psychiatric morbidity in children with type 1 diabetes compared to the general population was tripled within 6 months after the onset of diabetes (hazard ratio, HR 3.0, 95% confidence interval, CI 2.7-3.4) and doubled within the total observation period (HR 2.1, CI 2.0-2.2). An increased risk was noted in suicide attempts (HR 1.7, CI 1.4-2.0) and in most categories of psychiatric disorders. The risk of psychiatric disorders in probands declined from HR 2.7 (CI 2.2-3.3) for those in the cohort born 1973-1986 to 1.9 (CI 1.8-2.0) in those born 1997-2009. The risk for any psychiatric disorders among siblings of patients with type 1 diabetes was estimated to be HR 1.1 (CI 1.0-1.1) and there was no increased risk in any of the specific category of disorders.

Conclusions Children with type 1 diabetes are at high risk of psychiatric disorders, which seems to be a consequence of the disease rather than due to a common familial etiology. The results support recommendations on comprehensive mental health surveillance in children with type 1 diabetes, especially in recently diagnosed children.

For decades, children with type 1 diabetes have been assumed to be at risk for psychiatric disorders. (1) Much of this assertion is based on clinical observations. (2-4) Also, large epidemiological studies have shown increased risks of psychiatric disorders in other chronic pediatric diseases (5; 6), and it is reasonable to assume that such associations may also be present for type 1 diabetes. Another theory has been that the threat of serious complications and strict treatment regimen put high demand on children and their caregivers, which in turn increase the risk for psychiatric disorders. (7) Nevertheless, the psychiatric disorders among children with type 1 diabetes have not yet been properly tested in large samples. Previous studies on the effect of childhood type 1 diabetes on the development of psychopathology have only used small and highly selected clinical samples. (7-12) These studies have produced equivocal and inconclusive findings. For example, three studies reported a two to threefold increased rate of psychiatric disorders in children with type 1 diabetes compared to their peers, (7-9) whereas other reports showed that there is no association. (11; 12)

Exploring the association between type 1 diabetes and risk of psychiatric disorders is of high importance for parents, pediatric endocrinologists and researchers and has implications for recommendations on care of children with type 1 diabetes. For example, are potential associations higher in connection with the onset of type 1 diabetes? Has the magnitude of the associations changed with changing treatment practice of type 1 diabetes during the last decades?

The main aim of our study was to assess the risk of psychiatric disorders in children with type 1 diabetes. To overcome limitations of previous studies we used Swedish registers with high coverage and prospectively collected information to study the risk of psychiatric disorders in a large, nationwide, population-based dataset. We hypothesized that children would be especially vulnerable to development of psychiatric disorders within a 6-month period after diagnosis of

type 1 diabetes. We also expected that secular changes in diabetes care and diagnostic practice in child psychiatry would influence the prevalence and risk of psychiatric disorders among children with type 1 diabetes. In addition, to investigate a possible mechanism behind the association between type 1 diabetes and psychiatric disorders we performed complementary analyses on the risk of psychiatric disorders among healthy siblings of probands. This enabled us to test the hypothesis that the association between psychiatric disorders and type 1 diabetes is caused by familial factors, where high risk of psychiatric disorders among healthy siblings of children with type 1 diabetes would support a familial effect.

RESEARCH DESIGN AND METHODS

Participants

We used data from the Swedish Pediatric Quality Registry (SWEDIABKIDS), Swedish National Diabetes Register (NDR), and the Swedish National Patient Register (NPR) to identify patients (probands) born in Sweden from 1964 onward with onset of type 1 diabetes before 18 years of age. Since 2000, the SWEDIABKIDS records data from all Swedish pediatric diabetes centers reaching 99% national coverage in 2007. (13) In 1996, the NDR was initiated as a quality measure in diabetes care at a national level. (14) Annual reports on patients treated for diabetes are delivered nationwide by hospitals as well as outpatient and primary care health centers. NDR provides information on type of diabetes, date of onset and insulin regimen. The NPR contains data on somatic and psychiatric inpatient health care since 1973 and outpatient care since 2001. (15)

For every patient with childhood onset type 1 diabetes we randomly selected 100 controls (unexposed individuals) from the Total Population Register. Probands and unexposed individuals were matched by sex, year and county of birth. The unexposed individuals were required to be born in Sweden after 1972, not have diabetes of any type before the age of 18 years, and be alive and living in Sweden at the time of diagnosis of diabetes of matched proband. (Description of study design on Supplementary Figure S1). Probands were divided into cohorts born 1973-1986, 1987-1996, and 1997-2009 based on the time of diagnosis of type 1 diabetes. These cohorts were chosen because they coincide with changes in ICD classification in Sweden (introduction of ICD-9 was 1987 and ICD-10 was in 1997). To investigate the mechanism behind the association between type 1 diabetes and childhood psychiatric disorders, we also studied psychiatric outcomes in full-siblings of the patients with type 1 diabetes (siblings of probands). Biological relationship with patients with type 1 diabetes was established through the Multi-Generation Register, which links children to their biological parents. (16) Healthy siblings of probands were defined as children of the same parents without a diagnosis of diabetes of any type before the age of 18. Similar to the comparisons between probands and unexposed, one hundred healthy control sibling pairs (unexposed siblings) were randomly selected and matched to each case-sibling pair by sex, year and county of birth of both siblings. Both subjects in the relative control pair were required to be free of a diabetes diagnosis of any type prior to the age of 18. (Supplementary Figure S2).

Exposure

Type 1 diabetes was defined as having such a diagnosis in the SWEDIABKIDS or NDR or an ICD code in the NPR (ICD-8: 250.00– 250.09; ICD-9: 250A–250X; ICD-10: E10). ICD-8 and 9 do not distinguish between type 1 and type 2 diabetes, but in our age range (<18 years) these

codes identify type 1 diabetes with high positive predictive value as type 2 diabetes is rather infrequent in the Swedish population up 18 years of age." (17) We excluded 70 children who were later re-diagnosed as having monogenic diabetes (not type 1 diabetes). Furthermore, 153 patients were diagnosed with type 1 diabetes outside Sweden and therefore excluded from further analysis due to uncertain date of diagnosis and psychiatric morbidity prior to diabetes.

Outcome variables

Outcome variables related to psychiatric disorders were obtained from the NPR. The variables were defined in accordance with ICD classifications: 1) any psychiatric disorders (ICD-8 codes 290-315; ICD-9 codes 290-319; ICD-10 codes F00-F99), 2) suicide attempt (ICD-8/ICD-9 codes E950-E959 or E980-E989; ICD-10 codes X60-X84 or Y10-Y34), 3) psychotic disorders (ICD-8 codes 295, 297-299; ICD-9 codes 295, 297, 298; ICD-10 codes F20-F29), 4) mood disorders (ICD-8 codes 296, 300.4; ICD-9 codes 296, 300E, 311; ICD-10 codes F30-F39), 5) anxiety, dissociative, stress-related, somatoform disorders (ICD-8 code 300 except 300.4, codes 307; ICD-9 code 300 except 300.E, or 308-309; ICD-10 codes F40-F45, F48), 6) eating disorders (ICD-9 codes 307B, 307F; ICD-10 code F50), 7) psychoactive substance misuse (ICD-8 codes 291, 303, 304; ICD-9 codes 291, 303, 304, 305A or 305X; ICD-10 codes F10-F19), 8) Attention deficit hyperactivity disorder (ADHD) (ICD-9 code 314; ICD-10 code F90), 9) Autism spectrum disorder (ASD) (ICD-9 code 299; ICD-10 code F84), 10) intellectual disability (ICD-8 codes 310-315; ICD-9 codes 317-319; ICD-10 codes F70-F79), and 11) other behavioral disorders (ICD-9 codes 312-313; ICD-10 codes F91-F98).

Covariates

Information on sociodemographic characteristics was obtained by linkage to the biological parents through the Multi-Generation Register. (16) Parental psychiatric morbidity was defined as at least one event of: psychiatric diagnosis (ICD-8 codes 290-315; ICD-9 codes 290-319; ICD-10 codes F00-F99) or suicide attempt (ICD-8/ICD-9 codes E950-E959; ICD-10 codes X60-X84 in the NPR) or death by suicide (obtained from the Cause of Death Register). (18) Data on parental country of birth came from the Migration Register. Parental level of education was extracted from the Education Register, the LISA database (the longitudinal integration database for health insurance and labor market studies by Swedish acronym), and the Population Censuses from the years of 1970, 1975, and 1985. (19; 20) In all patients, the highest level of education obtained by either parent was used in the multivariate analyses. The Medical Birth Register provided data on perinatal factors. (21)

Statistical analysis

Baseline characteristics were compared between probands and controls by a chi^2 test or Student t test for mean values (Supplementary Table S1). Because of baseline differences between groups, not fully controlled by matching, subsequent analyses were additionally adjusted for covariates. The risk of psychiatric disorders (outcome) related to diagnosis of type 1 diabetes (exposure) was estimated with Cox's proportional-hazards model conditioned on the matching variables (sex, year and county of birth). Follow-up began on diagnosis of diabetes (the date of first dose of insulin) and ended with first reported event of the diagnosis of psychiatric disorder, emigration from Sweden, death, or end of the study period (31st January 2010). Censoring dates of death or emigration were extracted from the Cause of Death Register and the Migration Register, respectively. (18; 22) To control for censored observations prevalence of psychiatric disorder was calculated by the Kaplan-Meier method. The prevalence of psychiatric disorders was

estimated for the 10-year period after the onset of diabetes. This enables further comparison of estimates between cohorts and previously reported clinical samples.

Likewise, using the sibling data, we analyzed the relation between exposure (having a sibling with type 1 diabetes) and outcome of psychiatric disorders with Cox's model. The sibling cohorts were observed since their birth to the end of observation defined as above. Similarly, siblings of controls were observed from birth. As a side note, this will automatically result in a slightly higher prevalence among the controls to probands compared to controls of siblings. A robust sandwich estimator function was used to adjust for family clusters. Missing data were not replaced by any method but categorized as "unknown" for analyses. Statistical analyses were undertaken with SAS software (version 9.3; Cary, NC, USA). The study was approved by the Regional Ethics Committee at Karolinska Institutet, Stockholm, Sweden.

RESULTS

Baseline characteristics

The mean age at onset of type 1 diabetes was 9.3 years; SD: 4.5. The median follow-up time of the patients with type 1 diabetes was 5.8 (IQR 2.8-9.4) years.

Baseline characteristics of probands with type 1 diabetes, their healthy siblings and their matched controls are presented in Supplementary Table 1. Parents of probands were more likely to be over 35 years of age at the time of child's birth, have Scandinavian origin and upper secondary level of education compared to the parents of their peers. Probands seemed to more often be born moderate to late preterm (32 – 36 gestational age), with high birth weight (>3500g) and large for gestational age. In 403 (2.4%) probands psychiatric disorders were recognized before the onset

of type 1 diabetes, significantly more often than among controls in the same age (N=33928, 2.0%). Subsequent analyses were adjusted to those discrepancies between groups.

The risk for psychiatric disorders

In total, psychiatric disorders were recognized in 1428 (8.3%) probands, of whom 259 had more than one disorder. After adjustment for sociodemograhic and perinatal factors, probands were 2.1 times more likely to receive psychiatric diagnoses and 1.7 times more likely to attempt suicide than controls (table 1). Probands had an increased risk for mood disorders (hazard ratio, HR 2.0, 95% CI 1.8 - 2.3), anxiety disorders (HR 1.6, CI 1.4 - 2.0), eating disorders (HR 2.2, CI 1.8 - 2.6), substance misuse (HR 2.6, CI 2.4 - 2.9), attention deficit hyperactivity disorder (HR 1.5, CI 1.3 - 2.7), behavioral disorders (HR 2.2, CI 2.0 - 2.4), autism spectrum disorder (HR 1.7, CI 1.4 - 2.0), and intellectual disability (HR 1.8, CI 1.5 - 2.1) compared with healthy peers.

Increased risk of suicidal attempts was significant only for diagnoses from inpatient (HR 1.8, CI 1.5 - 2.2), but not for outpatient care (HR 1.4, CI 1.0 - 2.0; p=0.07). Other psychiatric diagnoses were significant for both in- and outpatient care (data not shown).

Overall, risk of psychiatric disorders increased with age at onset of type 1 diabetes (age of onset < 7 years: HR 1.9, CI 1.7 to 2.0 vs age of onset > 12 years: HR 2.4, CI 2.1 - 2.6). The highest risk of psychiatric disorder in all age groups was noted within the first 6 months after diagnosis of type 1 diabetes and declined with time (table 2).

Changes in the prevalence and risk of psychiatric disorders in type 1 diabetes during 1973-2009

The overall prevalence of psychiatric disorders in probands was 11.4% (95% CI, 10.8% - 12.0%) in 10 years after the onset of type 1 diabetes in the entire sample. When analyzed by cohort, the 10-year prevalence of psychiatric disorders increased threefold over the period of the study

(Table 3). The prevalence was lowest in the cohort with onset of type 1 diabetes in 1973-1986 (4.6%, 95% CI, 3.7% - 5.7%), when psychiatric diagnoses were based on the 8th version of ICD classification. The prevalence of psychiatric disorders doubled in 1987-1996 with the 9th version of ICD (8.4%, 95% CI, 7.5% - 9.4%). Introduction of ICD-10 resulted in further increase in prevalence of psychiatric disorders (15.3%; 95% CI, 14.4% - 16.3%) in 1997-2009. This was true for all groups of disorders. A similar trend was observed in the healthy controls, where the 10-year prevalence of psychiatric disorders was 1.5 (95% CI, 1.5% - 1.6%), 3.1 (95% CI, 3.0% - 3.1%), 8.7 (95% CI, 8.7% - 8.8%), respectively for ICD-8, ICD-9 and ICD-10. Interestingly, the risk of psychiatric disorders among probands in comparison to controls actually declined (HR 2.7, CI 2.2 - 3.3 for ICD-8; HR 2.5, CI 2.6 - 2.7 for ICD-9; HR 1.9 CI 1.8 - 2.0 for ICD-10). This trend was particularly evident in suicide attempts, behavioral disorders and intellectual disabilities (Table 3).

Siblings of patients with type 1 diabetes

Psychiatric disorders were observed in 1059 (5.6%) siblings of probands and 191 of these children received two or more psychiatric diagnoses. The adjusted risk for childhood psychiatric disorders among healthy full siblings of a patient with type 1 diabetes was estimated at HR 1.1 (CI 1.0 - 1.1); for suicide attempts the HR was 1.2 (CI 1.0 - 1.4; p=0.12). When analyses were conducted separately for different categories of psychiatric disorders, none of the categories were statistically significant (table 4).

CONCLUSIONS

This is the first large scale population-based study on risk for psychiatric disorders in children with type 1 diabetes. Our findings support previous clinical observations that these patients are at

increased risk for psychiatric morbidity. (3; 4) We found increased risks for different diagnostic categories of disorders suggesting that psychological assessment restricted to mood and anxiety disorders probably is too limited. (23) Furthermore, our findings offer valuable insight into the etiology of psychiatric comorbidity in type 1 diabetes. Lack of risk of psychiatric disorders among siblings of patients suggests that there is no shared genetic susceptibility between those conditions. (24)

Results in relation to other studies

Our findings provide robust evidence for psychiatric comorbidity in pediatric patients with type 1 diabetes. Previous case-control studies have yielded inconsistent results, primarily due to insufficient power for dichotomous variables. (26-29)

Results from this study confirm previous observations on high risk for psychiatric disorders within the first 6 months of diabetes. This may be related to a crisis reaction hampering adjustment to treatment requirements, but it may also involve poor disease control in the initial phase. (4) A recent study by Cameron at al. demonstrated that impaired mental state in children with new-onset type 1 diabetes may be attributed to the brain injury related to severe ketoacidosis. (25)

Our data provide evidence for cohort effects in the prevalence and the risk of psychiatric disorders among children with type 1 diabetes. In our sample, the prevalence of psychiatric disorders 10 years after onset of type 1 diabetes tripled from 3.8% in those born 1973-1986 to 16.7% for the cohort born 1997-2009. The 10-year prevalence was studied previously by Kovacs et al, who found that 47.6% from cohort diagnosed with type 1 diabetes between 1981-1984 developed psychiatric disorders. (3) However, methodological discrepancies between register-

based and case-series observational studies make comparison with this study difficult. Changes in diabetic care such as more demanding insulin regimens and higher responsibility of youths and their caregivers for treatment decisions could theoretically be an explanation for the increased psychological burden in patients with type 1 diabetes in recent years. But, similar trends among controls suggest that more general factors are responsible for the increase rates of psychiatric disorders. Most likely, this trend is related to changes in ICD classification and secular drift in diagnostic praxis. A meta-analysis showed that in more recent studies the differences in psychiatric symptoms between children with diabetes and controls were actually smaller than observed previously. (26) When we stratified our analysis on the time of diabetes diagnosis, we noted steady decline in the relative risk of psychiatric disorders among probands compared to controls. This suggests that advances in diabetes care made over the past four decades, such as the introduction of an intensive insulin treatment in children allowing more flexible lifestyle and dietary freedom compared to conventional insulin regimen, might be associated with the reduced risk of mental health problems.

Implications

We showed that psychiatric comorbidity in children with type 1 diabetes is more complex than previously thought. Diabetes increased risk for most categories of psychiatric disorders and almost one fifth of children with diabetes and psychiatric disorders had two or more psychiatric disorders. This supports existing recommendations of comprehensive care of children with type 1 diabetes. (27) Regular screening for disorders with available simple measures (i.e mood and anxiety disorders) would be valuable. A close cooperation between pediatric diabetes teams and mental health professionals is needed to monitor the mental health in children with type 1 diabetes.

Our findings have also implications for etiological research, as comorbidity between two diseases may result from common etiological risk factors. Shared genetic susceptibility has previously been proposed as a rationale for higher risk of autism spectrum disorders in type 1 diabetes. (28) To assess whether this hypothesis may explain psychiatric comorbidity in type 1 diabetes, we evaluated the risk of different groups of psychiatric disorders also in healthy siblings of children with type 1 diabetes. We expected that healthy siblings should have, similar to their brothers and sisters with diabetes, higher risk of psychiatric disorders than general population. Slightly higher risk of any psychiatric disorder was noted among the siblings. However, despite adequate power (>80% for HR=1.2) no increased risk was found in any specific category of psychiatric disorders that might share genetic susceptibility with type 1 diabetes. These results suggest that associations between type 1 diabetes and psychiatric disorders are due to biological and/or psychological effects of diabetes (i.e., consistent with a causal effect) rather than common genetic risk factors or within family environmental factors.

Strength and limitations

Strengths of our study include large scale population-based design, prospectively collected data from nationwide registries, control for several possible confounders, follow-up period up to adulthood, definitions of outcome as diagnosed disorders justifying clinical intervention and analysis of genetically informed data on siblings. Nevertheless, our study does have some limitations related to register-based methodology. Children with type 1 diabetes are under the regular diabetological care. High risk of psychiatric diagnoses in this population may be biased by care-seeking attitudes of parents adjusted to high utilization of the health care system. Still, the results for healthy siblings do not suggest that families with diabetes were more likely to seek help for psychiatric care for their children. Furthermore, one may argue that diabetologists could

notice symptoms that otherwise would not have been recognized and initiated referral to mental health services and this diagnostic bias could account for higher rates of psychiatric disorders in children with type 1 diabetes. Lack of detailed clinical data was another limitation of the study. Non-compliance and persistent high level of glycated hemoglobin in type 1 diabetes is a risk factor for psychiatric co-morbidity and neurodevelopmental problems. (29-31) However, we had no data on metabolic control of disease since medical records were unavailable.

Summary

In summary, our results have important clinical implications. First, high risk of psychiatric disorders in children with type 1 diabetes highlights the need of mental health service as part of gold-standard medical management in this population, and psychological care should start from the date of diagnosis of diabetes. Second, our findings draw attention to the complexity of psychiatric disorders accompanying type 1 diabetes. Design of cost-effective algorithms aimed at identifying children at risk of having psychiatric comorbidity poses a challenge. Third, this report challenges the single-disease approach, which dominates the health systems, medical education, and clinical research. This attitude has recently been questioned and the need of comprehensive care has been recognized. (32) Although physical-mental health comorbidity is mostly attributed to the elderly, our study shows that the pediatric population is not free from such difficulties and child health care needs to rise up to this challenge.

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AB had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. AB conceived the idea, designed the study, performed statistical analyses, and wrote the first draft. LF, CA and BZ participated in discussion. PL supervised the study design and statistical analyses. All authors interpreted the results, revised the report, and approved the final version of the report. AB and PL act as guarantors.

This study was approved by the research ethics committee at Karolinska Institutet, Stockholm (No 2009/939)

Disclaimer: Results and views of the present study represent the authors and not necessarily any official views of the Medical Products Agency where one author is employed (BZ).

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Supplementary Table S1: Characteristics of patients with type 1 diabetes, their healthy siblings and matched controls. Data are no (%) of subjects.

Supplementary Figure S1: Flow diagram of study of patients with type 1 diabetes vs healthy (unexposed) individuals. Diagram includes detailed information on the excluded individuals.

Supplementary Figure S2: Flow diagram of study of siblings patients with type 1 diabetes vs siblings of healthy individuals (unexposed siblings). Diagram includes detailed information on the excluded sibling pairs.

Table 1: Hazard ratios (95% CI) for psychiatric disorders in childhood and adolescence in relation to diagnosis of type 1 diabetes

	Probands	**Unexposed individuals**		
			Univariate	Multivariate
Event	Patients with type 1 diabetes (n= 17122) No (%) with outcome	Control group (n= 1696611) No (%) with outcome	Hazard ratio (95% CI)*	Hazard ratio (95% CI)**
Any psychiatric disorder	1428 (8.3)	70483 (4.2)	2.1 (2.0 - 2.2)	2.1 (2.0 - 2.2)
Suicide attempt	129 (0.8)	7427 (0.4)	1.7 (1.4 - 2.0)	1.7 (1.4 - 2.0)
Psychotic disorders	7 (0.0)	791 (0.1)	0.9 (0.4 - 1.8)	0.9 (0.4 - 1.8)
Mood disorders	210 (1.2)	10286 (0.6)	2.0 (1.8 - 2.3)	2.0 (1.8 - 2.3)
Anxiety, dissociative, stress to related and somatoform disorders	178 (1.0)	10737 (0.6)	1.6 (1.4 - 2.0)	1.6 (1.4 - 2.0)
Eating disorders	102 (0.6)	4656 (0.3)	2.2 (1.8 - 2.7)	2.2 (1.8 - 2.6)
Substance misuse	370 (2.2)	13997 (0.8)	2.6 (2.4 - 2.9)	2.6 (2.4 - 2.9)
Attention-deficit hyperactivity disorders	211 (1.2)	13575 (0.8)	1.5 (1.3 - 1.8)	1.5 (1.3 - 2.7)
Other behavioural disorders	340 (2.0)	15477 (0.9)	2.2 (2.0 - 2.4)	2.2 (2.0 - 2.4)
Autism spectrum disorders	114 (0.7)	6924 (0.4)	1.6 (1.4 - 2.0)	1.7 (1.4 - 2.0)
Intellectual disability	127 (0.7)	7312 (0.4)	1.7 (1.4 - 2.4)	1.8 (1.5 - 2.1)

*- Conditional analysis adjusted to age at the time of recruitment, sex, year and county of birth by matching; **- Multivariate Cox regression additionally adjusted for socio-economic factors (maternal/paternal age at child birth, maternal/paternal psychiatric history, maternal/paternal country of birth, level of education of higher educated parent), perinatal variables (gestational age, birth weight, being born small for gestational age, being born large for gestational age, Apgar score) and history of psychiatric disorders prior to the recruitment.

Table 2: Hazard ratios (95% CI) for psychiatric disorders in relation to diagnosis of type 1 diabetes stratified by age at onset and duration of type 1 diabetes.

Age at onset of type 1 diabetes (years)	Duration of type 1 diabetes (years)			Total
	<0.5	0.5-4	>5	
<7	2.7 (1.9 - 3.7)	2.0 (1.7 - 2.3)	1.8 (1.6 - 2.0)	1.9 (1.7 - 2.0)
7 - 11	3.3 (2.6 - 4.1)	1.9 (1.7 - 2.2)	2.1 (1.8 - 2.4)	2.1 (1.9 - 2.3)
≥12	3.0 (2.5 - 3.6)	2.2 (1.9 - 2.5)	1.7 (0.8 - 3.5)	2.4 (2.1 - 2.6)
Total	3.0 (2.7 - 3.4)	2.0 (1.9 - 2.2)	1.9 (1.7 - 2.1)	2.1 (2.0 - 2.2)

Multivariate conditional analysis adjusted to age at the time of recruitment, sex, year and county of birth by matching and additionally adjusted for variables included in the model: socio-economic factors (maternal/paternal age at child birth, maternal/paternal psychiatric history, maternal/paternal country of birth, level of education of higher educated parent), perinatal variables (gestational age, birth weight, being born small for gestational age, being born large for gestational age, Apgar score) and history of psychiatric disorders prior to the recruitment. Observations were censored for any psychiatric disorder diagnosed in previous follow-up period after onset of type 1 diabetes.

Table 3: The prevalence 10 years after diagnosis of type 1 diabetes and hazard ratios for psychiatric disorders by diabetes diagnosis cohort

Measurement	**Prevalence, % (95% CI)**			**Hazard ratio (95% CI)****		
Diagnosis cohort	1973-1986	1987-1996	1997-2009	1973-1986	1987-1996	1997-2009
Any psychiatric disorder	3.8 (3.0 - 4.8)	8.8 (7.8 - 9.8)	16.7 (15.4 - 18.1)	2.7 (2.2 - 3.3)	2.5 (2.3 - 2.8)	1.9 (1.8 - 2.0)
Suicide attempt	0.5 (0.2 - 0.9)	1.1 (0.8 - 1.6)	1.4 (1.0 - 1.9)	2.1 (1.4 - 3.2)	1.7 (1.3 - 2.2)	1.6 (1.3 - 2.1)
Psychotic disorders	0.1 (0.0 - 0.1)	0.1 (0.0 - 0.4)	0.1 (0.0 - 0.3)	1.3 (0.3 - 5.1)	0.7 (0.2 - 2.9)	0.9 (0.3 - 2.7)
Mood disorders	0.2 (0.0 - 0.5)	0.7 (0.5 - 1.1)	3.4 (2.7 - 4.3)	2.2 (1.0 - 5.2)	2.0 (1.6 - 2.6)	2.0 (1.7 - 2.4)
Anxiety, dissociative, stress to related and somatoform disorders	0.6 (0.3 - 1.0)	0.6 (0.4 - 0.9)	1.2 (0.9 - 1.7)	2.0 (0.9 - 4.4)	1.6 (1.2 - 2.2)	1.6 (1.4 - 1.9)
Eating disorders	0.3 (0.1 - 0.7)	0.6 (0.4 - 0.9)	1.5 (1.1 - 2.1)	2.3 (1.1 - 4.7)	2.2 (1.6 - 3.1)	2.1 (1.7 - 2.8)
Substance misuse	0.6 (0.4 - 1.1)	3.3 (2.7 - 4.0)	4.5 (3.8 - 5.5)	2.3 (1.6 - 3.3)	3.0 (2.5 - 3.5)	2.4 (2.1 - 2.8)
Attention-deficit hyperactivity disorders	0.0 (0.0 - 0.0)	1.0 (0.7 - 1.4)	3.2 (2.7 - 3.9)	1.0 (0.1 - 6.7)	2.3 (1.7 - 3.1)	1.4 (1.2 - 1.6)
Other behavioural disorders	1.3 (0.8 - 1.9)	1.9 (1.5 - 2.5)	4.5 (3.9 - 5.3)	3.5 (2.3 - 5.2)	2.5 (2.0 - 3.1)	2.0 (1.8 - 2.3)
Autism spectrum disorders*	-	0.4 (0.2 - 0.7)	1.7 (1.3 - 2.1)	-	1.7 (1.1 - 2.6)	1.7 (1.4 - 2.1)
Intellectual disability	0.3 (0.1 - 0.6)	0.6 (0.4 - 1.0)	1.2 (1.0 - 1.6)	2.2 (1.2 - 4.2)	2.0 (1.4 - 2.9)	1.7 (1.4 - 2.1)

*- In ICD-8 autism spectrum disorders were classified as a schizophrenia in psychotic disorders.**- Multivariate adjusted hazard ratios (95% CI) for psychiatric disorders in children with type diabetes when comparing with matched unexposed individuals. Multivariate Cox regression adjusted for socio-economic factors (maternal/paternal age at child birth, maternal/paternal psychiatric history, maternal/paternal country of birth, level of education of higher educated parent), perinatal variables (gestational age, birth weight, being born small for gestational age, being born large for gestational age, Apgar score) and history of psychiatric disorders prior to the recruitment.

Table 4: Hazard ratios (95% CI) for psychiatric disorders in childhood and adolescence when comparing siblings of patients with type 1 diabetes and siblings of healthy individuals.

	Siblings of Probands	**Unexposed siblings**		
			Univariate	Multivariate
Event	Siblings of patients with type 1 diabetes (n= 18847) No (%) with outcome	Siblings of healthy individuals (n= 1077951) No (%) with outcome	Hazard ratio (95% CI)*	Hazard ratio (95% CI)**
Any psychiatric disorder	1059 (5.6)	56366 (5.2)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.1)
Suicide attempt	107 (0.6)	5152 (0.5)	1.2 (1.0 - 1.5)	1.2 (1.0 - 1.4)
Psychotic disorders	7 (0.0)	520 (0.1)	0.8 (0.4 - 1.7)	0.8 (0.4 - 1.7)
Mood disorders	117 (0.6)	6774 (0.6)	1.0 (0.8 - 1.2)	1.0 (0.8 - 1.2)
Anxiety, dissociative, stress-related and somatoform disorders	122 (0.7)	7348 (0.7)	1.0 (0.8 - 1.2)	0.9 (0.8 - 1.1)
Eating disorders	85 (0.5)	4592 (0.4)	1.1 (0.9 - 1.4)	1.1 (0.9 - 1.4)
Substance misuse	193 (1.0)	9713 (0.9)	1.2 (1.0 - 1.4)	1.2 (1.0 - 1.3)
Attention-deficit hyperactivity disorders	151 (0.8)	8523 (0.8)	1.1 (1.0 - 1.3)	1.1 (0.9 - 1.2)
Other behavioral disorders	265 (1.4)	13801 (1.3)	1.1 (1.0 - 1.3)	1.1 (1.0 - 1.2)
Autism spectrum disorders	82 (0.4)	4845 (0.5)	1.0 (0.8 - 1.2)	1.0 (0.8 - 1.2)
Intellectual disability	123 (0.7)	6164 (0.6)	1.2 (1.0 - 1.4)	1.2 (1.0 - 1.4)

*- Conditional analysis adjusted to age at the time of recruitment, sex, year and county of birth by matching; **- Multivariate Cox regression additionally adjusted for socio-economic factors (maternal/paternal age at child birth, maternal/paternal psychiatric history, maternal/paternal country of birth, level of education of higher educated parent), perinatal variables (gestational age, birth weight, being born small for gestational age, being born large for gestational age, Apgar score. Confidence intervals for all outcomes except any psychiatric disorder include 1.0.

Supplementary Table S1: Characteristics of patients with type 1 diabetes, their healthy siblings and matched controls. Data are no (%) of subjects.

Characteristics	**Probands**	**Unexposed individuals**	***P* value**	**Siblings of Probands**	**Unexposed siblings**	***P* value**
	Patients with type 1 diabetes (n=17122)	Healthy individuals (n=1696611)		Siblings of patients with type 1 diabetes (n= 18847)	Siblings of healthy individuals (n= 1077951)	
Sex						
Male	9261 (54.1)	915255 (53.9)		9755 (51.8)	564167 (52.3)	
Female	7861 (45.9)	781356 (46.1)	0.7102	9092 (48.2)	513784 (47.7)	0.1152
Maternal age at delivery (years)						
<35	14984 (87.5)	1497374 (88.3)		16589 (88.0)	964059 (89.4)	
≥35	2129 (12.4)	197201 (11.6)		2244 (11.9)	112954 (10.5)	
Unknown	9 (0.1)	2036 (0.1)	0.0002	14 (0.1)	938 (0.1)	<0.0001
Paternal age at delivery (years)						
<35	12675 (74.0)	1271546 (74.9)		14086 (74.7)	814229 (75.5)	
≥35	4363 (25.5)	413371 (24.4)		4743 (25.2)	262480 (24.4)	
Unknown	84 (0.5)	11694 (0.7)	<0.0001	18 (0.1)	1242 (0.1)	<0.0001
Maternal psychiatric history						
Yes	1427 (8.3)	140957 (8.3)		1120 (5.9)	39321 (3.6)	

No	15695 (91.7)	1555654 (91.7)	0.9239	17727 (94.1)	1038630 (96.4)	<0.0001
Paternal psychiatric history						
Yes	1214 (7.1)	125177 (7.4)		992 (5.3)	34474 (3.2)	
No	15908 (92.9)	1571434 (92.6)	0.1517	17855 (94.7)	1043477 (96.8)	<0.0001
Mothers region of birth						
Sweden	15562 (90.9)	1481231 (87.3)		16969 (90.0)	923785 (85.7)	
Scandinavia	754 (4.4)	66927 (3.9)		781 (4.1)	42059 (3.9)	
Europe	348 (2.0)	68580 (4.1)		377 (2.0)	45279 (4.2)	
Africa	165 (0.9)	14912 (0.9)		341 (1.8)	18192 (1.7)	
Asia	212 (1.2)	47974 (2.8)		287 (1.5)	38218 (3.6)	
Other	72 (0.4)	14951 (0.9)		78 (0.4)	9480 (0.9)	
Unknown	9 (0.1)	2036 (0.1)	<0.0001	14 (0.1)	938 (0.1)	<0.0001
Fathers region of birth						
Sweden	15475 (90.4)	1462436 (86.2)		16943 (89.9)	912443 (84.7)	
Scandinavia	625 (3.7)	57241 (3.4)		648 (3.4)	36090 (3.4)	
Europe	397 (2.3)	79544 (4.7)		419 (2.2)	54934 (5.1)	
Africa	227 (1.3)	20100 (1.2)		418 (2.2)	21644 (2.0)	
Asia	228 (1.3)	48014 (2.8)		311 (1.7)	39921 (3.7)	
Other	86 (0.5)	17582 (1.0)		90 (0.5)	11677 (1.1)	
Unknown	84 (0.5)	11694 (0.7)	<0.0001	18 (0.1)	1242 (0.1)	<0.0001
Parental education						
Primary and lower secondary	982 (5.7)	101041 (6.0)		954 (5.1)	58341 (5.4)	
Upper secondary	8337 (48.7)	804271 (47.4)		9049 (48.0)	490072 (45.5)	
Post-secondary	3081 (18.0)	302323 (17.9)		3374 (17.9)	195540 (18.1)	

Postgraduate	4707 (27.6)	485837 (28.6)		5459 (30.0)	332088 (30.8)	
Unknown	15 (0.1)	3139 (0.2)	<0.0001	11 (0.1)	1910 (37.2)	<0.0001
Psychiatric disorders prior to recruitment						
Yes	403 (2.4)	33928 (2.0)		-	-	-
No	16719 (97.6)	1662683 (98.0)	0.001	-	-	-
Perinatal and somatic indicators						
Gestational age (wk)						
<32	73 (0.4)	10431 (0.6)		150 (0.8)	7317 (0.7)	
32-36	973 (5.7)	83622 (4.9)		963 (5.1)	49470 (4.6)	
≥37	15807 (92.3)	1572576 (92.7)		17433 (92.5)	1000574 (92.8)	
Unknown	269 (1.6)	29982 (1.8)	<0.0001	301 (1.6)	20590 (1.9)	<0.0001
Child small for gestational age (SGA)						
SGA	418 (2.4)	47204 (2.8)		428 (2.3)	25492 (2.4)	
No SGA	16080 (93.9)	1577638 (93.0)		17511 (92.9)	1001581 (92.9)	
Unknown	624 (3.6)	71769 (4.2)	<0.0001	908 (4.8)	50878 (4.7)	0.5864
Child large for gestational age (LGA)						
LGA	695 (4.1)	52611 (3.1)		830 (4.4)	36170 (3.4)	
No LGA	15803 (92.3)	1572231 (92.7)		17109 (90.8)	990903 (91.9)	
Unknown	624 (3.6)	71769 (4.2)	<0.0001	908 (4.8)	50878 (4.7)	<0.0001
Birth weight (grams)						
<1500	62 (0.4)	8336 (0.5)		115 (0.6)	5998 (0.6)	
1500-2499	544 (3.1)	58356 (3.4)		615 (3.3)	33656 (3.1)	
2500-3499	7173 (41.9)	716745 (42.3)		7357 (39.0)	438331 (40.7)	

≥3500	9076 (53.0)	882711 (52.0)		10443 (33.4)	578169 (53.6)	
Unknown	267 (1.6)	30463 (1.8)	<0.0001	317 (1.7)	21797 (2.0)	<0.0001
Apgar score at 5 min after birth						
≥7	15634 (91.3)	1541636 (90.8)		17338 (92.0)	994305 (92.2)	
<7	162 (1.0)	16103 (1.0)		205 (1.1)	10829 (1.0)	
Unknown	1326 (7.7)	138872 (8.2)	<0.0001	1304 (6.9)	72817 (6.8)	0.3449