Association and Familial Coaggregation of Childhood-Onset Type 1 Diabetes With Depression, Anxiety, and Stress-Related Disorders: A Population-Based Cohort Study

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OBJECTIVE

To estimate the association and familial coaggregation of childhood-onset type 1 diabetes with depression, anxiety, and stress-related disorders.

RESEARCH DESIGN AND METHODS

This was a population-based cohort study with use of data from Swedish nationwide registers. A total of ~3.5 million individuals born in Sweden 1973–2007 were linked to their biological parents, full siblings and half-siblings, and cousins. Cox models were used to estimate the association and familial coaggregation of type 1 diabetes with depression, anxiety, and stress-related disorders.

RESULTS

Individuals diagnosed with childhood-onset type 1 diabetes (n = 20,005) were found to be at greater risks of all outcomes: any psychiatric diagnosis (adjusted hazard ratio [aHR] 1.66 [95% CI 1.59–1.72]) or specific diagnoses of depression (1.85 [1.76–1.94]), anxiety (1.41[1.33–1.50]), and stress-related disorders (1.75 [1.62–1.89]), as well as use of antidepressants or anxiolytics (1.30 [1.26–1.34]), compared with individuals without type 1 diabetes. Overall, relatives of individuals with type 1 diabetes were at elevated risks of developing these outcomes, with the highest risks seen in parents (aHRs 1.18–1.25), followed by full siblings (aHRs 1.05–1.20), and the magnitudes of risk estimates appear proportional to familial relatedness.

CONCLUSIONS

These results support existing evidence that children and adolescents with type 1 diabetes are at greater risks of developing depression, anxiety, and stress-related disorders and indicate that shared familial factors might contribute to these elevated risks. Our findings highlight the need for psychological consulting for children and their families in diabetes care. Quantitative and molecular genetic studies are warranted to further understand the etiology of these psychiatric disorders in type 1 diabetes.

Type 1 diabetes is one of the major chronic conditions in childhood. Children and adolescents with type 1 diabetes are at a heightened risk of mental health problems

(1–3). Depression, anxiety, and stress-related disorders account for significant proportions of mental health problems in type 1 diabetes and are associated with less optimal diabetes management, reduced health-related quality of life, increased risk of complications, and premature mortality (4–7).

Current diabetes guidelines recommend screening for mental health problems in pediatric diabetes care (8,9), as it is vital for the affected children and adolescents to receive timely and adequate diagnoses with appropriate therapies and psychological support to minimize potential adverse effects on diabetes management.

Understanding the etiology of depression, anxiety, and stress-related disorders in type 1 diabetes is crucial to tailor clinical follow-ups and prevention intervention programs. Although the emotional, behavioral, and biological impacts of diabetes have been recognized to contribute to the risk of these psychiatric disorders (10), the exact etiology concerning the high co-occurrence seems to be multifactorial, intricate, and still only partially understood (11,12). One unexplored possibility is that type 1 diabetes and depression, anxiety, and stress-related disorders might share genetic and/or environmental risk factors. Type 1 diabetes and these psychiatric disorders aggregate in families (13–16), and familial factors—both genetic and environmental—were found to contribute substantially to susceptibility for each disease (17–19). However, whether type 1 diabetes and these psychiatric disorders coaggregate within families remains uninvestigated, and this investigation is often the essential first step in exploring whether type 1 diabetes and these conditions share underlying etiology (20).

Therefore, we conducted this population-based cohort study to assess the association of childhood-onset type 1 diabetes with subsequent depression, anxiety, and stress-related disorders and to investigate their familial coaggregation pattern across different types of relatives, aiming to facilitate understanding of potentially shared etiological aspects between type 1 diabetes and these psychiatric conditions.

RESEARCH DESIGN AND METHODS
Study Design and Subjects
This study was a population-based cohort study with use of data from several nationwide Swedish registers (details of these registers are presented in Supplementary Table 1). The cohort construction process is shown in Supplementary Fig. 1. Individuals born in Sweden between 1973 and 2007 with identifiable biological parents were included. We excluded individuals who were diagnosed with a chromosomal abnormality (using ICD-8, ICD-9, and ICD-10 codes presented in Supplementary Table 2) or emigrated or died before age 5 years, leading to a main cohort of 3,482,655 individuals. We linked the biological parents to each individual, using the Swedish Multi-Generation Register, and identified within-generation relatives from the main cohort, resulting in five relative subcohorts: parents, full siblings, maternal half-siblings, paternal half-siblings, and cousins. Twins and higher multiples were excluded from the full sibling subcohort since their familial factors (more shared genetic and prenatal environment) differ from those of other full siblings.

We also retrospectively constructed a matched subsample from the main cohort to demonstrate the aggregated incidence of the outcome across the observation period, which is from birth to 31 December 2013 or earlier if censored due to death or emigration. For each individual diagnosed with type 1 diabetes during the observation period, 10 reference individuals without type 1 diabetes, matched on sex and birth year, were randomly selected. We also constructed matched subsamples for each relative type, according to a detailed process described in Supplemental File 1.

Ethics approval for this study was granted by the regional ethics review board in Stockholm, Sweden (Dnr2013/862-31/5). No informed consent from participants was required, given the register-based nature of this study.

Type 1 Diabetes
Childhood-onset type 1 diabetes was defined as diagnosis with type 1 diabetes between 6 months and 18 years of age in Swediabkids database (21) or the Swedish National Diabetes Register (22). Both data sources have demonstrated validity in capturing type 1 diabetes in the Swedish population (23–25).

Outcomes
Clinical diagnoses of depression, anxiety, and stress-related disorders were obtained from the National Patient Register (NPR), which captured records from inpatient care since 1973, and outpatient and specialist health care facilities since 2001, with use of corresponding ICD-8, ICD-9, and ICD-10 codes listed in Supplementary Table 2. The primary outcome was defined as receiving any of the diagnoses, given their high co-occurrence and similarities in the neurobiological mechanisms and pharmacological treatment. The secondary outcomes were specific diagnoses of depression, anxiety, or stress-related disorders.

A tertiary outcome of using any antidepressants or anxiolytics was examined among individuals who remained living in Sweden after July 2005 (the start time of the Swedish National Prescribed Drug Register [PDR]). Information on the usage of prescribed antidepressants and anxiolytics was obtained from PDR with use of corresponding Anatomical Therapeutic Chemical (ATC) codes (Supplementary Table 2). Use of antidepressants was further examined with three predefined groups, including nonselective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, and other types of antidepressants, based on the ATC classifications (26).

Statistical Analysis
Demographic characteristics and incidence of outcomes were described separately for individuals with and without type 1 diabetes. Kaplan-Meier (KM) curves were plotted in the matched subsamples to show the aggregated incidence for the outcomes between individuals with and without childhood-onset type 1 diabetes and their relatives.

Association Between Type 1 Diabetes and the Outcomes
First, we compared the risk of all outcomes between individuals with and without childhood-onset type 1 diabetes in the main study cohort. Cox models were used to estimate hazard ratios (HRs) and 95% CIs, with age used as the underlying time scale (i.e., we compared individuals of the same age). Type 1 diabetes was modeled as a time-varying exposure: individuals were regarded as unexposed before being diagnosed with type 1 diabetes and exposed afterward. Follow-up time was calculated from birth until the first observed diagnosis of the outcome condition,

censoring (death or emigration), or 31 December 2013—whichever occurred first and separately for each outcome. HRs were adjusted for sex and birth cohort (in 5-year intervals).

Familial Coaggregations of Type 1 Diabetes and the Outcomes

Second, we examined the familial coaggregation of type 1 diabetes with all outcomes by comparing the risks in relatives of individuals with type 1 diabetes with those of the relatives of individuals without type 1 diabetes, using similar Cox models. Type 1 diabetes was also modeled as a time-varying exposure, where the relative of an individual was considered unexposed before the individual's diabetes diagnosis and exposed after that. If the relative developed the outcome before the individual's type 1 diabetes diagnosis, the relative would contribute only to the person-time of being unexposed. HRs were adjusted for sex and birth cohorts of both the individual and the relative.

Higher risk of outcomes in relatives of individuals with type 1 diabetes indicates that the phenotypic association between type 1 diabetes and the outcomes may be attributed to shared familial liability, and the differences in the magnitude of associations across types of relatives suggest the source of familial liability, i.e., genetic or environmental. Interpretations of the familial coaggregation pattern were made, consistent with previous studies (27–30), based on the following assumptions: on average, 1) parents share ~50% of additive genetic factors with their children and provide the early rearing environment, 2) full siblings share ~50%, half-siblings share ~25%, and cousins share <12.5% additive genetic factors; and 3) full siblings and maternal half-siblings share a similar extent of shared environmental factors (nongenetic factors that makes siblings alike), while paternal half siblings share less and cousins share nearly none. The assumption on the shared environment was made given that, during the observation period, children predominately reside with the mothers after the parental separation (31) and cousins rarely resided together in Sweden (32). Therefore, if an association is greater in full siblings than in maternal half-siblings, contributions from shared genetic factors in the familial liability can be indicated. If

an association is greater in maternal than in paternal half-siblings, contributions from shared environmental factors can be suggested. Moreover, no difference between maternal and paternal half-siblings in combination with a significantly stronger association in full siblings would highlight the importance of genetic factors. Also, we expect to see the association increase proportionally to the increased familial relatedness if familial liability is present.

Sensitivity Analysis

In sensitivity analyses, to examine whether the observed familial coaggregation between type 1 diabetes and the examined outcomes could be explained by direct effects of one condition on the other, we adjusted for type 1 diabetes in the relatives. If the associations remain positive after the adjustment, the existence of familial liability between type 1 diabetes and the outcomes would be further supported (20). We stratified analyses by sex to explore differences between males and females (33). For all analyses,

a cluster-robust (sandwich) estimator was used for SE calculation to control for interfamilial correlation within the data, where clusters were identified through family-specified identifiers. Tests were two tailed and conducted at the 0.05 significance level. Data management was conducted in SAS 9.4 (SAS Institute, Inc.), and statistical analyses were performed with use of survival package in R, version 4.0.5.

RESULTS

Distributions of demographic characteristics and incidence of outcomes in the main cohort are presented in Table 1. Out of the main cohort, 20,005 (0.6%) individuals were diagnosed with childhood-onset type 1 diabetes during the observation period, with a median onset age of 9.7 years (interquartile range 6.1, 13.0). Characteristics and incidence of outcomes across relative subcohorts are reported in Supplementary Table 3.

Fig. 1 displays KM curves with survival functions of outcomes comparing individuals with type 1 diabetes and

Table 1—Characteristics and subsequent common psychiatric disorders in the main cohort

	Type 1 diabetes*	No type 1 diabetes*
Total *N*	20,005 (0.6)	3,462,650 (99.4)
Sex		
Male	10,790 (53.9)	1,777,843 (51.3)
Female	9,215 (46.1)	1,684,807 (48.7)
Birth cohort		
1973–1977	2,255 (11.3)	501,114 (14.5)
1978–1982	2,261 (11.3)	457,323 (13.2)
1983–1987	2,705 (13.5)	476,745 (13.8)
1988–1992	3,944 (19.7)	580,303 (16.8)
1993–1997	3,868 (19.3)	499,891 (14.4)
1998–2002	3,093 (15.5)	443,632 (12.8)
2003–2007	1,879 (9.4)	503,642 (14.5)
Age at type 1 diabetes diagnosis		
Mean (SD)	9.6 (4.4)	N.A.
Median (IQR)	9.7 (6.1, 13.0)	N.A.
Any diagnosis of common psychiatric disorders	2,159 (10.8)	237,748 (6.9)
Depression	1,381 (6.9)	135,163 (3.9)
Anxiety	1,082 (5.4)	133,881 (3.9)
Stress-related disorders	642 (3.2)	67,967 (2.0)
Using antidepressants or anxiolytics†	3,827 (19.5)	542,795 (16.1)

Data are *n* (%) unless otherwise indicated. IQR, interquartile range. Statistically significant differences were detected for all categorical variables, with *P* values all <0.05. *Type 1 diabetes: individuals from the main cohort diagnosed with childhood-onset type 1 diabetes during the observation period. No type 1 diabetes: individuals from the main cohort not diagnosed with childhood-onset type 1 diabetes during the observation period. †Use of antidepressants or anxiolytics was assessed among individuals who remained resident in Sweden since 2005.
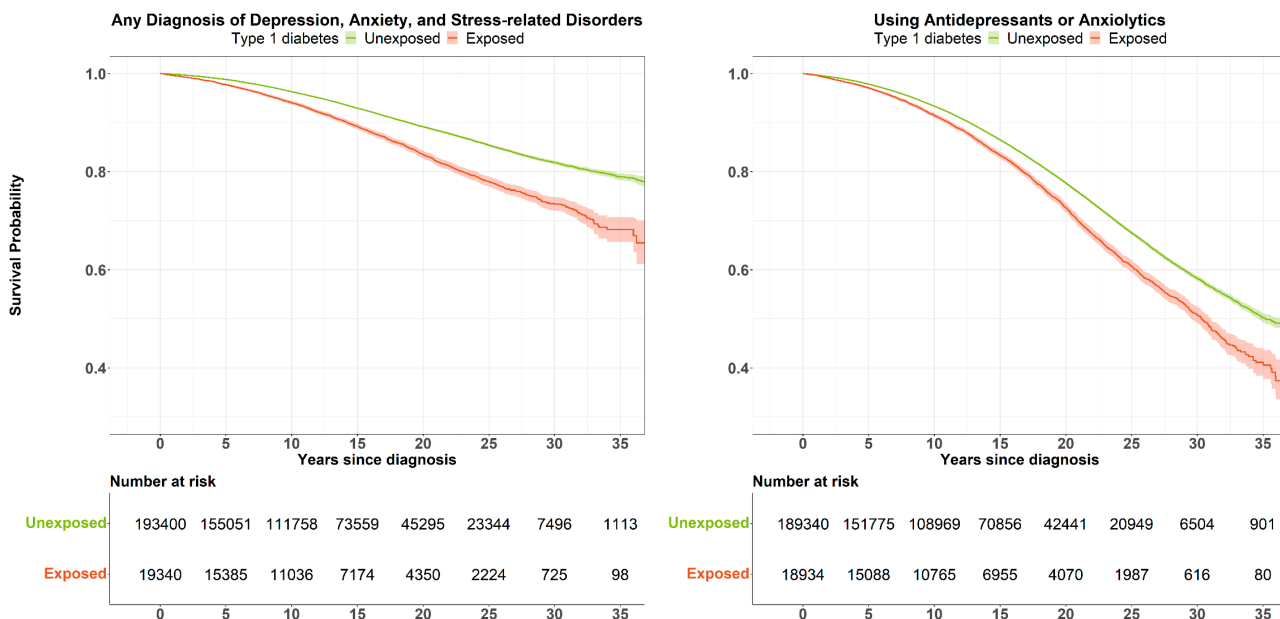
Figure 1—Survival curve of receiving any diagnosis of common psychiatric disorders and using antidepressants or anxiolytics for individuals diagnosed with childhood-onset type 1 diabetes compared with matched reference individuals. *Survival curves of receiving a specific diagnosis of depression, anxiety, or stress-related disorders and using antidepressants and using anxiolytics are presented in Supplementary Fig. 2. Use of antidepressants and anxiolytics was analyzed for individuals who remained residing in Sweden since 2005.

matched individuals without type 1 diabetes. The differences in proportion started to be visible around the second year after diabetes diagnosis and increased steadily for all outcomes. At 30 years of follow-up, 26.6% of individuals with type 1 diabetes had received at least one diagnosis of depression, anxiety, or stress-related disorder compared with 18.1% in the matched individuals. For those who remained residing in Sweden after 2005, 49.2% of individuals with type 1 diabetes have used antidepressants or anxiolytics compared with 31.7% of matched reference individuals. KM curves comparing relatives of individuals with type 1 diabetes and relatives of individuals without type 1 diabetes are presented in Supplementary Figs. 3–7.

Association and Familial Coaggregation Between Type 1 Diabetes and the Outcomes

Associations between childhood-onset type 1 diabetes and all outcomes and their familial coaggregation are shown in Fig. 2. Individuals with childhood-onset type 1 diabetes had a higher risk of receiving any diagnosis (adjusted HR [aHR] 1.66 [95% CI 1.59, 1.72]) and specific diagnoses of depression (1.85 [1.76, 1.94]), anxiety (1.41 [1.33, 1.50]), and stress-related disorders (1.75 [1.62, 1.89]). They were also more likely to use antidepressants or

anxiolytics (1.30 [1.26, 1.34]) than the individuals without type 1 diabetes, with the risk of using antidepressants (1.40 [1.35, 1.46]) being even higher than that of using anxiolytics (1.24 [1.19, 1.29]). When looking at specific types of antidepressants, individuals with type 1 diabetes showed increased risks of using all types of antidepressants: nonselective monoamine reuptake inhibitors (1.58 [1.37, 1.82]), selective serotonin reuptake inhibitors (1.36 [1.31, 1.43]), and other types of antidepressants (1.54 [1.40, 1.69]) (Supplementary Table 5).

In the familial coaggregation analyses, the highest risks were observed for the parents of individuals with type 1 diabetes, with statistically significant aHRs ranging from 1.16 to 1.25. Full siblings also showed statistically significantly increased risks of all outcomes, but with slightly attenuated aHRs ranging from 1.05 to 1.20. In other types of relatives, statistically significant associations were only observed for using antidepressants and anxiolytics in paternal half-siblings and for depression and using anxiolytics in cousins.

Sensitivity Analysis

Additional adjustment for the presence of type 1 diabetes in the relatives yielded similar results (Supplementary Table 6). Observed associations remained statistically significant for parents but were

slightly attenuated in full siblings, where the significantly elevated risks were only observed for any diagnosis and specific diagnoses of anxiety and stress-related disorders. Sex-stratified analyses revealed comparable patterns of results in females and males, with wider and overlapping CIs (Supplementary Table 7).

CONCLUSIONS

To our knowledge, this is the largest population-based familial coaggregation study exploring the co-occurrence of type 1 diabetes with depression, anxiety, and stress-related disorders. We observed that individuals with childhood-onset type 1 diabetes are at heightened risks of developing depression, anxiety, and stress-related disorders, as well as using antidepressants and anxiolytics. We also demonstrated familial coaggregation patterns between type 1 diabetes and these psychiatric outcomes across parents, full siblings, maternal and paternal half-siblings, and cousins.

Our findings not only strengthen the existing evidence on elevated risks of these psychiatric outcomes in individuals with childhood-onset type 1 diabetes but also suggest that such elevated risks appear soon after the diabetes diagnosis. The estimated risks for depression, anxiety, and stress-related disorders are similar to those of previous population-based
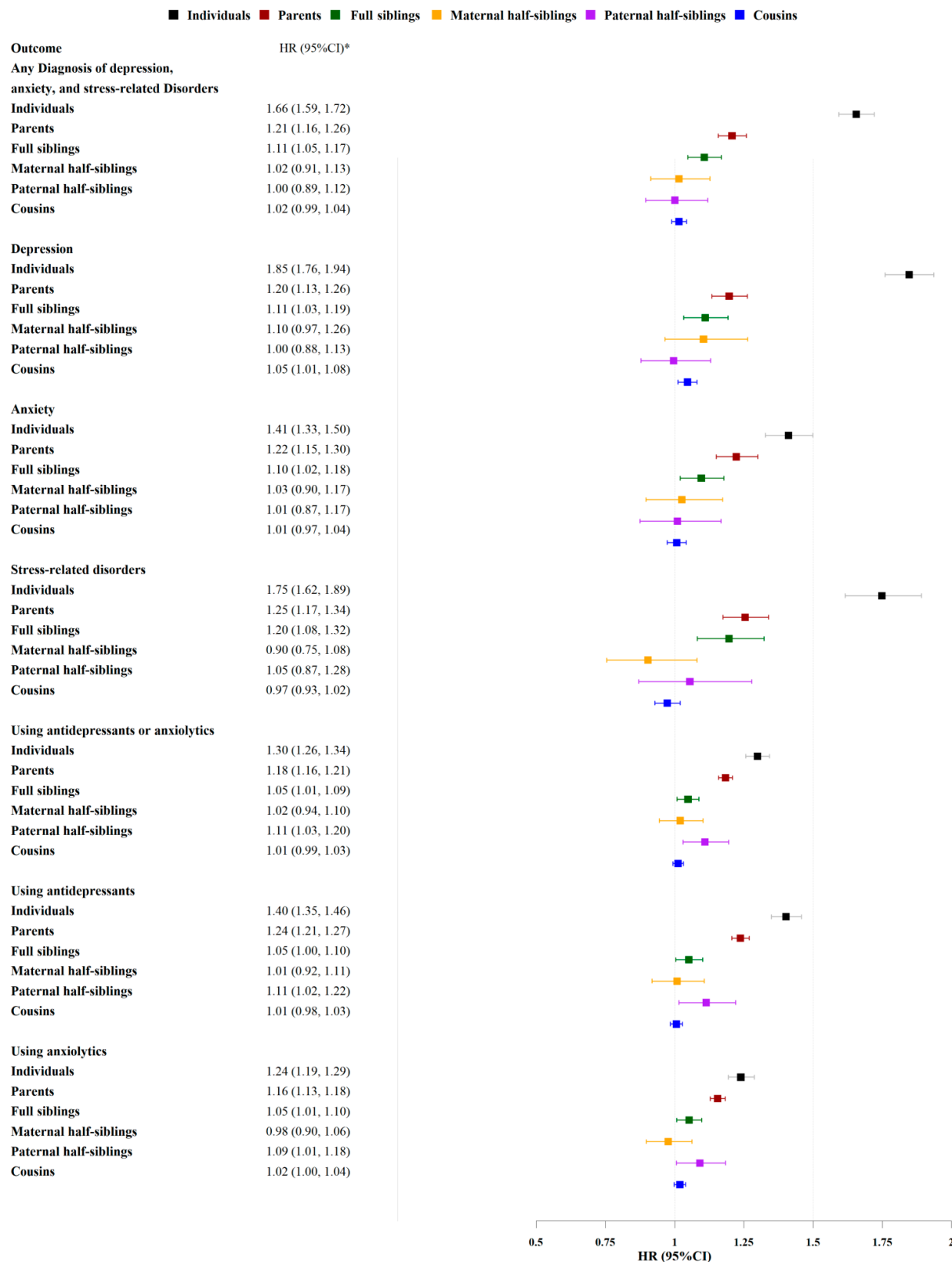
Individuals ■ **Parents** ■ **Full siblings** ■ **Maternal half-siblings** ■ **Paternal half-siblings** ■ **Cousins** ■

Outcome	HR (95%CI)*
Any Diagnosis of depression, anxiety, and stress-related Disorders	
Individuals	1.66 (1.59, 1.72)
Parents	1.21 (1.16, 1.26)
Full siblings	1.11 (1.05, 1.17)
Maternal half-siblings	1.02 (0.91, 1.13)
Paternal half-siblings	1.00 (0.89, 1.12)
Cousins	1.02 (0.99, 1.04)
Depression	
Individuals	1.85 (1.76, 1.94)
Parents	1.20 (1.13, 1.26)
Full siblings	1.11 (1.03, 1.19)
Maternal half-siblings	1.10 (0.97, 1.26)
Paternal half-siblings	1.00 (0.88, 1.13)
Cousins	1.05 (1.01, 1.08)
Anxiety	
Individuals	1.41 (1.33, 1.50)
Parents	1.22 (1.15, 1.30)
Full siblings	1.10 (1.02, 1.18)
Maternal half-siblings	1.03 (0.90, 1.17)
Paternal half-siblings	1.01 (0.87, 1.17)
Cousins	1.01 (0.97, 1.04)
Stress-related disorders	
Individuals	1.75 (1.62, 1.89)
Parents	1.25 (1.17, 1.34)
Full siblings	1.20 (1.08, 1.32)
Maternal half-siblings	0.90 (0.75, 1.08)
Paternal half-siblings	1.05 (0.87, 1.28)
Cousins	0.97 (0.93, 1.02)
Using antidepressants or anxiolytics	
Individuals	1.30 (1.26, 1.34)
Parents	1.18 (1.16, 1.21)
Full siblings	1.05 (1.01, 1.09)
Maternal half-siblings	1.02 (0.94, 1.10)
Paternal half-siblings	1.11 (1.03, 1.20)
Cousins	1.01 (0.99, 1.03)
Using antidepressants	
Individuals	1.40 (1.35, 1.46)
Parents	1.24 (1.21, 1.27)
Full siblings	1.05 (1.00, 1.10)
Maternal half-siblings	1.01 (0.92, 1.11)
Paternal half-siblings	1.11 (1.02, 1.22)
Cousins	1.01 (0.98, 1.03)
Using anxiolytics	
Individuals	1.24 (1.19, 1.29)
Parents	1.16 (1.13, 1.18)
Full siblings	1.05 (1.01, 1.10)
Maternal half-siblings	0.98 (0.90, 1.06)
Paternal half-siblings	1.09 (1.01, 1.18)
Cousins	1.02 (1.00, 1.04)

HR (95%CI)
0.5   0.75   1   1.25   1.5   1.75   2

Figure 2—Within-individual and within-family associations of childhood-onset type 1 diabetes with common psychiatric disorders and use of antidepressants or anxiolytics. *HRs (95% CI), with adjustment for sex and birth cohort of the index individual and the relative. †Crude HRs and 95% CIs are presented in Supplementary Table 4.

studies (1,3), with a nearly doubled risk of depression and ~1.6 times higher risk of anxiety and stress-related disorders. Our observed increased risk of using anti-depressants is also in line with another population-based study (34), whereas the risk of using anxiolytics in type 1 diabetes has not been reported before. Additionally, KM curves demonstrated that a

larger proportion of individuals with childhood-onset type 1 diabetes develop these psychiatric outcomes than their age- and sex-matched peers immediately after diabetes onset, and this proportion difference increased over time. This finding reflects that the early onset of type 1 diabetes places the affected children and adolescents at risk for psychiatric disorders from a young age and suggests that psychological follow-ups should be considered from the initial diabetes diagnosis and be continuously offered to affected children and adolescents, regardless of age at onset.

The observed familial coaggregation patterns, with the strength of estimated associations decreasing proportionally to the degree of relatedness, suggest that shared familial liability could underlie the etiology of the co-occurrence between type 1 diabetes and these psychiatric outcomes. This finding was also supported by the associations being largely unchanged even after adjustment for the direct influences of type 1 diabetes on the outcomes. Contributions from shared genetic factors were indicated by the estimated aHRs being generally higher in full-siblings than maternal half siblings. However, depression is an exception because the familial coaggregation pattern gives a less clear suggestion of shared genetic factors. This observation is somewhat in line with previous genomic studies that yielded inconclusive results on shared genetic susceptibility between depression and autoimmune disorders (including type 1 diabetes) (35,36). A contribution from shared environmental factors cannot be concluded, as the associations observed in maternal and paternal half-siblings were generally not statistically significant and were comparable in strength. Nevertheless, interpretations of the observed familial coaggregation pattern require caution because of the inherent limitation of the assumptions on the shared environment (31) and the limited statistical power. More familial studies with larger sample sizes are warranted to validate the findings from the current study.

Strengths and Limitations
The strengths of this study include the population-based cohort design with a large sample size and extended follow-up. The usage of nationwide registers

with prospectively collected data minimized the risk of selection, recall, and report bias. In particular, the completeness of the Swedish Multi-Generation Register allowed us to ascertain the familial coaggregation in five distinct relative subcohorts representing different degrees of shared genetic and familial environmental factors.

Several limitations should be noted. Firstly, as the Swedish NPR contains only inpatient and specialized outpatient records, we were likely to capture people with more severe psychiatric symptoms but may have missed those who did not seek medical help or whose symptoms were solely managed in primary care. Though a recent study shows that ~70% of adult patients with depression or anxiety treated in primary care can be captured on the basis of using prescribed antidepressants or anxiolytics (37), which were examined in the current study, we acknowledge that children and adolescents may have lower use of antidepressants/anxiolytics than adults, and our study may therefore have underestimated the prevalence of psychiatric outcomes. Secondly, we could not rule out the possibility of using antidepressants or anxiolytics for other reasons, such as long-term pain related to diabetes complications. Also, we were not able to capture those who used these medications before July 2005, since the PDR was only introduced at that time. Thirdly, it is plausible that the increased clinical contacts for children with type 1 diabetes may facilitate the identification of psychological symptoms and, therefore, referrals to mental health professionals; similarly, the diabetes team may promote the availability of mental health support for the family members to the parents, resulting in diagnostic bias. Additionally, we could not evaluate whether the most recent change in pediatric diabetes care, the increasing usage of insulin pumps and continuous glucose monitoring, had any influence on the patients' psychological experiences. Nevertheless, this issue is unlikely to affect the interpretation of the observed familial coaggregation. Last but not least, even with a considerable sample size of ~3.5 million individuals, statistical power was inadequate to detect possible differences between maternal and paternal half-siblings, reflected by the wide 95% CIs.

Clinical Implications
Our study lends strength to the existing recommendation for psychological screenings in children and adolescents with type 1 diabetes, as they are at heightened risks of depression, anxiety, and stress-related disorders. The observed KM curves signify that these screenings need to be considered soon after diagnosis, and continuous psychological follow-ups should be encouraged. Moreover, we noticed that 35.7% of individuals with type 1 diabetes developed more than one outcome after diabetes onset, with comorbid depression and anxiety being the most frequent (Supplementary Table 8). Thus, professionals working with children and adolescents with type 1 diabetes should be vigilant for the early onset of depression and anxiety and their tendency to co-occur. Also, more research is needed to optimize appropriate screening tools, tailor follow-up plans, and design therapeutic strategies. Furthermore, professionals should be aware that factors not related to diabetes management, such as familial liabilities, can contribute to the high co-occurrence between type 1 diabetes and these psychiatric disorders, as this may inform case management and treatment decisions. For example, mental health education and family support should be available for families with affected children and adolescents (38).

In conclusion, our study confirmed current evidence on the elevated risks of depression, anxiety, and stress-related disorders in childhood-onset type 1 diabetes. The findings of familial coaggregation constitute an important step toward a better understanding of the etiology behind the co-occurrence of type 1 diabetes with these psychiatric outcomes. Future studies with genetically informative designs, such as quantitative genetic studies and genome-wide association studies, can also be valuable to evaluate contributions from shared genetic, shared, and nonshared environmental factors to etiology between type 1 diabetes and these psychiatric conditions.

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