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ORIGINAL ARTICLE

Psychiatric medication use before and after the onset of type 1 diabetes in children and adolescents: A population-based cohort study

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Background: Several studies showed a bidirectional association between type 2 diabetes and psychiatric disorders in adults. Because there is limited information on the association between type 1 diabetes (T1D) and psychiatric disorders (including psychiatric medication use) in children and adolescents, we assessed frequency of use of these medications before and after the onset of T1D.

Methods: A population-based cohort study was conducted in the Dutch PHARMO Record Linkage System (1999-2009). Children and adolescents (<19 years) with at least 2 insulin dispensings from community pharmacies (T1D cohort, *N* = 925) were matched by age and sex (reference cohort without insulin use, *N* = 3591). The 5-year prevalence of psychiatric medication use (psycholeptics [ATC N05] and psychoanaleptics [ATC N06]) before and after onset of T1D were estimated, compared, and stratified by age, sex, and medication subgroup.

Results: The mean age of study participants was 10.1 years and 51% were boys. The 5-year prevalence of psychiatric medication use before the index date was significantly higher in the T1D cohort than in the reference cohort (7.2% vs 4.7%, respectively; *P* = .002) with the same pattern after developing T1D (10.4% vs 7.9%, respectively; *P* = .015). In both cohorts, adolescents (15-19 years) and boys had higher prevalences of use. This increased prevalence of psychiatric medication use both before and after the index date in T1D cohort was mainly driven by an increased use of psycholeptics (predominantly anxiolytics).

Conclusions: Children with T1D were more likely to use psychiatric medication in the years before and after the onset of T1D which was mainly driven by psycholeptic use.

KEYWORDS

adolescents, children, prevalence, psychiatric medication, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes (T1D) is one of the most common autoimmune disorders in children and adolescents.[1,2] In 2015, an estimated 542 000 children and adolescents aged <15 years old had T1D worldwide, and the global incidence of T1D in this age category has increased annually by 3% since the 1980s.[3,4]

T1D has been previously linked to a range of psychosocial problems.[5–7] A meta-analysis by Reynolds and Helgeson[8] concluded that children with diabetes were more likely to experience various psychological difficulties compared with their healthy peers. Other studies reported that T1D in children and adolescents was associated with an increased risk of developing psychiatric disorders (10%-20%), depressive symptoms, eating disturbances (8%-30%), increased alcohol use, sleep disorders, and a reduced quality of life.[6,9–14]

Several studies reported bidirectional association between type 2 diabetes (T2D) and psychiatric disorders in adults[15–17] and recently a large study which used 2 twin registries from Sweden and Denmark demonstrated a significant genetic overlap between T2D and depression.[18] Not only psychiatric disorders but also several psychiatric

medications (eg, olanzapine and risperidone) are seen as a risk factor for developing diabetes with different mechanisms such as increasing fasting glucose concentration or obesity.[7,19,20]

Compared to T2D, there is limited data available on the association between T1D and psychiatric disorders (and its temporal direction) in children and adolescents. Evaluating psychiatric medication utilization patterns in children and adolescents both before and after the onset of T1D and comparing the findings with a diabetes-free reference population can provide more information on this possible association.

2 | METHODS

2.1 | Data source, study design, and population

We used the population-based Dutch PHARMO Record Linkage System (RLS)[21] which covers the whole country and includes high quality and complete information linked on a patient level of, among other data, patient demographics, drug dispensing records from community pharmacies of more than 4 million inhabitants of the Netherlands (approximately 24% of the Dutch population) together with hospital discharge records.[22,23] The drug dispensing records consist of data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. The drugs are coded according to the anatomical therapeutic chemical codes (ATC codes).[24]

Patients younger than 19 years old with at least 2 insulin dispensings from the community pharmacies (based on the ATC codes for insulin preparations [A10A]) between January 1999 and December 2009 were selected as T1D cohort.[25] The date of first insulin prescription was selected as the index date (cohort entry date or date of diagnosis of T1D). For the comparative analysis, for each patient in the T1D cohort, up to 4 diabetes-free children and adolescents (without any prescription of glucose-lowering medications [ATC code A10] or hospitalization for diabetes [ICD-9-CM code 250] during the study period) with the same sex, age, and calendar time distribution (same cohort entry date and duration of follow-up time in the database) were randomly sampled from the PHARMO RLS (reference cohort). Patients in both cohorts were eligible for inclusion in the study if they had at least 12 months of exposure history before the index date (cohort entry date)—to ensure that they were incident insulin users—and at least 12 months of follow-up after the index date (cohort entry date). Patients in the T1D cohort were excluded from the study if they ever used oral glucose-lowering medications (in order to exclude potential patients with T2D [ATC code A10B]) or glucagon prior to the cohort entry date (glucagon [ATC code H04AA01]). Glucagon is usually prescribed for patients with diabetes to manage hypoglycemia; therefore, in patients who had prescriptions of glucagon before the insulin prescriptions, the date of first insulin prescription was not clear.[25] Both cohorts were followed from the index date for a maximum of 5 years. For all included study participants, data for the period before the index date (cohort entry date) were retrieved as long as possible (with a maximum of 5 years).

2.2 | Use of psychiatric medications statistical analysis

The prevalence of psychiatric medication use in each cohort (T1D and the reference cohort) was defined as the number of children and adolescents with at least 1 dispensing of a psychiatric drug (for ATC codes, see Table 1) in a particular year (or years) divided by the total number of children and adolescents in that cohort during that follow-up period. The overall prevalence of psychiatric medication use was calculated in each cohort from the index date until the end of follow-up and compared with Pearson's chi-square test. Furthermore, the overall prevalences of any psychiatric medication use (from the index date until the end of follow-up) were stratified by different sex and age categories based on the age at the onset of T1D (using age bands 0-4, 5-9, 10-14, and 15-18 years). To assess the patterns over time, annual prevalences of any psychiatric medication use was calculated from 5 years prior to the index date up to 5 years after the index date in both cohorts. Psychiatric medications were further categorized by therapeutic subgroups (Table 1).

Conditional logistic regression analysis was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between psychiatric medication use and the occurrence T1D. IBM Software package SPSS 19.0 for Windows was used for all statistical analysis in this study (Armonk, New York).

3 | RESULTS

During the study period, a total of 925 children and adolescents with T1D were identified and compared with a group of 3591 age- and sex-matched diabetes-free individuals (reference cohort). The mean age of the study population at the cohort entry date was 10.1 (SD: 4.5) years, and almost 51% of them were boys. The majority of patients with T1D in our study were 10 to 14 years old at the onset of the disease (Table 2).

The overall prevalence of any psychiatric medication use from the index date until the end of follow-up was significantly higher in the T1D cohort than in the reference cohort (10.4% vs 7.9%, respectively, $P = .015$). Figure 1A compares the annual prevalences of any psychiatric medication use between the 2 cohorts, showing a higher prevalence for the T1D cohort in all years after the diagnosis of diabetes and in almost all years before its onset. While for psycholeptic

TABLE 1 Codes used to identify psychiatric medications

Medication category	ATC code
Psycholeptics	N05
Antipsychotics	N05A
Anxiolytics	N05B
Hypnotics and sedatives	N05C
Psychoanaleptics	N06[1]
Antidepressants	N06A
Psychostimulants, agents used for ADHD and nootropics	N06B

Abbreviations: ADHD, attention deficit hyperactivity disorder; ATC, anatomical therapeutic chemical.

[1] Antidementia drugs (N06D) were not included in the study.

TABLE 2 Baseline characteristics of the study participants

Baseline characteristics		T1D cohort (n = 925)		Reference cohort (n = 3591)	
		N	%	*N*	%
Sex	Male	469	50.7	1817	50.6
	Female	456	49.3	1774	49.4
Age categories	0-4 y	135	14.6	537	15.0
	5-9 y	270	29.2	1043	29.0
	10-14 y	335	36.2	1295	36.1
	15-18 y	185	20.0	716	19.9
Year of cohort entry	1999-2004	385	41.6	1452	40.4
	2005-2009	540	58.4	2139	59.6
Number of participants in each year of the study period	5 y before the index date	381	41.2	1513	42.1
	4 y before the index date	487	52.6	1913	53.3
	3 y before the index date	610	65.9	2384	66.4
	2 y before the index date	741	80.1	2911	81.1
	1 y before the index date	925	100	3591	100
	First year of follow-up	925	100	3591	100
	Second year of follow-up	925	100	3587	99.9
	Third year of follow-up	812	87.8	3139	87.4
	Fourth year of follow-up	708	76.5	2726	75.9
	Fifth year of follow-up	605	65.4	2315	64.5

Abbreviation: T1D, type 1 diabetes.

medications prevalences were always higher in the T1D cohort (Figure 1B), the annual prevalences for psychoanaleptic medications were almost similar between the cohorts from 5 years before the index date until the second year of follow-up (Figure 1C). From the third year after the diagnosis of T1D, the prevalence of psychoanaleptic medication use was higher in the T1D cohort than in the reference cohort. In this study, we did not find any dispensing for psycholeptics and psychoanaleptics in combination (ATC code N06C).

Figure 2 displays the annual prevalence of different subgroups of psycholeptic and psychoanaleptic medications. Except for psychostimulants, the prevalence of other subgroups of psychiatric medications was higher in T1D cohort from 2 years before the diagnosis of diabetes until the fifth follow-up year. For the psychostimulants, the prevalence was higher in the reference cohort from 4 years before the index date until the second year after the index date and then increased by 60% in the third year after the index and continued to increase until the fifth follow-up year (Figure 2E).

The overall prevalence of any psychiatric medication use from 5 years before until the cohort entry date was significantly higher in the T1D cohort than in the reference cohort (7.2% vs 4.7%, respectively, P = .002). Having at least 1 dispensing for psychiatric medications in the period up to 5 years before the cohort entry date was significantly associated with developing T1D (OR = 1.5, 95% CI 1.1-2.0). This increased risk was completely driven by an increased use of psycholeptics.

For the period after the index date, prevalence of psychiatric medication use was stratified by sex and age. In both T1D and reference cohorts, boys and adolescents aged 15 to 19 years had higher prevalence of psychiatric medication use. Overall, the observed patterns in different sex and age categories were similar between the 2 cohorts. In all age categories and different sexes, children with T1D had higher prevalence of psychiatric medication use compared with the reference children (Figure 3).

4 | DISCUSSION

Our results showed that the overall prevalence of any psychiatric medication use from the index date (onset of T1D) until the end of the fifth follow-up year was significantly higher in the T1D cohort than among age and sex-matched diabetes-free individuals in the PHARMO RLS. The highest prevalences of psychiatric medication use were observed in boys and in the oldest age category (15-19 years) in both cohorts. In all age categories and different sexes, children with T1D had higher prevalence of psychiatric medication use compared with the reference children (Figure 3). Having at least 1 dispensing for psychiatric medications in the period up to 5 years before the cohort entry date was significantly associated with developing T1D and this increased risk was completely driven by an increased use of psycholeptic medications (eg, antipsychotics, anxiolytics, and hypnotics and sedatives).

4.1 | Psychiatric medication use before and after the onset of T1D

Psychiatric disorders might be a risk factor for developing diabetes. For example, adults with depressive symptoms and schizophrenia are more likely to develop T2D compared with adults without depressive symptoms.[19,26] This increased risk of diabetes might be associated with psychiatric diseases, psychiatric medication use, or both. Although complete mechanisms are unknown, several mechanisms have been proposed to explain this particular association. Antipsychotics (eg,

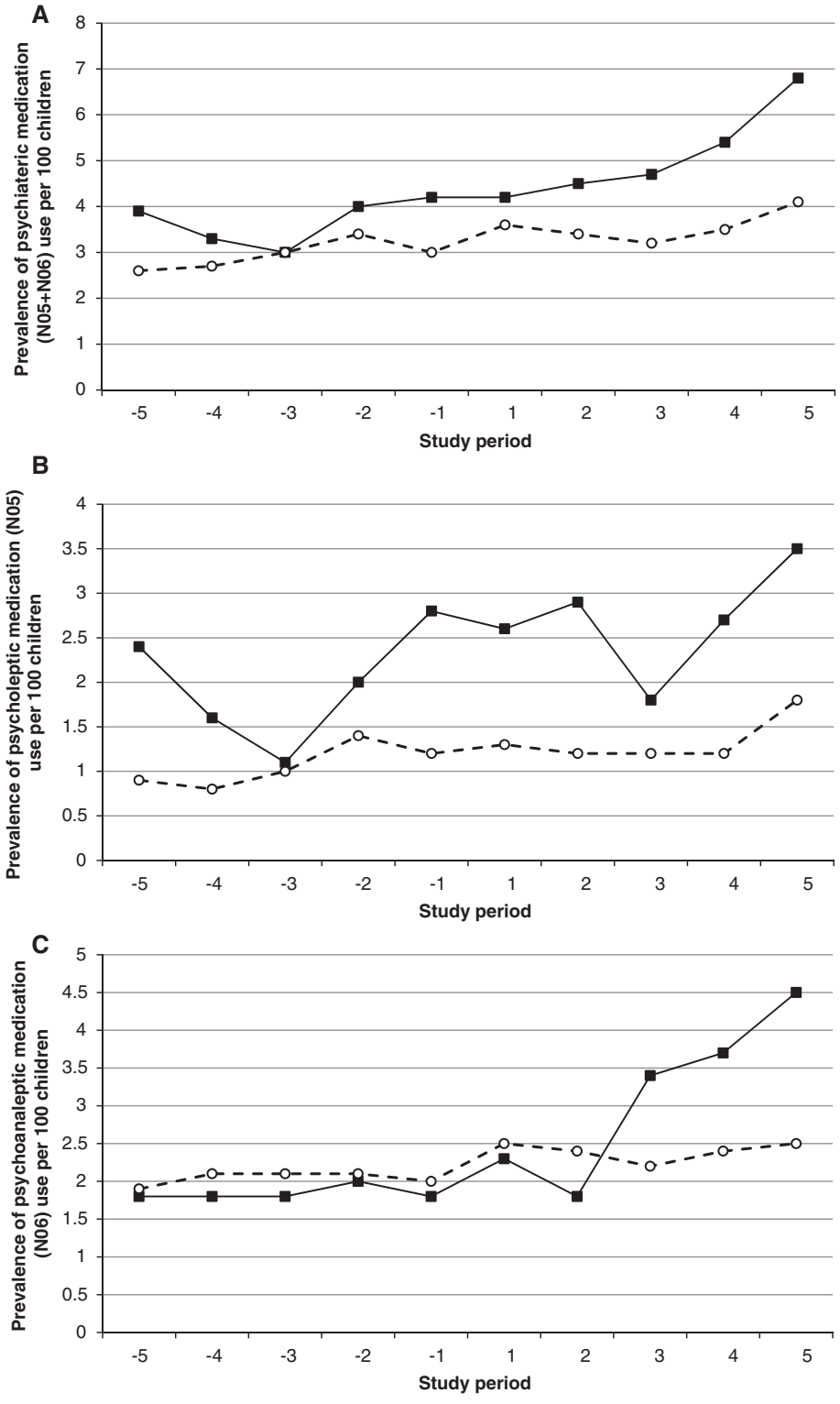

FIGURE 1 Annual prevalence of use of any psychiatric (N05 + N06) (A), any psycholeptic (N05) (B), and any psychoanaleptic (N06) (C) medications in the type 1 diabetes (–■–) and the reference (–○–) cohorts before and after the index date (minus signs refer to years before the index date)

olanzapine and risperidone) increase fasting glucose concentration and leptin levels, and can induce weight gain, insulin resistance and insulin deficiency, and acute pancreatitis.[26,27] A bidirectional association between T2D and depression has been previously reported,[15–17,28] and recently a large study demonstrated a significant genetic overlap between T2D and depression.[18] In the current study, we observed that having at least 1 dispensing for psychiatric medications in the period up to 5 years before the cohort entry date or diagnosis of T1D was significantly associated with developing T1D (OR = 1.5, 95% CI 1.1-2.0), this increased risk was completely driven by an increased use of psycholeptics. However, other large studies are needed to confirm the causal relation between psychiatric medication use and T1D. In addition, the prevalence of psychiatric medication use after the onset of T1D was significantly higher in the T1D cohort compared with the reference cohort (10.4% vs 7.9%, respectively; P = .015) which was in line with other studies that reported a variety of mental health problems such as depression, and anxiety, which were common in patients with T1D.[5,9,20,29] In a recent study, Cooper et al reported a 2.3 times higher

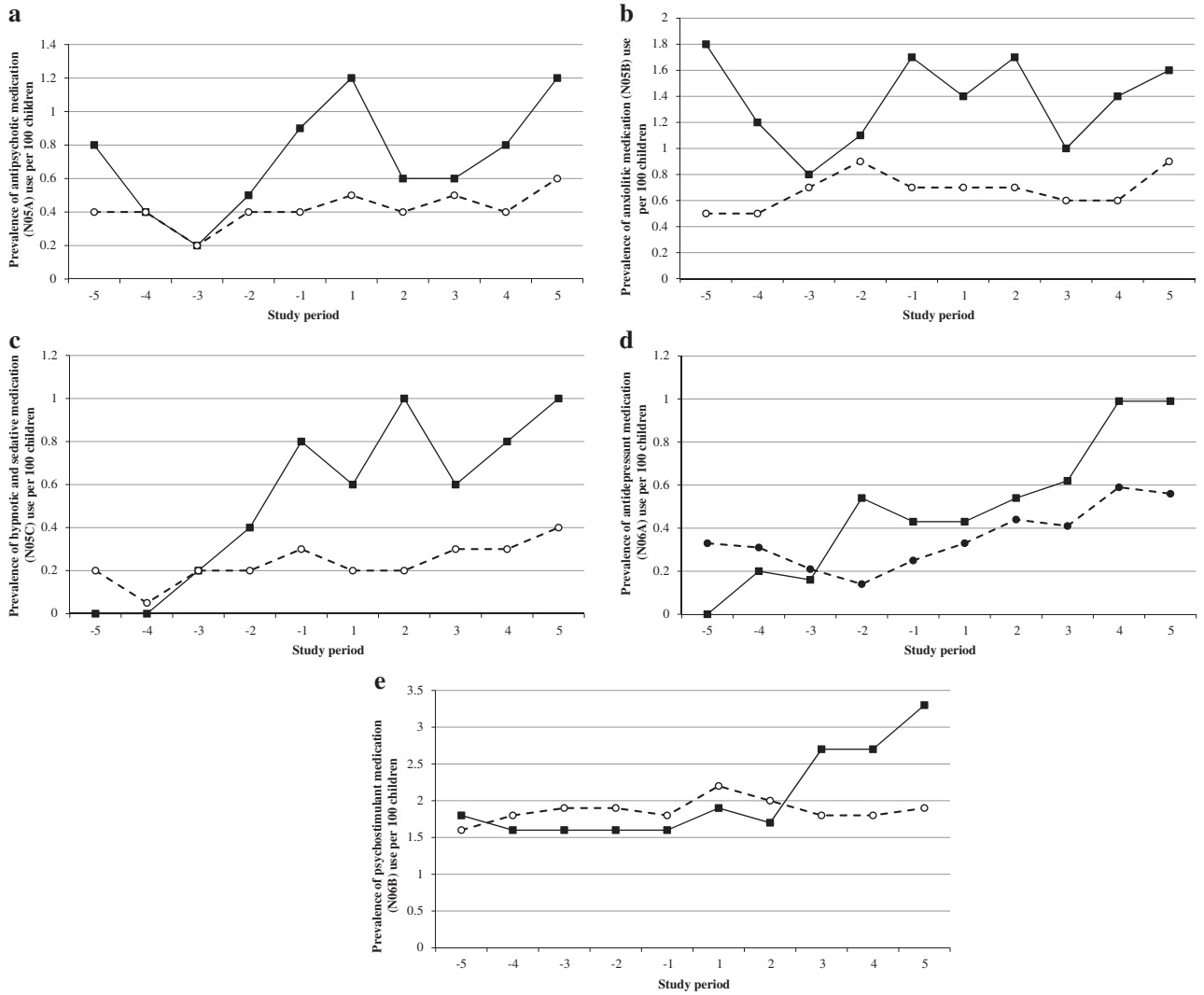

FIGURE 2 Annual prevalence of use of any antipsychotic (N05A) (A), anxiolytic (N05B) (B), hypnotic or sedative medication (N05C) (C), antidepressant (N06A) (D), and psychostimulant medication (N06B) (E) in the type 1 diabetes (–■–) and the reference (–○–) cohorts before and after the index date (minus signs refer to years before the index date)

risk of psychiatric disorders within a cohort of young adults with T1D compared with a non-diabetic reference cohort, with specifically diagnoses of anxiety, eating, mood, and personality and behavior disorders occurring more frequently within the T1D cohort.[30]

In one population-based cohort study, Knol et al showed an increased incidence of antidepressant and benzodiazepine use shortly after the initiation of diabetes medication in adults.[31] This increased use could be a consequence of the burden of diabetes as was noticed in previous papers.[28,31] In our study, we observed an elevated prevalence of antipsychotic, anxiolytic, hypnotic, or sedative medication, and antidepressant use in T1D cohort in the years after the onset of this disease especially the first year. We also observed that the prevalence of anxiolytic and hypnotic or sedative medication use in the year before the onset of T1D was higher than the first year after the diagnosis of this disease.

An increased use of psychostimulant medications was observed in the T1D cohort from the third year after the onset of T1D (Figure 2). This fining is in line with a recent study by Kapellen et al[32] that reported a higher prevalence of attention deficit hyperactivity disorder in children with T1D compared with diabetes-free children.

Diagnosis of T1D has a big impact on patients' life. Furthermore, patients are responsible for the control of their disease and this may cause depression.[33] In a recent meta-analysis, high prevalence of symptoms of depression and anxiety were observed in youth with T1D. Well-designed studies with large numbers of participants are needed to further explore the interaction of symptoms of psychiatric disorders (including depression and anxiety) in youth with T1D and also diabetes management and glycemic control.[12]

4.2 | Clinical relevance, implications, and suggestions for future research

Our findings that elevated psychiatric medication use in the T1D cohort exists before the onset of T1D warrants further research to identify the complete association of these 2 comorbidities and mechanisms.

Patients with T1D and depression (or other psychiatric disorders) showed poor metabolic control and higher rates of hospital admissions as well as longer inpatient stay.[34] Therefore, it is important to assess psychiatric health in pediatric patients with T1D.[34] Patients

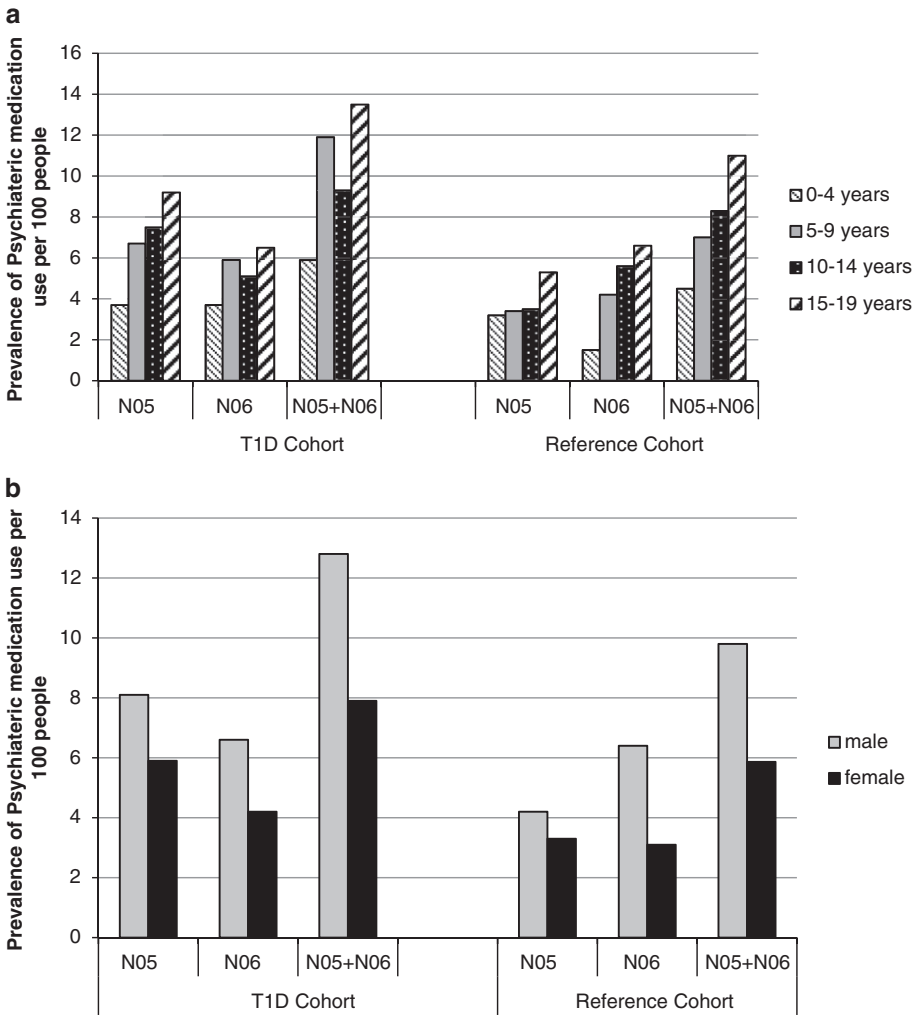

FIGURE 3 Prevalence of psychiatric medication use in the type 1 diabetes (T1D) and the reference cohorts (after the index date until the end of follow-up) stratified by age categories (age bands: 0-4, 5-9, 10-14, and 15-19 years) (A) and sex (B)

with T1D and depression receiving pharmacotherapy showed lower hemoglobin A1c levels. To better engage juvenile T1D patients in treatment for comorbid depression, collaborative care approaches need to be developed.[34]

It is also relevant to have more information on the type of health care providers (eg, general practitioners, endocrinologist, etc.) prescribing psychiatric medications for children with T1D. In future studies, researchers may consider investigating whether children with T1D have more frequent contact with psychiatric care clinics or whether psychiatric medications are prescribed within diabetes care clinics. Young patients might need support in the management of their pharmacotherapy. Concomitant use of diabetes and psychiatric medication may be accompanied with non-adherence to medication to control diabetes, which may lead to deterioration of diabetic control.[9] Adherence needs to be addressed in management of patients' pharmacotherapy and health care providers need to be aware of concomitant use of antidiabetic and psychiatric medications.

4.3 | Strengths and limitations

To the best of our knowledge, this is the first population-based study to investigate the prevalence of psychiatric medication use in children and adolescents with T1D in the period both before and after the onset of this disease. PHARMO RLS is a large population-based database which has been shown to be a representative of the Dutch population in several studies, and the population-based design of our study (without too many exclusion criteria) is its main strength.[22,23] Routinely collected detailed data on medication use reduced the probability of information bias and recall bias. Also, the use of insulin as a proxy for T1D is strong since the treatment of hyperglycemia is the only indication.[25] We assumed that most of the insulin users in our study had T1D, because other types of diabetes needing insulin (eg, latent autoimmune diabetes in adults, monogenic diabetes, mitochondrial diabetes, etc.) have a low prevalence compared with that of T1D. Therefore, misclassification of type of diabetes is probably a minor problem.[25,35] Furthermore, Bonferroni correction has been used to account for all tests that we used in this study, and the results remained still statistically significant.

There are several limitations in this study that must be addressed. We may have misclassified undiagnosed cases of T2D or children and adolescents with T2D who do not use any medication for T2D as diabetes-free children in the reference cohort. Furthermore, there are a few children and adolescents (N = 10) with only 2 insulin prescriptions during a longer follow-up time who may be misclassified as patients with T1D. As this number is low (1% of our patients with T1D), it has no material influence on our results. Another limitation of our study is related to our reference cohort. In this study, we randomly selected a group of age- and sex-matched

diabetes-free children and adolescents. We could not include diabetes-free children and adolescents who never obtained any prescription from pharmacies until the end of our study period (probably the healthiest children). The rates of psychiatric medication use we found in the reference cohort may therefore be overestimated for the general population of diabetes-free children and adolescents in the Netherlands, and the gap between children and adolescents with T1D and diabetes-free children and adolescents in the general population will be even higher than what we reported as the difference between the 2 cohorts. In this study, we used pharmacy dispensing data and unfortunately we did not have access to data on prescribed medication which were not dispensed. It is known that patients with T1D may better comply with psychiatric medication and by this way show higher prevalence of medication use. It is also possible that regular contact with the physician after the diagnosis of T1D increased the probability of diagnosing different disorders, which resulted in prescribing more psychiatric medications for these children during the period after cohort entry. But as can be seen in Figures 1 and 2, T1D patients already had increased use of psychiatric medications from about 2 years before the onset of T1D. Finally, we did not have data on use of psychiatric medicines during hospital admissions nor could we explore the indications for which psychiatric medications were prescribed in this study as our data were based on community pharmacy dispensings. For example, benzodiazepines might be used to reduce anxiety or to treat epilepsy.

4.4 | Conclusions

In conclusion, children and adolescents with T1D were more likely to use psychiatric medication in the years before and after the onset of diabetes compared with an age- and sex-matched diabetes-free reference cohort. This increased use was mainly driven by anxiolytics both before and after the onset of T1D. Our findings that elevated psychiatric medication use in the T1D cohort exists before and after the onset of T1D warrants further research to identify the complete association of these 2 comorbidities and mechanisms.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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