Chronic comorbidities in children with type 1 diabetes: a population-based cohort study

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ABSTRACT

Objective To determine the incidence of chronic comorbidities among children with type 1 diabetes (T1D) and to compare incidences with a group of children without diabetes.

Design Population-based cohort study.

Setting Dutch PHARMO database (1998–2010).

Patients All patients (<19 years old) with T1D between 1999 and 2009 (T1D cohort) and a group of age- and sex-matched (ratio: 1–4) children without diabetes (reference cohort).

Main outcome measure The incidence of nine common chronic comorbidities was assessed on the basis that they were treated pharmacologically and/or resulted in hospital admission. Cox proportional hazard analysis was used to estimate the strength of the association between T1D and comorbidities, expressed as HRs and 95% CIs.

Results A total of 915 patients with T1D and 3590 children in the reference cohort (51% boys, mean age of 10.1 (SD 4.5) years) were included. T1D was associated with an increased risk (HR; 95% CI) of hospitalisation for any comorbidity (3.7; 2.5 to 5.5), thyroid disease (14.2; 6.7 to 31.0), non-infectious enteritis and colitis (5.9; 3.0 to 11.5), cardiovascular disorders (3.1; 2.3 to 4.2), mental disorders (2.0; 1.4 to 3.1), epilepsy (2.0; 1.1 to 3.7) and (obstructive) pulmonary disease (1.5; 1.2 to 2.0). There was no significant difference in the incidences of other comorbidities (malignant disorders, anaemia and migraine) between the two cohorts.

Conclusions Our longitudinal study showed that incidences of six chronic diseases were significantly higher in T1D children during the early years of developing this disease compared with the reference children.

What is already known on this topic?

- Patients with diabetes are at increased risk for developing serious health problems and mortality.
- The increasing incidence of type 1 diabetes (T1D) in children worldwide, results in increasing number of children with serious health problems and chronic comorbidities.

What this study adds?

- We found significant increased risks of developing several chronic comorbidities in children with T1D.
- In a median of 5 years after diagnosis of diabetes, T1D children had significant increased risks of thyroid disorders (14-fold), non-infectious enteritis and colitis (sixfold), cardiovascular disease (threefold), mental disorders (twofold), epilepsy (twofold) and (obstructive) pulmonary disease (1.5-fold) compared with the age- and sex-matched reference cohort.

INTRODUCTION

Type 1 diabetes (T1D) is one of the most common autoimmune disorders in children, with a 3% annual increase in the global incidence rates since the 1980s.[1–3] Patients with diabetes are at increased risk of serious health problems and mortality.[4 5] Disrupting effects of diabetes on health, quality of life and use of medical services result in increased healthcare costs and economic burden.[6 7] Except for several well-described complications directly related to glucose metabolism such as retinopathy, nephropathy, peripheral neuropathy and cardiovascular disease, and associated autoimmune conditions such as coeliac disease, hypothyroidism/hyperthyroidism and Addison disease, little is known about the co-occurrence of other chronic comorbidities in children.[4 8 9] Furthermore, most previous studies were conducted in adult populations or did not specify the type of diabetes. Therefore, we conducted a population-based cohort study using a database of community pharmacy dispensing records linked to hospital admissions. This approach enabled us to estimate the incidence of multiple pharmacologically treated chronic comorbidities in T1D children at the same time and to compare the magnitude of risk of developing these comorbidities with a group of age- and sex-matched children without diabetes to estimate the excess burden of these comorbidities.

RESEARCH, DESIGN AND METHODS

Data source, study design and population

We used the validated population-based Dutch PHARMO Record Linkage System (RLS) (http://www.pharmo.nl) which covers the whole country and includes high-quality and complete information linked on a patient level of, among other data, patient demographics and drug dispensing records from community pharmacies of more than four million inhabitants of the Netherlands (approximately 24% of the Dutch population) together with hospital discharge records.[10 11] The drug dispensing records consist of data on the dispensed drug, the type of prescriber, the dispensing date,

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the amount dispensed and the written dose instructions. Hospital records are obtained from the Dutch National Medical Register (Landelijke Medische Registratie (LMR)), which comprises all hospital admissions in the Netherlands. Dates of hospital admissions and discharges, together with primary and secondary diagnoses, are documented in the hospital records. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (http://icd9cm.chrisendres.com), whereas the drugs are coded according to the Anatomical Therapeutic Chemical codes (ATC codes) (http://www.whocc.no/atc_ddd_index).

Patients (<19 years old) with incident T1D were selected based on having a history of hospital admission for T1D (ICD-9 code 250) and/or at least two insulin dispensings (ATC A10A) between January 1999 and December 2009 (T1D cohort).[10 12] Either the date of first insulin dispensing or the date of first hospital admission for T1D was selected as the index date (cohort entry date), whichever came first. Duration of diabetes is an important factor for developing other comorbidities; therefore, we decided to only include patients with incident diabetes to reduce biased estimates in the incidence and risk of developing comorbidities. To be sure that patients were really newly diagnosed with T1D, patients should be present in the database at least 1 year prior to the index date (except for children with a diagnosis of T1D before 1 year of age). Patients in the T1D cohort who used glucagon in the year prior to the cohort entry date, ever use of oral glucose-lowering medications (ATC A10B), or had history of cystic fibrosis were excluded.[10 12] For each patient in the T1D cohort up to four children without any dispensing for glucose-lowering medications or diabetes hospitalisation during the study period and with the same sex, age and follow-up time were randomly sampled from the database (reference cohort). Patients in both cohorts were only eligible for inclusion in the study if they had 12 months history before and at least 12 months follow-up after the index date. Both cohorts were followed from the index date till the end of data collection in PHARMO RLS, death or end of the study period (31 December 2010), whichever occurred first.

Chronic comorbidities

In this study, PHARMO RLS was used to identify all chronic conditions on the basis that they were treated pharmacologically and/or resulted in hospital admissions (see online supplementary table S1). Malignant neoplasms, anaemia, mental disorders, epilepsy, migraine, (obstructive) pulmonary disease and cardiovascular disorders were defined on the basis of hospitalisation of the patient for these conditions or at least two dispensings for the treatment of these conditions (see online supplementary table S1). For calculating incidence rates, the first hospital admission or first dispensing related to each chronic comorbidity after the index date (whichever occurred first) was counted as the first event. The medications used for the treatment of non-infectious enteritis and colitis are not specific enough, and only hospital admission data was used for the classification of this comorbidity. Since not all hospitalisations for non-infectious enteritis and colitis are related to inflammatory bowel disease (IBD), this category was further stratified into two subgroups: unspecified non-infectious colitis and regional enteritis and ulcerative colitis (probable IBD cases, see online supplementary table S1).

Statistical analysis

Baseline proportions of different diseases were calculated for the period 0–12 months prior to the index date and compared between two cohorts using a χ^2 test. For calculating incidence rates, patients with prevalent chronic disorder at baseline were removed from the at-risk population for that specific disease. Incidence rates per 1000 person-years (PY) with 95% CI were calculated for the total follow-up time. Kaplan–Meier hazard curves were used to compare cumulative incidences of comorbidities between the two cohorts, and Cox proportional hazards regression analyses were subsequently used to calculate HRs. The proportional hazards assumption was assessed prior to calculating HRs. All statistical analyses were carried out using SPSS V.19.0 statistical software (SPSS, Chicago, Illinois, USA).

RESULTS

A total of 915 patients with T1D and 3590 children in the reference cohort met the inclusion criteria. The mean age of the study population was 10.1 (SD 4.5) years and almost 51% of them were boys (table 1).

In the year prior to the index date, patients in the T1D cohort were hospitalised significantly more for any of these nine chronic diseases than the reference cohort with a prevalence of 1.3% and 0.25%, respectively (p<0.001). The occurrence of malignant neoplasms, cardiovascular disorders and thyroid diseases in the period 0–12 months prior to the index date was significantly higher in the T1D cohort compared with the reference cohort (table 1).

The median duration of follow-up was 5.2 years for both cohorts. Incidence rates for different chronic comorbidities in patients with T1D ranged from 0.6/1000 PY for malignant neoplasms to 22.3/1000 PY for (obstructive) pulmonary disease (table 2). Incidence rates of all chronic comorbidities were generally higher in the T1D cohort than in the reference cohort, resulting in an almost four times higher risk of being hospitalised for any of these nine comorbidities (HR 3.7, 95% CI 2.5

Table 1 Baseline characteristics of patients with type 1 diabetes (T1D cohort) and the reference cohort

Baseline characteristics	T1D cohort (N=915) N (%)	Reference cohort (N=3590) N (%)	p Value
Sex			
Male	466 (50.9)	1817 (50.6)	–
Female	449 (49.1)	1773 (49.4)	–
Age categories, years			
0–5	174 (19.0)	700 (19.5)	–
6–12	441 (48.2)	1716 (47.8)	–
13–18	300 (32.8)	1174 (32.7)	–
Year of cohort entry			
1999–2004	382 (41.6)	1452 (40.4)	–
2005–2009	533 (58.3)	2138 (59.6)	–
Proportion of chronic diseases already present in the year before the index date			
All malignant neoplasms	8 (0.9)	0 (0)	0.000
Anaemia	4 (0.4)	19 (0.5)	0.727
Mental disorders	28 (3.1)	76 (2.1)	0.090
Epilepsy	5 (0.5)	14 (0.4)	0.514
Migraine	1 (0.1)	10 (0.3)	0.354
(Obstructive) pulmonary disease	60 (6.6)	223 (6.2)	0.700
Non-infectious enteritis and colitis	0 (0)	2 (0.1)	0.475
Cardiovascular disease	8 (0.9)	12 (0.3)	0.011
Thyroid disease	9 (1)	3 (0.1)	0.000

T1D, type 1 diabetes.

Table 2 Incidence rates and HRs comparing comorbidities in the T1D cohort and the reference cohort

	T1D cohort (N=915)			Reference cohort (N=3590)				
Comorbidities	Events* (hospital admissions†)	Follow-up PY	IR/1000 PY (95% CI)	Events* (hospital admissions†)	Follow-up PY	IR/1000 PY (95% CI)	HR (95%CI)	p Value
All malignant neoplasms	3 (1)	5060	0.6 (0.2 to 1.7)	7 (3)	19 660	0.4 (0.2 to 0.7)	1.1 (0.2 to 5.3)	0.902
Anaemia	24 (1)	4995	4.8 (3.2 to 7.1)	62 (1)	19 298	3.2 (2.5 to 4.1)	1.5 (0.9 to 2.5)	0.097
Mental disorders	37 (11)	4810	8.9 (6.7 to 12.0)	70 (13)	19 063	4.3 (3.5 to 5.3)	2.0 (1.4 to 3.1)	0.001
Epilepsy	15 (6)	5019	3.0 (1.8 to 4.9)	29 (7)	19 491	1.5 (1.0 to 2.1)	2.0 (1.1 to 3.7)	0.029
Migraine	11 (0)	5056	2.2 (1.2 to 3.9)	27 (1)	19 526	1.4 (1.0 to 2.1)	1.5 (0.7 to 3.2)	0.249
(Obstructive) pulmonary disease	94 (6)	4209	22.3 (18.3 to 27.3)	280 (4)	16 954	16.5 (14.7 to 18.6)	1.5 (1.2 to 2.0)	0.002
Non-infectious enteritis and colitis	21 (21)	5025	4.2 (2.7 to 6.4)	14 (14)	19 616	0.7 (0.4 to 1.2)	5.9 (3.0 to 11.5)	0.000
Cardiovascular disease	76 (2)	4747	16.0 (12.8 to 20.0)	103 (2)	19 189	5.4 (4.4 to 6.5)	3.1 (2.3 to 4.2)	0.000
Thyroid disease	30 (0)	4978	6.0 (4.2–8.5)	8 (0)	19 633	0.4 (0.2–0.8)	14.2 (6.7–31.0)	0.000

*Total number of events.
†Number of hospital admissions.
IR, incidence rate; PY, person-years; T1D, type 1 diabetes.

to 5.5). HRs ranged from a similar risk of 1.1 (95% CI 0.2 to 5.3) for malignant neoplasms to a 14.2-fold (95% CI 6.5 to 31.0) increased risk for thyroid disorders. Statistically significant increased risks were observed for non-infectious enteritis colitis (HR 5.9, 95% CI 3.0 to 11.5), cardiovascular disorders (HR 3.1, 95% CI 2.3 to 4.2), mental disorders (HR 2.0, 95% CI 1.4 to 3.1), epilepsy (HR 2.0, 95% CI 1.1 to 3.7) and (obstructive) pulmonary disease (HR 1.5, 95% CI 1.2 to 2.0) (table 2). Figure 1 presents Kaplan–Meier hazard function curves for the cumulative incidences of all the above-mentioned comorbidities after the index date in both cohorts.

Children with T1D were more hospitalised for neurotic disorders such as anxiety, and alcohol or drug dependence syndromes (1.1% in the T1D vs 0.3% in the reference cohort) and they used more psycholeptic (1.8% vs 0.8%) and psychoanaleptic (1.7% vs 1.1%) medications (such as antipsychotics, anxiolytics, hypnotics and sedatives) compared with those in the reference cohort. Cardiovascular medication use was higher in the T1D than in the reference cohort for β blockers (3.5% vs 2.3%), agents acting on the renin–angiotensin system (3.3% vs 0.4%), lipid-modifying agents (2.2% vs 0.3%) and diuretics (1.6% vs 0.2%). While there was a significant association between non-infectious enteritis colitis and T1D, we did not find an increased risk for developing regional enteritis and ulcerative colitis (HR 0.7, 95% CI 0.1 to 6.3). However, children with T1D were hospitalised 10 times more frequently than the reference children for unspecified non-infectious gastroenteritis and colitis (HR 9.8, 95% CI 4.3 to 22.3).

DISCUSSION

This is the first population-based cohort study investigating the risk of developing chronic comorbidities in children with T1D compared with children without diabetes. Using the validated Dutch PHARMO RLS enabled us to measure the incidence rates of nine disorders at the same time. Our results indicate that there is a significant increased risk of thyroid disorders (14-fold), non-infectious enteritis and colitis (sixfold), cardiovascular disease (threefold), mental disorders (twofold), epilepsy (twofold) and (obstructive) pulmonary disease (1.5-fold) in a median of 5 years after the start of T1D. We did not observe a difference in risks of anaemia, migraine and malignant neoplasms between the two cohorts.

The association between T1D and thyroid disorders has been well described in previous studies and our results confirm the findings of these studies.[13–17] However, long-term observational studies to evaluate the incidence of thyroid disorders in children with T1D were lacking.[15] Unfortunately, we were unable to check whether these thyroid dysfunctions were immune related.

An association between paediatric IBD and (immune-mediated) diabetes has been previously reported.[18] We found a six times higher risk of hospitalisation for non-infectious enteritis and colitis in our T1D cohort. However, the majority of the discharge diagnoses were recorded as unspecified non-infectious gastroenteritis and colitis. It is not clear whether these hospital admissions were due to IBD (general and unspecified terms might be used in medical records) or they were related to other types of colitis or even coeliac disease which is highly frequent in patients with T1D.[8] Furthermore, unspecified non-infectious gastroenteritis and colitis could have been misdiagnosed in some cases of diabetes ketoacidosis (DKA).[19] Moreover, T1D children were hospitalised more frequently for non-infectious gastroenteritis and colitis, which may be the consequence of diarrhoea and vomiting resulting in difficulty to control T1D and consequently hospitalisation. Therefore, to reveal the real association between IBD and T1D more studies are needed.

We also found increased risks for cardiovascular and nervous system medication use, which is consistent with previous studies showing increased risks of cardiovascular and mental disorders in patients with diabetes.[20–22] Thus, the well-known associations in adults between diabetes and cardiovascular disease and mental disorders, especially depression and anxiety, may already present in childhood, although some of these medications may have been used (off-label) for other indications.[23 24] Therefore, early detection and adequate treatment of cardiovascular and mental disorder risk factors in children with T1D is important.

Increased risks in comorbidities such as epilepsy and (obstructive) pulmonary disease, and although statistically not significant, anaemia, migraine and malignant neoplasms all have been reported to some extent in the literature. In some cases biological explanations exist, but inconsistencies have been noted across the literature.[25–32] Some anti-neoplasm treatments (eg, corticosteroids, L-asparaginase, etc) can induce hyperglycaemia and subsequent use of insulin might be misclassified as for T1D.[33] However, the number of children with a low number of insulin dipensings (three or less) was very low (4.7% of all patients in the T1D cohort).

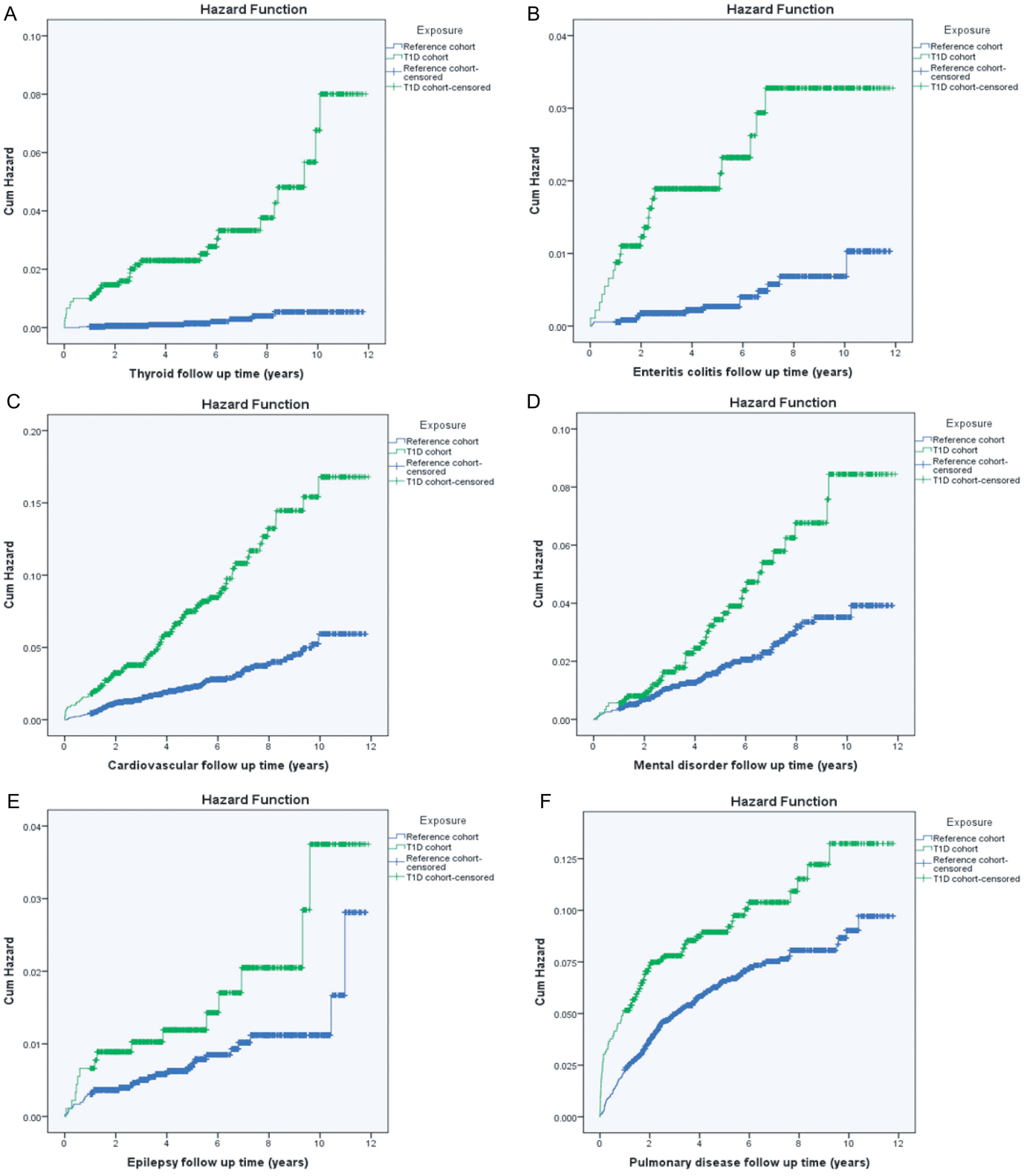

Figure 1 Cumulative hazard of developing (A) thyroid diseases, (B) enteritis colitis, (C) cardiac diseases, (D) mental disorders, (E) epilepsy and (F) (obstructive) pulmonary diseases, for the T1D (——) and reference cohorts (——).

Different chronic comorbidities and medications used for treating those comorbidities could interfere with the maintenance of normal blood glucose in patients with diabetes; therefore, appropriate treatment regimens should be selected in these patients.[4 34 35] Further studies are required to find out more information and risk factors for developing different complications in children with T1D. This knowledge is relevant for informing guidelines, applying prevention programmes, evaluating the impact of these chronic comorbidities on glycaemic control and making appropriate decisions related to healthcare costs.

This is the first population-based cohort study that evaluated the risk of several chronic comorbidities (at the same time) in a

cohort of T1D children compared with an age- and sex-matched reference cohort. The main strengths of our study are the population-based cohort design without many exclusion criteria, reasonable sample size, longitudinal data collection and a limited probability of information bias and recall bias.[10 12] Using insulin as a proxy for T1D is another strength for this study since the treatment of hyperglycaemia is the only indication and it has been validated as a proxy for identifying cases of T1D.[2] We assumed that most of insulin users in our study had T1D, because patients with cystic fibrosis at baseline were removed from the study population and other types of diabetes needing insulin (eg, mitochondrial diabetes) have low prevalences compared with T1D.[36] Therefore, misclassification of the type of diabetes is probably a minor problem.

It is likely that our results underestimate the prevalence of a number of comorbidities which did not lead to hospitalisation and for which no specific drugs were prescribed (under-ascertainment). While there might be misclassification of drugs and diseases, several studies have validated the exposure of drugs retrieved from pharmacy dispensing records and hospital discharge records in the Netherlands showing good sensitivity and specificity.[37–39] Information on drugs used in hospital, as well as on over-the-counter drugs was not available (under-ascertainment). Although the PHARMO RLS covers almost 24% of the Dutch population, the numbers of some prescribed drugs and hospital admissions were still low, leading to wide CIs. In the present paper we have quantified the problem of comorbidities and only discussed nine of them but we did not have information on the severity of these diseases and/or glycaemic control in patients with T1D. We cannot rule out that patients with T1D more often visit doctors and are more frequently screened for other complications (eg, thyroid disease, coeliac disease, cardiovascular risk factors, etc) than children without diabetes, which increases the chance of diagnosing other diseases and having more prescriptions (under-ascertainment for the reference cohort). Patients who used hyperglycaemia-inducing medications such as steroids or atypical anti-psychotics might have used a few doses of insulin to reduce hyperglycaemia, and these patients might be misclassified as T1D. However, there are a few children with temporary use of insulin in our study. The last limitation of our study is related to our reference cohort. In the current study, we randomly selected an age- and sex-matched reference cohort from the PHARMO RLS. In our reference cohort, we could not include those who never obtained any prescription from pharmacies until the end of our study period (probably the most healthy children). The rates of chronic comorbidities we found in the reference cohort are therefore not generalisable to the general population of children in the Netherlands, and the gap between children with T1D and children in the general population will be even larger than what we reported as the difference between the two cohorts.[10]

In conclusion, this study showed that risks of thyroid disorders, non-infectious enteritis and colitis, cardiovascular disease, mental disorders, epilepsy and (obstructive) pulmonary disease were significantly higher in children with T1D during the early years after developing diabetes. There was no significant difference in the risk of malignant neoplasms, migraine and anaemia between the two cohorts. Therefore, more studies are required in children and adolescents to further clarify the association between T1D and other chronic comorbidities and their mechanism and the effect of adequate blood glucose control on the postponement of these comorbidities in young patients.

Contributors SFF contributed to the study design, analysed the data and wrote the manuscript. PCS created the data matrix. PCS, MMJV, CAJK, AB and AKM contributed to the study design and the discussion and edited the manuscript. All authors take full responsibility for the contents of the manuscript.

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