New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic

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ABSTRACT

Background Viral infections may trigger type 1 diabetes (T1D), and recent reports suggest an increased incidence of paediatric T1D and/or diabetic ketoacidosis (DKA) during the COVID-19 pandemic.

Objective To study whether the number of children admitted to the paediatric intensive care unit (PICU) for DKA due to new-onset T1D increased during the COVID-19 pandemic, and whether SARS-CoV-2 infection plays a role.

Methods This retrospective cohort study comprises two datasets: (1) children admitted to PICU due to new-onset T1D and (2) children diagnosed with new-onset T1D and registered to the Finnish Pediatric Diabetes Registry in the Helsinki University Hospital from 1 April to 31 October in 2016–2020. We compared the incidence, number and characteristics of children with newly diagnosed T1D between the prepandemic and pandemic periods.

Results The number of children admitted to PICU due to new-onset T1D increased from an average of 6.25 admissions in 2016–2019 to 20 admissions in 2020 (incidence rate ratio [IRR] 3.24 [95% CI 1.80 to 5.83]; p=0.0001). On average, 57.75 children were registered to the FPDR in 2016–2019, as compared with 84 in 2020 (IRR 1.45; 95% CI 1.13 to 1.86; p=0.004). 33 of the children diagnosed in 2020 were analysed for SARS-CoV-2 antibodies, and all were negative.

Conclusions More children with T1D had severe DKA at diagnosis during the pandemic. This was not a consequence of SARS-CoV-2 infection. Instead, it probably stems from delays in diagnosis following changes in parental behaviour and healthcare accessibility.

What is already known on this topic?

- During the COVID-19 pandemic, an increased incidence and a more severe clinical presentation of type 1 diabetes in children have been reported.
- It is unclear whether the observed changes in the incidence and/or clinical presentation of type 1 diabetes are directly associated with SARS-CoV-2 infection.

What this study adds?

- During the pandemic, there was an increase in the number of children admitted to paediatric intensive care unit due to new-onset type 1 diabetes with severe ketoacidosis.
- A smaller increase in the incidence of new-onset type 1 diabetes diagnoses was observed.
- As no SARS-CoV-2 antibodies were detected in these children, indirect effects of the pandemic are more plausible causes for an altered presentation of new-onset type 1 diabetes.

INTRODUCTION

An increase in the number of children with newly diagnosed type 1 diabetes (T1D) has been reported during the COVID-19 pandemic,[1] and several reports from regions heavily impacted by the pandemic suggest that more children with new-onset T1D now present with severe diabetic ketoacidosis (DKA).[1–6] Lacking epidemiological studies, it is unclear whether there is a true increase in the T1D incidence, or rather an exacerbation of the disease presentation. Furthermore, the mechanisms of a potential association between COVID-19 and new-onset T1D are unknown.[7 8]

Finland has the highest incidence of T1D in the world,[9] whereas the number of paediatric COVID-19 cases remained low during the first wave of the COVID-19 pandemic.[10 11] Nevertheless, strict infection control measures affecting children were put in place from mid-March 2020: schools were closed, elective healthcare appointments cancelled or changed to eHealth outpatient visits and families advised to avoid unnecessary contacts.

Despite a low local COVID-19 infection rate, also we noticed that more children were admitted to the paediatric intensive care unit (PICU), Helsinki University Hospital (HUH) for newly diagnosed T1D from May 2020 onward. We set out to assess whether the occurrence of T1D had increased, or the disease presentation at diagnosis worsened, conceivably due to delays in seeking or receiving medical attention. Furthermore, as the COVID-19 might function as a trigger of the manifestation of T1D,[12] we analysed SARS-CoV-2 antibodies in children with newly diagnosed T1D. As the baseline seroprevalence of SARS-CoV-2 antibodies in the region was only 0.6%,[10] we hypothesised that this approach would enable us to infer whether the observed increase in new T1D cases or DKA at diagnosis was directly associated with preceding SARS-CoV-2 infection.

METHODS

Study design

This retrospective cohort study consists of two datasets of children newly diagnosed with T1D during 1 April–31 October 2020 (*the pandemic period*) and corresponding periods (1 April–31 October) in 2016–2019 (*the prepandemic periods*). The first dataset includes all children admitted to the PICU in The New Children's Hospital, HUH for new-onset T1D with severe DKA. The second dataset comprises all children prospectively enrolled to the Finnish Paediatric Diabetes Registry (FPDR) from the HUH district. In addition, serum samples for SARS-CoV-2 antibody testing were available from a subset of children enrolled in the registry cohort during the pandemic period.

Setting

The study was conducted in the HUH district (total population 2 188 253, paediatric population 369 807 (31 December 2019)) in Finland (population 5 525 292, paediatric population 872 996 (31 December 2019),[13] which is a Nordic welfare state with universal healthcare for residents. Private or outpatient care for new-onset T1D for children is not available in Finland. The New Children's Hospital is the only provider of PICU care in the HUH district. Thus, the incidence of severe DKA in this population can be calculated from the number of patients treated in the HUH. During the pandemic, the PICU admission criteria did not change. Our PICU was not used to treat adults with COVID-19 or any other new patient groups.

Participants

With the consent of the patient and/or the caregiver, Finnish children and adolescents with newly diagnosed T1D may participate in the FPDR. This includes prospectively collecting structured data on patient history, clinical presentation, including biochemistry and serology at diagnosis, details about in-hospital care[14] and storage of biological samples including serum. In 2016–2019, approximately 90% of newly diagnosed T1D children were registered, and 72% consented to donate a serum sample. Thus, the number of registered patients reflects the incidence of T1D in children in the area.

For the PICU cohort, we reviewed records of all newly diagnosed T1D children ≤15 years, treated in the HUH PICU during the pandemic period (1 April–31 October 2020), and those from the corresponding prepandemic periods 2016–2019, from the PICU electronic patient record (Clinisoft, GE). In the registry cohort, we reviewed records of all newly diagnosed children from the HUH district registered in the FPDR during the corresponding pandemic and prepandemic periods.

Data collection and definitions

We collected patient characteristics, duration of symptoms, the length of stay and biochemical findings on presentation (tables 1 and 2). As markers of severity of DKA, we recorded blood pH, plasma osmolality, β-hydroxybutyrate and glucose concentration in the PICU cohort, and pH and glucose concentration in the registry cohort. As markers of a possible diagnostic delay, we included the duration of symptoms before diagnosis, and the glycosylated haemoglobin value at diagnosis.

Details of SARS-CoV-2 antibody tests,[15–18] other laboratory tests and patient selection for PICU admission are included in the online supplemental data file.

Statistical methods

We compared the pandemic study period (1 April–31 October 2020) to corresponding time periods in the four preceding years (2016–2019) to evaluate possible pre-existing trends and to account for seasonal variation in the occurrence of T1D. As the observational periods were 7 months each year, we scaled

Table 1 Characteristics and laboratory values of the children admitted to the PICU in the Helsinki University Hospital for newly diagnosed type 1 diabetes during the pandemic period 1 April to 31 October 2020, and the corresponding periods in 2016–2019

	Prepandemic period 2016–2019 (n=25)	Pandemic period 2020 (n=20)	P value
Number of patients per study period, n	6.25*	20	
Incidence, per 100 000 person-years (95% CI)	2.89 (1.95–4.27)	9.35 (6.03–14.49)	0.0001
Age, median (IQR), years	9.5 (6.2–11.4)	10.0 (8.1–12.3)	0.42
Female sex, n (%)	10 (40)	9 (45)	0.77
Previously healthy, n (%)†	20 (83)	15 (75)	0.71
Duration of symptoms, n (%)			
<7 days	5 (20)	2 (10)	0.09
7–13 days	8 (32)	5 (25)	
14–20 days	7 (28)	2 (10)	
21–27 days	0	3 (15)	
≥28 days	5 (20)	8 (40)	
Altered level of consciousness, n (%)	7 (28)	4 (20)	0.73
Severe DKA (blood pH <7.10), n (%)	19 (76)	15 (75)	1.00
Laboratory values			
pH, median (IQR)	7.05 (6.97–7.10)	7.02 (6.91–7.13)	0.37
β-hydroxybutyric acid, median (IQR), mmol/L	6.2 (5.4–7.2)	8.0 (8.0–8.0)	0.004
Glucose, median (IQR), mmol/L	33.5 (25.0–37.3)	24.0 (22.2–34.8)	0.05
HbA1C, median (IQR), mmol/mol	112 (97–130)	116 (106–130)	0.42
HbA1C, median (IQR), %	12.4 (11.0–14.0)	12.8 (11.8–14.0)	0.42
Osmolarity, median (IQR), mmol/kg	320 (310–351)	329 (314–346)	0.78

*Mean number of patients per study period during prepandemic study periods 2016–2019.
†No underlying chronic medical conditions requiring medication or ongoing medical attention present at the time of T1D diagnosis.
HbA1C; glycated haemoglobin; DKA, diabetic ketoacidosis; PICU, paediatric intensive care unit; T1D, type 1 diabetes.

Table 2 Characteristics and laboratory values of children registered to the Finnish Paediatric Diabetes Registry in the Helsinki University Hospital district during the pandemic period (1 April–31 October 2020) and during corresponding prepandemic periods in 2016–2019

	Prepandemic periods 2016–2019 (n=231)	Pandemic period 2020 (n=84)	P value
Number of patients per period, n	57.75*	84	
Incidence, per 100 000 person-years (95% CI)	38.68 (34.00 to 44.00)	56.00 (45.22 to 69.34)	0.004
Age, median (IQR), years	8.0 (4.0–11.9)	8.2 (4.4–11.2)	0.53
Female sex, n (%)	103 (45)	36 (43)	0.80
Previously healthy, n (%)†	215 (93)	74 (88)	0.17
Duration of symptoms, n (%)			
less than 7 days	39 (18)	18 (22)	0.29
7–13 days	70 (32)	24 (30)	
14–20 days	34 (15)	14 (18)	
21–27 days	28 (13)	12 (15)	
28 days or more	51 (23)	12 (15)	
Admitted to PICU, n (%)	15 (6)	16 (19)	0.002
Severe DKA (blood pH <7.10), n (%)	20 (9)	13 (16)	0.10
Laboratory values			
pH, median (IQR)	7.36 (7.25–7.39)	7.36 (7.18–7.39)	0.34
β-hydroxybutyric acid, median (IQR), mmol/L	3.1 (0.7–6.0)	4.5 (0.9–6.1)	0.23
Glucose, median (IQR), mmol/L	25.8 (18.9–34.3)	23.4 (18.0–29.9)	0.04
HbA1C, median (IQR), mmol/mol	104 (84–129)	103.0 (82–119)	0.46
HbA1C, median (IQR), %	11.7 (9.9–14)	11.6 (9.7–13.0)	0.46

*Mean number of patients per study period during prepandemic study periods 2016–2019.
†No underlying chronic medical conditions requiring medication or ongoing medical attention present at the time of T1D diagnosis.
DKA, diabetic ketoacidosis; HbA1C, glycated haemoglobin; PICU, paediatric intensive care unit; T1D, type 1 diabetes.

the yearly population sizes to 7-month person-times in order to calculate and compare incidences in both cohorts between prepandemic and pandemic periods. Incidences were calculated based on the size of the paediatric population (children aged ≤15 years) at risk separately for each year.

We compared continuous and ordinal variables with the Mann-Whitney U test and categorical variables with the Fisher's test. A p value <0.05 was considered statistically significant.

Ethical aspects

Written informed consent was obtained from the participants and/or caregivers in the registry. The patients in the PICU cohort were not contacted for the purposes of the study.

RESULTS

During the pandemic period 1 April–31 October 2020, 20 children with newly diagnosed T1DM were admitted to the PICU, as compared with four to nine (mean 6.25) children during the corresponding prepandemic periods in 2016–2019. The incidence of PICU admission due to new-onset T1D increased from 2.89/1 00 000 person years (PY) in 2016–2019 to 9.35 /100 000 PY in 2020 with an incidence rate ratio (IRR) of 3.24 (95% CI 1.80 to 5.83); p<0.001 (figure 1, table 1, online supplemental table 1). The increase was not explained by a pre-existing trend (figure 1) or a lower admission threshold, as the severity of acidosis and hyperosmolarity were equal in all periods (table 1). During the pandemic period, 11/20 (55%) of the children

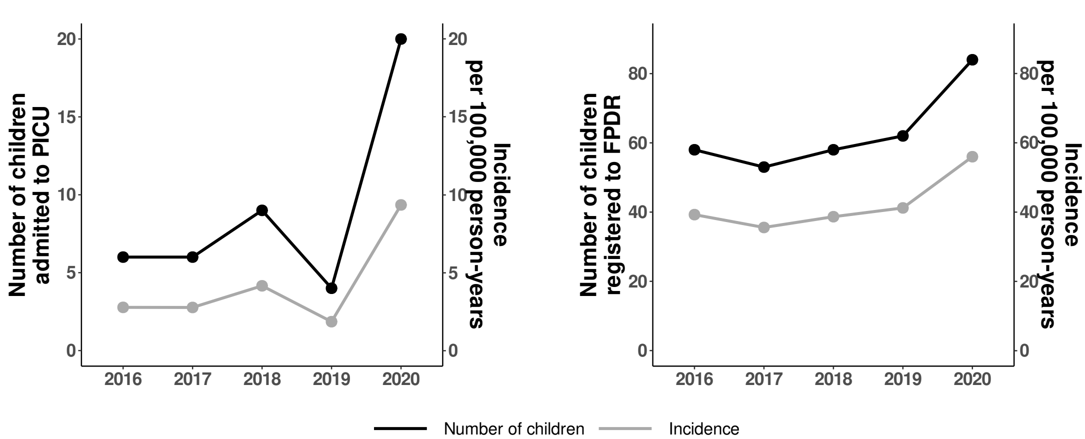

Figure 1 Number (y-axis left) and incidence (y-axis right) of children admitted to PICU (A) or registered in the Finnish Paediatric Diabetes Registry (B) with newly diagnosed type 1 diabetes between 1 April and 31 October each year 2016–2020 (x-axis). PICU, paediatric intensive care unit.

admitted to PICU had been symptomatic for at least 3 weeks, as compared with 5/25 (20%) during prepandemic periods, but the difference was not statistically significant (p=0.087, table 1, online supplemental figure 1). SARS-CoV-2 RT-PCR test from nasopharyngeal swab was performed in 7/20 (35%) of the PICU patients. All tests were negative. Four tests had been ordered as infection control measures, and three because symptoms of DKA had been mistaken for symptoms of acute infection but without a medical visit. In a tachypnoeic child with DKA, COVID-19 had been tested twice. Another child with abdominal pain had not been allowed to book a medical appointment without a negative test.

During the pandemic period, 84 children with newly diagnosed T1D from the HUH district were registered to the FPDR, as compared with 53–62 (mean 57.75) children each year in the prepandemic periods 2016–2019. The incidence of children registered to FPDR increased from 38.7/100 000 PY in 2016–2019 to 56.0 /100 000 PY in 2020 with an IRR of 1.45 (95% CI 1.13 to 1.86); p=0.004 (figure 1, table 2, online supplemental table 2).

Monthly numbers of children with newly diagnosed T1D admitted to the PICU and of those registered to the FPDR during the prepandemic and pandemic periods are shown in figure 2.

A serum sample was available from 33 children in the FPDR during the pandemic period. The median time from diagnosis to serum sample collection was 7 days (IQR 5–10 days). All samples were first tested for SARS-CoV-2 spike IgG antibodies using ELISA and 32/33 were negative. One sample with a weak positive result in ELISA was further tested with a microneutralisation assay and no neutralising antibodies were detected.

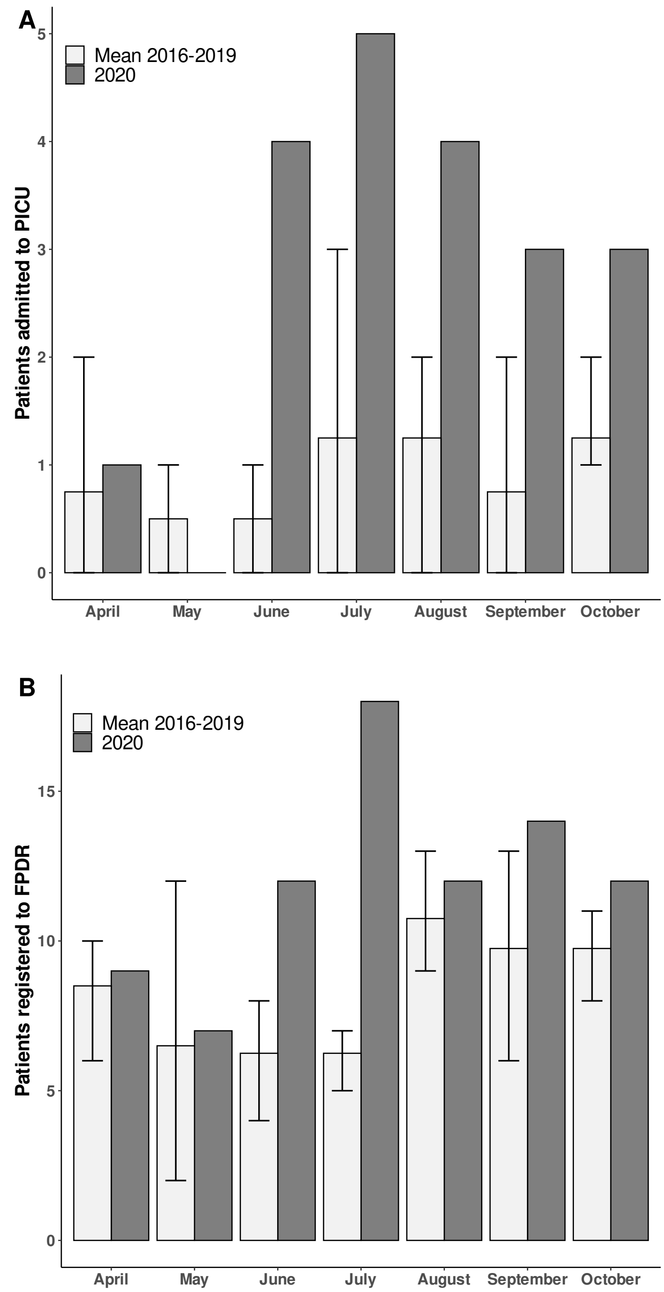

Figure 2 Monthly number of patients (y-axis) admitted to PICU (A) or registered in the Finnish Paediatric Diabetes Registry (B) with newly diagnosed type 1 diabetes during the pandemic period 1 April–31 October 2020 (dark grey) and mean of corresponding pre-pandemic periods in 2016–2019 (light grey). Error bars represent ranges. PICU, paediatric intensive care unit.

DISCUSSION

In this retrospective cohort of children with newly diagnosed T1D during the COVID-19 pandemic, we noticed a significant increase in the number of children requiring PICU care for severe ketoacidosis. The number of children registered to FPDR with newly diagnosed T1D also increased, but this smaller increase was unlikely to explain the increase in PICU admissions. None of the children tested had SARS-CoV-2 antibodies, suggesting that SARS-CoV-2 infection was not the primary trigger for more severe presentation of T1D or for the increase in children diagnosed with T1D.

Our findings are in line with recent Italian, German, UK and Australian studies reporting an increased incidence of DKA in children with new-onset T1D during the COVID-19 pandemic[1 3 4 6] and a recent report from UK[1] suggesting that also the incidence of paediatric T1D had increased. In contrast, a German study reported no increase in the incidence of T1D.[19] All the published studies except for one[20] found that the clinical presentation of T1D had changed. In the absence of population-based studies over a longer period, a worsened clinical presentation at diagnosis may create false impression of increasing incidence of T1D. However, the increase we observed in the total number of children with new-onset T1D is surprising, as the incidence of T1D in Finnish children has been declining since 2010.[21] A longer follow-up is needed to confirm the change in the T1D incidence. Furthermore, we cannot exclude the possibility that the pandemic could have influenced the participation or recruitment to the FPDR.

As T1D may be triggered by viral infections in susceptible individuals, the potential association of SARS-CoV-2 with either increasing incidence of T1D or more severe disease presentation needs to be addressed. Studies on cell cultures, animal and organoid models have indicated that the primary SARS-CoV-2 entry receptor ACE2 and viral entry coreceptors transmembrane serine protease 2 (TMPRSS2) and neuropilin-1 (NRP1) are expressed in pancreatic beta cells.[22–25] Human stem cell derived beta cells were also permissive to SARS-CoV-2 infection.[23] However, in a recent study combining data from multiple transcriptomic datasets and human pancreatic tissue sections, ACE2 and TMPPRS2 expression was detected in pancreatic microvasculature and ductal cells but not in beta cells, suggesting that ACE2 mediated direct beta cell cytotoxicity due to SARS-CoV-2 is unlikely.[26]

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Among children with newly diagnosed T1D in UK, SARS-CoV-2 was detected by PCR in 2/21 and SARS-CoV-2 antibodies in 3/16 children tested.[1] Without a control group or a population-based approach, it is difficult to interpret these results. As we noticed a similar change in the presentation of T1D in a population less affected by the pandemic and with no detectable SARS-Cov-2 antibodies in any of the newly diagnosed children, it seems likely that the virus plays no direct role in the increased incidence or more severe presentation of T1D in children. As long-term consequences of SARS-CoV-2 infection remain to be seen and not all patients infected with SARS-CoV-2 develop antibodies,[27] long-scale population-based studies are needed to confirm these findings.

Delays in the diagnostic process of T1D are likely to explain the increase in the number of children with DKA, as many of the children admitted to the PICU had been symptomatic for longer than the patients in previous years. Several patients with DKA had been tested for COVID-19 without a medical examination, as they presented with tachypnoea, fatigue or abdominal pain. Thus, in our setting, the delayed diagnosis did not result from medical care providers mistaking the symptoms of T1D for COVID-19.[28] Instead, more complex associations, influencing the threshold of families to seek medical attention and the accessibility of health services, seem to have been involved.

The pandemic and the infection control measures abruptly changed practices in child healthcare, and the behaviour of families with children. In regions with high COVID-19 infection rates, with seroprevalence rates above 5% early in the pandemic,[29] the infection control measures led to severe delays in the diagnosis and treatment of critically ill children.[3 6 30 31] Alarmingly, our results show the same phenomenon in a setting with low COVID-19 incidence. With a 0.6% seropositivity[10] and 2.7% positivity of COVID-19 in children with acute infections in the emergency department (ED),[11] the capacity of our healthcare system was not overburdened. On the contrary, our paediatric ED visits decreased by 45% after the start of the pandemic.[32] Instead, social distancing measures, prioritisation of COVID-19 infection control in healthcare and, possibly, unfounded parental fears of their child contracting COVID-19 seem to have needlessly impaired the functioning of the healthcare system.

In the future waves of the pandemic, guidance to the public promoting social distancing and staying home must be balanced against the risks of such advice and practices to families with children. Public awareness of the symptoms of paediatric critical illness should be increased. Also, healthcare providers must learn to prioritise their functions so that patients at risk for critical illness are not missed. Otherwise, children continue to be at risk of becoming collateral damage of infection control measures designed to protect adults. The actual impact of control measures should be evaluated for all subpopulations and the measures reasonably targeted in order to avoid causing unnecessary harm.

Our study is limited by its single-centre setting. However, as all children with new-onset T1D are cared in the same healthcare system including a single PICU, we covered all children requiring intensive care in the region. Furthermore, the study was conducted in the largest metropolitan area of the country with the highest incidence of childhood T1D in the world. This allowed us to analyse a significant number of cases despite the single centre design. Although serum samples were not available from all patients, none had SARS-CoV-2 antibodies detected. As the population seroprevalence is low, it is highly unlikely that more samples would have altered the conclusions. Last, as the FPDR is based on voluntary participation and the follow-up period was limited, larger, population-based studies with longer follow-up are needed to confirm the increased incidence of T1D observed in our study. The strengths of the study include prospectively collected clinical data from the FPDR and structured review of medical records from a single PICU. Furthermore, prospectively collected serum samples allowed us to analyse the presence of SARS-CoV-2 antibodies uniformly at the time of T1D diagnosis.

CONCLUSIONS

As compared with previous years, more children with newly diagnosed T1D presented with severe ketoacidosis in 2020. This change took place in a setting of low incidence of COVID-19 infections in the paediatric population and without detectable SARS-CoV-2 antibodies in children with newly diagnosed T1D. The total number of children with new-onset T1D in the same area also increased but not sufficiently to explain the increase in DKA.

The higher incidence of DKA is unlikely a direct consequence of COVID-19 infection. Instead, it may stem from changes in the functionality of the healthcare system, the availability of healthcare services and from parental fears over contracting COVID-19. These changes may have created barriers in the accessibility of the healthcare, leading to a delayed diagnosis and aggravated presentation of T1D.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol for the FPDR was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (Helsinki, Finland).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data collected for this study, including deidentified participant data and metadata that underlie the results reported in this article, may be shared with other investigators after approval of methodologically sound proposal. Proposals should be directed

to corresponding author (ORCID 0000-0002-0565-0593). To gain access, data requestors will need to sign a data access agreement.

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