EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

The COVID-19 Pandemic Affects Seasonality, With Increasing Cases of New-Onset Type 1 Diabetes in Children, From the Worldwide SWEET Registry

Felix Reschke,[1,2] Stefanie Lanzinger,[3,4] Vivien Herczeg,[5] Priya Prahalad,[6,7] Riccardo Schiaffini,[8] Dick Mul,[9] Helen Clapin,[10] Bedowra Zabeen,[11] Julie Pelicand,[12,13] Moshe Phillip,[14,15] Catarina Limbert,[16,17] and Thomas Danne,[1,2] on behalf of the SWEET Study Group*

OBJECTIVE

To analyze whether the coronavirus disease 2019 (COVID-19) pandemic increased the number of cases or impacted seasonality of new-onset type 1 diabetes (T1D) in large pediatric diabetes centers globally.

RESEARCH DESIGN AND METHODS

We analyzed data on 17,280 cases of T1D diagnosed during 2018–2021 from 92 worldwide centers participating in the SWEET registry using hierarchic linear regression models.

RESULTS

The average number of new-onset T1D cases per center adjusted for the total number of patients treated at the center per year and stratified by age-groups increased from 11.2 (95% CI 10.1–12.2) in 2018 to 21.7 (20.6–22.8) in 2021 for the youngest age-group, <6 years; from 13.1 (12.2–14.0) in 2018 to 26.7 (25.7–27.7) in 2021 for children ages 6 to <12 years; and from 12.2 (11.5–12.9) to 24.7 (24.0–25.5) for adolescents ages 12–18 years (all $P < 0.001$). These increases remained within the expected increase with the 95% CI of the regression line. However, in Europe and North America following the lockdown early in 2020, the typical seasonality of more cases during winter season was delayed, with a peak during the summer and autumn months. While the seasonal pattern in Europe returned to prepandemic times in 2021, this was not the case in North America. Compared with 2018–2019 (HbA$_{1c}$ 7.7%), higher average HbA$_{1c}$ levels (2020, 8.1%; 2021, 8.6%; $P < 0.001$) were present within the first year of T1D during the pandemic.

CONCLUSIONS

The slope of the rise in pediatric new-onset T1D in SWEET centers remained unchanged during the COVID-19 pandemic, but a change in the seasonality at onset became apparent.

[1]Children's Hospital Auf Der Bult, Hannover Medical School, Hannover, Germany
[2]SWEET e.V., Hannoversche Kinderheilanstalt, Hannover, Germany
[3]Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany
[4]German Centre for Diabetes Research (DZD), Munich-Neuherberg, Germany
[5]1st Department of Pediatrics, Semmelweis University, Budapest, Hungary
[6]Division of Pediatric Endocrinology, Stanford University, Stanford, CA
[7]Stanford Diabetes Research Center, Stanford, CA
[8]Diabetes Unit, Bambino Gesù Children's Hospital, Rome, Italy
[9]Diabeter, Center for Type 1 Diabetes Care and Research, Rotterdam, the Netherlands
[10]Department of Diabetes and Endocrinology, Perth Children's Hospital, Nedlands, Western Australia, Australia
[11]Changing Diabetes in Children and Life for a Child, Department of Paediatrics, Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders, Dhaka, Bangladesh
[12]Pediatric and Adolescent Diabetes Program, Department of Pediatrics, San Camilo Hospital, San Felipe, Chile
[13]Medicine School, Universidad de Valparaíso, San Felipe, Chile

Postmortem coronavirus disease 2019 (COVID-19) whole-body studies identified the human islet cells as a target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1,2). Controversy remains as to whether this may cause

acceleration of an underlying and potentially pathogenic feature associated with traditional diabetes pathogenesis (i.e., type 1 [T1D] or type 2 [T2D] diabetes) or a novel disease mechanism for diabetes involving either acute β-cell destruction or impairment of insulin secretion (3) when the individual has reached a stage of critically decreased insulin secretory capacity (i.e., the transition from stage 2 to stage 3 T1D). Diabetes be a risk factor for a severe form of COVID-19 disease, but infections in general could also trigger diabetes manifestation. If SARS-CoV-2 infection leads to insulin resistance or impaired insulin secretion, this could explain the frequently described enormous insulin requirement in many patients with a severe course of infection (4). Since T1D is also associated with viral infections (5), this could account for the higher T1D incidence during winter months (6). Thirty children in hospitals across North West London were diagnosed with new-onset T1D during the peak of the first wave of the COVID-19 pandemic in 2020, double the average number of cases seen in previous years during this period (7). The working group of the Diabetes Prospective Follow-up registry (Diabetes-Patienten-Verlaufsdokumentation [DPV]) evaluated the initial pediatric manifestation data between March 13 and May 13 of each year for diagnosis between 2011 and 2020, corresponding to the lockdown in Germany in 2020 (8). However, an extended analysis studying the expected T1D incidence from 1 January 2020 to 30 June 2021 based on data from 2011 to 2019 showed an increase in the T1D incidence following the peak of the pandemic by ∼3 months (9). Moreover, the Centers for Disease Control and Prevention in the U.S. recently published results from two large databases showing that the risk of developing diabetes, without

being distinction between T1D and T2D, increased by 31% or 116% in children <18 years within 30 days after being infected with SARS-CoV-2 (10).

The worldwide SWEET (Better control in Pediatric and Adolescent diabeteS: Working to crEate CEnTers of Reference) registry was initiated in 2008 to improve outcomes in pediatric diabetes (11). As of March 2022, the SWEET registry includes 94,676 participants and 1,093,175 visits from 126 diabetes centers worldwide. Data are collected biannually. Although this center-based registry does not allow calculation of population-based incidence rates, comparison of data uploaded prior to and following the start of the COVID-19 pandemic allows investigation of changes in the number of new cases and the severity at onset of T1D in children in a large number of participating centers.

RESEARCH DESIGN AND METHODS

This analysis was based on data from the international, prospective, multicenter diabetes SWEET registry. SWEET (clinical trial reg. no. NCT04427189, ClinicalTrials.gov) was approved by the ethics committee of Hannover Medical School and is associated with the Diabetes Centre for Children and Adolescents, Children's Hospital Auf Der Bult, which coordinates the SWEET collaboration. Each center must meet specific entry criteria showing diabetes expertise and compliance with the International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines. The local institutional review boards of the participating centers approved the pseudonymized data collection.

The SWEET database combines data from distinct sources. Data are collected locally through clinical databases, electronic health record systems, and the standardized SWEET DPV documentation software (https://sweet.zibmt.uni-ulm.de/

software.php) or centers download data from existing longitudinal registries. Twice yearly, data are transmitted to the central database hosted by the Institute of Epidemiology and Medical Biometry, ZIBMT. The prospectively collected data are then combined into a common database. Inconsistent, improbable, or missing data are reported back to the centers for correction. For meeting General Data Protection Regulation (GDPR), data are then aggregated into an anonymized, cumulative database used for clinical research, scientific analysis, and nationwide benchmarking.

Criteria for inclusion in this analysis were centers providing data from individuals with new-onset T1D in 2018–2021 aged between 6 months and ≤18 years. The number of incident cases was adjusted for the total number of patients treated at the center. Additionally, we stratified the analyses by age-groups (<6, 6 to <12, and 12 to ≤18 years). For analysis of the effect of seasonality, the monthly rates of new cases were calculated for each complete year, both in the total cohort as well as separately for the two regions of the northern hemisphere.

Glycemic control, assessed as the first value measured within 2 weeks of onset and the average of all values during the first year after onset, was assessed with HbA_{1c} measured locally in each center. For adjustment for differences between laboratories, the multiple of the mean method was used to standardize local HbA_{1c} mathematically. BMI was chosen as a measure of severity at onset (weight loss) and metabolic compensation during the initial year of treatment. BMI was expressed as SD score (SDS) values calculated with use of the international pediatric reference data from the World Health Organization (WHO) (https://www.who.int/childgrowth/standards/bmi_for_age/en/) to adjust for age and sex.

[14]The Jesse Z and Sara Lea Shafer Institute of Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

[15]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[16]Unit of Paediatric Endocrinology and Diabetes, Hospital Dona Estefânia, Lisbon, Portugal

[17]Nova Medical School, Universidade Nova de Lisboa, Lisbon, Portugal

Corresponding author: Thomas Danne, danne@hka.de

Statistical Analysis

Descriptive data are presented as median with quartiles or percentages. The Wilcoxon test was used to compare continuous variables, and the χ^2 test was used for binary variables. Linear repeated-measurement models with an autoregressive covariance structure considering that closer measurements in time are more highly correlated than measurements further apart were used to study the number of new-onset T1D cases per year. Models were adjusted for the total number of patients treated at the center per year with stratification by age-groups. Results are presented as adjusted means together with 95% CIs. In addition, new-onset cases were modeled by month to study seasonality per year. Month of diabetes onset was included as second-degree B-splines, and an interaction between month of onset and year was added to the linear regression model. A two-sided P value <0.05 was defined as statistically significant. P values were corrected for multiple testing with the false discovery rate method. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Overall, 92 centers from 47 countries submitted data to the study. In 2021, a total of 2,100 new cases were reported from 52 centers in Europe, 536 from 21 centers in Asia/Middle East/Africa, 211 from 6 centers in Australia/New Zealand, 746 from 8 centers in North America/Canada, and 114 from 5 centers in South and Middle America. As center size differed considerably, with Canadian and U.S. centers being the larger, the linear regression model was adjusted for total number of patients, confirming the significant increase in the overall yearly rate of T1D year by year in all age-groups (Fig. 1) (linear regression model, adjusted $P < 0.001$).

The average number of new-onset T1D cases per center increased from 11.2 (95% CI 10.1–12.2) in 2018 to 21.7 (20.6–22.8) in 2021 in the youngest age-group, <6 years ($P < 0.001$) (Fig. 1). Moreover, we observed an increase in new-onset cases from 13.1 (12.2–14.0) in 2018 to 26.7 (25.7–27.7) in 2021 in
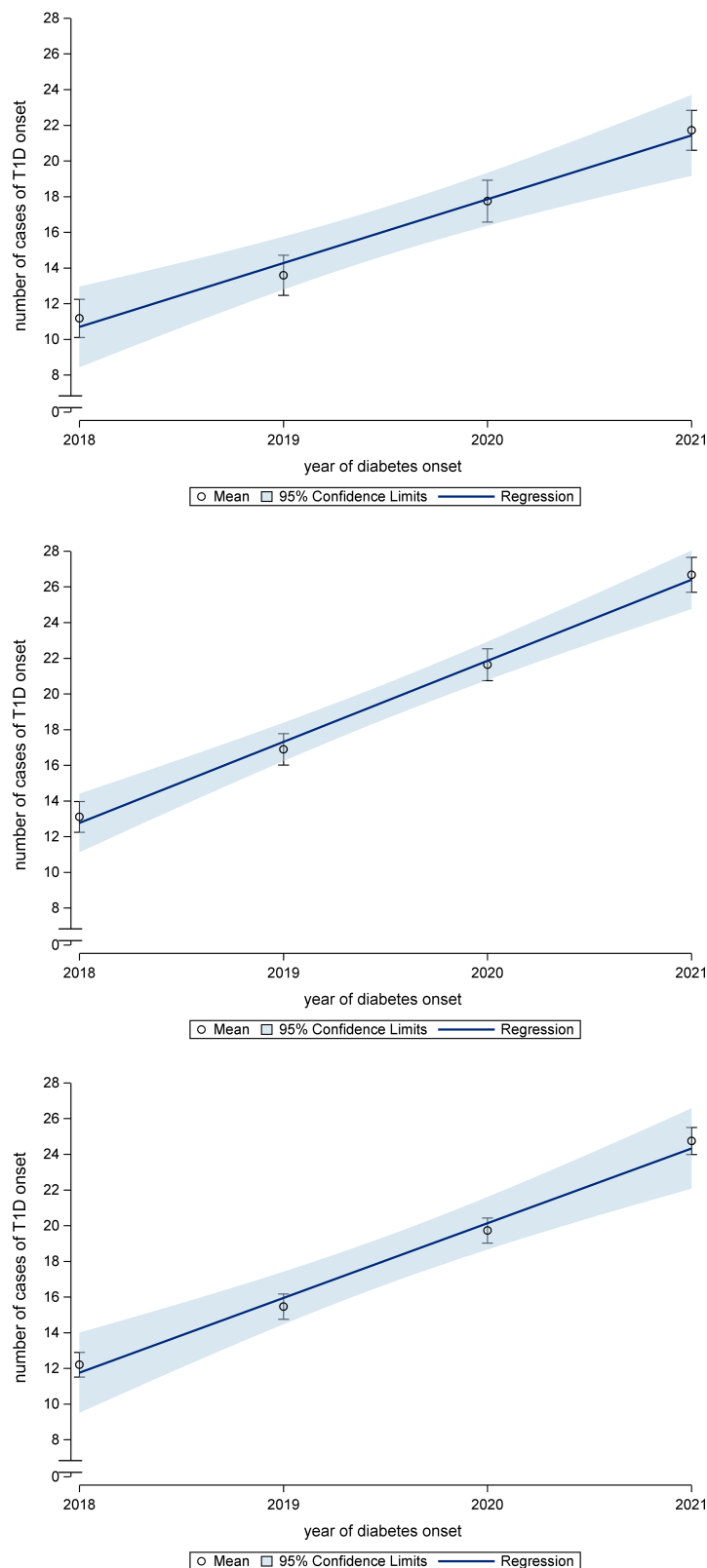

Figure 1—Linear regression model of new T1D onset cases presented as adjusted means with 95% CIs of children ages <6 years (top panel), 6–12 years (middle panel), and >12 years, bottom panel). Linear or logistic regression models were used with adjustment for number of patients treated at the center per year.
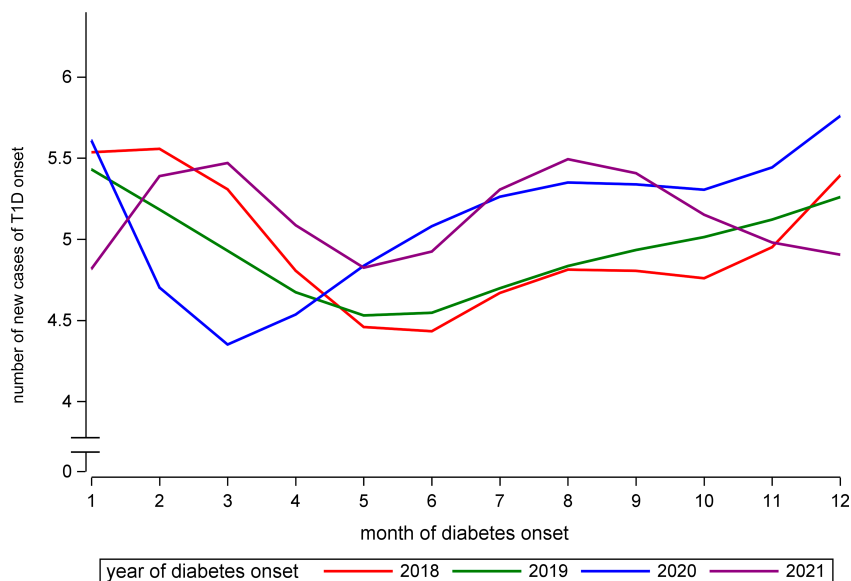
Figure 2—Seasonality of new cases in 92 centers of the worldwide SWEET project. Smoothed plot of the number of new T1D onset cases by month and year with second-degree B-splines.

children ages 6 to <12 years and from 12.2 (11.5–12.9) to 24.7 (24.0–25.5) in adolescents ages 12–18 years (all $P <$ 0.001).

A change in seasonality is seen in a linear regression model for new-onset T1D (center mean) in association with year and month of diabetes onset (Fig. 2). The effect of seasonality is mainly driven by the centers in the Northern hemisphere (Fig. 3), where a drop in new cases between March 2020 and May 2020, which corresponded to the first lockdown, was followed by an increase in cases later that year. While this shift returned to the prepandemic pattern in Europe in 2021, similar patterns were observed in North America in 2020 and 2021. Seasonality was less apparent in the other areas (data not shown).

In looking at the BMI SDS and HbA$_{1c}$ at onset of diabetes, no differences were apparent between different years. As expected, there were regional differences in clinical parameters at onset and in the first year of diabetes, which remained unchanged (Table 1). Of note, a slight but significantly higher HbA$_{1c}$ at onset was reported from European and African/Asian centers, while all centers except those in Australia/New Zealand reported higher average HbA$_{1c}$ levels within the first year of diabetes.

CONCLUSIONS

Results of the analysis of new-onset cases during the first 18 months of the COVID-19 pandemic in a large number of pediatric diabetes centers worldwide do not support the hypothesis that SARS-CoV-2 has acute effects on the development of T1D (6), but the analysis revealed evidence of a changing seasonal pattern in the Northern hemisphere. Indeed, the numbers of children with newly diagnosed T1D increased significantly in the participating centers around the world in all age-groups over the past 4 years with an unchanged slope, in line with reports of increasing worldwide incidence (12,13).

This is in contrast to reporting from a second analysis of population-based data from Germany of an increase in the observed versus expected incidence of T1D in children and adolescents during the COVID-19 pandemic (8). The increase of cases remained linear in 2020 in all age groups, and no further increase was seen in 2021, as in the recent German (12), Finnish (14) and U.S. data (15). Of note, in line with the German data, we found a shift in the seasonality driven by centers in the Northern hemisphere, where more cases are usually seen in cold months (4). While the seasonal pattern in Europe returned to prepandemic times in 2021, the seasonal shift with more cases in the summer months was still visible in the North American data, in line with temporal differences of COVID-19 disease burden between Europe and North America during the second wave (16). Thus, these findings demonstrate the importance of monitoring the course of the pandemic in the longer term and caution with regard to early observations of local increases in the number of T1D manifestations, which may only reflect a seasonal shift (5,13,17,18). Another aspect that will have to be taken into account in the future is the potential influence of vaccinations in school and adolescent pediatric populations.

Three potential pathophysiological pathways have been discussed as to how SARS-CoV-2 could be associated with T1D onset: first, directly causing T1D by damaging β-cells; secondly, as accelerator of an already ongoing autoimmune process; or lastly, as final step of stage 2 diabetes, when a viral disease with fever precipitates the clinical presentation. COVID-19–associated hygiene measures (19) and social distancing may have additionally reduced viral infections during the lockdown in the winter/spring season, decreasing the impact of viral triggers for T1D onset in those potentially susceptible. Although it is believed that psychological stress may also accelerate T1D onset (20) and increased psychological strain during the pandemic is experienced by many children (21), this appears not to have a short-term effect on T1D incidence.

Before the emergence of COVID-19, the influences of a pandemic influenza infection on clinically reported and incident T1D had been studied. While there was no clear association with manifest disease, a twofold excess of incident diabetes was found in the subgroup with laboratory-confirmed pandemic influenza A (H1N1) (22). In this regard, the case description of the occurrence of insulin-dependent diabetes in a diabetes antibody–negative 19-year-old male 5–7 weeks after COVID-19 infection triggered discussions (23). Moreover, results of a population-based screening program for pandemic monitoring in capillary blood from 15,771 children aged 1–18 years living in Bavaria, Germany, showed a sixfold higher SARS-CoV-2 antibody prevalence in April 2020 compared with the authority-reported cases (156 per 100,000 children) (24). However, from January to October 2020, the prevalence of SARS-CoV-2 antibodies was not different in children and adults with and without T1D in Colorado (25). Also, in another study investigators found no evidence that the COVID-19 pandemic
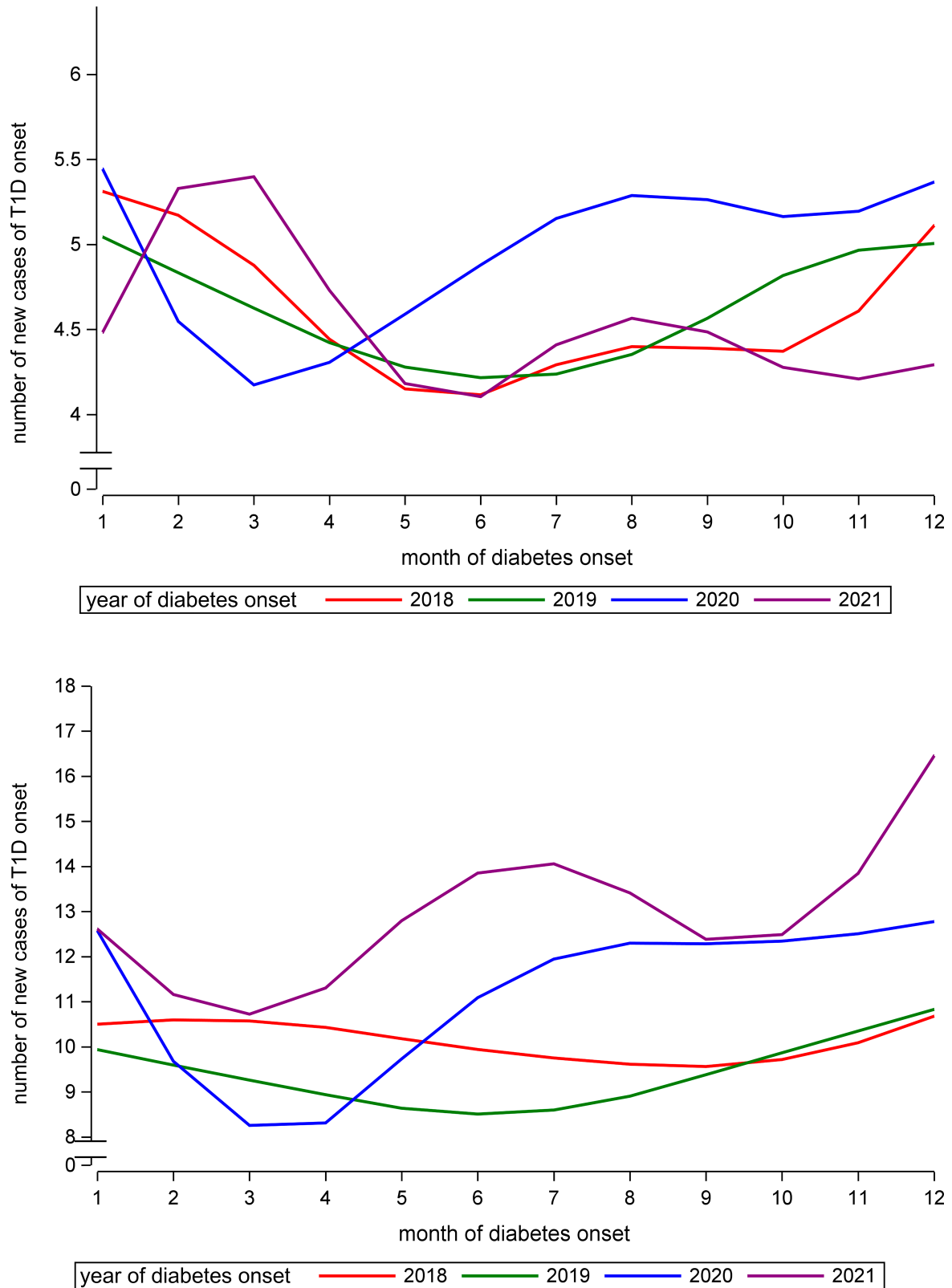
Figure 3—Seasonality of new cases in the centers from the Northern hemisphere: 52 European centers (top panel) and 8 centers from U.S./Canada (bottom panel). Smoothed plot of the number of new T1D onset cases by month and year with second-degree B-splines.

leads to a significantly increased number of new cases of autoantibody-negative T1D in children, adolescents, and young adults, also arguing against an increase of nonautoimmune T1D potentially related to subclinical SARS-CoV-2 infection (26).

Our center-based observations are in agreement with more systematic country-wide analyses from Italy (27), Canada (28),

Table 1—Clinical characteristics of new-onset pediatric T1D patients ages ≤18 years documented in 2018–2021 in the total cohort and regional distribution

	2018	2019	2020	2021	P*
Total cohort (92 centers)					
N	4,671	4,419	4,483	3,707	
Male sex	52.4	53.8	52.8	55.2	0.060
Age (years)	11.3 (8.0, 14.2)	10.8 (7.2, 13.8)	10.6 (7.0, 13.5)	10.1 (6.5, 13.2)	<0.001
HbA$_{1c}$ at diagnosis (mmol/mol)	95.7 (76.8, 119.1)	96.1 (75.6, 120.2)	99.0 (79.2, 120.9)	98.0 (78.0, 121.4)	0.070
HbA$_{1c}$ at diagnosis (%)	10.9 (9.2, 13.1)	11.0 (9.1, 13.1)	11.3 (9.5, 13.2)	11.2 (9.5, 13.2)	0.003
HbA$_{1c}$ (mmol/mol)	60.1 (51.6, 72.1)	60.4 (51.5, 73.7)	64.9 (53.8, 81.7)	70.0 (55.4, 93.5)	<0.001
HbA$_{1c}$ (%)	7.7 (6.9, 8.8)	7.7 (6.9, 8.9)	8.1 (7.1, 9.6)	8.6 (7.2, 10.7)	<0.001
BMI SDS at diagnosis	0.1 (−0.8, 1.0)	0.1 (−0.9, 1.0)	0.0 (−1.0, 1.0)	0.1 (−0.9, 1.0)	0.090
BMI SDS	0.5 (−0.2, 1.2)	0.4 (−0.4, 1.2)	0.4 (−0.5, 1.2)	0.3 (−0.6, 1.2)	<0.001
Europe (52 centers): Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, U.K., France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden					
N	2,623	2,579	2,709	2,100	
Male sex	53.8	55.5	54.3	55.4	0.546
Age (years)	11.0 (7.7, 14.0)	10.7 (7.0, 13.7)	10.3 (6.8, 13.3)	10.0 (6.1, 13.1)	<0.001
HbA$_{1c}$ at diagnosis (mmol/mol)	94.6 (76.1, 114.9)	93.5 (73.9, 115.9)	97.9 (78.3, 118.1)	97.9 (79.1, 117.8)	<0.001
HbA$_{1c}$ at diagnosis (%)	10.8 (9.1, 12.7)	10.7 (8.9, 12.8)	11.1 (9.3, 13.0)	11.1 (9.4, 12.9)	<0.001
HbA$_{1c}$ (mmol/mol)	56.3 (49.2, 65.9)	56.9 (49.1, 67.6)	62.6 (51.9, 78.7)	68.0 (54.3, 91.4)	<0.001
HbA$_{1c}$ (%)	7.3 (6.6, 8.2)	7.4 (6.6, 8.3)	7.9 (6.9, 9.4)	8.4 (7.1, 10.5)	<0.001
BMI SDS at diagnosis	0.1 (−0.8, 1.0)	0.0 (−1.0, 0.9)	−0.1 (−1.0, 0.9)	0.1 (−0.9, 1.0)	0.081
BMI SDS	0.5 (−0.2, 1.2)	0.4 (−0.3, 1.1)	0.4 (−0.5, 1.1)	0.3 (−0.5, 1.2)	<0.001
Asia/Middle East/Africa (21 centers): Bangladesh, Cameroon, Egypt, India, Iran, Israel, Korea, Kuwait, Mali, Mauritius, Nepal, Tanzania, Thailand, Turkey					
N	738	629	541	536	
Male sex	45.9	45.5	47.3	52.1	
Age (years)	11.4 (7.8, 14.4)	10.9 (7.4, 14.0)	10.8 (7.2, 13.5)	10.3 (6.9, 13.7)	0.002
HbA$_{1c}$ at diagnosis (mmol/mol)	95.1 (72.7, 118.6)	104.4 (86.9, 126.2)	110.6 (85.2, 131.0)	103.4 (86.9, 123.1)	0.002
HbA$_{1c}$ at diagnosis (%)	10.9 (8.8, 13.0)	11.7 (10.1, 13.7)	12.3 (10.0, 14.1)	11.6 (10.1, 13.4)	0.002
HbA$_{1c}$ (mmol/mol)	77.1 (58.5, 104.4)	79.2 (62.8, 105.8)	84.7 (64.5, 108.2)	86.9 (67.0, 113.4)	0.009
HbA$_{1c}$ (%)	8.8 (7.6, 10.8)	9.1 (7.7, 11.2)	9.3 (7.9, 11.5)	10.1 (8.2, 11.9)	<0.001
BMI SDS at diagnosis	−0.4 (−1.4, 0.7)	−0.2 (−1.5, 0.7)	−0.5 (−1.5, 0.6)	−0.7 (−1.8, 0.7)	0.188
BMI SDS	−0.1 (−1.0, 0.9)	−0.2 (−1.2, 0.8)	−0.1 (−1.2, 0.8)	−0.4 (−1.5, 0.7)	0.003
Australia/New Zealand (6 centers)					
N	266	284	261	211	
Male sex	51.5	51.1	53.6	54.5	0.921
Age (years)	12.0 (8.1, 14.3)	10.3 (7.1, 13.8)	10.6 (6.2, 13.3)	10.1 (6.5, 12.8)	0.001
HbA$_{1c}$ at diagnosis (mmol/mol)	77.0 (67.0, 94.6)	77.0 (65.9, 98.9)	71.5 (60.4, 89.1)	76.5 (62.7, 84.1)	0.538
HbA$_{1c}$ at diagnosis (%)	9.2 (8.3, 10.8)	9.2 (8.2, 11.2)	8.7 (7.7, 10.3)	9.2 (7.9, 9.9)	0.538
HbA$_{1c}$ (mmol/mol)	61.0 (54.3, 69.2)	60.4 (52.7, 69.4)	60.4 (52.4, 68.3)	59.2 (51.3, 69.2)	0.691
HbA$_{1c}$ (%)	7.7 (7.1, 8.5)	7.7 (7.0, 8.5)	7.7 (6.9, 8.4)	7.6 (6.8, 8.5)	0.691
BMI SDS at diagnosis	0.5 (−0.1, 1.3)	0.6 (−0.1, 1.3)	0.6 (−0.1, 1.4)	0.6 (−0.1, 1.5)	0.921
BMI SDS	0.7 (−0.1, 1.5)	0.9 (0.1, 1.6)	0.7 (0.1, 1.5)	0.7 (−0.1, 1.6)	0.921
U.S./Canada (8 centers)					
N	963	854	867	746	
Male sex	54.8	56.2	52.0	57.4	0.269
Age (years)	11.9 (8.8, 14.6)	11.4 (7.8, 14.4)	11.4 (7.9, 14.4)	10.5 (7.3, 13.8)	<0.001
HbA$_{1c}$ at diagnosis (mmol/mol)	104.9 (83.5, 134.2)	103.0 (79.0, 131.7)	106.0 (83.5, 134.0)	105.3 (79.0, 129.4)	0.411
HbA$_{1c}$ at diagnosis (%)	11.8 (9.8, 14.4)	11.6 (9.4, 14.2)	11.9 (9.8, 14.4)	11.8 (9.4, 14.0)	0.411
HbA$_{1c}$ (mmol/mol)	64.4 (55.2, 75.2)	64.2 (54.7, 76.8)	67.0 (55.4, 82.3)	69.6 (55.4, 92.1)	<0.001
HbA$_{1c}$ (%)	8.0 (7.2, 9.0)	8.0 (7.2, 9.2)	8.3 (7.2, 9.7)	8.5 (7.2, 10.6)	<0.001
BMI SDS at diagnosis	0.2 (−0.6, 1.1)	0.2 (−0.7, 1.2)	0.3 (−0.7, 1.4)	0.2 (−0.7, 1.2)	0.529
BMI SDS	0.7 (−0.1, 1.4)	0.6 (−0.1, 1.4)	0.7 (−0.1, 1.4)	0.5 (−0.3, 1.4)	0.038
South/Central America (5 centers): Chile, Costa Rica, Ecuador, Haiti, Mexico					
N	81	73	105	114	
Male sex	39.5	46.6	46.6	53.5	0.431

Table 1—Continued

	2018	2019	2020	2021	P*
Age (years)	10.6 (7.8, 12.8)	10.2 (7.3, 11.5)	10.4 (6.3, 12.0)	8.8 (5.9, 11.7)	0.217
HbA$_{1c}$ at diagnosis (mmol/mol)	109.0 (88.5, 126.1)	102.9 (86.9, 113.5)	109.0 (95.7, 122.2)	111.2 (95.7, 125.5)	0.052
HbA$_{1c}$ at diagnosis (%)	12.1 (10.2, 13.7)	11.6 (10.1, 12.5)	12.1 (10.9, 13.3)	12.3 (10.9, 13.6)	0.052
HbA$_{1c}$ (mmol/mol)	61.5 (54.3, 75.9)	69.2 (57.6, 83.6)	81.8 (66.7, 91.3)	92.4 (78.7, 113.9)	<0.001
HbA$_{1c}$ (%)	7.8 (7.1, 9.1)	8.5 (7.4, 9.8)	9.6 (8.3, 10.5)	10.6 (9.4, 12.6)	<0.001
BMI SDS at diagnosis	0.3 (−0.6, 1.5)	−0.1 (−0.8, 0.9)	0.1 (−1.2, 1.4)	0.3 (−0.8, 1.8)	0.619
BMI SDS	0.5 (−0.2, 1.3)	0.3 (−0.3, 1.0)	0.4 (−0.4, 1.4)	0.5 (−0.5, 1.8)	0.801

Data are median (quartile 1, quartile 3) or percentages unless otherwise indicated. HbA$_{1c}$ at diagnosis refers to the first value measured within 2 weeks of diabetes onset, and HbA$_{1c}$ refers to the average of all values during the first year after diabetes onset. *Kruskal-Wallis test for continuous variables and χ^2 test for binary variables, with adjustment for multiple comparisons with false discovery rate.

Finland (13), Germany (7), and Israel (29) demonstrating a delay in the diagnosis related to the lockdown. Thus, the temporary rise of cases during 2020 appears to be a result of the disruption of access to care during COVID-19 rather than an effect of (subclinical) viral infection. This is supported by higher HbA$_{1c}$ at onset in some regions and overall poorer diabetes control in newly diagnosed patients during the first year in many centers participating in the present analysis. This is in contrast to children with established T1D who were able to maintain glycemic control in most SWEET centers (30).

The reported effect of COVID-19 in an increase in cases in the Centers for Disease Control and Prevention cohort may be driven by new-onset T2D, as diabetes types could not be reliably differentiated in this study (8) and was not captured in our analysis. In a pediatric tertiary care center in Washington, DC, the incidence of T1D increased modestly (15%), while incident cases of T2D increased 182% during the first year of the pandemic (31). Furthermore, neither study had results from serological testing or PCR results available. Thus far, no studies have shown direct correlation of current or prior SARS-CoV-2 infection in children with subsequent development of T1D.

Our study has limitations: SWEET participants are primarily at larger centers with multidisciplinary care (9) and data cannot be considered representative of the incidence of a country or region. However, we found no evidence of notable regional differences except for glycemic control and seasonality. The observed seasonal effect might be due to a delay in diagnosis and not to a real delay in disease onset, as already described elsewhere (19–21). Diabetic ketoacidosis rates at onset were not available in several of these centers, and severity

at onset had to be assessed according to HbA$_{1c}$ alone. Another limitation is the lack of SARS-CoV-2 serology in our cohort. It is noteworthy that the overall number of total new cases decreased both in the European and North American centers in 2021 despite overall increasing numbers. This may be caused by a delay of referral or delay of data entry in the centers during the pandemic. Nevertheless, this is an unprecedented analysis of individual clinical data in a large number of new-onset T1D patients on a global scale for 2 years before and 2 years during the pandemic.

Within the limitations of an observational study the results are in line with the ongoing increase of pediatric T1D worldwide (10). Although the rate of T1D is increasing, the lack of a trend in recent years is predicated on the assumption that the prior trend would have continued. If there would have been flattening, as has been suggested from the Finnish data (32), the increase would be attributable to COVID-19. The increasing number of T1D cases in 2020 and 2021 follows the increasing trend observed in 2018 and 2019 without significant up- or downward deviation, indicating no short-term influence of the COVID-19 pandemic or SARS-CoV-2 infections leading to changes in the frequency of new-onset T1D in children. Thus, strong direct virus-related effects seem very unlikely. In any case, for future analysis the disruption of the seasonal pattern through direct or indirect influences of the pandemic needs to be taken into account in looking at incidence trends in childhood T1D.

References

1. Steenblock C, Richter S, Berger I, et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun 2021;12:3534

2. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021;3:149–165

3. van der Heide V, Jangra S, Cohen P, et al. Limited extent and consequences of pancreatic SARS-CoV-2 infection. Cell Rep 2022;38:110508

4. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546–550

5. Filippi CM, von Herrath MG. Viral trigger for type 1 diabetes: pros and cons. Diabetes 2008; 57:2863–2871

6. Gerasimidi Vazeou A, Kordonouri O, Witsch M, et al.; SWEET Study Group. Seasonality at the clinical onset of type 1 diabetes-lessons from the SWEET database. Pediatr Diabetes 2016; 17(Suppl. 23):32–37

7. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020;43:e170–e171

8. Tittel SR, Rosenbauer J, Kamrath C, et al.; DPV Initiative. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? Diabetes Care 2020;43:e172–e173

9. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic in Germany: results from the DPV registry. Diabetes Care 2022;45:1762–1771

10. Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years - United States, March 1, 2020-June 28, 2021. MMWR Morb Mortal Wkly Rep 2022;71:59–65

11. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther 2021;23:491–499.

12. Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia 2019;62:408–417

13. Green A, Hede SM, Patterson CC, et al. Type 1 diabetes in 2017: global estimates of incident and prevalent cases in children and adults. Diabetologia 2021;64:2741–2750

14. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. Arch Dis Child 2022;107:180–185

15. Gottesman BL, Yu J, Tanaka C, Longhurst CA, Kim JJ. Incidence of new-onset type 1 diabetes among US children during the COVID-19 global pandemic. JAMA Pediatr 2022;176:414–415

16. Tao S, Bragazzi NL, Wu J, Mellado B, Kong JD. Harnessing artificial intelligence to assess the impact of nonpharmaceutical interventions on the second wave of the coronavirus disease 2019 pandemic across the world. Sci Rep 2022; 12:944

17. Vlad A, Serban V, Timar R, et al. Increased incidence of type 1 diabetes during the COVID-19 pandemic in Romanian children. Medicina (Kaunas) 2021;57:973

18. Dilek SÖ, Gürbüz F, Turan İ, Celiloğlu C, Yüksel B. Changes in the presentation of newly diagnosed type 1 diabetes in children during the COVID-19 pandemic in a tertiary center in Southern Turkey. J Pediatr Endocrinol Metab 2021;34:1303–1309

19. Esposito S, Principi N. To mask or not to mask children to overcome COVID-19. Eur J Pediatr 2020;179:1267–1270

20. Sharif K, Watad A, Coplan L, Amital H, Shoenfeld Y, Afek A. Psychological stress and type 1 diabetes mellitus: what is the link? Expert Rev Clin Immunol 2018;14:1081–1088

21. Bussières EL, Malboeuf-Hurtubise C, Meilleur A, et al.; PRISME-COVID Team. Consequences of the COVID-19 pandemic on children's mental health: a meta-analysis. Front Psychiatry 2021;12: 691659

22. Ruiz PLD, Tapia G, Bakken IJ, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. Diabetologia 2018;61: 1996–2004

23. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab 2020;2:1021–1024

24. Hippich M, Holthaus L, Assfalg R, et al. A public health antibody screening indicates a 6-fold higher SARS-CoV-2 exposure rate than reported cases in children. Med (N Y) 2021;2: 149–163.e4

25. Jia X, Gesualdo P, Geno Rasmussen C, et al. Prevalence of SARS-CoV-2 antibodies in children and adults with type 1 diabetes. Diabetes Technol Ther 2021;23:517–521

26. Kamrath C, Rosenbauer J, Tittel SR, et al. Frequency of autoantibody-negative type 1 diabetes in children, adolescents, and young adults during the first wave of the COVID-19 pandemic in Germany. Diabetes Care 2021;44: 1540–1546

27. Rabbone I, Schiaffini R, Cherubini V, Maffeis C; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care 2020;43:2870–2872

28. Ho J, Rosolowsky E, Pacaud D, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatr Diabetes 2021;22:552–557

29. Goldman S, Pinhas-Hamiel O, Weinberg A, et al. Alarming increase in ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the first wave of the COVID-19 pandemic in Israel. Pediatr Diabetes 2022;23:10–18

30. Danne T, Lanzinger S, de Bock M, et al. A worldwide perspective on COVID-19 and diabetes management in 22,820 children from the SWEET project: diabetic ketoacidosis rates increase and glycemic control is maintained. Diabetes Technol Ther 2021;23:632–641

31. Marks BE, Khilnani A, Meyers A, et al. Increase in the diagnosis and severity of presentation of pediatric type 1 and type 2 diabetes during the COVID-19 pandemic. Horm Res Paediatr 2021;94:275–284

32. Parviainen A, But A, Siljander H; Finnish Pediatric Diabetes Register. Decreased incidence of type 1 diabetes in young Finnish children. Diabetes Care 2020;43:2953–2958