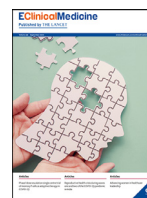




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Research paper

## Type 1 diabetes onset in Lombardy region, Italy, during the COVID-19 pandemic: The double-wave occurrence

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### ABSTRACT

**Background:** The Italian Lombardy region has been the epicenter of COVID-19 since February 2020. This study analyses the epidemiology of pediatric type 1 diabetes (T1D) onset during the first two pandemic waves and three previous years.

**Methods:** All the 13 pediatric diabetes centers in Lombardy prospectively evaluated charts of children at T1D onset (0–17 years), during year 2020. After calculating the annual incidence, the data were compared with those of the 3 previous years, using generalized linear models, adjusted for age and sex. Monthly T1D new onsets and diabetic ketoacidosis (DKA) were investigated yearly from 2017 to 2020. Data were extracted from outpatients charts of the pediatric diabetes centers and from the database of the national institute of statistics.

**Findings:** The estimated incidence proportion of T1D was 16/100,000 in 2020, compared to 14, 11 and 12 in 2019, 2018 and 2017, respectively. When adjusting for age and gender, the incidence was significantly lower in 2018 and 2017 compared to 2020 (adjusted incidence ratio: 0.73 and 0.77 respectively, with 95% CI: 0.63 to 0.84, and 0.67 to 0.83;  $p = 0.002$  and  $p = 0.01$ ), but no difference was found between the years 2020 and 2019. A reduction trend in the percentage of T1D diagnosis during the first wave (March–April) over the total year diagnoses was observed compared to previous years (11.7% in 2020, 17.7% in 2019, 14.1% in 2018 and 14.4% 2017). No difference was observed during the second wave (October–December) (32.8% in 2020, 33.8% in 2019, 34% in 2018, 30.7% in 2017). The proportion of DKA over the total T1D diagnoses during the second wave had higher trend than the first one (41.7% vs 33.3%), while severe DKA over the total DKA appeared higher during the first wave (60% vs 37.1%).

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*Interpretation:* The study suggests an increase in the incidence of pediatric T1D in Lombardy throughout the past five years. Pandemic waves may have affected the clinical presentation at onset.

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## Research in context

### *Evidence before this study*

The effect of the COVID-19 pandemic on type 1 diabetes onset is still debated, with contrasting results. Most of the studies were conducted in the early phase of the pandemic and were focused only on a few months of observation and on limited clinical aspects, like diabetic ketoacidosis (DKA).

### *Added value of this study*

Our data collected in the Lombardy region of Italy that experienced the deadliest COVID-19 outbreaks, suggests that pediatric T1D incidence significantly increased in 2020 compared to the 3 previous years. Indeed, the number of T1D diagnoses, DKA at onset, severe DKA and pediatric intensive care unit admissions differed between the first and the second COVID-19 waves.

### *Implications of all the available evidence*

The incidence of pediatric T1D is increasing in the Lombardy region.

## 1. Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still having a severe global impact. The Lombardy region, in Northern Italy, with more than 1.6 million cases and 55,000 deaths, has consistently remained the highest incidence of COVID-19 [1,2]. The coronavirus pandemic pressured the Lombardy's health system which was unprepared and struggled with a lack of space, resources, and staff. Especially during the first wave (March/April 2020), it was close to a collapse of the health system [3]. On 9th March 2020, the Italian government imposed the first lockdown and completely reorganized its health-care system to face the pandemic [3]. Following the peak of the epidemic in mid-March, the curve slowly fell due to lowering down of the cases, and restrictions were loosened on May 4th 2020. When the first wave seemed to have passed, the health care system adapted to cope with the new wave which occurred five months later starting in October, reached its peak in November and slowed down in a bell-shaped curve in the following months. Lombardy was again the epicenter of the second wave and a new lockdown was imposed [1,2].

While it seems obvious that in 2020 the social attention and health resources were mainly directed to COVID-19, it is important to remember that chronic conditions, like type 1 diabetes (T1D), need to be always addressed, especially in case of type 1 diabetes onset [4].

We hypothesized that the COVID-19 pandemic might have affected the epidemiology of T1D in Lombardy, especially during the two waves observed because of the lockdown [5]. We prospectively collected incidence data about the new-onset T1D in pediatric age in the Lombardy region during the calendar year 2020, comparing them to the 3 previous years (2017, 2018 and 2019). The frequency of new-onset T1D, diabetic ketoacidosis (DKA) and pediatric intensive care unit (PICU) admission in children and adolescents aged 0–17 years were investigated, focusing on the first and second waves.

## 2. Methods

### 2.1. Data sources

To estimate the incidence and to describe the clinical presentation of pediatric T1D during the calendar year 2020, a prospective multi-center study was performed using 2 data sources: the outpatient charts of all the pediatric diabetes centers in Lombardy (Italy) [6] and the demographic data of the Lombardy Region retrieved from the page (<http://demo.istat.it/>) referencing to the national institute of statistics (ISTAT). The available information consisted in the amount of the resident population in Lombardy on January 1st for each year of interest, also stratified by gender and age. Data were compared with those of the 3 previous calendar years (2017–2019).

To describe the COVID-19 related hospitalization curve during the pandemic, we extracted data from the public repository provided by "Dipartimento della Protezione Civile-Presidenza del Consiglio dei Ministri" (<https://github.com/pcm-dpc/COVID-19>).

### 2.2. Procedures

All the pediatric diabetes centers in the Lombardy region were contacted to participate in the study, and they gave their consent. The centers are located in all Lombardy provinces ( $n = 9$ ) and cover the whole regional area. According to the Organization of the Medical Assistance for Diabetes in Lombardy, the pediatric diabetes centers take care of children affected by T1D, aged 0–17 years.

All centers were asked to prospectively collect data from outpatient charts concerning new pediatric (age 0–17 years) T1D onset (gender, date of birth, date of diagnosis), its clinical presentation (pH and bicarbonates), the possible admission in the intensive care unit, coma, death and cerebral edema from March 1st, 2020 to December 31st, 2020. The same data were retrospectively collected for patients diagnosed in 2017, 2018, 2019 and between January 1st and February 29th, 2020.

T1D was diagnosed according to the guidelines of the International Society for Pediatric and Adolescent Diabetes. DKA was defined as a pH level below 7.3 and/or bicarbonate level below 15 mmol/L, and severe diabetic ketoacidosis as a pH level below 7.1 and/or bicarbonate level below 5 mmol/L [7]. Patients with non-T1D and patients with new onset diabetes, for whom the type of diabetes was unclear, were excluded from the data collection.

During pandemic (March – December 2020) children and adolescents at T1D onset were tested for SARS-COV-2 infection by swab at hospital admission according to regional protocol. Confirmed COVID-19 was defined as detection of SARS-CoV-2 by RT–PCR in nasopharyngeal samples.

According to the Regional epidemiological data of the COVID-19 pandemic, the first wave of COVID-19 was between the months of March and April 2020, and the second one between October and December 2020 [1].

### 2.3. Outcomes and statistical analysis

The principal outcome was the yearly incidence of clinically diagnosed T1D for the year 2020, compared with the 3 previous years. Incidences were calculated as the ratio, for each year, of incident cases (T1D onsets) and the respective population aged 0–17 years [8]. The incidence proportions in years from 2017 to 2020 were

**Table 1**

Characteristics of pediatric new onset T1D in 13 centers in Lombardy from 2017 to 2020. The last column shows the results from the tests of comparison among the four years: mean ages were compared by the F test for ANOVA models; medians of pH were compared by the Wald test for quantile regression models; for any other variables, the comparisons were performed by Fisher's exact test for proportions. Dec: December; Apr: april; Mar: march; Nov: november; Oct: october; Q: quartile; SD: standard deviation; ys: years.

	year				p-value
	2020	2019	2018	2017	
<b>All</b>	256	231	191	202	
<b>Gender: female</b>	110 (43.0%)	114 (49.4%)	88 (46.1%)	91 (45.0%)	0.5631
<b>Age at diagnosis (ys)</b>					
<b>mean, SD</b>	8.5, 4.2	8.9, 4.1	8.7, 3.9	8.7, 4.3	0.3186
0–5 ys	69 (27.0%)	51 (22.1%)	38 (19.9%)	51 (25.2%)	0.3064
6–11 ys	122 (47.7%)	112 (48.5%)	106 (55.5%)	91 (45.0%)	0.1963
12–18 ys	65 (25.4%)	68 (29.4%)	47 (24.6%)	60 (29.7%)	0.5180
<b>pH</b>					
<b>median, Q1-Q3</b>	7.33, 7.23–7.37	7.33, 7.20–7.37	7.32, 7.21–7.37	7.31, 7.18–7.35	0.3383
<b>COVID-19 waves</b>					
First (Mar/Apr)	30 (11.7%)	41 (17.7%)	65 (34.0%)	62 (30.7%)	0.3118
Second (Oct/Nov/Dec)	84 (32.8%)	78 (33.8%)			0.8890

estimated using generalized regression models with Poisson distribution, with new onsets as dependent variable, year as independent variable and the amount of population as offset [8,9]. All incidence proportions were expressed as the number of incident cases per 100,000 subjects in the target population. To evaluate if the incidence in 2020 was significantly different compared to the incidences in the previous years, the independent variable “year” was included in the model using dummy coding, with 2020 as reference. The null hypothesis that the incidence proportions in the four years are equal was assessed by the Likelihood Ratio test. After this, comparisons were performed by Wald tests and by adjusting the p-values for test multiplicity using the Bonferroni rule. Furthermore, to account for potential confounding effect of age and gender, the estimates of yearly incidence ratios were adjusted by including gender and age in the Poisson model, and the test procedure above described was performed on the new model. Gender was included by dummy coding, age was considered as numerical variable, and a potential non-linear effect was assessed by restricted cubic splines with 9 knots [10]. The model results were reported in terms of incidence ratios, with a respective 95% confidence interval (CI). Statistical significance was deemed for  $p < 0.05$ . DKA and severe DKA numbers were calculated on monthly bases, and graphically represented in order to highlight the variations within each year. The proportions of DKA over the total T1D cases, and the proportions of severe DKA over the total DKA were calculated within the period March 1st December 31th, in order to account for the pandemic period in 2020; the same was done for years 2017 to 2019, in order to allow the comparison. Similar calculations were performed for the proportions of T1D cases admitted in PICU. Fisher's exact test was adopted for the comparisons. However, since they involve low numbers of subjects, the statistical evidence support is also limited as expected and the conventional significance should be considered with caution accounting for the nature of the study and the tests multiplicity issue. Only major trends are therefore discussed.

The statistical analysis was performed using the R software release 4.0.4 and the Knime Analytic Platform release 4.2.3 [11,12].

### 3. Ethic statement

The analysis of anonymized data was approved by the Ethics Committee of the ASST-Fatebenefratelli-Sacco, Milan, Italy.

#### 3.1. Role of the funding source

There was no funding source for this study. The corresponding author (CM) had full access to the data, and the corresponding author made the final decision to submit for publication.

### 4. Results

All 13 pediatric diabetes Centers of the Lombardy region agreed to participate in the study.

We presented the epidemiological and clinical data of 880 new-onset pediatric patients with T1D, registered before (years 2017–2018–2019) and during the COVID-19 pandemic (year 2020).

SARS-CoV-2 RT-PCR test from nasopharyngeal swab was performed in 193/202 patients (95%). Eight patients were tested positive to COVID-19 (4.1%).

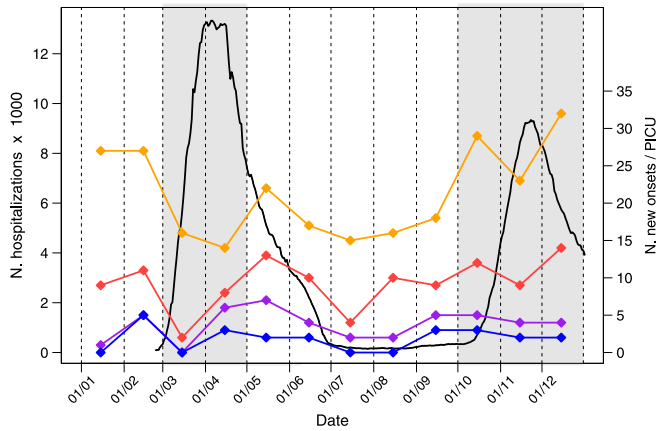
#### 4.1. Epidemiology of T1D from 2017 to 2020

Overall, the new pediatric T1D diagnoses were 256 in 2020, 231 in 2019, 216 in 2018 and 202 in 2017 (Table 1). The incidence proportion was 16/100,000 in the calendar year 2020, compared to 14, 11 and 12, respectively for the years 2019, 2018 and 2017 ( $p = 0.00,274$ ) (Table 2). From the tests related to the incidence ratios, it emerged that the incidence of T1D was significantly lower in 2018 and 2017 compared to 2020 [incidence ratio equal to 0.73 (95%CI 0.63 to 0.84)

**Table 2**

Assessment of incidence of T1D over the years 2020, 2019, 2018 and 2017 by Poisson regression models. Estimates of incidence were expressed as per 100,000 subjects in the target population. est = estimate, C.I. = Confidence Interval, \*  $p < 0.05$ , \*\*adjusted for age and gender.

year	Incidence est (95% C.I.)	Unadjusted Incidence Ratio		Adjusted **Incidence Ratio	
		est (95% C.I.)	p-value	est (95% C.I.)	p-value
<b>2020</b>	16 (14 - 18)	reference		reference	
<b>2019</b>	14 (12 - 16)	0.89 (0.78, 1.02)	0.64642	0.89 (0.78, 1.02)	0.65373
<b>2018</b>	11 (10 - 13)	0.73 (0.63, 0.84)	0.00265 *	0.73 (0.63, 0.83)	0.00297 *
<b>2017</b>	12 (10 - 14)	0.77 (0.67, 0.88)	0.01340 *	0.77 (0.67, 0.88)	0.01604 *



**Fig. 1.** Trends of daily hospitalizations due to COVID-19, and monthly new onsets of T1D, DKA, severe DKA and PICU admission in 2020. Dates are reported in month, first day. Solid black line: daily hospitalizations (period: 24/02/2020 to 31/12/2020); orange line: monthly number of new onsets of type 1 diabetes; red line: all diabetic ketoacidosis (DKA); purple line Severe DKA; blue line: pediatric intensive care unit admission. The gray regions represent the periods of two pandemic waves (from 01/03 to 30/04, and from 01/10 to 31/12).

and 0.77 (95%CI 0.67 to 0.88), respectively], but no difference was found between the years 2020 and 2019. Similar results were found from the tests related to the incidence ratios adjusted for gender and age (overall test:  $p = 0.003,302$ ) with very similar estimates of incidence ratios (Table 2). Furthermore, the estimate of male-to-female incidence ratio (accounting for year and age) was 1.11 ( $p = 0.109$ ). The average age at onset was similar across years (8.7, 8.7, 8.9 and 8.5 for 2017 to 2020 respectively), however the percentage of the new diagnosis in the youngest children of new onset was the highest in 2020 (Table 1).

No coma, death and cerebral edema were reported during the study period.

The data of the monthly new onsets of T1D, DKA and severe DKA for the years 2017 to 2020 are presented in Figure S1.

**4.2. Clinical presentation of pediatric T1D new-onset during pandemic waves**

During the first wave (March-April 2020), we recorded a reduction trend in the percentages of new diagnoses of T1D (11.7% of all diagnosed children presented with T1D in 2020) compared to the same months of the previous years (17.7% in 2019, 14.1% in 2018 and 14.4% 2017). (Table 1). During the second wave, 32.8% of the total new-onsets were diagnosed, similarly to the same period of the previous years (33.8% in 2019, 34% in 2018, 30.7% in 2017). A decrease in

**Table 3**

Characteristics of Ketoacidosis (DKA, SEVERE DKA) and PICU in Lombardy From March 1st Through December 31, 2020, During the COVID-19 Pandemic, and During the Same Period in 2019, 2018 and 2017. For diabetic ketoacidosis (ALL DKA) results were expressed as: number of cases of ketoacidosis / total number of T1D with available pH and/or HCO<sub>3</sub>; for SEVERE DKA, results were expressed as: number severe ketoacidosis / total number of ALL DKA; for PICU results were expressed as number of recovery in PICU / total number of T1D onsets. Tests of comparison between the four years were performed by Fisher's exact test for proportions, only for the whole groups ("All"). Dec: December; Apr: april; Mar: march; N: number Nov: november; Oct: october; PICU: pediatric intensive care unit; Q: quartile; T1D: type 1 diabetes; ys: years.

	Year	ALL DKAN/T1D (%)	SEVERE DKAN/DKA (%)	PICUN/T1D (%)	
All	2020	91/201 (45.3%)	39/91 (42.9%)	17/202 (8.4%)	
	2019	65/189 (34.4%)	24/65 (36.9%)	10/194 (5.2%)	
	2018	63/150 (42.0%)	20/63 (31.7%)	8/154 (5.2%)	
	2017	56/163 (34.4%)	18/56 (32.1%)	7/166 (4.2%)	
	p-value	0.0712	0.4594	0.3596	
Gender:					
Female	2020	35/82 (42.7%)	13/35 (37.1%)	6/82 (7.3%)	
Male	2019	32/92 (34.8%)	14/32 (43.8%)	4/95 (4.2%)	
	2018	25/68 (36.8%)	10/25 (40.0%)	5/71 (7.0%)	
	2017	28/76 (36.8%)	10/28 (35.7%)	3/78 (3.8%)	
	2020	56/119 (47.1%)	26/56 (46.4%)	11/120 (9.2%)	
	2019	33/97 (34.0%)	10/33 (31.2%)	6/99 (6.1%)	
Age:	2018	38/82 (46.3%)	10/38 (26.3%)	3/83 (3.6%)	
	2017	28/87 (32.2%)	8/28 (28.6%)	4/88 (4.5%)	
	0-5 ys	2020	23/54 (42.6%)	12/23 (52.2%)	11/54 (20.4%)
	6-11 ys	2019	12/43 (27.9%)	8/12 (66.7%)	3/44 (6.8%)
		2018	16/31 (51.6%)	8/16 (50.0%)	5/31 (16.1%)
12-18 ys	2017	14/40 (35.0%)	8/14 (57.1%)	3/41 (7.3%)	
	2020	44/94 (46.8%)	19/44 (43.2%)	5/95 (5.3%)	
	2019	27/93 (29.0%)	7/27 (25.9%)	1/93 (1.1%)	
	2018	27/78 (34.6%)	9/27 (33.3%)	3/82 (3.7%)	
	2017	24/78 (30.8%)	4/24 (16.7%)	2/80 (2.5%)	
COVID-19 waves	2020	24/53 (45.3%)	8/24 (33.3%)	1/53 (1.9%)	
	2019	26/53 (49.1%)	9/26 (34.6%)	6/57 (10.5%)	
	2018	20/41 (48.8%)	3/20 (15.0%)	0/41 (0.0%)	
	2017	18/45 (40.0%)	6/18 (33.3%)	2/45 (4.4%)	
	First (Mar/Apr)	2020	10/30 (33.3%)	6/10 (60.0%)	3/30 (10.0%)
Second (Oct/Nov/Dec)	2019	11/39 (28.2%)	8/11 (72.7%)	3/41 (7.3%)	
	2018	10/25 (40.0%)	2/23 (8.7%)	1/27 (3.7%)	
	2017	10/29 (34.5%)	2/10 (20.0%)	2/29 (6.9%)	
	2020	35/84 (41.7%)	13/35 (37.1%)	7/84 (8.3%)	
	2019	26/77 (33.8%)	11/26 (42.3%)	3/78 (3.8%)	
2018	23/64 (35.9%)	6/27 (22.2%)	2/65 (3.1%)		
2017	27/61 (44.3%)	11/27 (40.7%)	4/62 (6.5%)		



new diagnoses was observed in correspondence with the peak of hospitalizations for COVID-19 in both waves (April and November 2020) (Fig. 1).

During the first wave the percentage of all DKA over the respective amount of T1D new onsets appeared lower than during the second one (33.3% vs 41.7%), in contrast to severe DKA over the respective all DKA, which showed a higher trend in the first wave (60% vs 37.1%) (Table 3). Both DKA and severe DKA peaked when the Covid-19 hospitalization fell during the first wave, whereas during the second wave severe DKA cases were stable (Fig. 1).

The frequency of PICU admission reached the highest value in the first wave (10% of T1D new-onset) compared to the second wave (8.3%) of 2020 and also compared to the same months of the previous years (7.3% in 2019, 3.7% in 2018, 6.9% in 2017) (Table 3).

## 5. Discussion

Our study describes clinical features related to T1D onset during the pandemic in Lombardy, a region which was the epicenter of the COVID-19 pandemic in Italy.

Firstly, we showed that pediatric T1D follows the increasing trend observed between 2017 and 2020. Such data are in line with the most recent worldwide reports on this topic [13-16]. The similar incidence in 2019 and 2020 suggests no short-term influence of the COVID-19 on T1D new-onsets, as well as the low percentage of children and adolescents tested positive for SARS-CoV-2 at hospital admission at disease onset. Moreover, diabetes onset is the result of a pathological process that starts many months before the clinical symptoms. The relationship between viral infections and T1D onset is complex and far from being completely understood, and, at present, cause-effect relationship between the pandemic and T1D onset cannot be identified, and long-term follow up studies are needed [17].

In Lombardy, the incidence of T1D in pediatric age has increased by 128% in 31 years from 7/100.000 in 1989 to 16/100.000 in 2020 (about 4%/year) in a non-linear manner with an increase in the years 1990–2000 and then stable oscillating around 15/100.000 in the last 15 years [18,19]. Especially young children 0–4 years seemed to be slightly more affected, similarly to our findings [18]. Therefore, in the next few years we are expecting to diagnose and manage an increasing number of children and adolescents affected by T1D. Hence, a coherent implementation approach should be taken into consideration when planning health resources.

Secondly, our findings, for the first time to our knowledge, suggests that pandemic waves have affected the epidemiology of new T1D diagnosis. In the first wave we observed a decrease in new diagnoses compared to the previous years, despite the increase in the annual incidence of T1D in 2020. This relative decrease in new diagnoses peaked in correspondence with the highest rate of COVID-19 hospitalizations during the first wave. This could be the reason that led to the highest number of severe DKA in 2020, as also described elsewhere, when the COVID-19 hospitalization curve fell and the lockdown restrictions were loosened [20,21]. As consequence the percentage of PICU admission reached the higher value in the first wave than in the second wave of 2020 and also compared to the same months of the previous years, in line with data reported by Salmi et colleagues[22].

Our data support the observation that COVID-19 pandemic has changed many aspects related to the access to medical care, diagnosis, and treatment of many pediatric diseases around the world [5,23]. Regarding T1D, the first emerging lesson that can be drawn from the experiences in the early phase of the pandemic is the importance of not delaying the diagnosis, which resulted in an increased burden on DKA [20,21,24-27].

During the second wave, we observed a different pattern. The trajectory of T1D onset and DKA was similar, with the nadir of both

diagnoses being reached in correspondence with the peak of COVID-19 hospitalizations and the peak when the COVID-19 hospitalization curve fell. We hypothesize that different knowledge, attitudes, behaviors, and practices towards the pandemic at multiple levels could have contributed to these epidemiological differences.

During the first wave, Lombardy experienced a strict lockdown, the mediatic attention was constantly directed to fighting COVID-19, the health care system and medical staff were unprepared and suffered from lack of resources which were mainly directed to treat COVID-19 patients, and the population experienced a high degree of anxiety about getting into contact with potentially infected persons in medical services. These complex interactions may have resulted in delayed access to seek medical care in hospitals. On the other hand, during the second wave, the health care system was better reorganized to treat not only COVID-19 patients thanks to experiences collected in the early phases of the pandemic, and clinicians may have been more organized to operate at different front.

However, even in this 'difficult' scenario, neither death nor permanent damage was observed for the whole observation period, notwithstanding the several challenges imposed by the COVID-19 pandemic.

Finally, our study has some limitations to consider. The incidence calculated is the minimal one because we lack a second capture/recapture system. However, the 13 centers cover the whole region and, even if a few cases might have been missed, we are confident that more than 90% of cases have been recorded. Due to the access regulation to emergency departments, the missing patients could be part of the 14–17.99 age range, with the possibility that the incidence in this age group could have been underestimated. Finally, the increased incidence of T1D observed, could be explained as cyclical variations in incidence, with periodicities of between 4 and 6 years, as previously described by Patton and colleagues[28]. Further studies will be needed to evaluate the nature of the incidence variations in the medium- long-term period. Lastly, not all patients performed the nasopharyngeal swab for SARS-CoV-2, preventing any evaluation about the relationship between diabetes onset and SARS-CoV-2 infection.

In conclusion, our data suggest that T1D incidence is rising in pediatric age. The COVID-19 pandemic might have affected its clinical presentation in pediatric age, especially during the pandemic waves. The frequency of T1D diagnosis, DKA, severe DKA and pediatric intensive care unit admission differed between the first and the second pandemic waves. These data suggest that we should be prepared to face an increased number of T1D patients in the next future with timely resources and action plans.

## Declaration of Competing Interest

AS has spoken for Sanofi and Abbott and has served on the advisory board for Medtronic and Movi. All other authors declare no competing interests.

## Funding

None.

## Data sharing statement

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available upon request to the corresponding author.

## Contributors

CM, MM, RB conceived the study.  
CM, AES, RB, GM wrote the manuscript.

GF, CP, BF, LPG, DS, PM, FCR, RC, MZ, VC, SS, EC, AC, IB, CP, AR collected data

EB, EL,PB,GM managed the data and performed the statistical analysis.

GZ, EB: revised the manuscript.

All authors and contributors collaborated in the interpretation of the results and discussing and revising the manuscript and approved its final version.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101067.

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