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SHORT COMMUNICATION

Increased incidence of type 1 diabetes in 2 years of COVID-19 pandemic

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Northern Italy has been the first European area to be hit by the SARS-Coronavirus-2 2019 (COVID-19) pandemic and suffered the highest toll in terms of hospitalization and death during the so-called first waves. One of the many negative aspects of COVID-19 virus is its possible role as diabetogenic virus which is supported by several initial short-period epidemiologic observations and pathogenetic studies based on limited series [1–3].

To clarify and quantify the possible impact of two years of pandemia on incidence of type 1 diabetes (T1D), we performed a rapid analysis of regional data of an entire Italian region.

The study population was the cohort of patients cared for by the NHS regional network of 19 diabetes care units and 4 Pediatric Units in Piedmont (4,400,000 inhabitants in northwest Italy). The electronic medical record of the network feeds the regional registry of diabetes (RRD) which provides information on type 1 diabetes trends since 2011. From RRD, we extracted the data of all patients aged 0–29 diagnosed with T1D from January 1, 2017, to December 31, 2021. As enrolment in RRD is mandatory for access to care, especially insulin and device prescriptions, the accurateness is high. In compliance with privacy law, patient data were pseudo-anonymized using the same encryption algorithm used by the technical service of the Regional Health Authority and enriched with a unique anonymous identifier. The data were then transmitted to the Epidemiology Unit for analysis, Incidence rates (IRs) were calculated dividing the reported number of cases of each year, sex and age band by the corresponding resident populations on January 1 of each year, as reported by the National Institute of Statistics (ISTAT). Incidence rate ratios (RRs) were calculated as the ratio between the incidence of each year with the appropriate incidences in 2017 (reference year). 95% confidence intervals were also calculated.

A total of 834 subjects were extracted, 501males and 333 females, with identical mean age of 14.6 ± 7.8 years. The number of cases for each year is shown in the column "Number" of Table 1. Key results are summarized in Table 1 where raw incidence rate (IR) and corresponding rate ratio (RR) are reported.

Our findings reveal that the stable trend in type 1 incidence from 2017 to 2020 is interrupted by a significant leap forward in 2021. The RR of type 1 diabetes was significantly augmented by 31% (Table 1, section A). Comparisons of pooled incidence between three non-COVID years (2017–2019) and the two COVID-19 years (2020–2021) confirm the above significant increase in the total population. We also split the analysis according to age band 0–14 and 15–29 and sex to explore possible differences due these factors. A significant peak of patients aged 0–14 years and boys 0–29 in 2021 emerged. (Table 1, sections B and C); 15–29 years subjects show a similar pattern but, probably due to the reduced numerousness of the samples, the statistical significance is not reached. No statistically difference in incidence by diabetes unit nor by 4-year-ageband was found.

In summary, our findings highlight a significant increase of T1D incidence during the pandemic years, especially in

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Table 1 Type 1 diabetes, Piedmont (Italy) raw incidence rates (IR) and rate ratios (RR) 2017–2021

Year	Sex	Ageband	Number	IR	RR	Lower CI 95%	CI 95% upper
A. Raw IRs 0–29 years by 100,000 residents and RRs with confidence intervals 95%							
2017	All	0–29	158	13.74	1		
2018	All	0–29	150	13.11	0.95	0.76	1.19
2019	All	0–29	161	14.21	1.03	0.83	1.29
2020	All	0–29	164	14.60	1.06	0.85	1.32
2021	All	0–29	201	18.04	1,31*	1.07	1.62
2017–2019	All	0_29	469	13.69	1		
2020–2021	All	0_29	365	16.31	1,19*	1.04	1.37
B. Raw IRs 0–29 years by ageband per 100,000 residents and RRs with 95% confidence intervals 95%							
2017	All	0_14	102	18.41	1		
2018	All	0_14	94	17.23	0.94	0.71	1.24
2019	All	0_14	89	16.63	0.90	0.68	1.20
2020	All	0_14	95	18.08	0.98	0.74	1.30
2021	All	0_14	126	24.33	1,32*	1.02	1.72
2017	All	15_29	56	9.4	1		
2018	All	15_29	56	9.36	1.00	0.69	1.45
2019	All	15_29	72	12.05	1.29	0.91	1.83
2020	All	15_29	69	11.54	1.23	0.87	1.75
2021	All	15_29	75	12.57	1.34	0.95	1.90
C. Comparisons of pooled IRs by 100,000 residents between 2017–2019 and the two Covid-19 years (2020–2021)							
2017–2019	Boys	0_29	277	15.64	1		
2020–2021	Boys	0_29	224	19.34	1,24*	1.04	1.47
2017–2019	Girls	0_29	192	11.60	1		
2020–2021	Girls	0_29	141	13.06	1.13	0.91	1.40

*$p < 0.05$

2021, and a possible slightly greater risk for patients aged 0–14.

To our knowledge, although a few prior studies have observed an increase in T1D and DKA during the COVID-19 pandemic [1–3], others have not [2], and most have been limited short time periods. Paterson et al. reported periodical fluctuations in T1D incidence in subjects 0–14 in Europe [4], but the entity of the variation (3.4% versus 31% in our data) makes it difficult to consider this hypothesis.

Three are the main novelties of our analysis: firstly, the extension of the analysis to patients aged 15–29 years which is a common age of onset of type 1 diabetes in Italy, secondly, the reliability of diagnosis made by trained diabetologists and pediatricians, which rules out the possible interference of insulin resistant young individuals as seen in the adult population and thirdly, the last-minute data of year 2021. By measuring a 24-month interval after the onset of the COVID-19 pandemic, our study accounted for seasonal variation and other possible delays in the onset of new T1D cases.

However, strong clues to link these facts to the COVID-19 pandemic are lacking and further studies are needed. Type 1 diabetes mellitus is caused by progressive autoimmune-mediated loss of pancreatic β-cell mass via apoptosis. The onset of T1D depends on environmental factors that interact with predisposing genes to induce an autoimmune aggression toward β cells. Viral infections can act as an environmental trigger for the start of insulitis. This process takes time and may justify why in our data the onset of new cases was delayed with respect to the start of pandemia in 2020 and became evident in 2021. However, other hypothesis of a direct cytotoxic effect on beta-cells by binding to the angiotensin converting enzyme 2 (ACE2) receptor or by proteolytic cleavage of the viral spike protein by a protease cannot be ruled out [5].

We must recognize important limitations. Unfortunately, we do not have information on positivity to swab testing for COVID-19 because, especially up to September 2021, children and young subjects rarely underwent the test which was mainly directed to patients aged 50 years and more.

Moreover, the present analyses lack information on the rate of specific T1D specific autoantibodies to explore the hypothesis that the virus may have had a direct effect on beta-cells, as well as on other covariates which could have affected the association between COVID-19 and incident diabetes.

Our findings enable us to conclude that there could have been an increased T1D risk among persons aged 0–29 years during the current COVID-19 pandemia. This finding appear mainly borne by year 2021 and should be monitored in the next months. If confirmed, this fact could support the importance of COVID-19 prevention strategies in this age group.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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