

# Letters

## RESEARCH LETTER

### Progression From Presymptomatic to Clinical Type 1 Diabetes After COVID-19 Infection

The incidence of type 1 diabetes increased during the COVID-19 pandemic.<sup>1</sup> Temporal relationships between COVID-19 infection and the incidence of type 1 diabetes as well as the development of islet autoimmunity are reported.<sup>2,3</sup> It remains unknown whether COVID-19 infection accelerates disease progression in children with preexisting islet autoimmunity. The study examined whether there is an association between COVID-19 infection and progression to clinical diabetes in youth with presymptomatic type 1 diabetes.

**METHODS** | From February 2015 to October 2023, youth aged 1 to 16 years with presymptomatic type 1 diabetes (persistent, confirmed positive results for 2 or more islet autoantibodies) were identified in the Fr1da-screening program conducted in Germany and were asked to participate in a follow-up program in which their progression to clinical diabetes was monitored at 3- to 6-month intervals.<sup>4</sup> Since 2020, parents were asked to report if and when their child had been infected with COVID-19. SARS-CoV-2 antibodies were confirmed in blood samples collected at study visits. The study was approved by the ethical review board at the Technical University Munich. Written informed consent was obtained from parents of each study participant.

The study outcome was the development of clinical type 1 diabetes according to the American Association of Diabetes criteria.<sup>5</sup> COVID-19 was defined by notification from the family or the appearance of antibodies to both SARS-CoV-2 receptor binding domain and nucleocapsid proteins.<sup>3</sup> Participants

were considered negative for COVID-19 until the day before their reported infection date, until their last SARS-CoV-2 antibody-negative sample, or until their type 1 diabetes diagnosis date if this occurred within a maximum of 1 month after the last COVID-19-negative assessment. Incidence rates for the development of clinical type 1 diabetes were compared using the  $\chi^2$  statistic with 2-tailed *P* values less than .05 considered significant. Data analyses were conducted using R version 4.3.0 and the package epitools (Ausvet).

**Results** | Of 591 youth identified with presymptomatic type 1 diabetes, 509 children (median age, 4.1 years; IQR, 3.0-5.3 years; 235 females) were included in the follow-up. Of these, 358 were followed up during the period prior to March 1, 2020 (prepandemic) and 396 were followed up from March 1, 2020 (pandemic). Type 1 diabetes developed in 57 participants during the prepandemic period and 113 in the pandemic period (Table). The incidence rate for the development of clinical type 1 diabetes was 6.4 (95% CI, 4.9-8.2) per 100 person-years in the prepandemic period and 12.1 (95% CI, 10.1-14.4) in the pandemic period (*P* < .001) yielding an incidence rate ratio of 1.9 (95% CI, 1.4-2.6; *P* < .001).

Of the 396 participants followed up since the pandemic, 353 had COVID-19 infection information. Of these, 236 had a COVID-19 infection (Table). The incidence rate of type 1 diabetes during the pandemic period was 8.6 (95% CI, 6.2-11.7; *P* = .16 vs prepandemic period) while participants had tested negative for COVID-19 and was 14.0 (95% CI, 9.9-19.2) after COVID-19 infection (*P* = .04 vs pandemic COVID-19 negative; *P* < .001 vs prepandemic period). Incidence rates were 15.3 (95% CI, 8.7-25.1) for participants with a reported infection and 13.7 (95% CI, 8.9-20.4) for participants who had evidence of a COVID-19 infection based on antibody measurements only.

Table. Progression to Type 1 Diabetes in Children With Presymptomatic (Multiple Islet Autoantibody Positive) Type 1 Diabetes Prior to and During the COVID-19 Pandemic

	February 2015 to February 2020	March 2020 to October 2023	<i>P</i> value	Pandemic COVID-19 negative	Pandemic COVID-19 positive	<i>P</i> value vs prepandemic	<i>P</i> value vs pandemic COVID-19 negative
No. of children	358	396 <sup>a</sup>		324 <sup>b</sup>	236		
Median follow-up (IQR), y	2.6 (1.1-3.9)	2.6 (1.4-4.3)		1.5 (0.6-2.0)	1.0 (0.6-1.4)		
Follow-up person-years	895.3	931.6		441.7 <sup>c</sup>	236.1 <sup>d</sup>		
Developed clinical diabetes, No.	57	113 <sup>e</sup>		38	33		
Incidence rate per 100 person-years (95% CI)	6.4 (4.9-8.2)	12.1 (10.1-14.4)	<.001	8.6 (6.2-11.7)	14.0 (9.9-19.2)	<.001	.04

<sup>a</sup> Includes 245 participants who were enrolled prior to March 1, 2020, and 151 participants newly enrolled from March 1, 2020.

<sup>b</sup> Of the 396 participants followed up from March 1, 2020, 353 had COVID-19 data, of whom 29 tested positive for SARS-CoV-2 antibodies at their first measurement, including 2 who had enrolled prior to March 1, 2020.

<sup>c</sup> Follow-up for participants who had at least 1 test result negative for COVID-19 was from March 1, 2020, for participants enrolled prior to this date if their first test result during the pandemic period was negative and was from the date of

the first negative test result among those enrolled after March 1, 2020.

<sup>d</sup> Follow-up among participants who had tested positive for COVID-19 was from the date of infection or first positive antibody test result.

<sup>e</sup> For 42 of the 113 children who developed type 1 diabetes since the pandemic, the COVID-19 status in the period prior to the onset of type 1 diabetes could not be determined. This included 19 of the 43 participants with no COVID-19 information and 23 with no determination of SARS-CoV-2 antibodies at least 1 month prior to the development of diabetes.

**Discussion** | Follow-up of youth with presymptomatic type 1 diabetes demonstrated that the COVID-19 pandemic was associated with an accelerated progression to clinical disease and that this acceleration was confined to those with COVID-19. The findings are consistent with previously reported acceleration of progression in children with presymptomatic type 1 diabetes by viral infection.<sup>6</sup> Study limitations include missing information on COVID-19 in 42 participants prior to their development of diabetes and no data for COVID-19 severity. Further studies are required to determine whether COVID-19 also accelerates progression to type 1 diabetes in adults and whether vaccination and monitoring for COVID-19 symptoms should be considered for individuals with presymptomatic type 1 diabetes.

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**Data Sharing Statement:** See Supplement 1.

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