RESEARCH LETTER

SARS-CoV-2 Infections and Presymptomatic Type 1 Diabetes Autoimmunity in Children and Adolescents From Colorado, USA, and Bavaria, Germany

An increased incidence of clinical diabetes has been reported in children with previous COVID-19.[1,2] It is plausible that the virus may trigger autoimmune response to the islets or hasten metabolic decompensation in persons with already established islet autoimmunity. We tested the hypothesis that previous SARS-CoV-2 infection was associated with autoimmunity, which predicts future type 1 diabetes.

Supplemental content

Methods | In 2020 and 2021, a cross-sectional screening for islet autoantibodies and SARS-CoV-2 antibodies was offered to children and adolescents aged 1 to 18 years participating in the Autoimmunity Screening for Kids (ASK)[3] in Colorado, US, and to children aged 1 to 10.9 years enrolled in the Fr1da study[4] in Bavaria, Germany. In addition, in Bavaria, autoantibody-negative children were followed up after detection of SARS-CoV-2 antibodies with blood sample collection every 3 months. Screening was approved by the respective institutional review boards. Written informed consent was obtained from parents of each study participant. The race and ethnicity of participants were reported by parents using the US Census categories and included to control for possible confounding.

Past SARS-CoV-2 infection was defined by the presence of antibodies to both SARS-CoV-2 receptor binding domain and nucleocapsid proteins,[5,6] with similar detection thresholds for positivity as assessed by the World Health Organization international standard. Autoantibodies to insulin,

Table 1. Baseline Characteristics of the Study Population

Characteristic	Previous SARS-CoV-2 infection, No. (%)			
	Colorado (n = 4717)		Bavaria (n = 47 253)	
	Yes (n = 1524)	No (n = 3193)	Yes (n = 2862)	No (n = 44 391)
Autoantibodies present				
Multiple islet autoantibodies	7 (0.46)	14 (0.44)	8 (0.28)	133 (0.31)
Single high-affinity islet autoantibody	11 (0.74)	15 (0.47)	4 (0.14)	50 (0.11)
Sex				
Female	767 (50.3)	1607 (50.3)	1410 (49.3)	21 670 (48.8)
Male	757 (49.7)	1586 (49.7)	1452 (50.7)	22 721 (51.2)
Age group, y				
1.0-4.9	381 (25.0)	868 (27.2)	1610 (56.3)	29 537 (66.5)
5.0-11.9	651 (42.7)	1473 (46.1)	1252 (43.7)	14 854 (33.5)
12.0-18.0	492 (32.3)	852 (26.7)	NA	NA
First-degree relative with type 1 diabetes				
Yes	49 (3.2)	188 (5.9)	111 (3.9)	1555 (3.5)
No	1475 (96.8)	3005 (94.1)	2751 (96.1)	42 836 (96.5)
Race and ethnicity[a]				
African American	114 (7.5)	208 (6.5)		
American Indian or Alaska Native	27 (1.8)	47 (1.5)		
Asian American	23 (1.5)	99 (3.1)		
Hispanic	1004 (65.9)	1198 (37.5)		
Native Hawaiian and Other Pacific Islander	4 (0.3)	7 (0.2)		
Non-Hispanic White	287 (18.8)	1400 (43.8)		
Other	43 (2.8)	138 (4.3)		
Unknown	22 (1.4)	55 (1.7)		
Received SARS-CoV-2 vaccine (before or after COVID-19 infection)				
Yes	192 (12.6)	345 (10.8)		
No	1317 (86.4)	2844 (89.1)	None has received vaccine	
Unknown	15 (1.0)	4 (0.1)		

Abbreviation: NA, not applicable.

[a] "Other" was one of the categories from which parents could choose in the survey. Race and ethnicity were not collected in Bavaria.

Table 2. Results of Multivariable Logistic Regression for an Association Between Autoantibodies and SARS-CoV-2 Antibody Status, Colorado and Bavaria (N = 51 970)

	All participants		Excluded siblings and offspring of people with type 1 diabetes		Excluded youths vaccinated against SARS-CoV-2	
Covariate[a]	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Multiple islet autoantibodies						
SARS-CoV-2 infection	1.06 (0.59-1.80)	.83	0.90 (0.44-1.65)	.74	1.37 (0.46-3.71)	.55
Sex (male)	1.05 (0.77-1.43)	.38	1.12 (0.80-1.59)	.51	0.69 (0.26-1.70)	.42
Age/y	1.02 (0.97-1.08)	.76	1.03 (0.97-1.09)	.34	1.00 (0.90-1.11)	>.99
First-degree relative with type 1 diabetes	6.34 (4.22-9.25)	<.001	NA	NA	4.65 (1.29-13.33)	.02
Racial and ethnic minority group[b]	0.50 (0.20-1.20)	.12	0.75 (0.28-2.13)	.58	0.46 (0.17-1.19)	.11
Study site (Colorado)	1.79 (0.91-3.23)	.09	1.53 (0.62-3.22)	.33	NA	NA
Single high-affinity islet autoantibody						
SARS-CoV-2 infection	1.34 (0.70-2.44)	.36	1.45 (0.75-2.67)	.25	1.61 (0.66-3.79)	.29
Sex (male)	0.66 (0.42-1.02)	.06	0.68 (0.43-1.07)	.10	0.90 (0.39-2.07)	.81
Age/y	1.10 (1.03-1.17)	.004	1.10 (1.03-1.17)	.005	1.07 (0.97-1.17)	.16
First-degree relative with type 1 diabetes	1.30 (0.39-3.14)	.63	NA	NA	2.11 (0.33-7.40)	.37
Racial and ethnic minority group[b]	0.99 (0.44-2.37)	.98	0.99 (0.43-2.49)	.99	1.05 (0.44-2.70)	.91
Study site (Colorado)	2.76 (1.18-5.78)	.02	2.60 (1.06-5.66)	.04	NA	NA

Abbreviation: NA, not applicable.

[a] Covariates included age, sex, family history of type 1 diabetes, and race and ethnicity (in Colorado).

[b] Racial and ethnic minority was defined as race or ethnicity other than non-Hispanic White.

glutamic acid decarboxylase, islet antigen 2, and zinc transporter 8 autoantibodies were measured using comparable methods (eMethods in the Supplement). Study outcomes included the presence of multiple or single high-affinity islet autoantibodies that carry, respectively, a 50% and 30% risk of progression to clinical diabetes in 5 years.

Statistical analyses were performed using R version 4.1.2 (R Core Team). Multivariable logistic regression was used to assess independent associations between previous SARS-CoV-2 infection and islet autoimmunity as well as testing for interactions by study site. Standardized assessments of exposure and outcomes permitted multivariable logistic regression analysis of combined data to maximize statistical power. Covariates included age, sex, family history of type 1 diabetes, and race and ethnicity. Sensitivity analyses were performed excluding siblings and offspring of people with type 1 diabetes and separately excluding youths vaccinated against SARS-CoV-2. Two-tailed *P* values less than .05 were considered significant.

Results | Prior SARS-CoV-2 infections were identified in 1524 (32.3%) of 4717 Colorado youths (median age, 8.6 years; 50.3% female) and in 2862 (6.1%) of 47 253 Bavarian children (median age, 3.9 years; 48.9% female) (**Table 1**). Multiple islet autoantibodies were detected in 21 Colorado youths (0.45%) and in 141 Bavarian children (0.30%). In addition, 26 (0.55%) and 54 (0.11%) Colorado and Bavarian youths, respectively, were positive for a single high-affinity islet autoantibody. The prevalence of multiple or single high-affinity islet autoantibodies did not significantly differ between youths with vs without previous SARS-CoV-2 infection in Colorado (1.18% vs 0.91%, *P* = .43) or Bavaria (0.42% vs 0.41%, *P* = .88). Previous SARS-CoV-2 infection was not significantly associated with the presence of multiple islet autoantibodies (odds ratio, 1.06 [95% CI, 0.59-1.80]; *P* = .83) or a single high-affinity islet autoantibody (odds ratio, 1.34 [95% CI, 0.70-2.44]; *P* = .36) controlling for confounders (**Table 2**).

There was no significant interaction between the study site and the association with SARS-CoV-2 infection, sex, age, or family history of type 1 diabetes. Sensitivity analyses excluding siblings and offspring of people with type 1 diabetes or vaccinated youths yielded similar results (Table 2). In Bavaria, 465 children were followed up longitudinally after first detection of SARS-CoV-2 antibodies for a median of 8.9 months (IQR, 3.4-10.3) and up to 2 years. None of these children developed islet autoantibodies.

Discussion | Screening of more than 50 000 youths in diverse populations of Colorado and Bavaria found no association of SARS-CoV-2 infection with autoimmunity related to development of type 1 diabetes. Study limitations include the low prevalence of autoantibodies, limiting the power to detect an increase in risk associated with SARS-CoV-2 infection. Moreover, the cross-sectional design did not allow determination of whether autoantibodies developed before or after SARS-CoV-2 infection. Long-term follow-up of persons with preexisting autoimmunity is necessary to determine whether SARS-CoV-2 accelerates progression to clinical diabetes.

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