Incidence of an Insulin-Requiring Hyperglycemic Syndrome in SARS-CoV-2–Infected Young Individuals: Is It Type 1 Diabetes?

Massimo Pietropaolo,[1] Peter Hotez,[2] and Nick Giannoukakis[3]

Diabetes 2022;71:2656–2663 | https://doi.org/10.2337/db21-0831

PATHOPHYSIOLOGY

Pancreatic ACE2 receptor expression, together with increased prevalence of insulin-requiring hyperglycemia in patients with coronavirus disease 2019 (COVID-19), suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pancreatic infection might trigger a β-cell–selective inflammation precipitating autoimmune type 1 diabetes (T1D). We examined T1D incidence in patients with COVID-19 inside a large, global population using a "big data" approach. The incidence in 0–30-year-old patients with confirmed COVID-19 over an ∼15-month period from the beginning of the COVID-19 pandemic was compared with an age-matched population without COVID-19 inside the TriNetX COVID-19 Research Network (>80 million deidentified patient electronic medical records globally). The cohorts were used to generate outcomes of T1D post-index. In those up to 18 years of age, the incidence of insulin-requiring diabetes that could represent T1D in patients with already diagnosed, confirmed COVID-19 was statistically indistinguishable from the control population without COVID-19. In contrast, in those aged 19–30 years, the incidence was statistically greater. These data suggest that the incidence of T1D among patients with COVID-19 <30 years of age, at least up to this time since the beginning of the pandemic, is not greater when compared with an age-, sex-, and BMI-matched population without COVID-19. Nevertheless, we caution that patients with COVID-19 could be asymptomatic of a diabetic/prediabetic state and therefore would not be expected to come to medical attention, remaining undiagnosed. Hence, it is still possible that asymptomatic virus-infected individuals could acquire β-cell autoimmunity, eventually progressing to dysglycemia and clinical T1D at higher rates.

While respiratory failure, cardiovascular pathology, and thrombotic events rank among the most common causes of severe morbidity and mortality in patients with coronavirus disease 2019 (COVID-19), serious manifestations are seen across multiple organs in infected people, including the pancreas. In particular, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can induce hyperglycemia and trigger diabetes onset and diabetic ketoacidosis (DKA) in some subjects (1–4). In many cases, the hyperglycemic syndromes in patients with COVID-19 that are insulin-requiring resemble type 1 diabetes (T1D). This has spawned a media-driven popular narrative centered on some scientific reports that suggested SARS-CoV-2 infection accelerates pancreatic β-cell–selective autoimmunity, resulting in a T1D-resembling insulin-requiring hyperglycemia (5). This narrative is additionally fueled by evidence of ACE2 expression in the pancreas, infection of β-cells resulting in their impairment and potentially directing some kind of transdifferentiative event (6–12). There is, however, some controversy concerning how SARS-CoV-2 directly affects β-cell function (13).

[1]Diabetes Research Center, Section of Endocrinology, Diabetes, and Metabolism, Baylor College of Medicine, Houston, TX
[2]Texas Children's Hospital Center for Vaccine Development, Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX
[3]Institute of Cellular Therapeutics, Allegheny Health Network, Pittsburgh, PA

Corresponding author: Nick Giannoukakis, nick.giannoukakis@ahn.org

Received 14 September 2021 and accepted 27 February 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.19323818.

This article is part of a special article collection available at https://diabetesjournals.org/journals/collection/43/Diabetes-and-COVID-19-Articles.

See accompanying article, p. 2480.

Umsworth et al. (5) reported an apparent increase in the incidence of new-onset insulin-requiring diabetes in children compared with prior, pre–COVID-19 years, raising the possibility that SARS-CoV-2 could precipitate diabetes reminiscent of T1D. A viral etiology as a trigger of a β-cell–selective autoimmune state leading to insulin-requiring diabetes is not a particularly new concept (14–16). A variety of virus pathogens, including coxsackievirus B and other enteroviruses, rotavirus, and mumps, among others, have been implicated (17). The possibility that SARS-CoV-2 could precipitate a similar outcome raised significant alarms given the pandemic caused by the pathogen. Whether SARS-CoV-2 could infect pancreatic cells, and specifically pancreatic β-cells, immediately became a priority question to address. ACE2, the putative receptor facilitating SARS-CoV-2 cell entry, was found to be expressed at higher levels in the pancreas than in the lungs (18). Within a few months of the start of the pandemic, three groups confirmed the expression of ACE2 on pancreatic acinar, duct, and endothelial cells. However, the data concerning ACE2 expression on β-cells were divergent (6,13,19). One of the reasons appears to be the nonspecificity of certain antibody clones used to detect ACE2. Kusmartseva et al. (13) demonstrated that the antibodies used by Fignani et al. (6) to identify ACE2 histologically exhibit variable specificity, which could explain why some find ACE2 inside β-cells (6,7), while others could not (13). Nevertheless, Fignani et al. (6) reported the presence of SARS-CoV-2 virions inside β-cells. Since those reports, data have accumulated that support a number of additional mechanisms by which SARS-CoV-2 could penetrate and affect β-cells (8–10,12).

Although recent data indicate perturbed glycometabolic control post–COVID-19 (11), other findings (4) showed that the incidence of insulin-requiring diabetes in patients with COVID-19 (without any previous history of diabetes) was not greater than the reported incidence in the general population (based on the most recent Centers for Disease Control and Prevention [CDC] and other published epidemiology data) (20). Lawrence et al. (4) followed the frequency of severe DKA and newly diagnosed insulin-requiring diabetes that they suggested reflected T1D during the first period of the COVID-19 pandemic in Australia (March to May 2020) and compared this to all pediatric presentations of severe DKA and newly diagnosed T1D under emergency-care conditions between 2015 and 2020 (pre–COVID-19) (4). Although the frequency of severe DKA was significantly higher in patients under emergency care inside the pandemic period compared with the prepandemic periods, with the overall frequency of DKA significantly higher during the pandemic period, there were no statistically distinguishable differences in the number of new autoantibody-verified T1D diagnoses in the pandemic period and prepandemic periods (11 in 2020 vs. a range of 6–10 in 2015–2019). Even when presentations to the emergency department were stratified by age, there were no differences in the incidence of T1D between the pandemic period and the prepandemic period (4).

In this study, and for the first time, we provide global health care organization population-level data demonstrating that the incidence of diabetes that is reflective of T1D in patients with COVID-19, specifically inside an age group that historically and epidemiologically exhibits the highest risk for and the highest incidence of β-cell autoimmunity (up to 30 years of age) is not different than the incidence in an age-matched population without COVID-19. We additionally offer a model that can reconcile the divergent data on SARS-CoV-2 infectivity of pancreatic endocrine cells. Although our analysis was conducted in a very large international population, we caution that vigilance should be maintained. Our conclusion is that additional molecular, histopathology, and mechanistic studies are imperative to formally refute or establish a definitive link between bona fide, β-cell–targeting, autoimmune T1D in the setting of proven evidence for SARS-CoV-2 infection.

RESEARCH DESIGN AND METHODS

To more robustly ascertain the incidence of potential/likely T1D in patients with confirmed COVID-19 and compare that to a population without COVID-19, we polled the TriNetX COVID-19 Research Network (21), a global federated network of electronic medical records (EMRs). At the time this analysis was performed (11 June 2021), data were available from >80 million patients across 60 health care organizations representing hospitals, primary care, and specialty treatment providers. This analysis was conducted entirely on the TriNetX platform, which displays only aggregated counts and statistical summaries of deidentified information. TriNetX is compliant with the Health Insurance Portability and Accountability Act of 1996, the U.S. federal law that protects the privacy and security of health care data. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System to ensure the protection of the health care data it has access to and to meet the requirements of the Health Insurance Portability and Accountability Act of 1996 Security Rule.

Using a time window of 1 January 2020–11 June 2021, patients were identified as either diagnosed with COVID-19 (PCR-based confirmation) or control subjects (one or more general examination visits [ICD-10 Z00] and no evidence of a COVID-19 diagnosis). Patients with a COVID-19 diagnosis were identified by either one or more positive COVID-19 PCR tests or ICD-10 diagnosis codes (U07.1, B34.2, B97.29, or J12.81) on or after 20 January 2020. PCR confirmation of SARS-CoV-2 infection preceded any diagnosis of T1D in our patient selection approach. Insulin prescription information, where available in the medical record, was an additional variable used to distinguish T1D. Where available, patient records with T1D autoantibody data were additionally considered in the inclusion process.

COVID-19 and control cohorts were stratified by age: 0–18 and 19–30 years. These age ranges were selected because the historical and epidemiological risk for and incidence of T1D is highest (22–24). Past 30 years of age, the incidence of T1D is low and would not be expected to affect our findings and analyses (22–24). Both COVID-19 and control age-stratified cohorts were used to generate outcomes of T1D and type 2 diabetes (T2D) postindex (COVID-19 diagnosis or general examination visit). Patients with T1D were excluded from cohorts when determining T2D outcomes, and patients with T2D were excluded in cohorts when determining T1D outcomes.

Incident T1D was considered to be at minimum 1 day after PCR confirmation of SARS-CoV-2 infection. The risk of incident T1D 1 day or any time after the index encounter was analyzed using measures of association: risk (number of patients with T1D/number of patients in the cohort), risk difference (risk for control cohort − risk for COVID-19 cohort), risk ratio (risk for control cohort/risk for COVID-19 cohort), and odds ratio (patients in control cohort with T1D/patients in COVID-19 cohort with T1D)/(patients in control cohort without T1D/patients in COVID-19 cohort without T1D). Only patients without a record of T1D in the preindex period were considered to have incident T1D. The 95% CI is reported for the risk difference, risk ratio, and odds ratio. The *z* statistic and *P* value are reported for the risk difference. Additionally, the analysis of association was repeated for each age cohort comparison after propensity score matching to control subjects for age, sex, race (White, Black or African American, or Asian), Hispanic ethnicity, comorbidity (grouped by ICD-10 chapter), and medication confounders (use of immunological agents or antineoplastics). Propensity score with 1:1 matching was performed on the TriNetX platform using a greedy nearest neighbor matching approach with a caliper distance of 0.1 SD. The analysis was repeated for T2D.

As part of hypothesis testing, in order to ascertain if the global spread of the SARS-CoV-2 virus influenced the incidence of T1D, we investigated the possibility of apparent differences in the T1D incidence in the populations positive or negative for SARS-CoV-2 in the period from March 2020 to July 2021 with the incidence of the last two previous 12-month periods (2018–2019 and 2019–2020), in which the incidence of T1D was followed up with documented persistence of the T1D condition as medical history in the EMRs.

Data and Resource Availability

The data were acquired from deidentified EMRs accessible inside the TriNetX data platform. Proposals for access to the data should be directed to jennifer.stacey@trinetx.com. Data requestors will need to sign an agreement with TriNetX that defines the scope of the variables accessible for each of the patient records and the scope of the overall data access.

RESULTS

Patient selection is shown in Fig. 1. Patient demographics for the overall cohorts and the age-stratified cohorts are shown in Tables 1 and 2. Adjusted T1D incidence outcomes are shown in Table 3. This is the incidence of T1D in propensity score-matched patients without T1D in the preindex period (i.e., those patients without a medical history, record, or diagnosis of T1D or T2D in the preindex period). The results of the consequent and comparative analysis concerning T2D incidence are shown in Table 4. In this study, we show the incidence of T2D in propensity score-matched patients without T2D or T1D (i.e., only patients without a medical history, record, or diagnosis of T1D or T2D in the preindex period). Inside the 0–18-year-old population, our analysis did not reveal any statistically distinguishable difference in the incidence of T1D between populations with COVID-19 and without COVID-19 (Table 3). However, our analysis did reveal a statistically distinguishable incidence between the two populations in the 19–30-year-old range. Concerning the incidence of T2D post–COVID-19, we did not identify any statistically distinguishable difference in the incidence of T2D between the populations with COVID-19 and without COVID-19 (Table 4). Subgroup analysis was not possible given the general deidentified nature of the available medical records and the limits in the deidentified data available for further analysis. We followed up the initial TriNetX-based data search and analysis, this time using the Epic Cosmos federated database (>139 million individual records). The outcomes in this second, larger database supported our initial findings (no statistically distinguishable difference in the incidence of T1D between COVID-19 and non–COVID-19 populations [Supplementary Table 1]). Additionally, the incidence of T1D in COVID-19 subjects for the period 1 March 2020 to 15 July 2021 was below the annual historical U.S. and global incidence (20–24) and that in the calendar year periods 2018–2019 and 2019–2020 (Supplementary Table 1).

DISCUSSION

Sathish et al. (25) have reported the results of a meta-analysis of published clinical data to identify the proportion of patients with COVID-19 with newly diagnosed diabetes. All of the data were derived from retrospective cohort studies and covered only up to the first 5 months of the pandemic (January 2020–May 2020). The mean/median age varied from 47 to 65.5 years. The findings indicated that up to 14% of patients with COVID-19 were also diagnosed with new-onset diabetes (25). This study was limited in terms of analyzable populations affecting the findings' generalizability. Additionally, other studies that could offer insight into the incidence of specifically T1D and T2D were small in patient numbers (25). Our findings, instead, are based on an approach that included a wider time frame (15 months), a study population from the very young to up to 30 years of age, and an EMR-

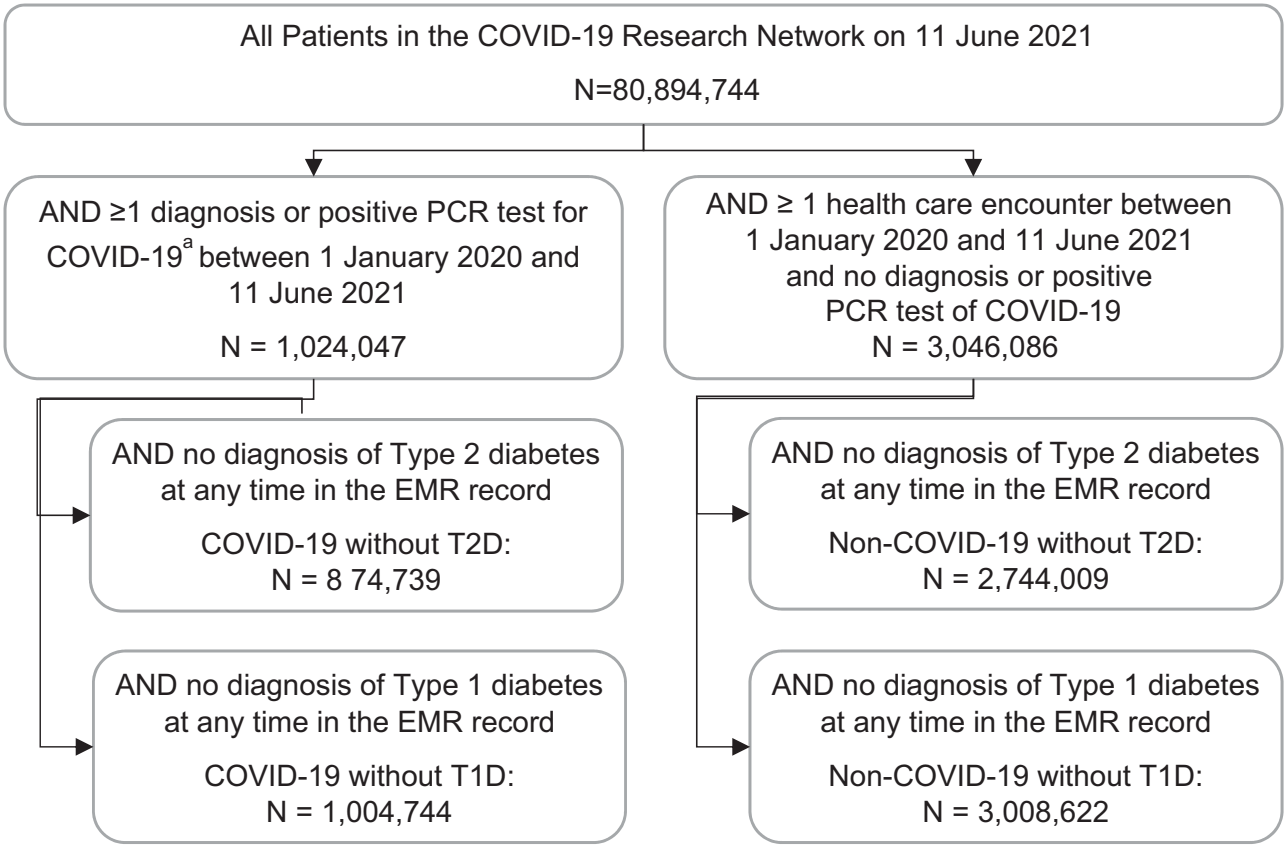

Figure 1—Patient selection. [a]Either one or more positive COVID-19 PCR tests or ICD-10 diagnosis codes (U07.1, B34.2, B97.29, or J12.81) on or after 20 January 2020.

based definition of "newly diagnosed disease" based on ICD diagnosis codes in an analysis that uses EMR as the source of data (>80 million patient EMRs across 60 geographically distinct major health care providers globally) for a sequential diagnosis of diabetes following COVID-19 confirmation. In our search and analysis to detect any differences in the incidence of diabetes (diagnosed T1D or T2D), even though we did not detect an incidence generally greater than the current epidemiological data (20,22–24,26,27) in the 0–18-year-old population (Table 3), we did uncover a statistically distinguishable difference in the 19–30-year-old age range (Table 3) after propensity score matching (43 of 163,749 patients with COVID-19 vs. 23 of 163,791 patients without COVID-19; $P = 0.0138$). While these incidences (in both populations inside the 19–30-year-old age range) are not statistically different from the CDC and other reported T1D incidence data (20,22–24,26,27), that they cluster inside an age

Table 1—Age, sex, and BMI of patients in the overall cohorts

	All patients		All patients without T2D		All patients without T1D	
Measure	COVID-19 (*N* = 1,024,047)	Non–COVID-19 (*N* = 3,046,086)	COVID-19 (*N* = 874,739)	Non–COVID-19 (*N* = 2,744,009)	COVID-19 (*N* = 1,004,744)	Non–COVID-19 (*N* = 3,008,622)
Age (years), mean ± SD	44.4 ± 21.4	37.8 ± 25.9	41.5 ± 21	35 ± 25.4	44.2 ± 21.4	37.6 ± 25.9
BMI						
≤19.9, adult (Z68.1)	40,445 (3.9)	370,166 (12.2)	37,293 (4.3)	364,821 (13.3)	39,645 (3.9)	368,465 (12.2)
20–29, adult (Z68.2)	213,055 (20.8)	809,068 (26.6)	178,369 (20.4)	722,210 (26.3)	206,873 (20.6)	796,015 (26.5)
30–39, adult (Z68.3)	174,862 (17.1)	504,625 (16.6)	124,449 (14.2)	385,934 (14.1)	167,736 (16.7)	490,440 (16.3)
≥40, adult (Z68.4)	70,696 (6.9)	158,600 (5.2)	43,814 (5.0)	106,646 (3.9)	67,107 (6.7)	152,209 (5.1)
Unavailable or pediatric	524,989 (51.3)	1,203,627 (39.5)	490,814 (56.1)	1,164,398 (42.4)	523,383 (52.1)	1,201,493 (39.9)
Sex	465,716 (45.5)	1,364,449 (44.8)	392,289 (44.8)	1,222,212 (44.5)	456,465 (45.4)	1,346,656 (44.8)

Data are *N* (%) unless otherwise indicated.

Table 2—Age and sex of patients in the age-stratified cohorts

	Age group (years)	Cohort	*N*	Age (years), mean ± SD	Sex, *N* (%)
Age stratifications among patients without T2D	0–18	COVID-19	112,204	10.2 ± 5.66	56,754 (50.6)
		Non–COVID-19	974,861	7.36 ± 5.6	492,627 (50.5)
	19–30	COVID-19	178,907	23.9 ± 3.49	74,412 (41.6)
		Non–COVID-19	298,711	23.7 ± 3.63	116,159 (38.9)
Age stratifications among patients without T1D	0–18	COVID-19	112,211	10.2 ± 5.66	56,749 (50.6)
		Non–COVID-19	974,782	7.36 ± 5.6	492,468 (50.5)
	19–30	COVID-19	181,147	23.9 ± 3.49	75,106 (41.5)
		Non–COVID-19	301,072	23.8 ± 3.63	116,784 (38.8)

range in which the epidemiological incidence of T1D was low prior to the COVID-19 pandemic raises a number of questions that we believe are worth addressing. For example, it is possible that this incidence may reflect insulin-requiring hyperglycemia and/or ketoacidosis secondary to virus-induced systemic inflammation and concomitant destabilization of glucose homeostasis in hospitalized subjects who may not have any underlying β-cell–selective autoimmunity or even any evidence of virus infection of pancreatic cells. Also, and not mutually exclusive, older individuals (i.e., >18 years of age) may be at risk for a more "aggressive" response of the innate arm of the immune system in response to SARS-CoV-2 (compared with other known seasonal pathogens in past years). This more aggressive inflammation may be more efficient in overriding lymphocyte networks that otherwise maintain β-cell–reactive lymphocytes in a state of anergy. Even though the prevalence of cytokine storm–affected patients in our analyzed populations is expected to be low, an unnaturally increased concentration of proinflammatory cytokines in persons >18 years of age, even in patients with mild COVID-19, might be theoretically able to breach metabolic control, resulting in insulin resistance and β-cell insufficiency that ends up being an insulin-requiring condition. Still other mechanisms (28) are related to nonenzymatic glycosylation and other covalent modifications of either human or viral proteins, as well as age-related shifts in biological clocks, NAD^+ levels, and the epigenome. Although currently not addressable due to privacy matters and policies that restrict access to deeper levels of data (e.g., laboratory test results that could shed light into these mechanistic possibilities) inside federated databases of health records, we are cautiously optimistic that such searching will become a reality in the not-too-distant future.

Whether SARS-CoV-2 can directly infect β-cells and whether this can drive the impairment of a substantial mass of β-cells unable to sustain normoglycemic homeostasis remain to be fully confirmed. Only in patients genetically at risk for T1D (e.g., HLA and *IDDM2* high-risk alleles) (29,30) have intercurrent viral infections been suspected to "paralyze"/stress β-cell function to the point of failure. These patients are mostly young to adolescent (up to 18 years old). Thus, if COVID-19 can predispose to and establish a chronic, autoimmunity-activating, β-cell–selective, and possibly lifelong T1D, SARS-CoV-2 would indeed be a unique pathogen. One would therefore expect that the lineage-related SARS-CoV-1 virus might have also been associated with the incidence of diabetes and indeed

Table 3—Incidence of T1D in propensity score–matched patients without T2D

	Age range (years)		
	0–18	19–30	Additional incidence data
T1D incidence, patients with outcome/total cohort (%)			
Non–COVID-19	30/110,139 (0.027)	23/163,791 (0.014)	Reported global incidence (0–19 years of age): 14.8–27.4/100,000 (0.0148–0.0274)***
COVID-19	26/110,058 (0.024)	43/163,749 (0.026)	
Risk difference, % (95% CI)	0.004 (−0.01, 0.017)	−0.012 (−0.022,−0.002)	
z value	0.532	−2.463	
P value	0.5948	0.0138	
Risk ratio (95% CI)	1.153 (0.682, 1.949)	0.535 (0.322, 0.887)	
Odds ratio (95% CI)	1.153 (0.682, 1.95)	0.535 (0.322, 0.887)	

***See Mayer-Davis et al. (22), Norris et al. (23), and Rogers et al. (24).

Table 4—Incidence of T2D in propensity score–matched patients without T1D

	Age range (years)	
	0–18	19–30
T2D incidence, patients with outcome/total cohort (%)		
Non–COVID-19	57/110,473 (0.052)	350/165,584 (0.211)
COVID-19	46/110,369 (0.042)	356/164,766 (0.216)
Risk difference, % (95% CI)	0.01 (−0.008, 0.028)	−0.005 (−0.036, 0.027)
z value	1.079	−0.292
P value	0.2804	0.7703
Risk ratio (95% CI)	1.238 (0.84, 1.825)	0.978 (0.844, 1.134)
Odds ratio (95% CI)	1.238 (0.839, 1.826)	0.978 (0.844, 1.134)

T1D. However, thus far, the data linking SARS-CoV-1 are inconclusive (31). If COVID-19 were to cause β-cell loss in patients with an underlying, latent, β-cell–selective autoimmunity, an excess incidence of T1D in the highest-risk population (0–18 years of age) would have already been obvious at this time in the pandemic. The data from Lawrence et al. (4) and our own findings in this study do not appear to support this (32). Furthermore, two published studies, in a population that is at high risk for T1D, support our findings. In the first, Kamrath et al. (33) did not establish any increased frequency of autoantibody-negative T1D cases inside a population of children, adolescents, and young adults following the onset of the COVID-19 pandemic in Germany compared with cases in the preceding decade. Neither did they observe any differences in the number of new cases during the pandemic when compared with the known prepandemic epidemiological annual trends (34). The second study was conducted retrospectively inside a Finnish population of children (35). In that study, Salmi et al. (35) determined that, during the pandemic, even though there was an increase in the number of children with new-onset T1D admitted to pediatric intensive care units for severe ketoacidosis, none of them tested positive for SARS-CoV-2 antibodies.

As shown in Supplementary Table 1, the incidence of T1D in subjects with COVID-19 for the period 1 March 2020 to 15 July 2021 was significantly less than in the parallel population without COVID-19 (Supplementary Table 1) and significantly below the annual historical U.S. and global incidence (20–24) while the incidence of T1D in individuals without COVID-19 in the same time period was not statistically different than the incidence in the 2018–2019 and 2019–2020 calendar years (Supplementary Table 1). At this time, we cannot identify the reasons for the significantly lower incidence in the population with COVID-19 in the time period 1 March 2020 to 15 July 2021 when compared to the population without COVID-19 in the same period. Nevertheless, we cannot formally exclude an undercounting of T1D incidence since many SARS-CoV-2–infected patients tend to avoid medical care at academic medical institutions, seeking to self-quarantine and/or to seek care from primary health providers, which is not expected to result in capturing signs of β-cell–selective autoimmunity.

In Table 4, we present a summary of our findings on the incidence of T2D in individuals first diagnosed with SARS-CoV-2 infection. In the two age ranges we polled, the incidence of T2D between those with SARS-CoV-2 positivity compared with those without is statistically indistinguishable. This is not particularly surprising since T2D is not a common finding in children or adolescents, even though there is a global increase in obesity in adolescents and young adults. Nevertheless, the evidence showing an increase in glucometabolic impairment in patients with COVID-19 postrecovery (36) should be an area of clinical investigational focus going forward, especially in those individuals in whom significant system inflammation due to the response to the virus possibly caused a new homeostasis tilted toward impaired glucose tolerance and insulin sensitivity.

Very recently, Barrett et al. (36) reported a higher incidence of diabetes in individuals <18 years of age in COVID-19–positive compared with COVID-19–negative populations. It is important to note that this retrospective study did not discern whether the incident diabetes was T1D or T2D. Unlike this study, Barrett et al. (36) did not specifically address the incidence of T1D in their study population. Also, the basis of analysis was data obtained from claims databases of two multiparameter health data brokers (IQVIA and Health Verity). Claims data are notoriously subject to multiple revisions and, depending on when the data were retrieved, what the authors considered claims due to a diagnosis and/or treatment for T1D could have been longitudinally corrected to another health condition (e.g., treatment for nondiabetic ketoacidosis, T2D, or other insulin-requiring conditions). Moreover, the analysis was conducted on only hospitalized cases. Individuals hospitalized for COVID-19 <18 years of age as of the present time (24 January 2022) represent ∼0.09% of all COVID-19 diagnoses (CDC COVID Data Tracker: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network). This is a very small sampling of the total population that is positive for SARS-CoV-2 confirmed by PCR and thus artificially inflates the outcome due to a small denominator (small

noninclusive base population). Also, hospitalized patients are at risk for glucometabolic episodes that are captured in claims data as diabetes, when in fact these episodes, while insulin requiring, could consist of a variety of acute glucometabolic conditions for which claims information could be revised. Instead, our data are based on a diagnosis that is then confirmed to remain as a persistent medical problem in the patient's EMR.

Our data, as important as they may be in addressing the question raised by many and unfortunately driven by an unhelpful media narrative, should nevertheless be treated with some caution. We recognize that approximately one-half of patients with COVID-19 are without symptoms of a diabetic state (and quite possibly prediabetic state) (37) and therefore would not be expected to come to medical attention, remaining undiagnosed. Even if SARS-CoV-2 directly infects β-cells, triggering a β-cell–selective autoimmunity in nonsymptomatic individuals, short of an acute and precipitous loss of a substantial mass of functional β-cells, younger age populations are more likely to remain largely asymptomatic for T1D, in line with the established chronology of an asymptomatic autoimmunity progressing to dysglycemia (38,39) and, eventually, clinical onset. Thus, even though our data do not indicate an increased incidence in insulin-requiring diabetes potentially reflecting T1D among symptomatic, self-quarantined, and hospitalized patients with COVID-19, it is still possible that asymptomatic SARS-CoV-2–infected individuals could acquire β-cell autoimmunity and eventually progress to dysglycemia and clinical T1D at higher rates.

This study has some notable limitations. First, it is a retrospective analysis. Second, COVID-19 could be underreported even though we used specific ICD codes that, by the autumn of 2020, were already established in most, if not all, of the participating health care organizations. Third, given that the data from the EMR databases did not always provide T1D autoantibody test results, we could not include these variables in our search and analysis to firmly establish that our results represent authentic autoimmune T1D counts. In addition, we determined incident T1D in the outcomes by only counting patients who had no prior EMR encounter with a record of T1D; however, we cannot be certain patients were not receiving diabetes care in a health care organization outside the TriNetX network. Thus, we could be overreporting incident T1D. Fourth, the EMR data are also at risk for coding errors or the entry of the data when patient information was translated to ICD codes. Fifth, recording of the ICD codes could also vary by age, comorbidities, illness severity, and medications in addition to insulin. Sixth, due to the current limitations of the analytics available within the TriNetX and the Epic Cosmos systems, multivariate analyses to rule out confounders could not be conducted. Despite these limitations, this study's findings, we believe, are novel and valuable to the clinical and research community in helping it determine real-world outcomes related to the incidence of T1D in populations with COVID-19.

Note Added in Proof. Between initial publication of this article online and its final publication online and in print, reanalysis of data based on updated information from the Epic Cosmos database was conducted. Text in RESULTS and DISCUSSION and data in Supplementary Table 1 and its legend have been revised accordingly. The conclusions remain unchanged.

Acknowledgments. The authors thank Jennifer Stacey and Jessamine Winer-Jones, employees of TriNetX, for expert assistance in mining the TriNetX database and data and for the statistical analysis of the data.

Funding. This study was supported by the McNair Medical Institute at The Robert and Janice McNair Foundation (to M.P.).

Duality of Interest. P.H. is a developer of a COVID-19 vaccine construct, which was licensed by Baylor College of Medicine to Biological E Ltd., a commercial vaccine manufacturer for scale up, production, testing, and licensure. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. N.G. conceived the hypothesis and discussed it with M.P. and P.H. The initial draft of the findings into a manuscript was done by N.G. The interpretation of the data were discussed among all of the authors in all manuscript revisions. M.P. and P.H. reviewed the initial draft of the manuscript and data and revised and edited the initial and all subsequent versions of the manuscript. All authors agreed with the final version of the manuscript prior to submission by N.G. N.G. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021;17:11–30
2. Ebekozien O, Agarwal S, Noor N, et al. Inequities in diabetic ketoacidosis among patients with type 1 diabetes and COVID-19: data from 52 US clinical centers. J Clin Endocrinol Metab 2021;106:e1755–e1762
3. Gregory JM, Slaughter JC, Duffus SH, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. Diabetes Care 2021;44:526–532
4. Lawrence C, Seckold R, Smart C, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary centre during the COVID-19 pandemic. Diabet Med 2021;38:e14417
5. 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
6. Fignani D, Licata G, Brusco N, et al. SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β-cells and in the human pancreas microvasculature. Front Endocrinol (Lausanne) 2020;11:596898
7. 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
8. Wu CT, Lidsky PV, Xiao Y, et al. SARS-CoV-2 infects human pancreatic beta cells and elicits beta cell impairment. Cell Metab 2021;33:1565–1576.e1565
9. Tang X, Uhl S, Zhang T, et al. SARS-CoV-2 infection induces beta cell transdifferentiation. Cell Metab 2021;33:1577–1591.e1577
10. Steenblock C, Richter S, Berger I, et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun 2021;12:3534
11. Montefusco L, Ben Nasr M, D'Addio F, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. Nat Metab 2021;3:774–785
12. Millette K, Cuala J, Wang P, et al. SARS-CoV2 infects pancreatic beta cells in vivo and induces cellular and subcellular disruptions that reflect beta cell dysfunction. 20 July 2021 [preprint]. Res Sq:10.21203/rs.3.rs-592374/v1

13. Kusmartseva I, Wu W, Syed F, et al. Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab 2020;32:1041–1051.e6
14. Pietropaolo M, Trucco M. Viral elements in autoimmunity of type I diabetes. Trends Endocrinol Metab 1996;7:139–144
15. Luppi P, Zanone MM, Hyoty H, et al. Restricted TCR V beta gene expression and enterovirus infection in type I diabetes: a pilot study. Diabetologia 2000; 43:1484–1497
16. Hyöty H. Viruses in type 1 diabetes. Pediatr Diabetes 2016;17(Suppl. 22):56–64
17. Rodriguez-Calvo T. Enterovirus infection and type 1 diabetes: unraveling the crime scene. Clin Exp Immunol 2019;195:15–24
18. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol 2020;18:2128–2130.e2
19. Coate KC, Cha J, Shrestha S, et al.; HPAP Consortium. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. Cell Metab 2020;32:1028–1040.e4
20. U.S. Department of Health and Human Services. National Diabetes Statistics Report 2020: Estimates of Diabetes and its Burden in the United States, 2020. Accessed 20 January 2022. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
21. Turk MA, Landes SD, Formica MK, Goss KD. Intellectual and developmental disability and COVID-19 case-fatality trends: TriNetX analysis. Disabil Health J 2020;13:100942
22. Mayer-Davis EJ, Dabelea D, Lawrence JM. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017;377:301
23. Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. Lancet Diabetes Endocrinol 2020;8:226–238
24. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Med 2017;15:199
25. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Obes Metab 2021;23:870–874
26. Divers J, Mayer-Davis EJ, Lawrence JM, et al. Trends in incidence of type 1 and type 2 diabetes among youths - selected counties and Indian reservations, United States, 2002-2015. MMWR Morb Mortal Wkly Rep 2020; 69:161–165
27. Magliano DJ, Islam RM, Barr ELM, et al. Trends in incidence of total or type 2 diabetes: systematic review. BMJ 2019;366:l5003
28. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY) 2020;12:9959–9981
29. Morran MP, Vonberg A, Khadra A, Pietropaolo M. Immunogenetics of type 1 diabetes mellitus. Mol Aspects Med 2015;42:42–60
30. Redondo MJ, Steck AK, Pugliese A. Genetics of type 1 diabetes. Pediatr Diabetes 2018;19:346–353
31. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–199
32. DiMeglio LA, Albanese-O'Neill A, Muñoz CE, Maahs DM. COVID-19 and children with diabetes-updates, unknowns, and next steps: first, do no extrapolation. Diabetes Care 2020;43:2631–2634
33. 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
34. 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
35. Salmi H, Heinonen S, Hastbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. Arch Dis Child 2022;107:180–185
36. 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
37. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 transmission from people without COVID-19 symptoms. JAMA Netw Open 2021;4:e2035057
38. Nathan BM, Boulware D, Geyer S, et al.; Type 1 Diabetes TrialNet and Diabetes Prevention Trial–Type 1 Study Groups. Dysglycemia and Index60 as prediagnostic end points for type 1 diabetes prevention trials. Diabetes Care 2017;40:1494–1499
39. Sosenko JM, Palmer JP, Rafkin-Mervis L, et al.; Diabetes Prevention Trial-Type 1 Study Group. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. Diabetes Care 2009;32:1603–1607