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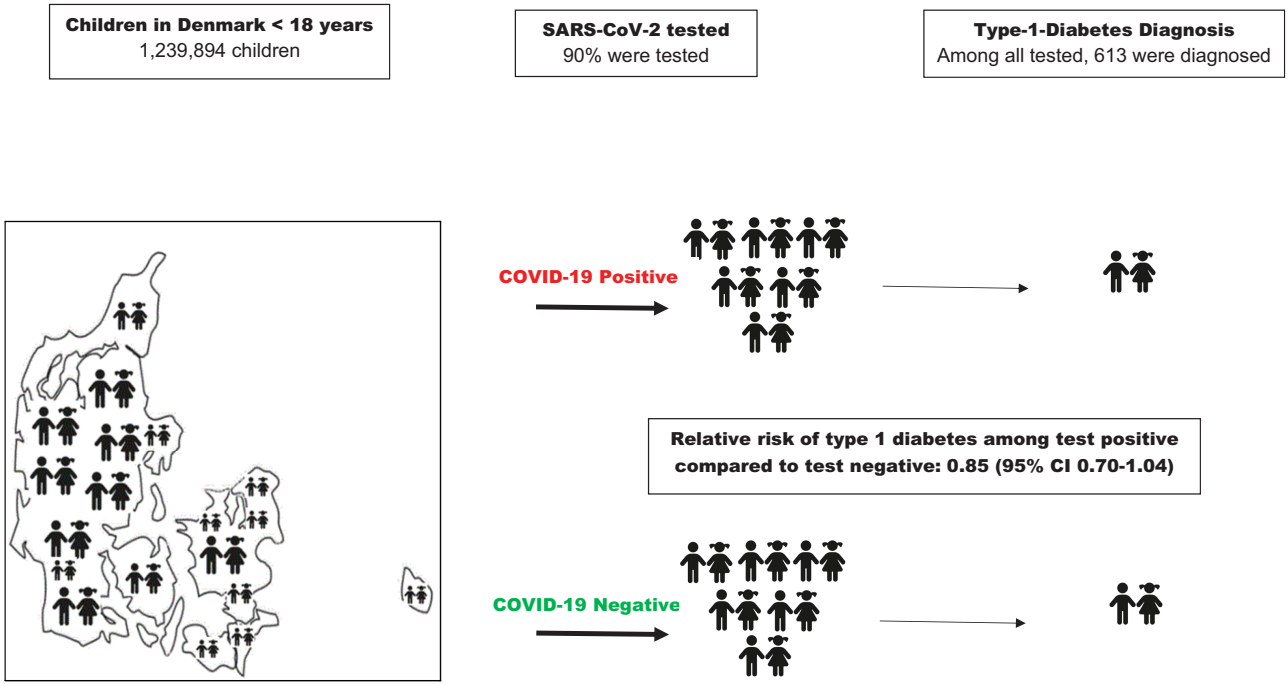

ARTICLE HIGHLIGHTS

- Studies have shown an association between SARS-CoV-2 infection and subsequent risk of type 1 diabetes, supporting the possibility of a viral etiology in type 1 diabetes and adding to concerns regarding adverse health consequences of COVID-19.
- We asked if the risk of new-onset type 1 diabetes increased among children in the period after SARS-CoV-2 infection.
- The relative risk of being diagnosed with type 1 diabetes after a positive compared with a negative SARS-CoV-2 test is 0.85 (95% CI 0.70–1.04).
- Our data do not support an association between SARS-CoV-2 infection and subsequent risk of type 1 diabetes among children.

Risk of Type 1 Diabetes in Children Is Not Increased After SARS-CoV-2 Infection: A Nationwide Prospective Study in Denmark

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OBJECTIVE

It has been hypothesized that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children can increase risk of developing type 1 diabetes.

RESEARCH DESIGN AND METHODS

We undertook a prospective, register-based analysis of children in Denmark by investigating the association between SARS-CoV-2 infection and subsequent risk of type 1 diabetes. During the pandemic, Denmark had one of the highest test rates per capita in the world, and 90% of all Danish children were tested.

RESULTS

Compared with children with a history of only negative SARS-CoV-2 tests, we did not observe a higher risk of first-time diagnosis of type 1 diabetes in children 30 days or more after a positive SARS-CoV-2 test (hazard ratio 0.85; 95% CI 0.70–1.04).

CONCLUSIONS

Our data do not support that SARS-CoV-2 infection is associated with type 1 diabetes or that type 1 diabetes should be a special focus after a SARS-CoV-2 infection in children.

A number of epidemiologic studies have reported an increased risk of diabetes after coronavirus disease 2019 (COVID-19) in children (1–3). We evaluated the association in nationwide registers in Denmark, which had one of the highest test rates per capita in the world during the pandemic (4,5). The matter is important because an association would support a possible viral etiology (6) of type 1 diabetes (T1D) and add to already existing worries regarding potential serious, adverse, long-term consequences of COVID-19 infection.

RESEARCH DESIGN AND METHODS

Our study was a nationwide, register-based cohort study that included all Danish residents aged 0 to 17 years during 1 March 2020 to 25 August 2022 with at least one severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test. Inhabitants in Denmark were identified from The Danish Civil Registration System (7). SARS-CoV-2 tests (both positive and negative results) were identified in the national COVID-19 surveillance system, which includes all Danish residents with RT-PCR tests for SARS-CoV-2 (8).

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T1D and diabetic ketoacidosis diagnoses were identified by ICD-10 codes (E10 and E101, respectively) in the National Patient Register (9). The validity of the T1D diagnosis among children in the Danish National Patient Register was validated earlier (10). Information was linked using the unique national identification number (i.e., the Danish Civil Registration System number) for all Danish citizens. Cohort members were followed from 30 days after the first registered SARS-CoV-2 test until end of the study (25 August 2022), their 18th birthday, death, emigration, or first diagnosis of T1D or diabetic ketoacidosis. Individuals with a registered T1D diagnosis or a diabetic ketoacidosis diagnosis prior to the study start (1 March 2020) were excluded.

Hazard ratios (HRs) of T1D diagnosis comparing follow-up among children with a positive SARS-CoV-2 test and children with only negative test results were estimated by Cox regression, with current age as the underlying time scale and with adjustment for sex, comorbidity (Charlson's comorbidity index ≥1: yes or no) at baseline, number of COVID-19 vaccines received (none, one, two or more) at baseline, parental history of T1D (yes or no) at baseline, and current calendar period (bimonthly categories). The first 30 days after first positive test were excluded from follow-up. HRs of T1D with and without simultaneous diabetic ketoacidosis diagnosis were estimated similarly with a competing risk setup.

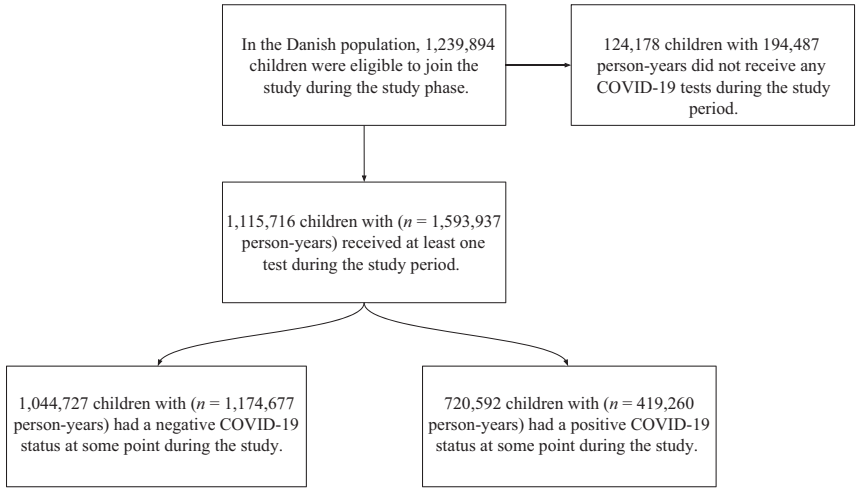

Figure 1—Flowchart for the study.

RESULTS

A flow chart and the study design are depicted in Fig. 1 and Fig. 2, respectively. In Denmark, 1,239,894 individuals aged <18 years contributed follow-up data during the study period, including 1,115,716 (90%) with at least one SARS-CoV-2 test. The 124,178 individuals with no tests were substantially younger and less likely to be vaccinated, and fewer had a parental history of T1D (Supplementary Table 1). Among the tested children, 613 were diagnosed with T1D during 1,593,937 observed person-years, corresponding to an incidence rate of 38.5 per 100,000 person-years.

We observed no significant difference in the hazard of being diagnosed with T1D in test-positive children compared with children with only negative test results (HR 0.85; 95% CI 0.70–1.04) (Table 1). We observed similar associations across age, sex, comorbidity, number of vaccine doses, parental history of T1D, and month of T1D diagnosis (Table 1). From 30 days to 6 months since testing positive, the HR was 0.88 (n = 102 events; 95% CI 0.70–1.12) and 0.79 (n = 42 events, 95% CI 0.57–1.09), respectively, for >6 months after testing positive compared with children with only negative SARS-CoV-2 tests. The HR of being diagnosed with T1D with and without a simultaneous diabetic ketoacidosis diagnosis was 0.61 (n = 17 events; 95% CI 0.35–1.08) and 0.89 (n = 127 events; 95% CI 0.72–1.11), respectively. We observed no difference between

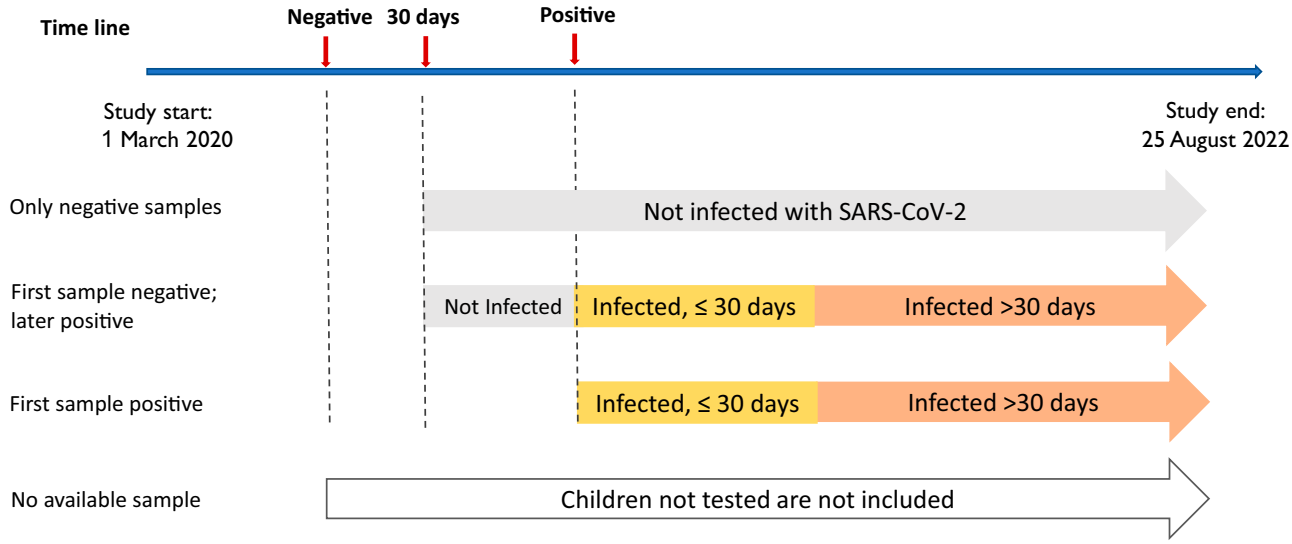

Figure 2—Design of the study. The study has a test-negative design, which means that people are only included if they have one or more tests. Follow-up starts 30 days after first test. People with an initial negative test will count as negative up until the point when they may have a positive test, after which they will count as positive for the remaining study period. The first 30 days after first positive test are excluded from the follow-up.

Table 1—HR of T1D by SARS-CoV-2 infection history according to characteristics at baseline in a cohort of 1,115,716 Danish children, 1 March 2020 to 25 August 2022

	SARS-CoV-2 positive*		SARS-CoV-2 negative†			
Characteristics at baseline	No. of T1D cases	Person-years of follow-up	No. of T1D cases	Person-years of follow-up	HR (95% CI)‡	*P* value§
All	144	419,260	469	1,174,677	0.85 (0.70–1.04)	
Age-group (years)						0.45
0–4	16	59,145	61	250,256	1.09 (0.62–1.89)	
5–10	56	148,612	157	376,710	0.91 (0.67–1.25)	
11–17	72	211,503	251	547,711	0.76 (0.58–1.00)	
Sex						0.47
Male	87	213,260	270	603,427	0.90 (0.70–1.16)	
Female	57	206,001	199	571,250	0.78 (0.58–1.06)	
Comorbidity						0.61
No	134	393,809	428	1,100,696	0.86 (0.70–1.06)	
Yes	10	25,451	41	73,981	0.72 (0.36–1.44)	
No. of vaccine doses received						0.74
0	88	257,445	370	925,346	0.84 (0.66–1.06)	
1	7	22,553	19	42,202	0.65 (0.27–1.56)	
≥2	49	139,262	80	207,129	0.92 (0.64–1.34)	
Parental history of T1D						0.19
No	134	413,430	418	1,157,960	0.88 (0.72–1.09)	
Yes	10	5,830	51	16,717	0.56 (0.28–1.11)	
Virus variant**						
Index	16	44,406	NA	NA	0.83 (0.50–1.38)	
α	8	18,193	NA	NA	1.04 (0.51–2.09)	
Δ	10	29,928	NA	NA	0.73 (0.39–1.37)	
o	82	235,593	NA	NA	0.91 (0.70–1.19)	

*History of at least one positive SARS-CoV-2 test. The first 30 days after first positive test were excluded from follow-up. †History of only SARS-CoV-2–negative tests. The first 30 days after first negative test were excluded from follow-up. ‡The HR is estimated with a time-dependent exposure (SARS-CoV-2 status) and adjusted for sex, comorbidity, vaccine doses, parental history of T1D, and calendar month of follow-up. The unadjusted HR was very similar to the adjusted estimates and, therefore, was omitted. §Test of homogeneity of the association between SARS-CoV-2 infection and T1D across subgroups (statistical interaction test). **Subgroup analyses divided by periods of variant predominance (i.e., Index, from 1 August 2020 to 31 December 2020; α, from 15 March to 30 June 2021; Δ, from 15 July to 15 November 2021; and o, from 28 December 2021 to 16 February 2022). NA, not applicable.

HRs in subgroups of periods of variant predominance (Table 1). The 10% participants without a SARS-CoV-2 test had a significantly lower risk of being diagnosed with T1D compared with children with only a negative test (HR 0.35; 95% CI 0.20–0.60; *P* = 0.0001). In the larger part of the study period, testing would have been mandatory at hospital visits; thus, children without any tests are less likely to have been in contact with the hospital system, which is a prerequisite for a T1D diagnosis in our study.

In a secondary analysis, we looked at the association between COVID-19–related hospitalization and subsequent T1D including all individuals 0 to 17 years of age living in Denmark between 1 March 2020 and 25 August 2022 (rather than limiting to tested individuals, as above). In this extended cohort, we observed a total of 936 children with T1D during 2,817,858 person-years, but we observed no T1D cases 30 days or more after a first COVID-19–related hospitalization (*n* = 939 person-years). In a secondary analysis, we also looked at the HR for receiving a T1D diagnosis within 29 days of the test relative to individuals who only tested negative and estimated the HR to be 0.99 (*n* = 22 events; 95% CI 0.63–1.55). Finally, inspection of annual incidences of T1D up to the pandemic suggested a weak increasing trend during the past 7 years (Supplementary Fig. 1).

CONCLUSIONS

We did not observe an excess risk of T1D after documented infection with SARS-CoV-2 in children, such as reported by U.S. Centers for Disease Control and Prevention (1) and, subsequently, by another study also undertaken in the U.S. (2) and one undertaken in Norway (3). Our results are more in line with a study conducted in Scotland (11). A fifth individual-level study was less informative because it did not present estimates of the association for children alone (12).

A principal problem common to the two U.S. studies (1,2) was that they both used adjudicated health care claims from primarily commercial health plans. Identifying exposed cases from such databases, and using patients exposed to health problems other than infection with SARS-CoV-2 as reference or comparison groups, can make it difficult to determine what relevant target population the relative risk estimates can be generalized to.

The studies conducted in Norway (3) and Scotland (11) and our own Danish study were based on national health registries for all children and adolescents in the three countries. According to the Norwegian data, the risk of being diagnosed with T1D 31 days or longer after a SARS-CoV-2 infection, compared with children who had tested negative for SARS-CoV-2

infection, was 1.63 (95% CI 1.08–2.47), whereas the Scottish estimate was 0.79 (95% CI 0.50–1.27), suggesting no association, as did also our estimate of 0.85 (95% CI 0.70–1.04).

An explanation for the clear difference between our Danish estimate and the Norwegian estimate could be related to the fact that Denmark had one of the highest test rates per capita in the world (11). In the age-groups 2–9 and 10–19 years, only 4.1% and 2.9%, respectively, had zero tests, whereas 62.3% and 59.8%, respectively, had 4 to 15 tests, and 15.8% and 25.5%, respectively, had >15 tests during the pandemic period (12). A substantially higher number of cases with an incident T1D diagnosis were identified among SARS-CoV-2–infected children in our study (n = 144) compared with only 28 (3) in the Norwegian and 19 (9) in the Scottish studies.

The confounder distributions might have differed across the three populations, resulting in different risk estimates. Few factors have been consistently identified as determinants of T1D, apart from the fact that it has a strong genetic component and exhibits substantial familial aggregation (13). Unlike the Norwegian and Scottish studies, we were able to adjust for parental T1D. This did not affect our estimates.

A strength of our study compared with the four earlier, individual-level studies (1–3,9) was that we were able to stratify our data according to periods of SARS-CoV-2 variant predominance. These analyses did not reveal any specific variant patterns.

A German study was one of the first to show an increased incidence of T1D during the pandemic, but a concomitant increase in the frequency of autoantibody negativity was not observed (14), suggesting that the increased T1D incidence may not be due to SARS-CoV-2 infection per se (14). Another study found no association between an infection with SARS-CoV-2 and the development of autoimmunity with regard to T1D (15).

Importantly, an increasing trend of 1.6% per year in the incidence rate during 1989–2013 has been reported for Denmark (16). If we extrapolate up to 2020 from the reported incidence of 27.0 per 100,000 for the 5-year period of 2009–2013 (a decade later), the high incidence of 38.5 per 100,000 person-years we observed during the pandemic is only partially explained (i.e., $1.016^{10} \times 27 = 32$) from the time trend seen over the past 30 years. A 20% increase during the pandemic corresponds well with observations reported in Germany (17) and Czechia (18). Our own observation (Supplementary Fig. 1) suggested an increasing annual incidence rate during the 7 years prior to 2020.

In conclusion, our data do not support an association between SARS-CoV-2 infection and subsequent risk of T1D among individuals younger than 18 years, or that T1D should be a special focus after a SARS-CoV-2 infection in children. However, some increase in the incidence of T1D in children and adolescents during the COVID-19 pandemic cannot be excluded.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. R.N., T.G.J., A.P.H., J.W., and S.F.O. were involved in the conception and design of the study. T.G.J. and J.W. were involved in the conduct of analyses. R.N., T.G.J., A.P.H., J.W., and S.F.O. were involved in the interpretation of the results. R.N. and S.F.O. wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. S.F.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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