Relation of Incident Type 1 Diabetes to Recent COVID-19 Infection: Cohort Study Using e-Health Record Linkage in Scotland

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Diabetes Care 2023;46:921–928 | https://doi.org/10.2337/dc22-0385

OBJECTIVE

Studies using claims databases reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection >30 days earlier was associated with an increase in the incidence of type 1 diabetes. Using exact dates of diabetes diagnosis from the national register in Scotland linked to virology laboratory data, we sought to replicate this finding.

RESEARCH DESIGN AND METHODS

A cohort of 1,849,411 individuals aged <35 years without diabetes, including all those in Scotland who subsequently tested positive for SARS-CoV-2, was followed from 1 March 2020 to 22 November 2021. Incident type 1 diabetes was ascertained from the national registry. Using Cox regression, we tested the association of time-updated infection with incident diabetes. Trends in incidence of type 1 diabetes in the population from 2015 through 2021 were also estimated in a generalized additive model.

RESULTS

There were 365,080 individuals who had at least one detected SARS-CoV-2 infection during follow-up and 1,074 who developed type 1 diabetes. The rate ratio for incident type 1 diabetes associated with first positive test for SARS-CoV-2 (reference category: no previous infection) was 0.86 (95% CI 0.62, 1.21) for infection >30 days earlier and 2.62 (95% CI 1.81, 3.78) for infection in the previous 30 days. However, negative and positive SARS-CoV-2 tests were more frequent in the days surrounding diabetes presentation. In those aged 0–14 years, incidence of type 1 diabetes during 2020–2021 was 20% higher than the 7-year average.

CONCLUSIONS

Type 1 diabetes incidence in children increased during the pandemic. However, the cohort analysis suggests that SARS-CoV-2 infection itself was not the cause of this increase.

A recent article from the U.S. Centers for Disease Control and Prevention (CDC) reported, based on medical claims databases (1), increased incidence of diabetes ≥30 days after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among those younger than 18 years. Such a finding, if replicated, would

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Received 24 February 2022 and accepted 3 May 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.20001458.

This article is part of a special article collection available at diabetesjournals.org/journals/collection/52/Diabetes-and-COVID-19.

See accompanying articles, pp. 913, 938, and 953.

imply a substantial increase in the burden of childhood-onset diabetes and might also alter the risk–benefit balance for coronavirus disease 2019 (COVID-19) vaccination in young children. The CDC study did not distinguish the type of diabetes, but in this age group, type 1 diabetes accounts for about 75% of cases in the U.S. (2). There is evidence that viral infections can play a primary causal role in type 1 diabetes through infection of pancreatic β-cells, triggering autoimmunity (3) and that viral infections can have a secondary causal role through accelerated autoimmunity, increasing the rate of progression to stage 3 type 1 diabetes in those with autoimmune β-cell destruction who are still normoglycemic. However, there are other possible explanations for the observed association, including misclassification of prevalent diabetes as incident in people who acquire SARS-CoV-2 infection; this is plausible given that type 1 diabetes is already known to be associated with increased risk of severe COVID-19 (4). Also, COVID-19 may cause diabetes to be diagnosed earlier, through precipitating metabolic decompensation or simply through causing urine or blood to be tested for diabetes. Furthermore, early symptoms of diabetes may lead to contact with health services and to testing for SARS-CoV-2, and thus to detection of infections that would otherwise go undetected.

In Scotland, health care is free at the point of delivery and all new diagnoses of type 1 diabetes in primary or secondary care are captured in the nationwide diabetes Scottish Care Information–Diabetes (SCI-Diabetes) registry (5) within 24 h of the diagnostic care encounter. Furthermore, the nationwide policy is that all children aged <16 years with suspected diabetes must be admitted for inpatient care to a specialist unit on the day of presentation. Adults with suspected type 1 diabetes are referred urgently to a hospital diabetes clinic and are seen within a few days. All PCR tests for COVID-19 have been captured in a national database by Public Health Scotland; during the study period, a confirmatory PCR test was mandatory for all those with a positive lateral flow test. This makes it possible to determine the temporal sequence of the relationship between detected SARS-CoV-2 infection and diagnosis of type 1 diabetes based on exact dates of first positive test and accurate dates of diagnosis of diabetes. The objectives of this study were as follows: *1*) to establish whether SARS-CoV-2 infection is associated with increased risk of incident type 1 diabetes, *2*) to determine the time interval over which risk is increased, and *3*) to examine how the incidence of type 1 diabetes has changed during the pandemic.

RESEARCH DESIGN AND METHODS

Construction of Cohort

The REACT-SCOT (Rapid Epidemiological Analysis of Comorbidities and Treatments as Risk Factors for COVID-19 in Scotland) study, described in detail elsewhere (6,7), was established by Public Health Scotland early in the epidemic as a matched case-control study of all diagnosed COVID-19 cases in Scotland with up to 10 control individuals per case, matched for age, sex, and general practice. The incidence density sampling design allows individuals to be sampled more than once as a control and subsequently as a case. The 3,938,454 individuals sampled in the REACT-SCOT study up to 22 November 2021 composed 72% of the estimated Scottish population in mid-2020, including all diagnosed cases of COVID-19. The cohort at risk for diabetes was formed from all 1,849,411 individuals sampled in REACT-SCOT who, at baseline, were younger than 35 years and had not been diagnosed with diabetes. Supplementary Fig. 1 shows a flowchart of the construction of the cohort. The baseline (entry) date for each individual was the later of 1 March 2020 (the start of the epidemic in Scotland) or the date of birth. Date of exit was the earliest of the latest date of extraction of linked data (22 November 2021), date of death, or date of any evidence of diabetes (e.g., dispensed prescription for a drug used in diabetes, hospital admission with discharge diagnoses including ICD-10 codes E10 to E14, or an outpatient consultation with specialty coded A81 for diabetes). COVID-19 vaccination records were obtained from a national database, the National Clinical Data Store.

Ascertainment of SARS-CoV-2 Infection

SARS-CoV-2 infection was defined by first positive PCR test for SARS-CoV-2 in the Electronic Communication of Surveillance in Scotland database, which captures all PCR tests for COVID-19 nationally. REACT-SCOT cases include some individuals with a definite clinical diagnosis of COVID-19 (ascertained via hospital-discharge diagnosis coding) who had never tested positive for the virus. These individuals who tested negative amounted to only 1% of individuals with COVID-19 in the cohort at risk for diabetes; the date of presentation with SARS-CoV-2 infection for these cases was set as 7 days before admission. Suspected reinfection was defined by the CDC criterion of a positive test ≥90 days after the first positive test (8).

Diabetes Ascertainment

Incident cases of type 1 diabetes in Scotland during 2015–2021 were ascertained based on date of diagnosis and type of diabetes as recorded by the clinician in the SCI-Diabetes registry. The clinical classification of type in SCI-Diabetes has previously been validated against detailed prescribing and hospital admission histories; in the years 2015–2019, we reclassified the type of diabetes as type 2, monogenic, or secondary in <2% of those younger than 16 years clinically labeled as having type 1 diabetes, for example. In a study of a consented cohort of adults with a clinical diagnosis of type 1 diabetes who are representative of those in the national SCI-Diabetes registry, we classified those with C-peptide levels >600 pmol/L and negative for three autoantibodies as "possible type 2" and validated this classification against genotypic scores (9). Only 3% of those with a clinical diagnosis of type 1 diabetes were reclassified as having "possible type 2."

Statistical Analysis

Incident cases of type 1 diabetes during the study period 1 March 2020 to 22 November 2021 were linked to the REACT-SCOT database. Those with preexisting diabetes of any type at baseline were excluded, using SCI-Diabetes records, supplemented with prescribing data (240-day lookback for British National Formulary subparagraph codes 0601011 or 0601012 for drugs for diabetes), hospital-discharge diagnoses (5-year lookback for any mention of ICD-10 codes E10 to E14 for diabetes), and outpatient records (any consultation with specialty code A81 for diabetes). As shown in Supplementary Table 1, almost all incident case patients have a first admission for diabetes within a few days of the date of diagnosis.

The association of type 1 diabetes with recent SARS-CoV-2 in REACT-SCOT was modeled in a Cox regression. COVID-19 status at the start of each person-time interval was coded as no prior COVID-19, first positive test in the last 30 days, or first positive test >30 days earlier. The 30-day cutoff was chosen for consistency with the CDC study, which excluded the first 30 days "to avoid effects on transient hyperglycemia" (1). Age at baseline was modeled as a natural spline with three degrees of freedom. Other covariates included in the model were sex and number of vaccine doses (0 to 3) given at least 14 days before. There were no missing values. To allow exact updating of time-varying covariates—SARS-CoV-2 status and vaccination status—observed person-time was split into 1-day intervals. Without thinning, this time splitting would generate a data table with >1 billion rows. To reduce computational requirements, the rows were thinned after splitting to retain a 1% sample of person-time intervals with no event and all person-time intervals with an event. There was no appreciable loss of information from this procedure, because even after thinning there were still >10,000 controls (i.e., person-time intervals with no event) for every case (i.e., person-time interval with an event).

A table of incident cases of type 1 diabetes in Scotland from 2015 to the end of 2021 was joined by date and age group to daily estimates of the total population of Scotland, obtained by fitting a spline function to publicly available midyear estimates. Incidence in a 56-day sliding window, centered on each day from 1 March 2015 to 1 October 2021, was calculated for age bands 0–14 and 15–34 years. Smoothed effects of seasonality and calendar time were estimated jointly from the counts of daily cases by age group, using the R package *mgcv* (10) to fit a generalized additive model, as described in the Supplementary Material.

Data and Resource Availability

The component data sets used in this study are available to researchers via application to the Public Benefits and Privacy Panel for Health and Social Care (https://www.informationgovernance.scot.nhs.uk/pbpphsc/). All final source code used for derivation of variables, statistical analysis and generation of this manuscript can be accessed at https://github.com/pmckeigue/covid-scotland_public.

RESULTS

Association of SARS-CoV-2 Infection With Incident Type 1 Diabetes

Among the 1,849,411 individuals in the cohort, 365,080 had a first detected SARS-CoV-2 infection between 1 March 2020 and 22 November 2021. There were 1,074 individuals who developed incident type 1 diabetes during follow-up. A total of 1,052 individuals were right censored for having developed other types of diabetes, and 447 were censored because they died before the end of the study period.

The age distribution of individuals in the cohort who developed type 1 diabetes and their COVID-19 status on or prior to their date of diagnosis of diabetes are shown in Table 1. Overall, SARS-CoV-2 infection had been detected in 69 incident case patients with type 1 diabetes up to their date of diagnosis. Of these, two had tested positive at least 90 days after their first positive test, meeting CDC criteria for suspected reinfection (8).

After splitting the data set into 1-day person-time intervals and thinning, as described in the preceding section, the data set used for Cox regression consisted of 11,553,301 person-time intervals. Table 2 lists the rate ratios for incident type 1 diabetes by COVID-19 status categorized as to timing of the SARS-CoV-2 infection. With no previous infection as reference category, the rate ratios for type 1 diabetes associated with prior SARS-CoV-2 infection were 2.62 (95% CI 1.81, 3.78) for infection in the last 30 days and 0.86 (95% CI 0.62, 1.21) for first positive test >30 days earlier. In those younger than 16 years, the corresponding rate ratios were 3.15 (95% CI 2.07, 4.79) and 0.79 (95% CI 0.50, 1.27). COVID-19 vaccination status was not associated with incidence of type 1 diabetes.

Pattern of Testing for COVID-19 in Relation to Type 1 Diabetes Presentation

To investigate if the association of incident diabetes with a first positive test in the last 30 days could be explained by higher testing rates around the date of diagnosis of diabetes, we plotted the dates of all RT-PCR tests (negative or positive) conducted for people with incident type 1 diabetes. As shown in Supplementary Fig. 2 and Fig. 1, there was increased frequency of testing, mostly negative, in the days before and after diagnosis of type 1 diabetes.

Population-Level Incidence Rates of Type 1 Diabetes

Figure 2 shows the observed incidence of type 1 diabetes in the Scottish population younger than 35 years over a 56-day sliding time windows during 2015–2021. The age bands 0–14 years and 15–34 years were used for compatibility with the age bands used for national population estimates. A pattern of peaks and troughs is seen in both age groups, with greater amplitude seen in the 0–14 years age band. To discern underlying patterns requires modeling of seasonality and calendar time effects, as described in the Supplementary Material. Figure 3*A* shows the fitted seasonal effect as the ratio of incidence per week of the year to the average rate, adjusted for calendar time. Incidence peaks in February and September and is lowest in July. Figure 3*B* shows the fitted effect of calendar time from 2015 through 2021 as the ratio of the incidence per day to the average rate,

Table 1—SARS-CoV-2 infection status at or before diagnosis in those diagnosed with type 1 diabetes during follow-up, by age at entry to cohort

	SARS-CoV-2 status, *n* (%)				
Age at entry (years)	No positive test	0–15 days	16–30 days	>30 days	All
0 to <16	592 (93)	14 (2)	10 (2)	19 (3)	635
16 to <35	413 (94)	4 (1)	3 (1)	19 (4)	439
All	1,005 (94)	18 (2)	13 (1)	38 (4)	1,074

Table 2—Rate ratios for new diagnosis of type 1 diabetes associated with time since testing positive for SARS-CoV-2[a]

Effect	No diabetes (n = 11,552,227), n (%)	Incident type 1 (n = 1,074), n (%)	Rate ratio (95% CI)	P value
Male sex	5,806,715 (50)	617 (57)	1.33 (1.17, 1.50)	5×10^{-6}
≥1 dose vaccine[b]	1,375,621 (12)	106 (10)	0.93 (0.73, 1.18)	0.5
Days since first testing positive for SARS-CoV-2[b]				
No positive test	11,006,334 (95)	1,005 (94)		
0–30	106,854 (1)	31 (3)	2.62 (1.81, 3.78)	3×10^{-7}
	439,039 (4)	38 (4)	0.86 (0.62, 1.21)	0.4

[a]Cox regression model with person-time split into 1-day intervals. Person-time intervals with no event thinned to a 1% random sample to reduce computation. Age at entry included in the model as a natural spline with three degrees of freedom. [b]Vaccination and SARS-CoV-2 status were coded as time-updated covariates.

adjusted for seasonality. In those aged 15–34 years, the relationship best supported by the data is a linear increase over 2015–2021. In those aged 0–14 years, the relationship best supported by the data is a curve with year to year variation, with a trough in mid-2019 at 0.9 times the long-term average followed by a rise to a peak in 2021 of 1.2 times the long-term average.

CONCLUSIONS

Principal Findings

The incidence of type 1 diabetes in those aged 0–14 years in Scotland increased during 2020–2021 to about 1.2 times the average over the study period. However, in this age group, incidence varied widely from year to year, with 2019, for example, having 0.9 times the long-term average incidence. In those aged 15–34 years, there was no evidence of an increase in 2020–2021 beyond the long-term upward trend in this age band.

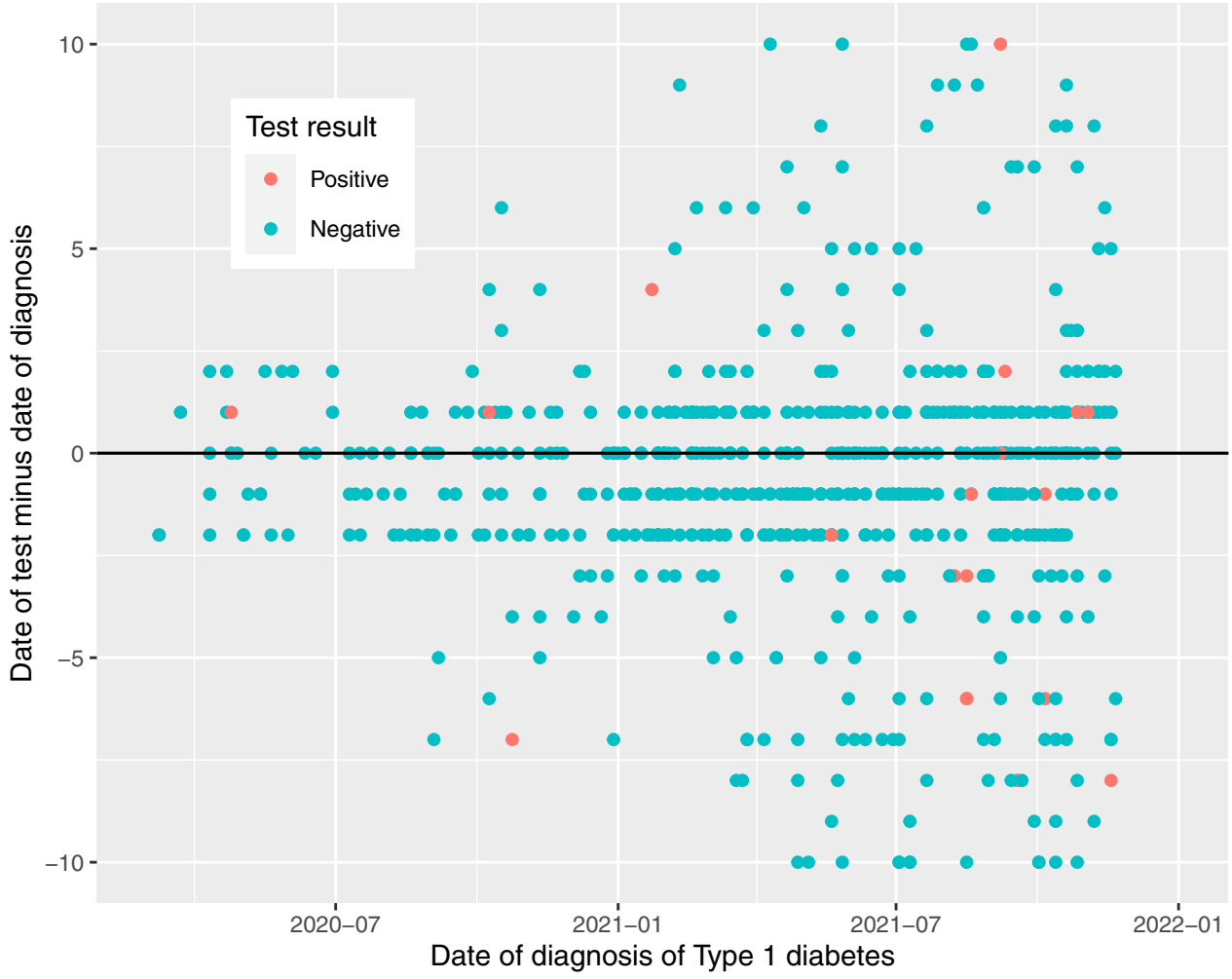

Figure 1—Dates of SARS-CoV-2 PCR tests minus date of diagnosis: zoomed plot from 10 days before to 10 days after date of diagnosis.

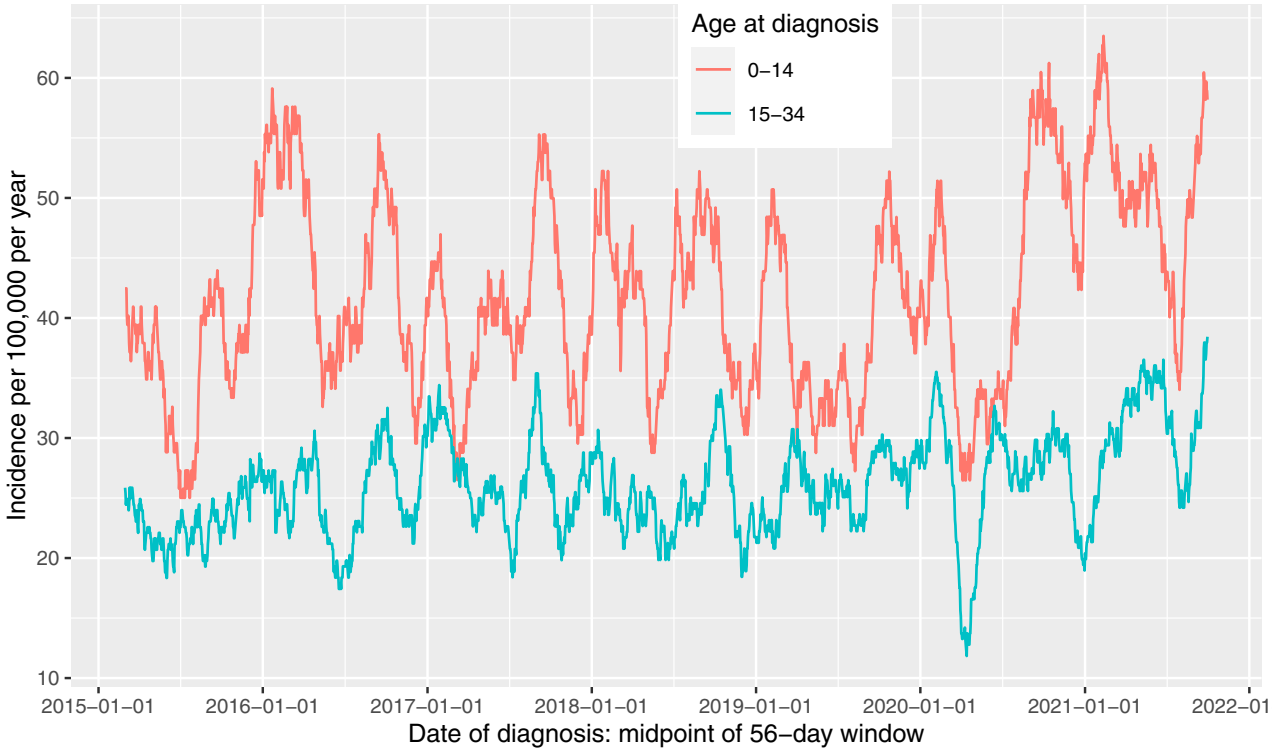

Figure 2—Incidence of type 1 diabetes in Scotland: sliding time windows of a width of 56 days, by age at diagnosis (years).

Using precise dates of diagnosis for type 1 diabetes, we found no association of SARS-CoV-2 infection >30 days previously with type 1 diabetes incidence overall or in those aged <16 years. Thus, our data do not replicate those in the report by the CDC of increased diabetes incidence >30 days after infection. The CDC report did not examine incidence <30 days after infection. We observed a strong association between a first positive SARS-CoV-2 test within the past 30 days and type 1 diabetes in both children and adults.

Infection-induced type 1 diabetes could arise within 30 days, but there are strong arguments against a causal effect of COVID-19 underlying this association. First, the increased frequency of recent negative, as well as positive, SARS-CoV-2 tests around the time of presentation with type 1 diabetes indicates that the association is partly attributable to higher detection of infection through increased testing around the time of presentation with type 1 diabetes.

Second, in England, the median time from onset of symptoms to diagnosis of type 1 diabetes before age 16 years was reported to be 25 days (11). Given this typical lag, it is likely that many of those who tested positive for SARS-CoV-2 <30 days before diagnosis of type 1 diabetes already had diabetes by the time of infection. Some of this association may be attributable to COVID-19 illness causing metabolic decompensation and precipitating diagnosis of incipient type 1 diabetes.

Third, the time course of the increase in incidence of diabetes in those aged 0–14 years predated most of the cumulative incidence of infection in this age group. From recent estimates of the time course of infections with SARS-CoV-2 in the population of England, based on combining multiple data sources (12), the cumulative proportion infected with SARS-CoV-2 in the 0–14 year age group in England was only about 8% up to the end of August 2020; it increased to 25% by the end of June 2021 and then increased more steeply to about 55% by the end of the study period (22 November 2021). No similar estimates have been published for Scotland, but the time course of the epidemic in this age group is likely to be similar to that in England. Thus, if the increase in incidence of type 1 diabetes in this age group had been caused by SARS-CoV-2 infection, most of the increase would have occurred after June 2021. Instead, Fig. 3*B* shows that the increase in incidence began in early 2020 and peaked by June 2021, consistent with the time course of social distancing rather than SARS-CoV-2 infection.

It is also relevant that the effect estimate for vaccination of 0.93 (95% CI 0.73, 1.18) does not provide support for a causal effect of COVID-19 on type 1 diabetes in adults, though power to detect subtle effects of vaccination less extreme than a rate ratio of 0.73 was limited. This effect estimate is based almost entirely on adults, because few children were vaccinated during the study period.

Increased incidence of type 1 diabetes could have several possible explanations other than SARS-CoV-2 infection itself. Of note, the levels of infection with other respiratory viruses has been altered over this period (13,14) and it is plausible that there may be changes in other pathogens, such as enteroviruses, that have been associated with altered risk of type 1 diabetes (15–19). Changes in other environmental factors, such as sunlight exposure and vitamin D levels, might also be relevant (20). It should be noted that the seasonal pattern with a peak in incidence in February and September is the same as previously reported for

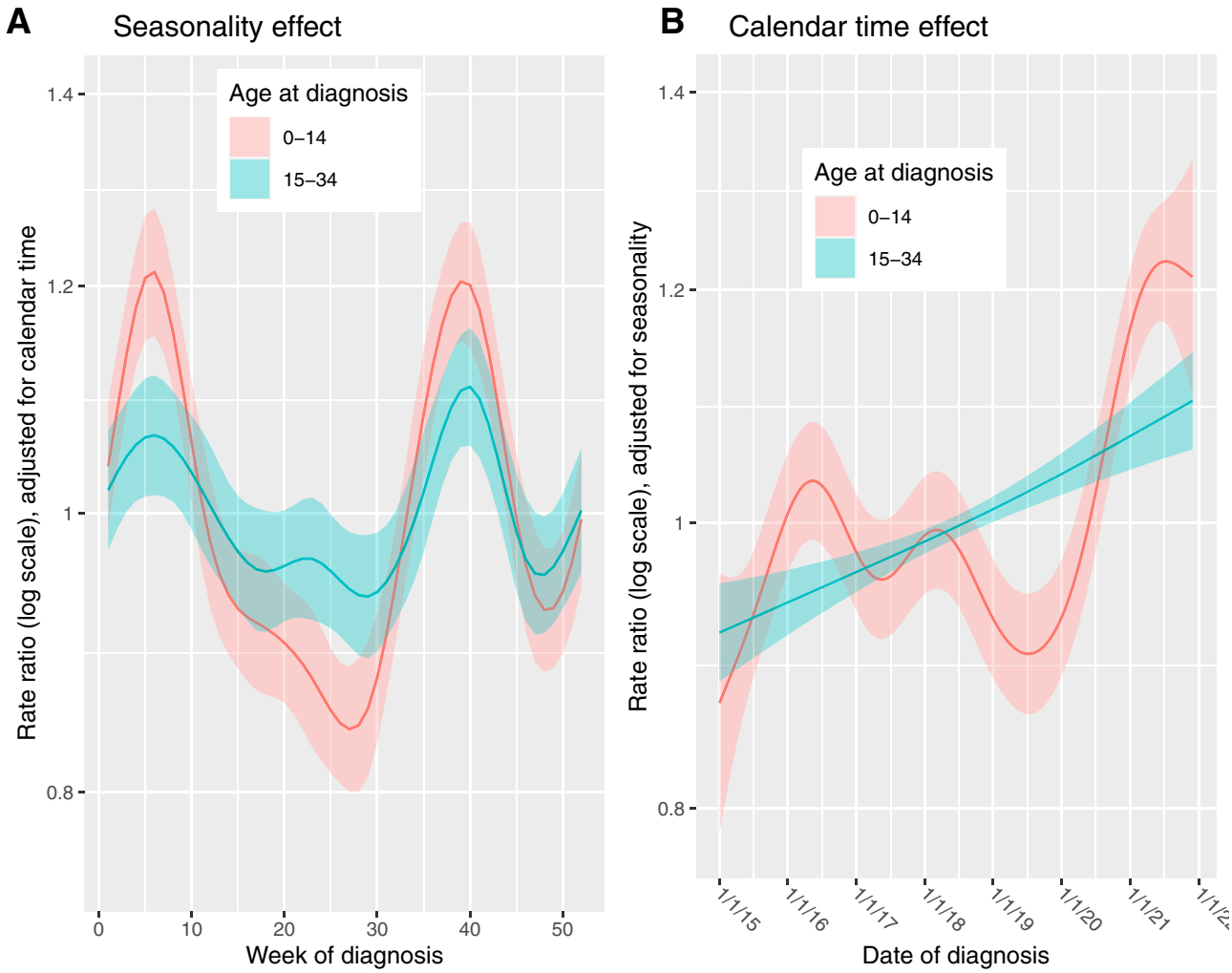

Figure 3—Fitted curves for relation of type 1 diabetes incidence in Scotland to (*A*) seasonality and (*B*) calendar time from 2015 through 2021. Ribbon edges are 1 SE above and below the fitted curve.

Denmark (21), and here we demonstrate it is observed in older-onset as well as childhood-onset type 1 diabetes, though at lower amplitude. It is of interest that the seasonal pattern was maintained during the pandemic despite altered seasonal social-mixing patterns.

Strengths and Limitations

Strengths of this study include the availability of individual-level data, comprehensive national coverage of PCR tests, the inclusion of data on the level of negative testing around the time of presentation, and most importantly, validation of the accuracy of dates of diagnosis of type 1 diabetes in the SCI-diabetes registry against date of first hospitalization for type 1 diabetes in pediatric case patients for whom the policy is to admit all newly diagnosed cases immediately. Limitations are that, because the numbers of incident case patients with type 1 diabetes exposed to SARS-CoV-2 infection were relatively small for formal modeling of the hazard ratio, we had to use fairly broad categories of 0–30 days and >30 days for the exposure period. However, the clustering of negative and positive tests around the date of diagnosis is obvious on inspection of scatter plots. Another limitation common to other studies of this question are that until mass testing was rolled out in the third quarter of 2020, most cases of SARS-CoV-2 in younger people were not detected. However, as noted above, it is estimated that about 85% of infections in children 0–14 years old during the study period occurred after August 2020, by which time mass testing was under way. Misclassification of exposed individuals as unexposed would only slightly reduce the rate ratios for type 1 diabetes associated with detected infection in this age group.

Comparison With Previous Studies

Our results do not confirm the association of incident diabetes before age 18 years with SARS-CoV-2 infection >30 days previously, as reported by the CDC (1). In that study, the rate ratio associated with COVID-19 exposure was estimated as 2.7 in the IQVIA database and 1.3 in the Health Verity database. It is not clear how accurately the date of diagnosis could be determined from these claims databases. The incidence rates of 337 in the IQVIA data set and 351 per 100,000 in the HealthVerity data set are far higher than the most recent incidence rates reported from the SEARCH (SEARCH for Diabetes in Youth Study) registry in the U.S.: 22 per 100,000 for type 1 diabetes in those aged 0–19 years and 5 per 100,000 for type 2

diabetes in those aged 10–19 years (22), and far higher than the rates in Scotland. Some case patients classified as incident in the CDC study on the basis of a first encounter for diabetes had a prior history of diabetic ketoacidosis. These aspects suggest that some prevalent cases may have been misclassified as incident. No other studies, to our knowledge, have directly tested the association at the individual level of SARS-CoV-2 infection with type 1 diabetes onset.

Two studies have reported increased incidence of type 1 diabetes during the pandemic. A cohort study in the Finnish Pediatric Diabetes Registry reported that annual incidence had increased from an average of 39 in the 2016–2019 period to 56 per 100,000 during April–October 2020 (23). Of 84 people with newly diagnosed diabetes during the pandemic who were tested for SARS-CoV-2 IgG, 33 were negative, suggesting a cause other than COVID-19 itself. A Romanian registry also reported a temporal increase of 13.3 per 100,000 in incident type 1 diabetes during the pandemic period compared with 11.0–12.3 per 100,000 for the 2015–2019 period (24). In contrast, authors of studies from Germany (25), Saudi Arabia (26), and Italy (27) found incidence was no higher during the pandemic than before. A recent study of data on U.S. veterans reported an increase in incident diabetes (>99% of which was type 2 diabetes) after COVID-19 infection (28). It would be of interest to establish whether changes in diabetes incidence by country are related to SARS-COV-2 infection rates or to the stringency of social-distancing measures.

Conclusion

We observed during the pandemic a 1.2-fold increase in the incidence of type 1 diabetes in those aged 0–14 years; there are several possible causes for this. In a cohort analysis, incident type 1 diabetes was not associated with SARS-CoV-2 infection >30 days previously; therefore, a causal effect of SARS-CoV-2 is not supported.

Ethics Approval and Data Governance. Approval for use of the diabetes data were provided by the Public Benefit and Privacy Panel (ref. 1617-0147; https://www.informationgovernance.scot.nhs.uk/pbpphsc/) and the West of Scotland Multicentre Research Ethics Committee (ref. 21/WS/0047). The REACT-SCOT study was performed within Public Health Scotland as part of its statutory duty to monitor and investigate public health problems and pandemic response. Under the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/) set out by the NHS Health Research Authority, this does not fall within the definition of research; therefore, ethical review was not required. This has been confirmed in writing by the NHS West of Scotland Research Ethics Service. Individual consent is not required for Public Health Scotland staff to process personal data to perform specific tasks in the public interest that fall within its statutory role. The statutory basis for this is set out in Public Health Scotland's privacy notice.

Funding. No specific funding was received for this study. H.M.C. is supported by an endowed chair from the AXA Research Fund. T.M.C. is supported by Diabetes UK grant 18/0005786. Authors were not precluded from accessing data in the study and they accept responsibility for submitting the article for publication.

Duality of Interest. P.M.M. declares stock ownership in the following: Bayer and Roche Pharmaceuticals. T.M.C. declares grant support from Diabetes UK. S.H.W. declares receiving meeting support from Novo Nordisk. T.M.C. is a trustee of the Edinburgh High Blood Pressure Fund. H.M.C. declares grants from Juvenile Diabetes Research Foundation International and Diabetes UK; meeting support from Eli Lilly and Company, Regeneron, and Sanofi; advisory board fees paid through her institution from Eli Lilly and Company, Regeneron, Sanofi, Astra-Zeneca, Novo Nordisk, and Bayer; and stock ownership in Bayer and Roche. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.M.M. and H.M.C. conceived and designed the study and made the decision to submit the work for publication. H.M.C., S.M., L.B., D.A.M., and S.H.W. contributed to retrieving or pre-processing data for the study. T.M.C. undertook literature searches. L.B. contributed to data interpretation. P.M.M. accessed and analyzed the data. S.N.W. oversaw the time-series modelling. H.M.C. accessed and verified the analysis and wrote the first draft of the manuscript. All authors contributed to reviewing and editing the manuscript for intellectual content. All authors approved the decision to submit. H.M.C. 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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