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ABSTRACT

To analyze the ecological relationship between COVID-19 incidence in the total population and type 1 diabetes (T1D) incidence in children and adolescents, spatiotemporal models were applied considering time lags from 0 to 12 months. The results do not indicate a positive correlation between COVID-19 incidence and T1D incidence.

1. Introduction

When coronavirus disease 2019 (COVID-19) caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic in March 2020, the health effects on children and adolescents were not foreseeable. An unexpected observation in the first months of the COVID-19 pandemic was that the incidence of pediatric type 1 diabetes (T1D) was higher than expected [1–3]. In the case of a causal relationship between SARS-CoV-2 infection and new-onset T1D, spatiotemporal relationships between both diseases should be detectable. In a previous study, we reported that the standardized incidence ratios (SIRs) of T1D and COVID-19 were not correlated in the periods associated with the pandemic waves until June 2022 [4]. However, others have reported a temporal relationship between COVID-19 incidence and pediatric T1D incidence, with a time lag of approximately three months in the general population [5], and an increased T1D incidence in COVID-19-positive children with presymptomatic T1D (median follow-up of 1.0 years) [6]. Therefore, we aimed to investigate the hypothesis that there was a time-lagged association of the COVID-19 pandemic waves with pediatric T1D incidence in Germany.

2. Methods

Nationwide data on new cases of T1D in individuals younger than 20 years were obtained from the German Diabetes Prospective Follow-up Registry [7] for the period from March 2020 to December 2023 (as of May 2024). The T1D cases were aggregated by district, month, year, sex and age at diagnosis (0–4, 5–9, 10–14, 15–19 years). Daily national district-level data on cases with newly detected SARS-CoV-2 infections by polymerase chain reaction for the period March 2020 to December 2022 were aggregated to calendar months and years [8]. Age- and sex-specific population data, geographical polygon data for mapping [9,10], indicators of area deprivation (German Index of Socioeconomic Deprivation [11,12]) and urban–rural typology data [13,14] were obtained at the district level.

To calculate T1D SIRs, district-level T1D incidence rates were

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indirectly age- and sex-standardized, with age- and sex-specific national T1D incidence rates over the period from March 2020 to December 2022 used as the reference rates. To calculate COVID-19 SIRs, district-level COVID-19 incidence rates were indirectly standardized, with the nationwide COVID-19 incidence over the same period used as the reference rate.

Partial Spearman correlation analyses and Bayesian spatiotemporal conditional autoregressive (CAR) Poisson models [4,15] were used to estimate the association between the COVID-19 SIR and the risk of subsequent T1D. Analyses were applied to cross-classified data from districts (n = 400) and one-month periods (n = 34) (for a total of n = 13,600 data points), allowing for time lags between the COVID-19 SIR and the T1D SIR of 0–12 months. All analyses were adjusted for area deprivation quintiles, the urban–rural typology of districts (predominantly rural regions, intermediate regions, and predominantly urban regions), and the geographical longitude and latitude of district centroids. A Bonferroni correction was applied to adjust for multiple inference. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.2 [16].

3. Results

Between March 2020 and December 2022 [December 2023], 12,073 [15,421] 0- to 19-year-olds with newly diagnosed T1D were identified. The T1D incidence showed a wave-like change during the pandemic, with a peak in 2021. The crude incidence per 100,000 person-years increased from 25.6 (95 % confidence interval [CI]: 24.7; 26.4) in 2020 to 28.9 (28.0; 29.7) in 2021 and then decreased to 27.4 (26.6; 28.2) in 2022 and to 21.1 (20.4; 21.8) in 2023. In contrast, the incidence of COVID-19 in the total population sharply increased in 2022: the crude incidence per 1,000 person-years increased from 25.2 (25.2; 25.3) in 2020 to 358.0 (357.8; 358.1) in 2022 (Supplemental Table S1). In Germany, a total of 37.4 million cases were documented to have COVID-19 from March 2020 to December 2022.

The descriptive evaluation of the spatiotemporal distribution by calendar month revealed no relevant temporal correlation between the COVID-19 SIR and the T1D SIR (Fig. 1), nor did the choropleth maps (Supplemental Fig. S1) or the scatterplot (Supplemental Fig. S2).

Partial Spearman correlation analyses revealed no significant association between the T1D SIR and the COVID-19 SIR for time lags of 0–7 months. For time lags of 8–12 months, a weak, albeit significant, inverse correlation was estimated. The spatiotemporal CAR models revealed no significant changes in the T1D SIR per doubling of the COVID-19 SIR for time lags of 0–6 months and a reduced T1D risk for time lags of 7–12 months (Table 1). However, when analyses were additionally adjusted for calendar year, a weak significant association remained only for time lags of 10 and 11 months and only in the partial Spearman correlation (Supplemental Table S2).

4. Discussion

This study analyzed for the first time the spatiotemporal associations between the waves of the COVID-19 pandemic and the incidence of T1D in children and adolescents, accounting for time lags of up to 12 months between the monthly COVID-19 incidence data and the T1D incidence data. The results provide no evidence of a positive association between T1D incidence and COVID-19 incidence. Our findings are limited by the ecological study design. However, these findings are consistent with the results of cohort studies in which no association between SARS-CoV-2 infection and the risk of developing T1D was found [17,18]. The observed inverse correlation between COVID-19 and T1D SIRs for time lags of 8–12 months was presumably attributable to the decreasing T1D incidence trend from 2021 to 2023. The emergence of rapid tests beginning in February 2021 and changes in regulations for PCR testing may have reduced the ascertainment of COVID-19 cases. However, this limitation can be presumed not to seriously bias the main findings. There is inconsistent evidence for a direct effect of SARS-CoV-2 on the development of islet autoimmunity and T1D, and the increasing incidence rate of T1D may also be the result of secondary effects of the pandemic, such as unfavorable lifestyle changes, social distancing, and psychosocial stress [19,20].

In conclusion, our findings provide no evidence that a causal relationship between COVID-19 incidence rates and T1D incidence rates among children and adolescents is likely.

CRediT authorship contribution statement

Anna Stahl-Pehe: Writing – review & editing, Writing – original draft, Conceptualization. **Christina Baechle:** Writing – review & editing. **Stefanie Lanzinger:** Writing – review & editing. **Clemens Kamrath:** Writing – review & editing. **Oliver Kuß:** Writing – review & editing. **Reinhard W. Holl:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Joachim Rosenbauer:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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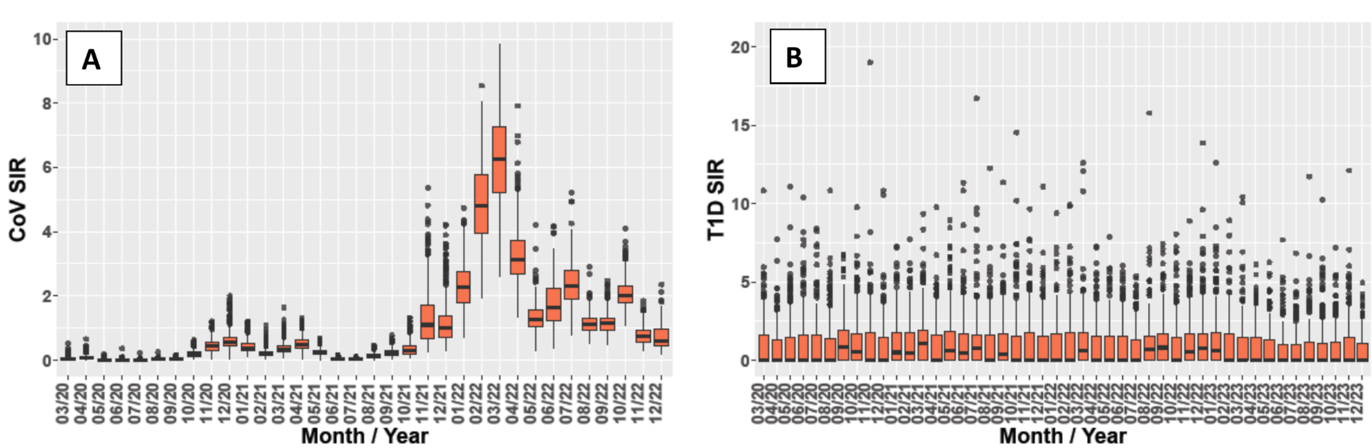

Fig. 1. Boxplots of the spatiotemporal distributions of the coronavirus disease 2019 (COVID-19) standardized incidence ratio (SIR) (A) and type 1 diabetes (T1D) SIR (B) across districts (n = 400) separately by month/year.

Table 1
Partial correlation and Bayesian spatiotemporal conditional autoregressive Poisson models for the associations of the COVID-19 SIR and T1D SIR per district and one-month periods considering time lags.

Period for COVID-19 SIR	Period for type 1 diabetes SIR	Time lag (months)	Partial Spearman correlation coefficient (95 % CI) *	p value *	Spatiotemporal CAR model Relative change in T1D SIR (95 % CI) per doubling of COVID-19 SIR **
03.2020–12.2022	03.2020–12.2022	0	−0.001 (−0.026; 0.024)	1.000	1.002 (0.992; 1.012)
	04.2020–01.2023	1	0.003 (−0.022; 0.028)	1.000	1.002 (0.993; 1.012)
	05.2020–02.2023	2	0.004 (−0.020; 0.029)	1.000	1.003 (0.992; 1.012)
	06.2020–03.2023	3	−0.001 (−0.026; 0.023)	1.000	1.001 (0.991; 1.012)
	07.2020–04.2023	4	−0.007 (−0.032; 0.018)	1.000	0.999 (0.990; 1.008)
	08.2020–05.2023	5	−0.007 (−0.032; 0.018)	1.000	0.999 (0.989; 1.009)
	09.2020–06.2023	6	−0.018 (−0.043; 0.006)	0.409	0.992 (0.993; 1.002)
	10.2020–07.2023	7	−0.018 (−0.043; 0.007)	0.473	**0.988 (0.978; 0.999)**
	11.2020–08.2023	8	**−0.027 (−0.052; −0.002)**	**0.022**	**0.980 (0.969; 0.990)**
	12.2020–09.2023	9	**−0.032 (−0.056; −0.007)**	**0.003**	**0.979 (0.968; 0.988)**
	01.2021–10.2023	10	**−0.041 (−0.065; −0.016)**	**<0.001**	**0.977 (0.967; 0.987)**
	02.2021–11.2023	11	**−0.048 (−0.072; −0.023)**	**<0.001**	**0.976 (0.965; 0.987)**
	03.2021–12.2023	12	**−0.062 (−0.087; −0.037)**	**<0.001**	**0.970 (0.961; 0.980)**

COVID-19: coronavirus disease 2019, T1D: type 1 diabetes, SIR: standardized incidence ratio, CI: confidence interval, CAR model: conditional autoregressive Poisson model. All analyses were adjusted for area deprivation, urban–rural typology, and geographical longitude and latitude of the district centroids.

* 95% confidence intervals and p values were adjusted for multiple inference (13 time lags) according to the Bonferroni method.

** Estimates are posterior medians and Bonferroni-adjusted 95% posterior credible intervals based on 2,000 Markov chain Monte Carlo (MCMC) samples (20,000 burn-in samples, 120,000 additional samples, thinning by 50) resulting from a spatiotemporal Poisson model with Leroux spatial and temporal dependence structure and spatiotemporal interactions (analysis of variance (ANOVA) structure).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111936.

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