Incidence of Type 1 Diabetes in Children and Adolescents During the COVID-19 Pandemic in Germany: Results From the DPV Registry

https://doi.org/10.2337/dc21-0969

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OBJECTIVE

The aim of this study was to investigate the incidence of type 1 diabetes in children and adolescents during the coronavirus disease 2019 (COVID-19) pandemic in Germany compared with previous years.

RESEARCH DESIGN AND METHODS

Based on data from the multicenter German Diabetes Prospective Follow-up Registry, we analyzed the incidence of type 1 diabetes per 100,000 patient-years in children and adolescents from 1 January 2020 through 30 June 2021. Using Poisson regression models, expected incidences for 2020/21 were estimated based on the data from 2011 to 2019 and compared with observed incidences in 2020/21 by estimating incidence rate ratios (IRRs) with 95% CIs.

RESULTS

From 1 January 2020 to 30 June 2021, 5,162 children and adolescents with new-onset type 1 diabetes in Germany were registered. The observed incidence in 2020/21 was significantly higher than the expected incidence (24.4 [95% CI 23.6–25.2] vs. 21.2 [20.5–21.9]; IRR 1.15 [1.10–1.20]; $P < 0.001$). IRRs were significantly elevated in June 2020 (IRR 1.43 [1.07–1.90]; $P = 0.003$), July 2020 (IRR 1.48 [1.12–1.96]; $P < 0.001$), March 2021 (IRR 1.29 [1.01–1.65]; $P = 0.028$), and June 2021 (IRR 1.39 [1.04–1.85]; $P = 0.010$).

CONCLUSIONS

A significant increase in the incidence of type 1 diabetes in children was observed during the COVID-19 pandemic, with a delay in the peak incidence of type 1 diabetes by ~3 months after the peak COVID-19 incidence and also after pandemic containment measures. The underlying causes are yet unknown. However, indirect rather than direct effects of the pandemic are more likely to be the cause.

The rate of new cases of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) increased remarkably during March 2020 and peaked in early April 2020 in Germany (1,2). In response to the pandemic, nationwide health policy measures to achieve social distancing, such as restrictions on social contacts, school closures, and the general recommendation

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Received 6 May 2021 and accepted 16 December 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.17282138.

to stay at home to contain the spread of SARS-CoV-2, were implemented. Thereafter, the incidence of COVID-19 in Germany stabilized at a lower level from June 2020 to September 2020. In early October 2020, however, COVID-19 cases showed another sharp increase in a second wave, with a peak in late December 2020, which was followed by a third wave starting in March 2021 and lasting until June 2021 (1,2).

Type 1 diabetes is a chronic autoimmune disease that is influenced by both genetic and environmental factors (3). The incidence of type 1 diabetes increased by an average annual rate of 3–4% over the past three decades (4). There is evidence for a role of infections in the pathogenesis of type 1 diabetes (5,6). Common respiratory infections in early childhood have been shown to be a risk factor for the development of type 1 diabetes (7–9). Infection with SARS-CoV-2 was suspected to lead to the development of new-onset diabetes in children (10). However, it is not known whether COVID-19 is associated with an increase in the incidence of type 1 diabetes (11,12). On the other hand, efforts to control the COVID-19 pandemic, such as social isolation, led to a marked decrease in common infections in children (13,14), and this could also affect the incidence of type 1 diabetes. It is therefore essential to clarify whether the incidence of type 1 diabetes changed during this pandemic. We have previously shown that there was no increase in the incidence in type 1 diabetes during the first wave of the COVID-19 pandemic in Germany from mid-March to mid-May 2020 (15).

The aim of this study was to extend this analysis with longer follow-up. We therefore investigated the frequency of new-onset type 1 diabetes in children and adolescents during the COVID-19 pandemic in 2020 and the first half of 2021 compared with the years 2011 to 2019 in Germany using a large population-based clinical database.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

This study used data from the DPV (German Diabetes Prospective Follow-up Registry; i.e., Diabetes-Patienten-Verlaufsdokumentation) of children and adolescents living in Germany and aged between 6 months and <18 years at the diagnosis of new-onset type 1 diabetes from 1 January 2020 through 30 June 2021. The control group consisted of 22,987 children and adolescents with new-onset type 1 diabetes in the same age range diagnosed from 2011 to 2019 in Germany. The DPV has a nationwide coverage of >90% of pediatric patients with type 1 diabetes in Germany and comprises 257 pediatric diabetes centers in Germany (16). Twice a year, locally collected longitudinal data are pseudonymized and transmitted for central plausibility checks and analyses to Ulm University, Ulm, Germany. Inconsistent data are reported back to participating centers for validation and/or correction. Data are then completely anonymized for analysis. Verbal or written informed consent for participation in the DPV was obtained from patients or their guardians. The ethics committee of Ulm University in Ulm, Germany, approved the analysis of anonymized data from the DPV. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies.

The severity of the COVID-19 pandemic was measured as the weekly incidence rates of new COVID-19 cases per 100,000 population. In accordance with the international standards of the World Health Organization, all laboratory confirmations of SARS-CoV-2, irrespective of the presence or severity of clinical symptoms, were considered as COVID-19 cases. The incidence of confirmed COVID-19 cases was derived from the official statistics of the Robert Koch Institute, Berlin, Germany (17); the population data were taken from the German Federal Statistical Office (18).

The Stringency index, which is a composite index containing nine indicators of containment and closure policies, originated from the Oxford Covid-19 Government Response Tracker (OxCGRT) (19).

Variables

Demographic data included year, month (and additionally week for 2018 to 2020/21 data), and age at diabetes onset, sex, and immigrant background (patient or at least one parent born outside of Germany). Clinical data from diabetes onset included BMI (calculated as weight in kilograms divided by height in meters squared), HbA_{1c} (% [mmol/mol]), and presence of autoantibodies. BMI values were transformed to SD scores based on German reference values (KiGGS [German Health Interview and Examination Survey for Children and Adolescents]) by applying the Box-Cox transformation method (20). In order to adjust for different laboratory methods, local HbA_{1c} values were mathematically standardized to the DCCT (Diabetes Control and Complications Trial) reference range (4.05–6.05%) using the multiple of the mean transformation method. Autoantibody measurements included autoantibodies against islet cells, glutamic acid decarboxylase, tyrosine phosphatase, insulin, and zinc transporter 8. Positive autoantibody status was defined as any measure of these autoantibodies above the upper limit of normal, according to the reference values of the respective laboratory of the treating center, at the diagnosis of diabetes.

We analyzed the incidence of type 1 diabetes for the whole period from 1 January 2020 to 30 June 2021, separately for the year 2020 and the first half of the year 2021, as well as for five different periods related to the activity of the COVID-19 pandemic: the prepandemic period, consisting of January and February 2020; the first wave of the pandemic, consisting of March to May 2020; a stable phase with a relatively low rate of new infections from June to September 2020; the second wave from October 2020 to February 2021; and the third wave from March 2021 the end of June 2021 (1). Furthermore, we examined the incidence of type 1 diabetes by month from January 2020 to June 2021.

Statistical Analysis

Medians and interquartile ranges (IQRs) are provided for the description of continuous variables, and frequencies and percentages are used for the description of categorical variables. For each timeframe analyzed (total period from January 2020 to June 2021, calendar years, the first halves of calendar years, COVID-19–related periods, or months), we related the number of new cases to the respective number of person-years at risk to estimate the incidence per 100,000 person-years with 95% CIs.

For the analysis of the incidence by calendar year, we applied a multivariable Poisson trend regression model

(model 1) to incidence data from 2011 to 2019 that included year at diabetes onset (as continuous term), age group at diabetes onset (6 months to <6 years, 6 to <12 years, and 12 to <18 years), and sex as independent variables. Based on this trend model, we estimated the expected incidence for 2011 to 2020/21, standardized for age group and sex, with the sum of person-years of each year between 2011 and 2020 as reference distribution.

We used a respective model with year at diabetes onset included as a categorical independent term (model 2) to estimate incidences for 2011 to 2019, standardized for age group and sex, using the same reference distribution of person-years at risk. Furthermore, we applied a multivariable Poisson regression model that included age group and sex as independent variables (model 3) to adjust the observed incidence in 2020/21 to the same reference distributions of the person-years at risk. Finally, a Poisson regression model that included a binary variable indicating observed and predicted data as independent variables (model 4) was used to compare the observed with the expected incidence of type 1 diabetes. The ratio between the observed and expected incidence of type 1 diabetes was presented as adjusted incidence rate ratio (IRR), with the corresponding 95% CIs and two-sided *P* values from the Wald test. CIs of observed and expected incidences in strata were adjusted for multiple inferences according to the Bonferroni procedure. CIs for estimated period/month-specific IRRs were adjusted for multiple inferences according to the Bonferroni procedure, and corresponding *P* values were adjusted for multiple testing using the Bonferroni-Holm method.

Furthermore, we analyzed the incidence data stratified by age group and sex, applying the same statistical approach (with necessary adaptations).

To analyze incidence data by period (January to February 2020, March to May 2020, June to September 2020, October 2020 to February 2021, and March to June 2021) or month (January 2020 to June 2021), the Poisson regression models described before were extended appropriately. For period-specific or month-specific analyses, models 1 and 2 were extended to include the period or month of diabetes onset and a term for an interaction of period or month at diabetes onset by year at diabetes onset. Model 3 was extended to include only period or month of diabetes onset. Model 4 additionally included a term for interaction of the binary variable indicating observed and predicted data and period or month.

Furthermore, rates of autoantibody negativity in patients with newly diagnosed type 1 diabetes in 2020/21 were compared with those in 2018 and 2019 via multivariable log-binomial regression, adjusted for age group, sex, and immigrant background and additionally for number of measured antibodies in cases of autoantibody negativity. The analysis of autoantibody negativity was performed for the whole period from January 2020 to June 2021 versus 2018/2019, total calendar years, for the first halves of the years, and stratified by periods based on the total onset cohorts.

Differences in frequencies of autoantibody negativity were presented as adjusted absolute percentage differences with the corresponding 95% CIs.

A two-sided *P* value <0.05 was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Data and Resource Availability

Access to the data is possible by remote data processing upon request and approval from the DPV board.

RESULTS

Study Cohort

In the period from 1 January 2020 to 30 June 2021, the DPV registered 5,162 children and adolescents (55.8% male) with new-onset type 1 diabetes from 236 diabetes centers in Germany, 3,338 patients from 2020 and 1,824 patients from the first half of 2021. The median age of the cohort was 9.7 years (IQR 5.9–12.8). The median HbA_{1c} level was 11.4% (IQR 9.9–13.1 [101.3 mmol/mol (84.8–119.6)]).

Table 1 provides a descriptive overview of the 2020/21 study population and a comparison with the 2018–2019 cohort. We compared the weekly numbers of cases of children and adolescents with new-onset type 1 diabetes in 2020 and the first half of 2021 with those of the 2 previous years. Figure 1 shows the weekly cumulative case numbers for each year. An increase in the case numbers in the years 2020 and 2021 compared with the years 2019 and 2018 is evident onward from calendar week 20 in 2020 and week 11 in 2021, respectively.

Annual Change in Incidence of Type 1 Diabetes From 2011 to 2019

From 2011 to 2019, the incidence of type 1 diabetes increased by 2.4% per year (95% CI 1.9–2.9; $P < 0.001$) (Fig. 2). This increase was higher in male than in female participants (male, 2.7% per year [95% CI 2.0–3.4]; $P < 0.001$ and female, 2.0% per year [95% CI 1.2–2.7]; $P < 0.001$). The increase in the incidence of type 1 diabetes between 2011 and 2019 was most pronounced among adolescents aged 12–17 years (4.3% per year [95% CI, 3.4–5.2]; $P < 0.001$), lower in those aged 6–11 years (1.7% per year [95% CI 0.9–2.5]; $P < 0.001$), and lowest in children aged <6 years (1.1% per year [95% CI 0.1 to 2.1]; $P = 0.033$).

Observed Compared With Expected Incidence of Type 1 Diabetes in 2020/21

For the period from 1 January 2020 through 30 June 2021, the observed incidence was 24.4 (95% CI 23.6–25.2). This observed incidence was significantly higher than the expected incidence of 21.2 (95% CI 20.5–21.9); the corresponding IRR was 1.15 (95% CI 1.10–1.20; $P < 0.001$) (Table 2). The IRR was similar for both sexes (female, 1.14 [95% CI 1.07–1.21]; $P < 0.001$ and male, 1.16 [95% CI 1.10–1.23]; $P < 0.001$) (Table 2).

The increase in the observed compared with the expected incidence in 2020/21 was significant in the age groups of children aged <6 years (IRR 1.23 [95% CI 1.13–1.33]; $P < 0.001$) and 6–11 years (IRR 1.18 [95% CI 1.11–1.26]; $P < 0.001$), while no significant increase could be detected in adolescents aged 12–17 years (IRR 1.06 [95% CI 0.98–1.13]; $P = 0.13$) (Table 2).

Separately for 2020 and for the first half of 2021, the observed incidences (23.7 [95% CI 22.8–24.6] and 25.8 [24.4–27.2], respectively) were each significantly higher than the expected incidences (20.9 [20.0–21.8] and 21.8 [20.5–23.1], respectively), with IRRs of 1.13 (1.08–1.19; $P < 0.001$) and 1.18

Table 1—Characteristics of patients with new-onset type 1 diabetes from 2020 and first half of 2021 and from 2018 and 2019

Variable	2020/21 (n = 5,162)	2018 (n = 2,740)	2019 (n = 2,903)
Median age at diabetes diagnosis (IQR), years	9.7 (5.9–12.8)	9.8 (6.0–13.1)	9.7 (5.9–12.9)
Male sex, %	55.8	55.0	54.9
Median HbA_{1c} at diabetes diagnosis (IQR), % [mmol/mol]	11.4 (9.9–13.1) [101.3 (84.8–119.6)]	11.0 (9.5–12.7) [97.2 (80.7–115.6)]	11.2 (9.7–12.9) [98.3 (82.7–117.4)]
Median BMI at diabetes diagnosis (IQR), SD score	−0.25 (−1.10 to 0.56)	−0.31 (−1.11 to 0.53)	−0.24 (−1.10 to 0.59)
Immigrant background, %	26.0	25.8	27.3

For the demonstration of the demographic and clinical data, the cohort of 2020/21 was compared with children and adolescents aged between 6 months and <18 years at the diagnosis of type 1 diabetes in the 2 previous years 2019 and 2018 in Germany.

(1.10–1.27; $P < 0.001$), respectively (Fig. 2 and Table 2).

Observed Compared With Expected Incidence of Type 1 Diabetes by Different Pandemic-Related Periods or Months in 2020/21

An analysis of the observed and expected incidences of type 1 diabetes in the five different periods related to the activity of the COVID-19 pandemic revealed a significantly higher observed than expected incidence in summer 2020 from June to September 2020 (IRR 1.27 [95% CI 1.13–1.43]; $P < 0.001$) and in spring 2021 from March to June 2021 (IRR 1.27 [1.13–1.42]; $P < 0.001$) (Fig. 3 and Supplementary Fig. 1). Stratified by age group, we found a significantly higher observed than expected incidence from June to September 2020 and from March to June 2021 for the children aged <12 years, while for adolescents aged 12–17 years, the observed incidence was only higher than the expected in the period from June to September 2020 (Table 2).

Figure 4 shows the monthly IRRs with the corresponding 95% CIs. Compared with the expected monthly incidence, the observed incidence was significantly higher in June 2020 (IRR 1.43 [95% CI 1.07–1.90]; $P = 0.003$), July 2020 (IRR 1.48 [1.12–1.96]; $P < 0.001$), March 2021 (IRR 1.29 [1.01–1.65]; $P = 0.028$), and June 2021 (IRR 1.39 [1.04–1.85]; $P = 0.010$). Supplementary Table 1 provides the observed and expected incidences by month from January 2020 to June 2021 and the corresponding IRRs. Compared with the 7-day incidence of COVID-19 cases, COVID-19–related deaths, and the Stringency index as a measure of the pandemic containment measures presented in Supplementary Fig. 2, the increase in the incidence of type 1 diabetes followed the peak incidences of the pandemic and the countermeasures taken to control it by ∼3 months.

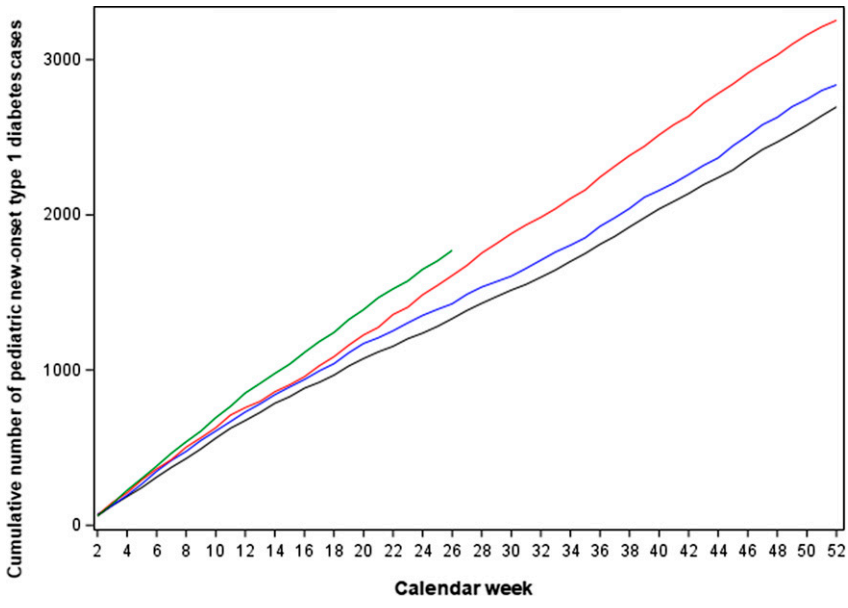

Figure 1—Cumulative number of new cases of type 1 diabetes in children and adolescents in Germany over the years 2018 (black), 2019 (blue), and 2020 (red) and the first half of 2021 (green). Week-specific information on the time of diabetes onset was missing for seven patients in 2021, 12 patients in 2020, and nine patients in 2019 and 16 patients in 2018. These patients were not included in the illustration.

Autoantibody Negativity in 2020/21 Compared With 2018–2019

Data of autoantibody measurements were available in 3,851 (74.6%) of 5,162 patients in 2020 and the first half of 2021 and in 4,205 (74.5%) of 5,643 patients in 2018 and 2019. For the period from 1 January 2020 through 30 June 2021, the adjusted rates of autoantibody negativity did not differ from 2018 and 2019 (2020/21 vs. 2018/19, 6.1% [95% CI 5.3–7.0] vs. 6.4% [5.7–7.3]; absolute difference 2020/21 vs. 2018/19, −0.3% [−1.1 to 0.6]; $P = 0.47$). In addition, separately for the year 2020 and for the first half of 2021, the adjusted rates of autoantibody negativity did not differ from 2018 and 2019 (difference 2020 vs. 2018/19, −0.5% [−1.5 to 0.5]; $P = 0.32$ and difference first halves of 2021 vs. 2018/19, −0.2% [−1.5 to 1.2]; $P = 0.83$).

Moreover, during both periods with an increased incidence of type 1 diabetes, there was also no significant difference for the adjusted rate of autoantibody negativity (absolute difference June to September 2020 vs. June to September 2018/19, 0.7% [95% CI −1.0 to 2.4]; $P = 0.40$ and absolute difference February to June 2021 vs. February to June 2018/19, −0.1% [−1.7 to 1.6]; $P = 0.95$).

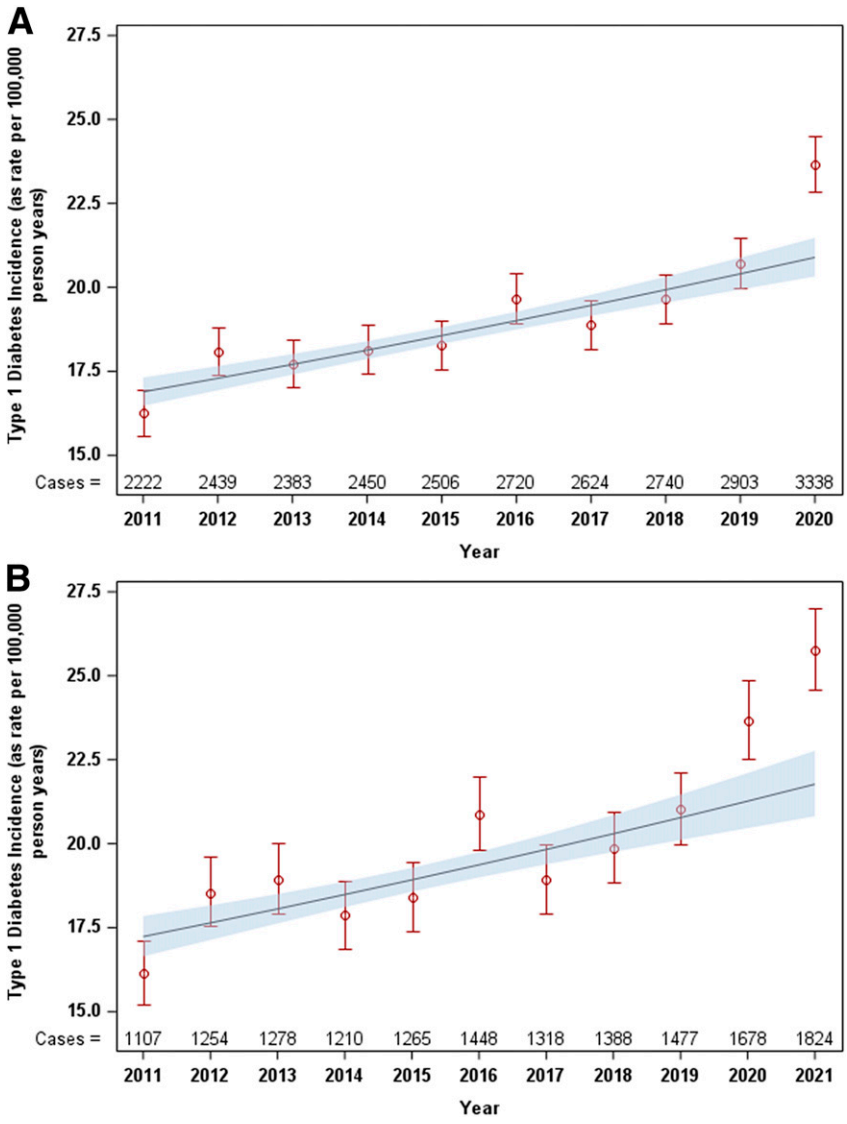

Figure 2—Incidence of type 1 diabetes in children in the year 2020 (A) and the first half of 2020 and 2021 (B) compared with the years 2011 to 2019. Based on a multivariable Poisson trend regression model on data from 2011 to 2019 that included year at diabetes onset (as continuous term), age group at diabetes onset, and sex as independent variables, the expected incidence (as rate per 100,000 person-years) for 2011 to 2020, as well for the first half of the years 2011 to 2021, standardized for age group and sex, with the sum of person-years of each year between 2011 and 2020/21 as reference distribution, was estimated (dark blue line with corresponding 95% CI ([ight blue area]). A multivariable Poisson regression model with year at diabetes onset included as categorical independent term was used to estimate incidences for 2011 to 2019 standardized for age group and sex using the same reference distribution of person-years at risk (red circles). Furthermore, a multivariable Poisson regression model that included age group and sex as independent variables was applied to adjust the observed incidence in 2020 and the first half in 2021 to the same reference distributions of the person-years at risk (red circles). The vertical bars indicate the corresponding 95% CIs of the estimated observed incidences. The number of children registered in DPV with new-onset type 1 diabetes is presented for every year from 2011 to 2020 (A) and for every first half of the years 2011 to 2021 (B).

CONCLUSIONS

This population-based study found an increase in the observed versus expected incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic. The peak incidence of type 1 diabetes followed the peak incidence of COVID-19 and also the pandemic containment measures by ∼3 months. Except for the increase in March 2021, the increase in the incidence of type 1 diabetes was mainly due to the lack of a seasonal decline during the summer months.

Reports from diabetes registries in Norway (21) and Austria (22) indicate that the incidence of type 1 diabetes in children aged <15 years stopped rising from 2004 to 2012 and from 2012 to 2017, respectively, especially in young children. In contrast, our study shows a preserved increase in the incidence of type 1 diabetes in childhood between 2011 and 2019. Consistent with the studies from Norway and Austria mentioned above, the increase declined with decreasing age at diabetes onset. In contrast to this trend in recent years, the most pronounced increase of incidence of type 1 diabetes during the COVID-19 pandemic was observed in this youngest age group.

The results of this study are different from those presented in a previous short communication from our group, demonstrating no increase in type 1 diabetes incidence during the first wave of the COVID-19 pandemic (15). However, this is not a contradiction. The previous observation interval was limited to the first 2 months of the pandemic and the lockdown from mid-March to mid-May (calendar week 20). As this extension of the observation period shows, the incidence increased just after the end of the previous observation period. This also demonstrates the importance of monitoring the course of the pandemic in the longer term.

Our study is consistent with the results of a smaller study from Finland (23). In this study, children with new-onset type 1 diabetes from 1 April to 31 October from 2016 to 2020 in the Helsinki University Hospital were analyzed. During the pandemic period, 84 children with newly diagnosed type 1 diabetes were registered, as compared with 53–62 children each year in the prepandemic periods of 2016 to 2019. As in our study, the most significant increase in the number of cases occurred in the 2 summer months of June and July 2020. Importantly, all 33 children diagnosed in 2020 who were tested for SARS-CoV-2 antibodies were negative. In contrast to this report and our results, a study involving 13 pediatric diabetes centers in Lombardy, Italy, found no significant increase in the incidence of type 1 diabetes in 2020 compared with 2019 (24). The reported new case number of 256 in 2020 was not significantly

Table 2—Observed versus expected incidence of type 1 diabetes (per 100,000 person-years) during year 2020 and first half of 2021, as well as during both periods with increased observed incidence

	Observed incidence in 2020/21 (95% CI)	Expected incidence for 2020/21 based on data from 2011–2019 (95% CI)	IRR for observed vs. expected incidence (95% CI)	*P*
1 January 2020 to 30 June 2021*				
All patients	24.4 (23.6–25.2)	21.2 (20.5–21.9)	1.15 (1.10–1.20)	**<0.001**
Male patients	26.6 (25.5–27.8)	22.9 (21.9–24.0)	1.16 (1.10–1.23)	**<0.001**
Female patients	21.9 (20.9–23.0)	19.2 (18.2–20.2)	1.14 (1.07–1.21)	**<0.001**
Aged <6 years	18.6 (17.5–19.8)	15.1 (14.1–16.2)	1.23 (1.13–1.33)	**<0.001**
Aged 6–11 years	32.7 (31.2–34.3)	27.7 (26.3–29.2)	1.18 (1.11–1.26)	**<0.001**
Aged 12–17 years	23.5 (22.2–24.8)	22.2 (21.0–23.5)	1.06 (0.98–1.13)	0.13
Year 2020*				
All patients	23.7 (22.8–24.6)	20.9 (20.0–21.8)	1.13 (1.08–1.19)	**<0.001**
Male patients	25.7 (24.3–27.0)	22.6 (21.4–23.9)	1.13 (1.06–1.21)	**<0.001**
Female patients	21.5 (20.3–22.8)	18.9 (17.7–20.1)	1.14 (1.06–1.23)	**<0.001**
Aged <6 years	17.8 (16.5–19.2)	15.2 (14.0–16.5)	1.17 (1.06–1.30)	**0.002**
Aged 6–11 years	31.4 (29.6–33.4)	27.3 (25.6–29.1)	1.15 (1.07–1.24)	**<0.001**
Aged 12–17 years	23.4 (21.8–25.1)	21.5 (20.1–23.2)	1.09 (1.00–1.19)	0.06
First half of year 2021*				
All patients	25.8 (24.4–27.2)	21.8 (20.5–23.1)	1.18 (1.10–1.27)	**<0.001**
Male patients	28.6 (26.6–30.6)	23.5 (21.7–25.4)	1.22 (1.11–1.33)	**<0.001**
Female patients	22.8 (21.0–24.7)	19.8 (18.1–21.6)	1.15 (1.04–1.28)	**0.008**
Aged <6 years	20.2 (18.2–22.4)	15.0 (13.4–16.9)	1.34 (1.17–1.54)	**<0.001**
Aged 6–11 years	35.4 (32.7–38.3)	28.4 (26.0–31.1)	1.24 (1.12–1.38)	**<0.001**
Aged 12–17 years	23.6 (21.4–26.0)	23.6 (21.4–26.0)	1.00 (0.89–1.13)	0.96
Period with increased incidence of type 1 diabetes in 2020 (June 2020 to September 2020)†				
All patients	24.0 (22.0–26.1)	18.9 (17.2–20.8)	1.27 (1.13–1.43)	**<0.001**
Male patients	25.4 (22.7–28.5)	20.6 (18.1–23.4)	1.23 (1.05–1.44)	**0.002**
Female patients	22.4 (19.8–25.4)	16.9 (14.7–19.6)	1.33 (1.11–1.58)	**<0.001**
Aged <6 years	17.8 (15.1–21.0)	13.2 (10.8–16.0)	1.35 (1.07–1.71)	**0.004**
Aged 6–11 years	32.6 (28.7–37.1)	25.9 (22.4–29.8)	1.26 (1.06–1.50)	**0.003**
Aged 12–17 years	23.5 (20.2–27.3)	19.0 (16.1–22.5)	1.23 (1.00–1.51)	**0.043**
Period with increased incidence of type 1 diabetes in 2021 (March 2021 to June 2021)†				
All patients	25.5 (23.5–27.7)	20.2 (18.4–22.1)	1.27 (1.13–1.42)	**<0.001**
Male patients	28.8 (25.9–32.1)	21.7 (19.2–24.6)	1.33 (1.14–1.55)	**<0.001**
Female patients	22.1 (19.5–25.1)	18.4 (16.0–21.1)	1.20 (1.01–1.43)	**0.023**
Aged <6 years	20.6 (17.6–24.0)	14.1 (11.7–17.0)	1.46 (1.17–1.83)	**<0.001**
Aged 6–11 years	34.0 (30.0–38.5)	26.2 (22.8–30.2)	1.30 (1.09–1.54)	**<0.001**
Aged 12–17 years	23.4 (20.2–27.2)	21.6 (18.5–25.2)	1.09 (0.89–1.32)	1.00

Using Poisson regression models, expected incidences for 2020 were estimated based on the data from 2011 to 2019 and compared with observed incidences in 2020 by estimating IRRs with 95% CIs and two-sided *P* values. Incidences are presented as rate per 100,000 person-years with corresponding 95% CIs. Bold font indicates significance. *CIs of observed and expected incidences were adjusted for multiple inferences using the Bonferroni method separately for each stratum. †CIs of observed and expected incidences and CIs of IRRs were adjusted for multiple inferences using the Bonferroni method, and *P* values were adjusted for multiple testing using the Bonferroni-Holm method.

higher than the 231 cases in 2019, but significantly higher than 216 and 202 new cases in 2018 and 2017, respectively. However, the number of cases was to small and the time trend analysis too short to draw clear conclusions. Some other studies with fewer patients showed inconsistent results regarding a change in the incidence of pediatric type 1 diabetes during the pandemic (10,25–28). Supplementary Table 2 gives an overview of studies on incidence or number of cases of pediatric new-onset type 1 diabetes during the COVID-19 pandemic compared with previous years.

A temporal association of the increased incidence of type 1 diabetes following the peak incidences of COVID-19 may be due to direct effects resulting from infections with SARS-CoV-2, but also to indirect effects resulting from the consequence of environmental changes caused by the pandemic itself or by pandemic containment measures.

In the case of direct effects, cytotoxic as well as immunologic effects could cause β-cell impairment. SARS-CoV-2 was suggested to cause diabetes through direct cytotoxicity of β-cells without autoimmunity (29). However, histopathologic studies showed conflicting evidence of whether SARS-CoV-2 directly affects pancreatic β-cells (30–33). In addition, this study found no increase in the frequency of autoantibody-negative type 1 diabetes in children and adolescents during those

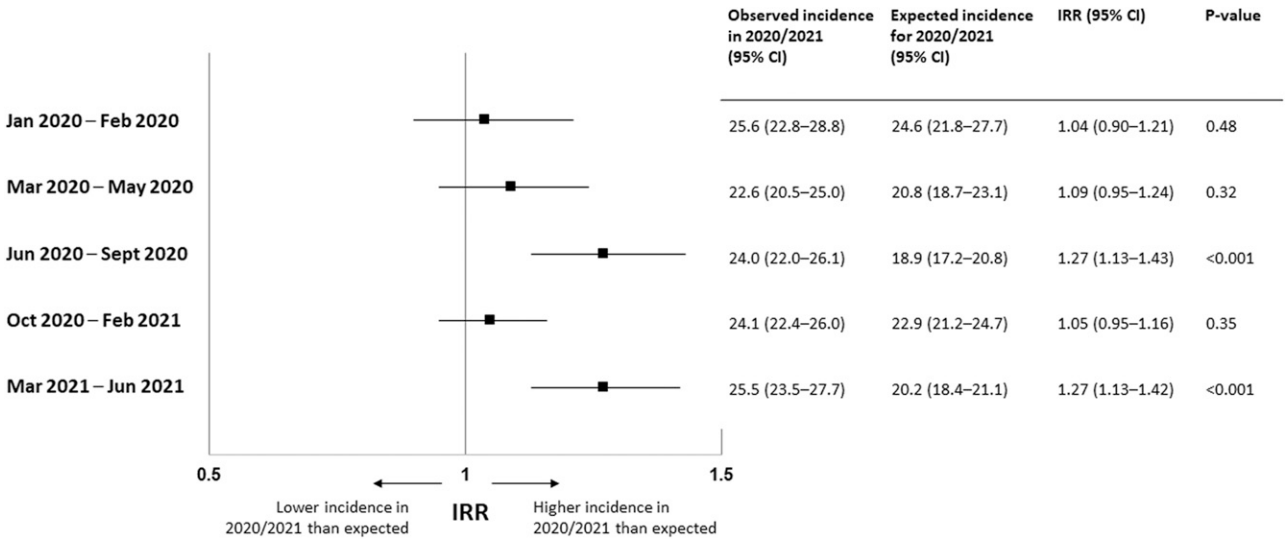

Figure 3—IRRs of observed versus expected incidence of type 1 diabetes in children and adolescents from January 2020 to June 2021 by different pandemic-related periods. Error bars indicate 95% CIs. For period-specific analyses, statistical models were extended to include the period of diabetes onset and a term for an interaction of period at diabetes onset by year at diabetes onset. A Poisson regression model that included a binary variable indicating observed and predicted data and period as independent variables was used to compare the adjusted observed with the adjusted expected incidence of type 1 diabetes. Confidence limits of IRRs and *P* values were adjusted for multiple testing using the Bonferroni and Bonferroni-Holm methods, respectively.

periods, for which an increased observed versus expected incidence of type 1 diabetes has been demonstrated. This is consistent with a previous detailed analysis of the first half of 2020 (34). Therefore, the increase in the incidence of type 1 diabetes in children appears to be due to immune-mediated type 1 diabetes. However, because autoimmunity and progressive β-cell destruction typically begin long before the clinical diagnosis of type 1 diabetes, we were surprised to see the incidence of type 1 diabetes followed the peak incidence of COVID-19 and also the pandemic containment measures by only ∼3 months.

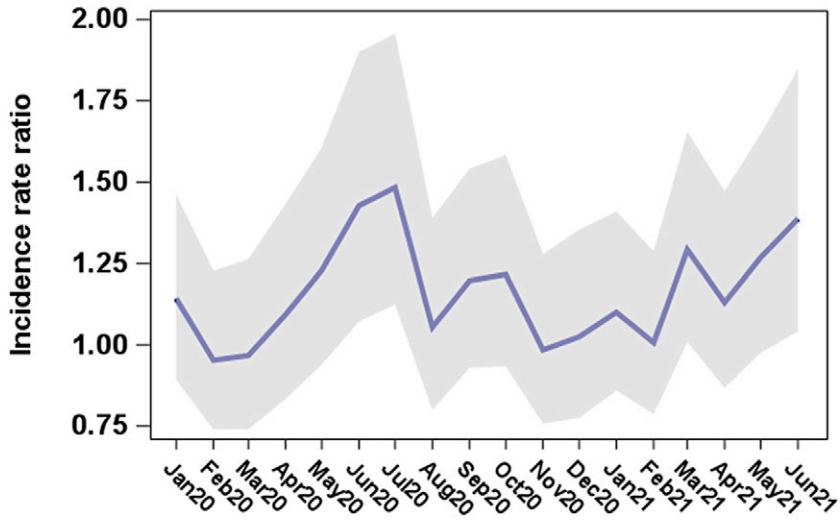

Figure 4—IRRs of observed versus expected incidence of type 1 diabetes in children and adolescents from January 2020 to June 2021 by month. IRRs estimated from trend models are presented as blue line with the corresponding 95% CI as gray area. For month-specific analyses, statistical models were extended to include the month of diabetes onset and a term for an interaction of period at diabetes onset by year at diabetes onset. A Poisson regression model that included a binary variable indicating observed and predicted data and month as independent variables was used to compare the adjusted observed with the adjusted expected incidence of type 1 diabetes. Confidence limits of IRRs and *P* values were adjusted for multiple testing using the Bonferroni and Bonferroni-Holm methods, respectively. IRRs were significantly elevated in June 2020 ($P = 0.003$), July 2020 ($P < 0.001$), March 2021 ($P = 0.028$), and June 2021 ($P = 0.010$).

Considering direct effects of COVID-19, infection with SARS-CoV-2 could trigger the development of new-onset type 1 diabetes in those with prediabetes with islet autoimmunity. Although infection with SARS-CoV-2 is typically very mild and often asymptomatic in children, a rare complication is multisystemic inflammatory syndrome (MIS-C) in children with COVID-19 (35). This hyperinflammatory disorder presents 1–2 months after acute infection with SARS-CoV-2 with high fever, organ dysfunction, markedly elevated inflammatory markers, and formation of multiple autoantibodies. The progress from prediabetes to overt type 1 diabetes could be due to the cytokine storm seen in children after COVID-19, possibly as a different course of MIS-C with a focus on autoimmunity. However, immunologic findings seen in children with MIS-C and with new-onset type 1 diabetes differ (36,37). Unfortunately, sufficient data about the history of COVID-19 infections in children with new-onset type 1 diabetes are currently not available in the DPV. As mentioned above, no evidence of past SARS-CoV-2 infection was found in children with new-onset type 1 diabetes in the Finnish study (23). Furthermore, we found no association between the COVID-19

incidences reported by the authorities and the increase in the observed over the expected incidence of type 1 diabetes in the following months. While numbers of COVID-19 cases were significantly higher in the second wave of the pandemic than in the first wave (1,2), the incidence of type 1 diabetes did not increase more after the second than after the first wave of the COVID-19 pandemic. Moreover, the seroprevalence for anti–SARS-CoV-2 antibodies in children and adolescents in Germany after the first wave of the pandemic was quite low, between 0.6 and 1.1% (38–40).

Considering indirect effects of COVID-19, the impact on type 1 diabetes incidence is not due to infection with SARS-CoV-2, but rather a consequence of environmental changes resulting from the pandemic itself or pandemic containment measures. Attention has been focused on the possibility that changes in lifestyle are a major factor in the rise of type 1 diabetes frequency (41). Because of social isolation, there was a drastic decrease in otherwise frequent and typical pediatric infectious diseases during the pandemic, such as viral respiratory and gastrointestinal tract infections (13,14). Common infections in early childhood have been shown to be a risk factor for the development of type 1 diabetes in children (5–9). This association would suggest a decrease in the incidence of type 1 diabetes. However, the opposite is the case; this study found an increase in the incidence of new-onset type 1 diabetes during the COVID-19 pandemic, despite the marked decrease in common pediatric infections.

It is important to note that infections could also protect against type 1 diabetes. According to the hygiene hypothesis, there is an inverse trend between the occurrence of infectious diseases in early life and the occurrence of autoimmune diseases (42). The biodiversity hypothesis, an extension of the hygiene hypothesis, states that decreased biodiversity in the external and internal exposure increases the risk of immune-mediated diseases (43). Therefore, the influence of environmental exposure on the risk of developing autoimmune diseases is of utmost importance (44). COVID-19 pandemic control efforts changed abruptly social contacts, the behavior of families with children, and child health care practices, which may have resulted in a dramatic decrease in biodiversity in children, particularly in young children (45,46). This change in total environmental exposure, the exposome, could be the link to the increased incidence of type 1 diabetes in young children seen in our study (47,48).

In addition, increased stress from the pandemic itself or social isolation and school closure has been reported in children and adolescents, leading to poorer mental health and a high prevalence of anxiety and depressive symptoms (49–51). Among the environmental variables that play a role in the development of type 1 diabetes, psychological stress has been linked to the onset of the disease, and a wide range of studies point to the role of psychological stressors in the pathogenesis of type 1 diabetes (52–54).

A strength of our study is the population-based data from German children and adolescents. Furthermore, for comparisons with observed incidence, the estimates of the expected incidence in 2020 were derived from appropriate statistical methods, considering the observed increase in the incidence of type 1 diabetes over the past decade. Limitations of our study include that the multivariable Poisson regression model included only some potential confounders. Thus, residual confounding resulting from patient-, area-, and population-level confounders cannot be excluded. Potentially confounding factors include socioeconomic status, history of COVID-19, or family members with COVID-19. In addition, we can only speculate about underlying factors. The analysis relating incidence of type 1 diabetes and occurrence of COVID-19 is an ecologic analysis and thus prone to ecologic bias. However, an analysis of this association using individual-level data could not be performed, because the COVID-19 status of the patients was only available for a small proportion, and a suitable control group of children and adolescents without type 1 diabetes but known COVID-19 status was not available.

Further research is needed to understand the reasons for the increased incidence of type 1 diabetes following the waves of the pandemic and the role of infection with SARS-CoV-2 and also the measures taken to control the COVID-19 pandemic with its consequences, such as social isolation or psychological stress. Additional longer-term studies on the incidence of type 1 diabetes during the pandemic are therefore essential.

In summary, this study found an increase in the incidence of type 1 diabetes in children and adolescents in Germany during the COVID-19 pandemic, with a time lag of ∼3 months to the peak incidences of COVID-19 but also to the pandemic containment measures. The possible causes of this association are manifold and still unclear. However, our results suggest that indirect rather than direct effects of the pandemic are more likely to be the cause.

Acknowledgments. The authors thank A. Hungele and R. Ranz for support and development of the DPV documentation software (clinical data managers, Central Institute of Epidemiology and Medical Biometry [ZIBMT], Ulm University, Ulm, Germany) and Sascha Tittel for help with data analysis. The authors thank all centers participating in the DPV project (a list is available in the data supplement). 2020 data was presented at the ESPE (European Society for Paediatric Endocrinology) online congress 2021.

Funding. The DPV is supported through the German Federal Ministry for Education and Research within the German Centre for Diabetes Research (DZD) (82DZD14A02). Further financial support was received by the German Diabetes Foundation (DDS) (FP-0438-2021), the German Robert Koch Institute (RKI), and the German Diabetes Association (DDG).

The funding organization had no role in design or conduct of the study, collection, management, analysis, or interpretation of the data, preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.K. conceptualized the study, interpreted the analyses, wrote the initial manuscript, and reviewed and revised the manuscript. J.R. analyzed the data, designed and supervised the statistical analysis, and critically reviewed and revised the manuscript. A.J.E. analyzed the data and designed the analyses, contributed to the interpretation of results, and reviewed and revised the manuscript. K.S., H.B., D.K., M.S., S.H. and V.L. collected data, contributed intellectually to the research topics of the DPV initiative, and critically reviewed the scientific content of the manuscript. R.W.H. conceptualized the study, coordinated and supervised data collection, acquired funding for the study, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. A.J.E. and R.W.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the

integrity of the data and the accuracy of the data analysis.

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