Incidence of COVID-19 and Risk of Diabetic Ketoacidosis in New-Onset Type 1 Diabetes

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abstract

OBJECTIVES: With this study, our aim was to quantify the relative risk (RR) of diabetic ketoacidosis at diagnosis of type 1 diabetes during the year 2020 and to assess whether it was associated with the regional incidence of coronavirus disease 2019 (COVID-19) cases and deaths.

METHODS: Multicenter cohort study based on data from the German Diabetes Prospective Follow-up Registry. The monthly RR for ketoacidosis in 2020 was estimated from observed and expected rates in 3238 children with new-onset type 1 diabetes. Expected rates were derived from data from 2000 to 2019 by using a multivariable logistic trend regression model. The association between the regional incidence of COVID-19 and the rate of ketoacidosis was investigated by applying a log-binomial mixed-effects model to weekly data with Germany divided into 5 regions.

RESULTS: The observed versus expected frequency of diabetic ketoacidosis was significantly higher from April to September and in December (mean adjusted RRs, 1.48–1.96). During the first half of 2020, each increase in the regional weekly incidence of COVID-19 by 50 cases or 1 death per 100 000 population was associated with an increase in the RR of diabetic ketoacidosis of 1.40 (95% confidence interval, 1.10–1.77; \( P = .006 \)) and 1.23 (1.14–1.32; \( P < .001 \)), respectively. This association was no longer evident during the second half of 2020.

CONCLUSIONS: These findings suggest that the local severity of the pandemic rather than health policy measures appear to be the main reason for the increase in diabetic ketoacidosis and thus the delayed use of health care during the pandemic.

WHAT'S KNOWN ON THIS SUBJECT: Significant delays in diagnosis and treatment were reported during the coronavirus disease 2019 pandemic, leading to increased rates of diabetic ketoacidosis in children. Temporal associations between delayed hospital presentations or treatment initiations and pandemic containment measures have been reported.

WHAT THIS STUDY ADDS: With this study, we found that the regional 7-day incidence of coronavirus disease 2019 cases and deaths, rather than nationwide pandemic containment measures such as social distancing, were associated with risk of ketoacidosis and in children with new-onset type 1 diabetes.

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread quickly across Europe and America during March and April 2020. Within Germany, however, there were large regional differences in the number of COVID-19 cases and deaths; the south, namely, the federal states of Bavaria and Baden-Württemberg, and the west, namely, North Rhine-Westphalia, of Germany were particularly affected at the beginning of the pandemic. In response to the pandemic, nationwide health policy measures to contain the spread of SARS-CoV-2 were swiftly implemented in Germany to achieve social distancing, such as restrictions on social contacts, school closures, and the general recommendation to stay at home. Although the rates of new cases of COVID-19 increased remarkably during March and peaked in early April, and deaths related to COVID-19 peaked in mid-April in Germany, the rates declined thereafter and stabilized at lower levels in May and June. In early October, however, COVID-19 cases showed another sharp increase in a second COVID-19 wave, with a peak in late December.

The pandemic has also resulted in harm to patients who were not affected by COVID-19. Admissions for health care during the pandemic have markedly declined. As a result, diagnoses were delayed, and diseases were identified at an advanced stage. This delay has been quantified for instance by an increase in the frequency of diabetic ketoacidosis at onset of type 1 diabetes in children and adolescents during the first 2 months of the COVID-19 pandemic in Germany. Ketoacidosis is an acute life-threatening complication of a delayed diagnosis of new onset of type 1 diabetes and could serve as a measure of delayed access to health care.

Our aim of this study was to quantify the relative risk (RR) of diabetic ketoacidosis at diagnosis of type 1 diabetes during the year of 2020 and to assess whether the increased risk was associated with the regional incidence of COVID-19 cases and COVID-19-related deaths. Knowledge of factors leading to a decrease in health care use and to a delay in diagnosis could help to prevent future health risks from non–COVID-19 diseases by taking countermeasures and by improving the resilience of outpatient and inpatient care to sudden massive challenges.

**METHODS**

**Data Source and Study Population**

For this study, we used data from the German Diabetes Prospective Follow-up Registry DPV (Diabetes-Patienten-Verlaufsdocumentation) of children and adolescents aged between 6 months and 18 years living in Germany with the diagnosis of new-onset type 1 diabetes during the year 2020. The control group consisted of 42,417 children and adolescents living in Germany with new-onset type 1 diabetes diagnosed during the years 2000–2019. The DPV registry has a nationwide coverage of >90% of pediatric patients with type 1 diabetes in Germany and comprises 257 pediatric diabetes centers (hospitals and practices) as of March 2021. 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 registry was obtained from patients or their guardians. The ethics committee of Ulm University approved the analysis of anonymized data from the DPV registry. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

The data of the pandemic were taken from the official statistics from the Robert Koch Institute, Berlin, Germany. In accordance with the international standards of the World Health Organization, all laboratory confirmations of SARS-CoV-2, irrespective of the presence and severity of clinical symptoms, were considered as COVID-19 cases.

**Variables**

Demographic data included year, month (additionally week for 2020 data) and age at diabetes onset, sex, and immigrant background (patient or at least 1 parent born outside of Germany).

For regional analysis, Germany was divided into 5 geographical regions: the north, consisting of the federal states of Schleswig-Holstein, Mecklenburg-Western Pomerania, Hamburg, Bremen, and Lower Saxony; the middle, consisting of Saarland, Rhineland-Palatinate, and Hesse; the west, consisting of North Rhine-Westphalia; the east, consisting of Thuringia, Saxony, Saxony-Anhalt, Berlin, and Brandenburg; and the south, consisting of Bavaria and Baden-Württemberg (Fig 1A). Patients were assigned to regions on the basis of their residence at diabetes onset if the information was available, and if this was not the case, they were assigned via the postal code of the first-care clinic.

Diabetic ketoacidosis was defined as a pH level <7.3 and/or a bicarbonate level <15 mmol/L, and severe ketoacidosis was defined as a pH <5.5. 

**Variables**

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level <7.1 and/or bicarbonate level <5mmol/L.14

The severity of the COVID-19 pandemic was measured as the weekly incidence rates of new COVID-19 cases and COVID-19–related deaths per 100 000 population.

**Statistical Modeling**

Median and interquartile range (IQR) are provided for the description of continuous variables, and frequencies and percentages are provided for the description of categorical variables. Continuous or categorical variables were compared among different groups via the Kruskal-Wallis test or the \( \chi^2 \) test, respectively, adjusted for multiple testing by using the Bonferroni-Holm method.

For the selection of possibly confounding variables, we controlled for covariates for which there is evidence for association with the outcome. Immigrant status, younger age, and female sex are known to increase the risk of ketoacidosis at diabetes onset.17

Applying a multivariable logistic trend regression model that included the year at diabetes onset (as a continuous term), the month of diabetes onset, and an interaction term of both, age group at diabetes onset (6 months to <6 years, 6–<12 years, and 12–18 years), sex, and immigrant background (as independent variables), we estimated the expected monthly rate of ketoacidosis, as well as severe ketoacidosis for 2020 based on data from 2000 to 2019, standardized for age group, sex, and immigrant background, with the total population of all type 1 cases with onset between 2000 and 2020 as reference.

In the same way, we applied a multivariable logistic regression model that included the month of diabetes onset, age group, sex, and immigrant background as independent variables to standardize the observed monthly rates in 2020 to the same reference distributions of the total study population. A log-binomial regression model that included the month of diabetes onset, a binary variable indicating observed and predicted data, and an interaction term of both as independent variables was used to compare the standardized observed
with the standardized expected monthly rates of ketoacidosis and severe ketoacidosis; the results are presented as adjusted RR with 95% confidence intervals (CIs) and corresponding P values of Wald tests.

To evaluate the association of the regional severity of the COVID-19 pandemic with the regional rate of ketoacidosis in children and adolescents with new-onset type 1 diabetes in the year 2020, we applied a multivariable log-binomial mixed-effects model with ketoacidosis as the dependent variable and the regional incidence rate of the COVID-19 pandemic as the exposure variable, adjusting for sex, age group, and immigrant background. Because data on the severity of the COVID-19 pandemic were available on a region-by-week pattern, all patients with type 1 diabetes onset within a specific region-by-week “cluster” were assigned the same severity level. Therefore, we included a region-by-week interaction as a normally distributed random intercept term in the model. The severity of the COVID-19 pandemic was measured as the weekly incidence rate of new COVID-19 cases and deaths related to COVID-19 per 100,000 population. To capture changes in the course of the pandemic, we conducted the described analysis separately for the first and second half of the year 2020 (calendar weeks 1–26 and 27–52, respectively), corresponding to the first and second wave of the pandemic. The results are presented as adjusted RRs with 95% CIs and corresponding P values of Wald tests. In addition, the probability of a ketoacidosis at type 1 diabetes onset estimated from the log-binomial model is plotted dependent on the incidence of COVID-19 cases or COVID-19–related deaths.

A 2-sided P value <.05 was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

During the year 2020, data of 3238 children and adolescents with new-onset type 1 diabetes were registered in DPV from 189 diabetes centers in Germany. The median age of our cohort was 9.8 years (IQR, 6.0–12.9 years). The proportion of male patients was 55.6%.

Ketoacidosis was present in 1094 patients (33.8%), of which 401 (12.4%) were severe. Table 1 provides a descriptive overview of the study population.

According to the applied multivariable logistic trend model, the standardized expected monthly proportions of ketoacidosis for the year 2020 ranged from 20.1% (95% CI, 16.1%–25.0%) in January to 25.3% (95% CI, 20.6%–31.0%) in October (Table 2). In contrast, the observed frequencies of ketoacidosis rates for 2020, the observed frequencies of ketoacidosis in the year 2020 were significantly higher from April to September and again in December with mean adjusted RRs ranging from 1.48 to 1.96 in these months (Table 2, Fig 2).

The observed frequencies of severe ketoacidosis during the pandemic compared with the expected frequencies were also increased in April (adjusted RR, 2.10 [95% CI, 1.27–3.48]; P = .004), May (adjusted RR, 2.50 [1.49–4.21]; P < .001), July (adjusted RR, 1.71 [1.06–2.75]; P = .03), August

### TABLE 1 Description of the Study Population

<table>
<thead>
<tr>
<th>Region</th>
<th>All, No. (%</th>
<th>No Diabetic Ketoacidosis</th>
<th>Diabetic Ketoacidosis (All)</th>
<th>Severe Ketoacidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3238 (100)</td>
<td>2144 (66.2)</td>
<td>1094 (33.8)</td>
<td>401 (12.4)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>9.8 (6.0–12.9)</td>
<td>9.9 (6.1–13.0)</td>
<td>9.8 (5.8–12.9)</td>
<td>9.4 (4.8–12.5)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>1799 (55.6)</td>
<td>1207 (56.3)</td>
<td>592 (54.1)</td>
<td>209 (52.1)</td>
</tr>
<tr>
<td>Immigrant background, No. (%)</td>
<td>808 (25.0)</td>
<td>486 (22.7)</td>
<td>322 (28.4)</td>
<td>134 (33.4)</td>
</tr>
<tr>
<td>Geographical regions, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>657 (20.3)</td>
<td>441 (67.1)</td>
<td>216 (32.9)</td>
<td>90 (13.7)</td>
</tr>
<tr>
<td>Middle</td>
<td>436 (13.5)</td>
<td>305 (70.0)</td>
<td>131 (30.0)</td>
<td>47 (10.8)</td>
</tr>
<tr>
<td>West</td>
<td>807 (24.9)</td>
<td>524 (64.9)</td>
<td>283 (35.0)</td>
<td>98 (12.1)</td>
</tr>
<tr>
<td>East</td>
<td>503 (15.5)</td>
<td>330 (65.8)</td>
<td>173 (34.4)</td>
<td>60 (11.9)</td>
</tr>
<tr>
<td>South</td>
<td>835 (25.8)</td>
<td>544 (65.1)</td>
<td>291 (34.9)</td>
<td>106 (12.7)</td>
</tr>
</tbody>
</table>

*P < .01 versus no diabetic ketoacidosis (Kruskal-Wallis test adjusted for multiple testing by using the Bonferroni-Holm method).

**P < .001 versus no diabetic ketoacidosis (χ² test adjusted for multiple testing by using the Bonferroni-Holm method).

The first column shows the percentage of patients in this region out of all patients; the following columns show the respective percentage based on the No. patients in the corresponding

cluster.
TABLE 2 Observed Versus Expected Rates of Diabetic Ketoacidosis, Severe Ketoadicosis, and Impaired Consciousness at Diagnosis of Type 1 Diabetes During the COVID-19 Pandemic in Germany From January 1 to June 30, 2020

<table>
<thead>
<tr>
<th>Month</th>
<th>Observed Rate in 2020 (N = 3238), % (95% CI)</th>
<th>Expected Rate for 2020 Based on Data From 2000 to 2019 (N = 42 417), % (95% CI)</th>
<th>Observed Versus Expected Rate, Adjusted RR (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic ketoacidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>22.6 (18.4–27.8)</td>
<td>20.1 (16.1–25.0)</td>
<td>1.13 (0.83–1.52)</td>
</tr>
<tr>
<td>February</td>
<td>30.5 (25.5–36.4)</td>
<td>22.9 (18.5–28.4)</td>
<td>1.33 (1.01–1.76)</td>
</tr>
<tr>
<td>March</td>
<td>28.1 (23.0–34.3)</td>
<td>24.6 (20.0–30.8)</td>
<td>1.13 (0.84–1.52)</td>
</tr>
<tr>
<td>April</td>
<td>41.1 (35.5–47.6)</td>
<td>20.9 (16.5–26.5)</td>
<td>1.96 (1.49–2.59)</td>
</tr>
<tr>
<td>May</td>
<td>39.0 (33.7–45.2)</td>
<td>21.3 (17.0–26.7)</td>
<td>1.83 (1.40–2.40)</td>
</tr>
<tr>
<td>June</td>
<td>31.8 (26.6–37.7)</td>
<td>21.3 (17.0–26.8)</td>
<td>1.48 (1.11–1.98)</td>
</tr>
<tr>
<td>July</td>
<td>39.7 (34.5–45.7)</td>
<td>21.9 (17.7–27.1)</td>
<td>1.82 (1.40–2.35)</td>
</tr>
<tr>
<td>August</td>
<td>43.5 (37.5–50.1)</td>
<td>24.2 (19.3–30.2)</td>
<td>1.79 (1.37–2.34)</td>
</tr>
<tr>
<td>September</td>
<td>36.0 (31.0–41.8)</td>
<td>24.5 (20.1–29.8)</td>
<td>1.47 (1.15–1.88)</td>
</tr>
<tr>
<td>October</td>
<td>29.7 (24.7–35.6)</td>
<td>25.3 (20.6–31.0)</td>
<td>1.17 (0.89–1.54)</td>
</tr>
<tr>
<td>November</td>
<td>27.8 (22.9–33.9)</td>
<td>20.8 (16.4–26.4)</td>
<td>1.34 (0.98–1.83)</td>
</tr>
<tr>
<td>December</td>
<td>33.5 (27.8–40.3)</td>
<td>22.6 (17.7–29.2)</td>
<td>1.48 (1.09–2.01)</td>
</tr>
<tr>
<td><strong>Severe diabetic ketoacidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>7.3 (4.9–10.9)</td>
<td>5.7 (3.7–9.0)</td>
<td>1.28 (0.70–2.32)</td>
</tr>
<tr>
<td>February</td>
<td>9.7 (6.8–13.9)</td>
<td>8.2 (5.8–12.2)</td>
<td>1.17 (0.69–2.00)</td>
</tr>
<tr>
<td>March</td>
<td>11.8 (8.4–16.8)</td>
<td>10.1 (7.0–14.7)</td>
<td>1.16 (0.70–1.92)</td>
</tr>
<tr>
<td>April</td>
<td>16.5 (12.3–21.5)</td>
<td>7.8 (5.1–11.9)</td>
<td>2.10 (1.27–3.48)</td>
</tr>
<tr>
<td>May</td>
<td>16.3 (12.4–21.2)</td>
<td>6.5 (4.2–10.2)</td>
<td>2.50 (1.49–4.21)</td>
</tr>
<tr>
<td>June</td>
<td>9.6 (6.5–15.8)</td>
<td>7.0 (4.5–10.8)</td>
<td>1.37 (0.78–2.41)</td>
</tr>
<tr>
<td>July</td>
<td>13.8 (10.4–18.3)</td>
<td>8.1 (5.5–11.9)</td>
<td>1.70 (1.06–2.75)</td>
</tr>
<tr>
<td>August</td>
<td>19.6 (15.2–25.3)</td>
<td>9.2 (6.2–13.7)</td>
<td>2.14 (1.33–3.43)</td>
</tr>
<tr>
<td>September</td>
<td>12.4 (9.2–16.7)</td>
<td>7.2 (4.8–10.8)</td>
<td>1.73 (1.05–2.85)</td>
</tr>
<tr>
<td>October</td>
<td>8.1 (5.4–12.0)</td>
<td>8.4 (5.7–12.5)</td>
<td>0.96 (0.55–1.67)</td>
</tr>
<tr>
<td>November</td>
<td>7.8 (5.2–12.0)</td>
<td>8.2 (5.5–12.4)</td>
<td>0.95 (0.53–1.71)</td>
</tr>
<tr>
<td>December</td>
<td>12.2 (8.6–17.4)</td>
<td>7.7 (4.9–12.2)</td>
<td>1.59 (0.89–2.83)</td>
</tr>
</tbody>
</table>

Diabetic ketoacidosis was defined as pH <7.3 and/or serum bicarbonate <15 mmol/L; severe diabetic ketoacidosis was defined as pH <7.1 and or serum bicarbonate <5 mmol/L. Immigrant background was defined as patient or at least 1 parent born outside of Germany.

a Multivariable logistic regression model that included the month of diabetes onset (January to June), age group (6 mo to <6 y, 6–<12 y, 12–18 y), sex, and immigrant background as independent variables, standardized for age group, sex, and immigrant background, with the total population of all type 1 cases with onset in the first half of each year between 2000 and 2020 as reference.

b The expected rate was estimated on the basis of data from 2000 to 2019 by using a multivariable logistic trend regression model that included the year and month, an interaction term of both, and age group, sex, and immigrant background as independent variables, standardized to the reference population defined in footnote a.

c Estimated from a log-binomial regression model that included the month of diabetes onset, a binary variable indicating observed and predicted data, and an interaction term of both, applied to the standardized observed and standard expected monthly frequencies.

The applied multivariable mixed-effects log-binomial model revealed a significant association between the regional weekly incidences of COVID-19 cases and COVID-19–related deaths and the corresponding rates of ketoacidosis at diagnosis of type 1 diabetes during the first half of the year 2020. The adjusted RR for the predicted rate of diabetic ketoacidosis was 1.40 (95% CI, 1.10–1.77; P = .006) per increase in the 7-day incidence of COVID-19 cases by 50 U/100 000 population and 1.23 (95% CI, 1.14–1.32; P < .001) per increase in the 7-day incidence of COVID-19–related deaths by 1 U/100 000 population. To illustrate these associations, Fig 3 shows the model-derived probability of a ketoacidosis at type 1 diabetes onset dependent on the incidence of COVID-19 cases (Fig 3A) or COVID-19–related deaths (Fig 3B) during the first half of the year 2020. In contrast, during the second half of the year 2020, there was an inverse association between the regional weekly incidences of COVID-19 cases and the corresponding rates of ketoacidosis at diagnosis of type 1 diabetes. The adjusted RR for the predicted rate of diabetic

(adjusted RR, 2.14 [1.33–3.43]; P = .002) September

(adjusted RR, 1.73 [1.05–2.85]; P = .03) (Table 2).

Subsequently, we compared the standardized monthly rates of ketoacidosis observed during the year 2020 with the corresponding standardized expected frequencies derived from 2000–2019 data for the 5 regions of Germany. The RR for ketoacidosis was significantly elevated in April, May, July, and August in the west and in the south of Germany and in the west additionally in October (Fig 2, Supplemental Table 3).
ketoacidosis was 0.92 (95% CI, 0.87–0.98; \(P = .007\)) per increase in the 7-day incidence of COVID-19 cases by 50 U/100 000 population (Fig 3C). In addition, the association between the 7-day incidence of COVID-19–related deaths and the corresponding rates of ketoacidosis at diagnosis of type 1 diabetes was not significant during the second half of the year 2020 (RR, 0.98 [95% CI, 0.93–1.03]; \(P = .42\)) (Fig 3D).

**DISCUSSION**

With this study, we found a significant increase in the risks of diabetic ketoacidosis and severe diabetic ketoacidosis in children and adolescents with new-onset type 1 diabetes during the coronavirus pandemic in Germany. Our finding of an increased risk of ketoacidosis during the COVID-19 pandemic is potentially indicative of a delayed admission to health care and is consistent with reports from different parts of the world.\(^\text{10,18,19}\)

At the time of the highest RR of ketoacidosis, the severity of the pandemic also reached its peak with
the highest incidence of new COVID-19 cases and deaths. During March, however, nationwide measures were also taken to contain the pandemic, such as restrictions on social contacts, school closures, and the general advice on staying at home (Supplemental Table 4). Because of the temporal parallelism of both, namely, the increase of the incidence of COVID-19 and pandemic containment measures, it is important to determine which factors could have affected the increase in diabetic ketoacidosis at diagnosis of diabetes type 1 and thus the delay in admission to health care and diagnosis during the COVID-19 pandemic because this would have implications for further measures during this pandemic, as well as for future pandemics or similar disasters. Although general measures to contain the pandemic affected the whole country in a similar way, both the severity of the pandemic and its development over time varied considerably between different regions within Germany; the south and the west of Germany were particularly affected during March and April (Supplemental Information, Fig 2). It is therefore not surprising that our study revealed that these 2 regions showed the most pronounced increases in the rates of diabetic ketoacidosis in the following months.

Our analysis could demonstrate that the regional COVID-19 incidences of new cases and deaths during the first wave of the pandemic were associated with the risk of ketoacidosis in children and adolescents at diagnosis of type 1 diabetes. During the rapid spread of SARS-CoV-2, there was a significant decrease in the number of children presenting in the emergency
Department, resulting in a diagnostic delay. Because the development of ketoacidosis is commonly caused by a delay in diagnosis in patients with type 1 diabetes, our study suggests that the incidence level of the pandemic may be associated with a delayed use of health services. We assume that a rapidly increasing number of COVID-19 cases and deaths could cause anxiety and insecurity among the population. As a result, contact with the health care system would be avoided as far as possible for fear of possible infection. It has been reported that the obvious concern about COVID-19 led to a decline in the use of life-saving evidence-based treatments. Therefore, our study suggests that an early onset and a rapid increase in COVID-19 cases and especially in COVID-19-related deaths might have led to a high level of uncertainty and fear among the population, which could explain the increase in diabetic ketoacidosis.

This study shows that the increased risk of ketoacidosis outlasted the first pandemic wave and also the first lockdown by several months. It can therefore be assumed that neither the lockdown nor an overload of the health care system was responsible for the increase in the rate of ketoacidosis observed in our study. From the findings that the higher observed versus expected rate of ketoacidosis continued through the summer, when COVID-19 infection rates were stable at a low level, it can be hypothesized that public concern and fear had persisted for a considerable time. It was not until September and October that there was a marked decrease in the observed compared with the expected rates of ketoacidosis. Thereafter, the risk of ketoacidosis then rose again while the incidence of COVID-19 cases and deaths increased during the second wave of the pandemic.

Because of the low incidence of COVID-19 cases and deaths during the summer months but the persistently high rates of ketoacidosis, the paradoxical result of an inverse association between COVID-19 incidence and risk of ketoacidosis in the second half of the year emerged. This indicates that the behavior of the population adapts to the changing environmental parameters such as the dynamic or severity of the pandemic after a certain delay. After the summer, the incidence of COVID-19 increased again from October onward. In contrast to the first wave, when there was a prompt increase in the rate of ketoacidosis, this increase was clearly delayed in the second wave. During the second wave of the pandemic, when a significantly higher incidence of COVID-19 has been documented by the authorities, there was a smaller increase in the observed to predicted rate of ketoacidosis compared with the first wave. Beside differences in COVID-19 test capacities between the first and the second wave, this may indicate that the behavior of the population in relation to health care use changed during the pandemic in the form of a habituation effect.

In a French registry study, researchers found a decrease in hospital admissions for myocardial infarction after the lockdown that was irrespective of the regional prevalence of COVID-19. We have previously reported that the number of children and adolescents with new-onset type 1 diabetes did not change during the lockdown from mid-March to mid-May in Germany. In contrast to the association between the decrease in hospital admission and the regional prevalence of COVID-19 in the French study, we investigated the association between the frequency of advanced disease as a measure of a delay in admission to health care and the weekly regional incidence of COVID-19, which better reflects the dynamics of the pandemic.

One strength of our study is that we analyzed data across the entire first year of the pandemic. Another strength of the current study includes the large sample size of a population-based cohort. Furthermore, for comparisons with observed frequencies, the estimates of the expected frequencies of diabetic ketoacidosis in 2020 were derived from appropriate statistical methods, considering the observed slight but significant increase in the frequency of diabetic ketoacidosis in children with new-onset type 1 diabetes over the past 2 decades. Limitations of our study include that the multivariable logistic regression models included only some potential confounders of the association between COVID-19 incidence and diabetic ketoacidosis. Thus, residual confounding due to both individual patient-level and population-level confounders cannot be excluded. Potentially confounding factors include socioeconomic status, distance to health facility, family members with COVID-19, or regional differences in health policy measures. In addition, we calculated associations without evidence of causality. Because we have not assessed the individual behavior of the patients’ families, we cannot prove whether our presumption that uncertainty and concern caused by the pandemic led to avoidance of health care and thus an increase in observed compared to expected rates of diabetic ketoacidosis is true. Further research is needed to understand the reasons for the increased rates of diabetic ketoacidosis during the COVID-19 pandemic.

CONCLUSIONS

With this study, we found a significant increase in the frequency
of ketoacidosis associated with the regional severity of the pandemic (ie, the incidence of COVID-19 cases and deaths). The increased risk of ketoacidosis has outlasted the first wave of the COVID-19 pandemic by several months. The measures taken to contain the spread of the virus were implemented nationwide, were limited in time, and do not explain the regional differences and the prolonged time in the risk of ketoacidosis seen in our study. Therefore, these nationwide health policy measures do not appear to be the main reason for the significant increase in diabetic ketoacidosis at presentation nor for the delayed use of health care. Instead, it could be that concern caused by the pandemic itself may have been a reason for avoiding contact with health care. It is therefore important that people regain confidence in hospitals and medical care. Information and education campaigns must communicate that avoiding the use of health care can lead to significant harm that is disproportionately higher than the negligible risk of contracting COVID-19.

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ABBREVIATIONS

CI: confidence interval
COVID-19: coronavirus disease 2019
DPV: Diabetes-Patienten-Verlaufs-dokumentation
IQR: interquartile range
RR: relative risk
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2


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