# Frequency of Autoantibody-Negative Type 1 Diabetes in Children, Adolescents, and Young Adults During the First Wave of the COVID-19 Pandemic in Germany

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## OBJECTIVE

The aim of this study was to investigate the frequency of newly diagnosed type 1 diabetes without evidence of autoimmunity and the respective frequencies of ketoacidosis in children, adolescents, and young adults during the coronavirus disease 2019 (COVID-19) pandemic in Germany compared with the previous decade.

## RESEARCH DESIGN AND METHODS

Based on data from the German Diabetes Prospective Follow-up Registry (DPV), we compared data from 715 children, adolescents, and young adults, newly diagnosed with type 1 diabetes during the COVID-19 pandemic in Germany between 1 March and 30 June 2020, with data from 5,428 children, adolescents, and young adults of the same periods from 2011 to 2019. Adjusted differences and relative risks (RRs) of negative β-cell autoantibody test results and diabetic ketoacidosis were estimated using multivariable log-binomial regression analysis. An upper noninferiority test (margin 1%) was applied to evaluate whether the autoantibody-negativity rate in 2020 was not higher than that in 2011 to 2019.

## RESULTS

The estimated frequencies of autoantibody negativity in 2020 and 2011–2019 were 6.6% (95% CI 5.1–8.4) and 7.2% (95% CI 6.5–8.0), respectively, with an absolute difference of −0.68% (90% CI −2.07 to 0.71; $P_{\text{upper noninferiority}}$ = 0.023). The increase of the estimated frequency of diabetic ketoacidosis during the COVID-19 pandemic was similar between autoantibody-negative and -positive type 1 diabetes (adjusted RRs 1.28 [95% CI 0.80–2.05] and 1.57 [1.41–1.75], respectively).

## CONCLUSIONS

This study found no evidence that the COVID-19 pandemic leads to a significantly increased number of new cases with autoantibody-negative type 1 diabetes in children, adolescents, and young adults. In addition, autoantibody-negative type 1 diabetes showed no particular susceptibility to ketoacidosis, neither before nor during the pandemic.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing the pandemic coronavirus disease 2019 (COVID-19), was posited to lead to the development of diabetes through direct cytotoxicity of β-cells without autoimmunity (1,2). ACE2 acts as the main receptor for SARS-CoV-2 (3). Ten years ago, positive immunostaining for ACE2 protein in the pancreatic islets led to the hypothesis that the SARS-CoV-1 tropism for the β-cell could cause direct damage to pancreatic islets (4). Reports of autoantibody-negative type 1 diabetes following COVID-19 support this hypothesis for SARS-CoV-2 (5,6). However, it is unclear whether patients develop autoantibody-negative type 1 diabetes (also called idiopathic or type 1B diabetes) as a consequence of infection with SARS-CoV-2 (7). Recent histopathological studies showed conflicting evidence as to whether SARS-CoV-2 directly affects pancreatic β-cells (8–11). Thus, it is imperative to clarify whether human pancreatic islets are susceptible to and affected by SARS-CoV-2 (11).

In addition, idiopathic type 1B diabetes was thought to be prone to ketoacidosis (12). As there is a significantly increased frequency of ketoacidosis at the onset of type 1 diabetes during the COVID-19 pandemic (13–15), we raised the question of whether there would also be an increase in the frequency of this acute life-threatening metabolic disturbance in new cases of idiopathic type 1B diabetes during the pandemic period.

The aim of our study was to investigate the frequency of newly diagnosed idiopathic type 1B diabetes and its association with ketoacidosis in children, adolescents, and young adults during the COVID-19 pandemic in Germany.

## RESEARCH DESIGN AND METHODS
### Data Source and Study Population
This study used data from the German Diabetes Prospective Follow-up Registry (DPV; Diabetes-Patienten-Verlaufsdokumentation) with nationwide coverage of >90% of pediatric patients with type 1 diabetes in Germany (16). Twice a year, locally collected pseudonymized longitudinal data are 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. The data are then anonymized for analysis. We selected children, adolescents, and young adults (≤25 years) from 194 diabetes centers in Germany with a new diagnosis of type 1 diabetes or clinically diagnosed type 2 diabetes or maturity-onset diabetes of the young (MODY), from 1 March 2020, when the number of COVID-19 cases in Germany began to rise, through 30 June 2020.

The control group consisted of children and adolescents with new-onset type 1 diabetes diagnosed between 1 March and 30 June of the years 2011 to 2019 from 282 diabetes centers in Germany. The frequencies of new-onset type 1 diabetes without evidence of β-cell autoimmunity, as well as type 2 diabetes and MODY, during the COVID-19 period and the same periods from 2011 through 2019 were analyzed. The frequencies of diabetic ketoacidosis observed at diagnosis of type 1 diabetes during the COVID-19 period and the same periods 2011–2019 were compared between patients with and without detected autoantibodies. DPV data on frequencies of diabetic ketoacidosis at diagnosis of type 1 diabetes during the first 2 months of the COVID-19 pandemic have previously been published (13).

Verbal or written informed consent for participation in the DPV registry was obtained from patients or their parents. The ethics committee of Ulm University approved the analysis of anonymized data from the DPV registry.

### Variables
Demographic data included age at diabetes onset, sex, immigrant background (patient or at least one parent born outside of Germany), and family history of diabetes (defined as at least one of the parents with diabetes of any type). Clinical data included BMI (calculated as weight in kilograms divided by height in meters squared), $HbA_{1c}$ (% [mmol/mol]), and presence of diabetic ketoacidosis and severe ketoacidosis. BMI values were transformed to SD scores (BMI-SDS) based on German reference values (German Health Interview and Examination Survey for Children and Adolescents [KiGGS]) by applying the

least mean squares method (17). In order to adjust for different laboratory methods, local $HbA_{1c}$ values were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range (4.05–6.05%) using the "multiple of the mean" transformation method (18). Diabetic ketoacidosis was defined as pH <7.3 and/or bicarbonate <15 mmol/L and severe diabetic ketoacidosis as pH <7.1 and/or serum bicarbonate <5 mmol/L (19). Autoantibodies included autoantibodies against islet cells (islet cell antibody [ICA]), GAD (anti-GAD), tyrosine phosphatase (anti-IA2), insulin (insulin autoantibody [IAA]), and zinc transporter 8 (anti-ZnT8).

### Statistical Analysis
Unadjusted outcomes were presented as median with interquartile range for the description of continuous variables and as percentages (%) for the description of categorical variables and were compared between groups via Wilcoxon rank sum test for continuous outcomes or $\chi^2$ test for dichotomous outcomes.

Further, rates of autoantibody negativity and diabetic ketoacidosis in patients with newly diagnosed type 1 diabetes over the last decade were analyzed via multivariable log-binomial regression, trends in the number of autoantibodies examined, and $HbA_{1c}$ at onset of type 1 diabetes via multivariable linear regression. Trends were investigated by including calendar year as a continuous term in regression models.

Regression analyses were adjusted for age group at diabetes onset (<6 years, 6 to <12 years, 12 to <18 years, and 18–25 years), sex, and immigrant background. Analyses of trends in the number of autoantibodies examined and $HbA_{1c}$ at onset of type 1 diabetes as well as frequencies of autoantibody negativity were additionally adjusted for BMI-SDS (20,21) and, in patients with type 1 diabetes, the number of autoantibodies investigated, according to VanderWeele's disjunctive cause criterion (22). The results of regression analyses are presented as adjusted means and adjusted relative risks (RRs) with the corresponding 95% CI and $P$ values of Wald-type tests. A two-sided $P$ value <0.05 was considered statistically significant.

To evaluate whether the proportion of autoantibody negativity in the year 2020 was not higher than that in the same periods in 2011–2019 (upper noninferiority), we estimated a 90% CI for the absolute difference of the frequencies of autoantibody negativity between 2020 and 2011–2019 and used the upper bound of this CI and the corresponding upper noninferiority test statistic, respectively, to determine noninferiority with an upper margin of 1% at an error level of 5% (23). Thus, our null ($H_0$) and alternative hypothesis ($H_A$) stated that the rate of autoantibody negativity in 2020 was at least or at most 1% higher than that in 2011–2019 ($H_0$: autoantibody negativity rate [2020] $\geq$ autoantibody negativity rate [2011–2019] + 0.01, equivalently: autoantibody negativity rate [2020] − autoantibody negativity rate [2011–2019] $\geq$ 0.01; $H_A$ autoantibody negativity rate [2020] < autoantibody negativity rate (2011–2019) + 0.01, equivalently: autoantibody negativity rate [2020] − autoantibody negativity rate [2011–2019] < 0.01). Thus, differences in frequencies were presented as absolute differences in percentage points with the corresponding 90% CI and corresponding $P$ values of Wald-like test statistics. A one-sided $P$ value <0.05 was considered statistically significant. Upper noninferiority testing was also performed in stratified analyses (by sex and age group) of the proportion of autoantibody negativity and for the proportion of T2D/MODY among all new-onset diabetes cases. 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.

### RESULTS
We obtained data of 1,072 children, adolescents, and young adults with new-onset type 1 diabetes during the COVID-19 pandemic from 1 March through 30 June 2020, and of 8,349 children, adolescents, and young adults newly diagnosed with type 1 diabetes during the same period from 2011 to 2019 in Germany (Table 1). Data of autoantibody measurements were available in 732 patients (68.3%) for the year 2020 and in 5,618 patients (67.3%)

for the years 2011 to 2019. Differences of demographic data between patients with or without available data on autoantibody status were found for 2020 only for familial diabetes background (5.1% in patients with vs. 1.5% in patients without available data; $P$ = 0.024) (Table 1).

We compared the characteristics of patients with positive and negative autoantibody test results from both periods studied. The median age at diagnosis of type 1 diabetes in 2020 was 10.5 years in patients with negative and 10.0 years in those with positive autoimmune test results ($P$ = 0.37) and 10.3 years or 10.0 years in 2011–2019, respectively ($P$ = 0.54). In both periods studied, no difference in sex frequency was found for patients with negative or positive autoantibody test results (56.7% males in autoantibody-negative vs. 58.9% males in autoantibody-positive patients in 2020 [$P$ = 0.73] and 55.3% vs. 53.9% in 2011–2019 [$P$ = 0.54]).

A total of 60 out of 732 patients (8.2% [95% CI 6.5–9.9]) in 2020 and 526 out of 5,618 patients (9.4% [95% CI 8.7–10.0]) in the periods from 2011 to 2019 had negative autoantibody test results at onset of type 1 diabetes, with an absolute difference of −1.2% (90% CI −2.95 to 0.62%). Table 1 gives an overview of the demographic data of the study cohort and of the respective number of different autoantibodies tested and corresponding frequencies for positive and negative results.

In 17 patients with new-onset type 1 diabetes from 2020 and in 190 patients from 2011 to 2019, data on BMI were missing, so that data of 715 and 5,428 patients, respectively, were included in the adjusted analysis of the autoantibody negativity rate. Over the past decade, the estimated adjusted mean number of autoantibodies examined has increased from 3.1 (95% CI 3.0–3.2) in 2011 to 3.7 (95% CI 3.6–3.8) in 2020 ($P$ < 0.0001). Despite this, the mean estimated proportion of autoantibody-negative cases of new-onset type 1 diabetes remained stable (trend analysis 2010 to 2020, $P$ = 0.27) (Fig. 1).

The estimated adjusted rate of autoantibody negativity in cases with new-onset type 1 diabetes was 6.6% (95% CI 5.1–8.4) in 2020 and 7.2% (95% CI 6.5–8.0) between 2011 and 2019. The

absolute difference in the adjusted autoantibody-negativity rate between 2020 and 2011–2019 was −0.68% (90% CI −2.07 to 0.71; upper noninferiority test, $P$ = 0.023). According to the upper limit of the 90% CI, it can be concluded that the autoantibody-negativity rate in 2020 was at most 0.71% higher than the autoantibody-negativity rate in 2011–2019, at a significance level of 5%. Further subanalysis stratified by sex and age groups is shown in Table 2A.

The estimated adjusted proportion of all new cases of diabetes that were type 2 or MODY was 2.1% in 2020 and 2.8% from 2011 to 2019. The absolute difference in the adjusted type 2 diabetes/MODY rate between 2020 and 2011–2019 was −0.72% (90% CI −1.31 to −0.13; upper noninferiority test, $P$ < 0.0001) (Table 2A).

The estimated adjusted frequencies of diabetic ketoacidosis and severe diabetic ketoacidosis from 2011 to 2019 were lower in patients with negative than in patients with positive autoantibody test results (for diabetic ketoacidosis, 19.5% in patients with negative autoantibodies vs. 23.5% in patients with positive autoantibodies; adjusted RR 0.83 [95% CI 0.69–0.99], $P$ = 0.039; and for severe diabetic ketoacidosis, 5.4% in patients with negative autoantibodies vs. 7.8% in patients with positive autoantibodies; adjusted RR 0.69 [95% CI 0.48–1.00], $P$ = 0.049) (Table 2B). During the COVID-19 pandemic, the differences did not reach the significance level (for diabetic ketoacidosis, 24.9% in patients with negative autoantibodies vs. 36.8% in patients with positive autoantibodies, adjusted RR 0.68 [95% CI, 0.43–1.06], $P$ = 0.087; and for severe diabetic ketoacidosis, 13.4% vs. 14.0%, respectively, adjusted RR 0.96 [95% CI 0.49–1.87], $P$ = 0.91) (Table 2). The increases in the frequencies of ketoacidosis and severe ketoacidosis during the COVID-19 pandemic were similar between patients with negative (for diabetic ketoacidosis, adjusted RR 2020 vs. 2011–2019: 1.28 [95% CI 0.80–2.05]; and for severe diabetic ketoacidosis, adjusted RR 2.49 [95% CI 1.20–5.18]) and positive (for diabetic ketoacidosis, adjusted RR 2020 vs. 2011–2019: 1.57 [95% CI 1.41–1.75]; and for severe diabetic ketoacidosis, adjusted RR 1.79 [95% CI 1.46–2.20]) autoantibody test results, respectively (Table 2B).

**Table 1—Characteristics of patients newly diagnosed with diabetes in Germany from 1 March through 30 June 2020 during the COVID-19 pandemic and during the same period from 2011—2019**

| Characteristics | 1 March to 30 June 2020 | 1 March to 30 June 2011–2019 | |
|---|---|---|---|
| | | Total period | Per year in the period (range) |
| All patients with new-onset type 1 diabetes, n | 1,072 | 8,349 | 948 (798–1,018) |
| Age (years), median (interquartile range) | 10.1 (6.6–13.4) | 10.4 (6.4–13.7) | 10.2 (10.1–10.8) |
| Male sex, n (%) | 628 (58.6) | 4,534 (54.3) | 522 (405–554) (54.3 [50.8–56.4]) |
| Immigrant background, § n (%) | 264 (24.6) | 1,920 (23.0) | 205 (162–245) (23.0 [19.4–24.4]) |
| Family history of diabetes,* n (%) | 42 (3.9) | 367 (4.4) | 39 (35–65) (4.4 [3.7–7.2]) |
| BMI-SDS, median (interquartile range) | −0.04 (−0.90 to 0.79) | −0.07 (−0.82 to 0.71) | −0.06 (−0.17 to 0.03) |
| Patients with new-onset type 1 diabetes and data on autoantibody measurements, n (% of all patients with new-onset type 1 diabetes) | 732 (68.3) | 5,618 (67.3) | 641 (517–705) (67.6 [61.7–71.0]) |
| ICA | 535 (73.1) | 3,865 (68.8) | 422 (314–525) (71.1 [58.2–75.9]) |
| IAA | 527 (72.0) | 3,728 (66.4) | 416 (289–504) (68.4 [55.9–71.5]) |
| Anti-GAD | 664 (90.7) | 5,150 (91.7) | 588 (473–660) (91.5 [89.8–93.9]) |
| Anti-IA2 | 613 (83.7) | 4,759 (84.8) | 533 (428–614) (84.4 [81.7–87.7]) |
| Anti-ZnT8 | 366 (50.0) | 1,602 (28.5) | 173 (97–290) (27.0 [16.9–41.1]) |
| Age (years), median (interquartile range)# | 10.0 (6.4–13.4) | 10.1 (6.2–13.3) | 10.1 |
| Male sex, n (%)# | 430 (58.7) | 3,033 (53.9) | 347 (260–388) (53.8 [50.3–56.2]) |
| Immigrant background,§ n (%)# | 187 (25.5) | 1,364 (25.1) | 141 (105–185) (25.1 [20.3–27.0]) |
| Family history of diabetes,* n (%)# | 37 (5.1) | 314 (5.2) | 36 (25–48) (5.2 [3.8–8.1]) |
| BMI-SDS, median (interquartile range)# | −0.03 (−0.87 to 0.80) | −0.07 (−0.82 to 0.69) | −0.07 (−0.15 to 0.07) |
| Number of autoantibodies measured, median (interquartile range)¶ | 4 (3–5) | 4 (3–4) | 4 (3–4) |
| Patients with one or more positive autoantibodies,¶ n (%) | 672 (91.8) | 5,092 (90.6) | 566 (446–625) (91.1 [88.8–93.0]) |
| Patients with type 1 diabetes and negative autoantibody test results, n of patients tested for each antibody (%) | 60 (8.2) | 526 (9.4) | 62 (41–74) (9.3 [7.3–11.8]) |
| ICA | 184 (34.4) | 1,350 (35.5) | 147 (112–195) (35.3 [28.3–40.9]) |
| IAA | 193 (36.6) | 1,457 (39.9) | 174 (86–206) (40.0 [29.8–42.6]) |
| Anti-GAD | 245 (36.9) | 1,886 (34.9) | 205 (165–295) (34.9 [32.1–44.7]) |
| Anti-IA2 | 243 (39.6) | 2,011 (42.1) | 220 (180–258) (42.1 [41.0–44.8]) |
| Anti-ZnT8 | 120 (32.8) | 455(29.3) | 42 (17–87) (29.3 [17.5–34.2]) |
| Patients with new-onset type 2 diabetes or MODY, n all [type 2 diabetes/MODY] | 36 (27/9) | 430 (317/113) | 45 (37–63) (33 [28–48]/13 [9–17]) |

§Immigrant background was defined as patient or at least one parent born outside Germany.
*Family history of diabetes was defined as at least one of the parents with diabetes of any type.
#Patients with new-onset type 1 diabetes and data on autoantibody measurements only.
¶Autoantibodies against islet cells, GAD, tyrosine phosphatase, insulin, and ZnT8.

The estimated adjusted mean HbA$_{1c}$ at diagnosis was higher during the COVID-19 pandemic (11.4% [101.2 mmol/mol]) than during the previous decade (11.1% [98.0 mmol/mol]; P = 0.001). Stratified by autoantibody status, the estimated mean HbA$_{1c}$ at diagnosis during the COVID-19 pandemic was 11.5% [101.8 mmol/mol] in patients with negative and 11.4% [101.1 mmol/mol] in patients with positive autoantibody test results (P = 0.83). In the periods from 2011 to 2019, the estimated mean HbA$_{1c}$ levels were 11.3% [100.5 mmol/mol] in patients with negative and 11.1% [97.8 mmol/mol] in patients with positive autoantibodies (P = 0.02).

## CONCLUSIONS

Our analysis presents the first population-based study that evaluates the frequency of autoantibody-negative type 1B diabetes during the COVID-19 pandemic.

This study found no evidence for a relevant increase in the frequency of autoantibody-negative type 1 diabetes in children, adolescents, and young adults in Germany during the COVID-19 pandemic compared with the previous decade. There was also no increase in other forms of diabetes, namely type 2 diabetes or MODY. We have previously reported that the number of new cases of type 1 diabetes did not differ significantly from the prediction based on the rising trend during the preceding 10 years during the first 2 months of the pandemic in Germany (24). Therefore, our data do not support the hypothesis that SARS-
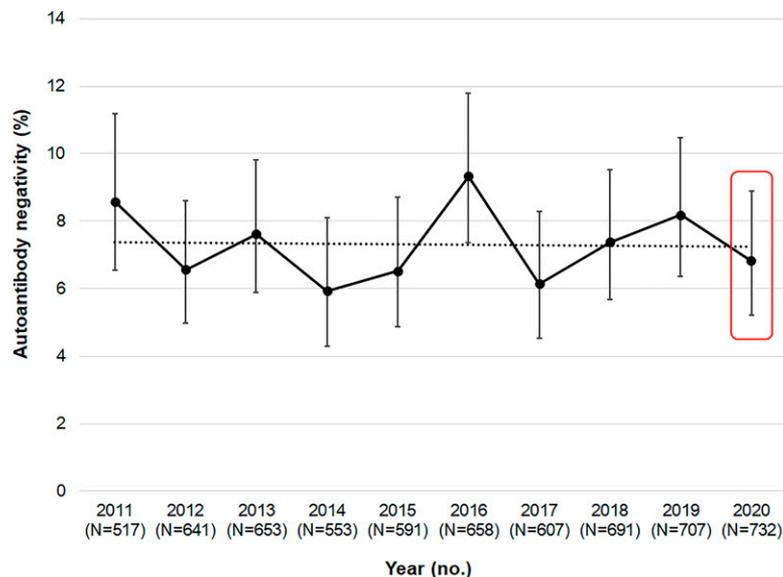
**Figure 1**—Adjusted mean frequencies (in percentages) with 95% CI (error bar) of autoantibody negativity of children, adolescents, and young adults with new-onset type 1 diabetes in Germany between 1 March and 30 June from 2011 to 2020 and the trend over the 10 years (dotted line) are estimated from a log-binomial regression model including year as categorical variable and adjusted for age group at diabetes onset (<6 years, 6 to <12 years, 12 to <18 years, and 18–25 years), sex, immigrant background, BMI-SDS, and the number of autoantibodies investigated. The numbers in parentheses after the years indicate the number of patients with new-onset type 1 diabetes and available data on autoantibody status.

CoV-2 triggers autoantibody-negative type 1 diabetes in a relevant number of patients. The main limitation of case reports of autoantibody-negative type 1 diabetes in temporal relation to SARS-CoV-2 infection is the lack of evidence of a causal association. Thus, our data show that strong direct diabetogenic effects of SARS-CoV-2 in children, adolescents, and young adults seem highly unlikely. However, we cannot exclude individual cases with SARS-CoV-2–related pathogenesis. Our study demonstrates that the frequency of autoantibody negativity for the time of the COVID-19 pandemic was at most 0.71% higher than in the years 2011 to 2019 at the error level of 5%. We observed 1,072 cases of new-onset type 1 diabetes during 1 March to 30 June 2020. Assuming a DPV coverage of 90% of all cases of type 1 diabetes in children, adolescents, and young adults in Germany, we could assume a number of about 1,200 cases of new-onset type 1 in children, adolescents, and young adults during these 4 months. Given a maximum increase in the frequency of antibody-negative cases of 0.71% compared with the previous years, this would result in at most 9 additional

cases of antibody-negative type 1B diabetes in children, adolescents, and young adults during the analyzed period of the COVID-19 pandemic.

The seroprevalence for anti–SARS-CoV-2 antibodies in children and adolescents in Germany ranged from 0.6 to 1.5% between the end of April and the end of June 2020 in different parts of Germany (25–28). It can be assumed that the estimated seroprevalence for anti–SARS-CoV-2 antibodies for children and adolescents at the beginning of June was approximately 0.8–1.0% for Germany as a whole. Given a population of 15.33 million children and adolescents <20 years of age, it can be concluded that at least 120,000 to 150,000 children and adolescents had been infected with SARS-CoV-2 by the beginning of June and were therefore also at risk for developing SARS-CoV-2–related autoantibody-negative type 1B diabetes by the end of our observation period by 30 June 2020. In contrast to immune-mediated type 1A diabetes, type 1B diabetes would be expected to develop within a short interval after infection with SARS-CoV-2 due to direct cytotoxicity to β-cells (5,6).

Assuming a maximum of 9 additional cases of autoantibody-negative type 1B diabetes in at least 120,000 to 150,000 at-risk individuals, the individual risk of developing type 1B diabetes after SARS-CoV-2 infection would be <1:13,000–17,000.

Although idiopathic type 1 diabetes is thought to be prone to ketoacidosis with fulminant presentation in some reports (12), our analysis in patients with new-onset autoantibody-negative type 1B diabetes over the last decade showed a slightly lower frequency of ketoacidosis, despite slightly higher levels of $HbA_{1c}$. Autoantibody-negative type 1B diabetes showed no particular susceptibility to ketoacidosis compared with immune-mediated type 1A, neither before nor during the pandemic, in Germany.

When considering outcomes during the pandemic, it is important to note that both patient care and patient behavior were affected by the COVID-19 pandemic. This, of course, also affects data collected during the pandemic and leads to changes compared with the years before. Admissions for health care during the pandemic have markedly declined (29–31). As a result, diagnoses were delayed and diseases were identified at an advanced stage (32,33). Therefore, during the COVID-19 pandemic, a significant increase in the frequency of ketoacidosis has been observed from different parts of the world (13–15). However, there was no greater increase in the frequency of ketoacidosis in patients with idiopathic than in patients with immune-mediated type 1 diabetes in our study.

Taken together, our population-based study does not support the hypothesis that SARS-CoV-2 led to a significant increase in new cases of autoimmune negative type 1B diabetes in the period studied. However, one limitation of our study is that we only covered the first wave of the pandemic in Germany over a period of 4 months. In addition, the infection rates during the first wave of the pandemic in Germany were lower than during the second wave, which is still ongoing while this article is being completed. However, testing was also much more restrictive at the beginning of the pandemic, especially among children and adolescents. A strength of our study is the

**Table 2—Estimated adjusted frequency and RR of autoantibody negativity and diabetic ketoacidosis in patients newly diagnosed with diabetes in Germany during the COVID-19 pandemic from 1 March through 30 June 2020 and during the same period from 2011 through 2019**

| Characteristics | 1 March to 30 June 2020 | 1 March to 30 June 2011–2019 | Absolute difference (90% CI), % | P value (upper noninferiority test)§ |
|---|---|---|---|---|
| A. Autoantibody negativity, % (95% CI) in type 1 diabetes [n of patients with negative autoantibody test result/n of patients analyzed] | | | | |
| All patients[a] | 6.6 (5.1–8.4) [59/715] | 7.2 (6.5—8.0) [502/5,428] | −0.68 (−2.07 to 0.71) | 0.023 |
| Sex[b] | | | | |
| Female | 7.3 (5.1–10.5) [22/297] | 6.8 (5.8–7.9) [169/2,503] | 0.51 (−1.75 to 2.78) | 0.36 |
| Male | 6.0 (4.3–8.3) [25/418] | 7.6 (6.6–8.7) 221/2,925] | −1.57 (−3.30 to 0.16) | 0.007 |
| Age groups, years[c] | | | | |
| <6 | 5.1 (2.8–9.3) [10/162] | 7.0 (5.5–8.8) [129/1,274] | −1.80 (−4.49 to 0.88) | 0.043 |
| 6–11 | 5.6 (3.8–8.3) [23/306] | 6.4 (5.4–7.5) [183/2,252] | −0.74 (−2.66 to 1.18) | 0.068 |
| 12–17 | 8.4 (5.7–12.2) [25/226] | 7.5 (6.3–8.9) [165/1,777] | 0.84 (−1.84 to 3.52) | 0.46 |
| 18–25 | 4.6 (0.7–31.7) [1/21] | 16.4 (10.4–25.8) [25/125] | −11.8 (−21.2 to −2.42) | 0.012 |
| Type 2 diabetes or MODY, %[d] | | | | |
| New-onset type 2 diabetes or MODY | 2.1 (1.5–2.9) [36/1,108] | 2.8 (2.4–3.2) [431/8,780] | −0.72 (−1.31 to −0.13) | <0.0001 |
| | | | RR (95% CI) | P value¶ |
| B. DKA, % (95% CI)[d] | | | | |
| DKA [severe DKA] in autoantibody negative | 24.9 (16.1–38.6) [13.4 (7.1–25.5)] | 19.5 (16.4–23.2) [5.4 (3.8–7.7)] | 1.28 (0.80–2.05) [2.49 (1.20–5.18)] | 0.31 [0.015] |
| DKA [severe DKA] in autoantibody positive | 36.8 (33.4–40.6) [14.0 (11.6–16.8)] | 23.5 (22.4–24.7) [7.8 (7.1–8.6)] | 1.57 (1.41–1.75) [1.79 (1.46–2.20)] | <0.0001 [<0.0001] |
| RR (95% CI) | 0.68 (0.43–1.06) [0.96 (0.49–1.87)] | 0.83 (0.69–0.99) [0.69 (0.48–1.00)] | | |
| P value | 0.087 [0.91] | 0.039 [0.049] | | |

Immigrant background was defined as patient or at least one parent born outside Germany. Diabetic ketoacidosis (DKA): pH <7.3 and/or serum bicarbonate <15 mmol/L; severe DKA: pH <7.1 and/or serum bicarbonate <5 mmol/L. §The upper bound of the 90% CI for the absolute difference of the frequencies between 2020 and 2011–2019 and the corresponding upper noninferiority test statistic was used to determine noninferiority with an upper margin of 1% at an error level of 5%. ¶Wald-type test statistic. [a]Frequency was adjusted for age at diabetes onset, sex, BMI-SDS, number of autoantibodies analyzed, and immigrant background. [b]Frequency was adjusted for age at diabetes onset, BMI-SDS, number of autoantibodies analyzed, and immigrant background. [c]Frequency was adjusted for sex, BMI-SDS, number of autoantibodies analyzed, and immigrant background. [d]Frequency was adjusted for age at diabetes onset, sex, and immigrant background.

population-based data, with the coverage of >90% of all diabetes manifestations during the observation period in Germany among children and adolescents.

Although our epidemiologic data do not support a significant role for COVID-19 in the pathogenesis of idiopathic type 1B diabetes at the current stage, the sheer magnitude of the pandemic and the multitude of unanswered questions regarding potential short-, medium-, and long-term health consequences for those affected make continued diabetes surveillance seem warranted.

and, as such, had full access to all of 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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