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Is COVID-19 to Blame? Trends of Incidence and Sex Ratio in Youth-Onset Type 2 Diabetes in Germany

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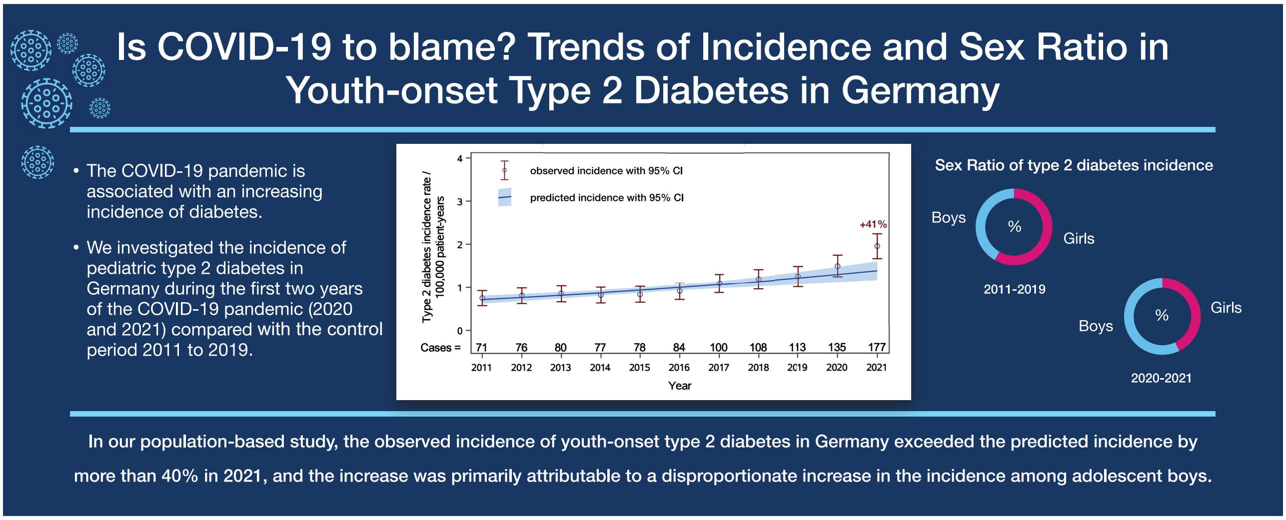

ARTICLE HIGHLIGHTS

- The COVID-19 pandemic is associated with an increasing incidence of diabetes.
- Epidemiological studies with nationwide coverage of type 2 diabetes incidence among children and adolescents during the COVID-19 pandemic are currently missing.
- In our population-based study, the observed incidence of youth-onset type 2 diabetes in Germany exceeded the predicted incidence by >40% in 2021, and the increase was primarily attributable to a disproportionate increase in incidence among adolescent boys, which led to a reversal of the pre–COVID-19 sex ratio.
- The COVID-19 pandemic seems to have significantly amplified the risk of type 2 diabetes in predisposed youth.

Is COVID-19 to Blame? Trends of Incidence and Sex Ratio in Youth-Onset Type 2 Diabetes in Germany

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OBJECTIVE

We investigated the incidence of pediatric type 2 diabetes (T2D) in Germany during 2 years of the coronavirus disease 2019 (COVID-19) pandemic (2020–2021) compared with the control period 2011–2019.

RESEARCH DESIGN AND METHODS

Data on T2D in children (aged 6 to <18 years) were obtained from the DPV (German Diabetes Prospective Follow-up) Registry. Poisson regression was used to estimate incidences for 2020 and 2021 based on data from 2011 to 2019, and these were compared with observed incidences in 2020 and 2021 by estimating incidence rate ratios (IRRs) with 95% CIs.

RESULTS

Incidence of youth-onset T2D increased from 0.75 per 100,000 patient-years (PYs) in 2011 (95% CI 0.58, 0.93) to 1.25 per 100,000 PYs in 2019 (95% CI 1.02, 1.48), an annual increase of 6.8% (95% CI 4.1, 9.6). In 2020, T2D incidence increased to 1.49 per 100,000 PYs (95% CI 1.23, 1.81), which was not significantly higher than predicted (IRR 1.15; 95% CI 0.90, 1.48). In 2021, the observed incidence was significantly higher than expected (1.95; 95% CI 1.65, 2.31 vs. 1.38; 95% CI 1.13, 1.69 per 100,000 PYs; IRR 1.41; 95% CI 1.12, 1.77). Although there was no significant increase in incidence in girls in 2021, the observed incidence in boys (2.16; 95% CI 1.73, 2.70 per 100,000 PYs) significantly exceeded the predicted rate (IRR 1.55; 95% CI 1.14, 2.12), leading to a reversal of the sex ratio of pediatric T2D incidence.

CONCLUSIONS

In Germany, incidence of pediatric T2D increased significantly in 2021. Adolescent boys were more affected by this increase, resulting in a reversal of the sex ratio of youth-onset T2D.

A growing number of studies suggest the coronavirus disease 2019 (COVID-19) pandemic is associated with an increasing incidence of diabetes (1). Incident diabetes has been reported as a complication of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (2), and emerging data support the possibility that the risk of diabetes manifestation may also be increased in the postacute phase of the disease (3–5). To our knowledge, data on trends of pediatric type 2 diabetes incidence during the pandemic are currently available only from the U.S. A

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ORIGINAL ARTICLE

recent analysis of OneFlorida+ Network data showed an increase in youth-onset type 2 diabetes from March 2020 to mid 2021, exceeding the predicted incidence by ~10 to 25% (6). Several retrospective case series from U.S. diabetes centers have uniformly reported a steep rise in incident pediatric type 2 diabetes (from +50 to +231%) since the start of the COVID-19 pandemic, predominantly affecting ethnic minority youth. Similar to observations in pediatric type 1 diabetes (7), youth with new-onset type 2 diabetes present significantly more often with diabetic ketoacidosis (DKA) compared with prepandemic observations (8–14).

Pathophysiological hypotheses for the association between SARS-CoV-2 and diabetes onset range from direct impairment of β-cell function, either by viral infection or by release of proinflammatory cytokines (15,16), to worsening of insulin resistance by persistent low-grade inflammation and dexamethasone-induced hyperglycemia. Since March 2020, incisive public health measures such as school closures and restrictions on participation in both recreational and amateur sports could have fostered weight gain and physical inactivity in children. This hypothesis is supported by an observed acceleration of weight gain during the first months of the pandemic in Germany, particularly in primary school–aged children and in youth who were already obese before the pandemic (17,18); a marked decrease in physical activity and a corresponding temporal increase in sedentary behavior during the pandemic were also observed (19–22). Whether these changes also led to an increase in pediatric type 2 diabetes incidence is currently unclear. Our study aimed to investigate the development of type 2 diabetes incidence in children and adolescents during the COVID-19 pandemic in Germany (2020–2021), analyze differences between sexes, and describe potential changes in clinical presentation at diagnosis.

RESEARCH DESIGN AND METHODS

Data Sources and Study Population

DPV (German Diabetes Prospective Follow-up) Registry data on children living in Germany and aged 6 to <18 years at the time type 2 diabetes diagnosis from 1 January 2011 to 31 December 2021 were analyzed. The age restriction to children aged >6 years was chosen because of the extremely low incidence of type 2 diabetes in younger children. Type 2 diabetes diagnoses were made by health care professionals at participating diabetes centers based on guideline-defined diagnostic criteria (23). Diabetes diagnoses are regularly updated in the DPV Registry as new information becomes available (e.g., antibodies, genetic findings). As part of the quality control system, regular correction runs are performed in which ambiguous or potentially erroneous data are reviewed at the participating centers, and revised data are then sent back to the study center. The final sample included all newly diagnosed type 2 diabetes cases documented in the DPV Registry within 3 months of diagnosis. For the current analysis, data from 219 German diabetes centers were available. Using data from the regional North Rhine Westphalian (NRW) Diabetes Registry, which covers 20 to 25% of the population in Germany, the median registration coverage of youth-onset type 2 diabetes cases in the DPV Registry was estimated to be 81% (interquartile range 68–86%) from 2011 to 2020 based on a three–data source log-linear model (24,25).

Verbal or written consent to participate in the DPV Initiative was obtained from patients or their legal guardians. Biannually, pseudonymized longitudinal data collected locally at contributing centers are transmitted to Ulm University for central plausibility checks and analyses. Analysis of anonymized data from the DPV Registry was approved by the Ethics Committee of the University of Ulm (application no. 314/21; Ulm, Germany). This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Current population data were obtained from the Federal Statistical State Office of Germany (26).

Variables

Study population data included year of and age at diabetes diagnosis, sex, and migration background (patient or at least one parent born outside Germany). Clinical data at diabetes onset included BMI, HbA_{1c} (% [mmol/mol]), and incident DKA. DKA was defined as venous or capillary pH <7.30 or bicarbonate level <15 mmol/L documented within ≤10 days of diabetes diagnosis.

BMI values were converted to *z* scores based on German reference values using Box-Cox transformation (27). To account for different laboratory methods, local HbA_{1c} values were standardized to the Diabetes Control and Complications Trial reference range (4.05–6.05%) using multiple-of-the-mean transformation.

Statistical Analysis

Continuous variables are presented as medians and interquartile ranges. Frequencies and percentages are provided for categorical variables. Group comparisons of demographic and anthropometric variables were performed between all children newly diagnosed with type 2 diabetes from 1 January 2018 to 31 December 2019 and children newly diagnosed with type 2 diabetes from 1 January 2020 to 31 December 2021 using the Kruskal-Wallis test for continuous variables and an χ^2 test for dichotomous variables.

Per calendar year, the number of new type 2 diabetes cases was related to the respective number of person-years (PYs) at risk to estimate age- (6 to <12 and 12 to <18 years) and sex-specific incidence rates per 100,000 PYs with 95% CIs assuming a Poisson distribution. The division into only two age groups was chosen because of the overall low number of cases of T2D. Annual incidence rates with 95% CIs were directly age and sex standardized, and proportions of boys with incident type 2 diabetes with 95% CIs were directly age standardized using the 2021 population as standard.

To compare the observed incidence rates in 2020 and 2021 with the predicted annual incidence rates estimated from the prepandemic period, 2011 to 2019, a multivariable Poisson trend regression model accounting for over- or underdispersion by inflating or deflating the variance regression parameter estimates (deviance or degrees of freedom; SAS option dscale) was applied, including year of onset (as continuous term), age at onset (categorized as 6 to <12 or 12 to <18 years), and sex as independent variables. Predicted annual incidence rates for 2011 to 2021 were then estimated based on this trend model, standardized for age group and sex, with the 2021 population data as reference. Next, using a Poisson regression model with a binary variable indicating observed and predicted data as independent variable, the observed incidence of type 2 diabetes was compared with the predicted incidence. The annual proportion of boys with incident type 2 diabetes from 2011 to 2019 was analyzed using a log-binomial trend regression model including the independent variables year of onset and categorized age at onset, allowing us to estimate the expected proportion of boys in 2020 and 2021. For both years, observed versus predicted proportions of boys were then compared using log-binomial regression models with an independent binary variable specifying observed and predicted data. As sensitivity analysis, we performed additional joinpoint analyses of type 2 diabetes incidence in the total study population and in girls and boys separately, estimating number and time of joinpoints from the data according to the Bayesian information criterion (Supplementary Material).

Clinical presentation at diabetes onset was analyzed by applying multivariable linear trend regression models, with categorized age group, sex, and year of diabetes onset as independent variables, to HbA_{1c} and BMI *z* score from 2011 to 2019. Predicted values for HbA_{1c} and BMI *z* score at diagnosis for 2020 and 2021 were then estimated from these trend models, using the 2011 to 2019 sample of new-onset cases with available HbA_{1c} and BMI *z* score values as reference. Linear regression models including a binary variable denoting observed and predicted data were applied to compare the observed values with each predicted value.

CIs of the observed and predicted incidence rates and HbA_{1c} and BMI z score values in each stratum were adjusted for multiple inference using the Bonferroni method. The ratios between the observed and predicted incidence rates and the differences between observed and predicted HbA_{1c} and BMI *z* score values were expressed as adjusted incidence rate ratios (IRRs) or adjusted differences, respectively, with corresponding 95% CIs. All analyses were carried out for the total population and for sex or age group. Age- and sex-specific analyses were performed by including a term for the interaction of year by sex or age group in the trend regression models and by including a term for the interaction of the indicator variable of observed and predicted data by sex or age group in the respective models stratified by calendar year. In all statistical procedures, statistical significance was assessed from 95% CIs.

Data and Resource Availability

Aggregated data might be made available upon reasonable request via e-mail to the corresponding author.

RESULTS

Trends in Type 2 Diabetes Incidence From 2011 to 2019

In the prepandemic period from 2011 to 2019, we observed an annual type 2 diabetes incidence increase of 6.8% (95% CI 4.1, 9.6). The annual increase was more pronounced in boys (11.2% per year; 95% CI 7.2, 15.4) than in girls (3.8% per year; 95% CI 0.7, 7.0; ratio of sex-specific annual increases in boys vs. girls 1.07; 95% CI 1.02, 1.12). Results of the joinpoint analyses largely confirmed these findings. (Supplementary Figs. 1–3). Furthermore, a significant increase was detected only in participants aged 12 to $<$18 years (6.9% per year; 95% CI 4.0, 9.9), not in those aged 6 to $<$12 years (6.1% per year; 95% CI $-$2.2, 15.2). However, the increase in participants aged 12 to $<$18 years was not significantly different from that in those aged 6 to $<$12 years (ratio of age-specific IRRs in those aged 12 to $<$18 vs. 6 to $<$12 years 1.01; 95% CI 0.92, 1.10). The absolute case numbers of new-onset type 2 diabetes in children in Germany for all years from 2011 to 2021 are shown in Figs. 1 and 2.

Observed Versus Predicted Type 2 Diabetes Incidence in 2020 and 2021

In 2020, the observed type 2 diabetes incidence continued to increase to 1.49 per 100,000 PYs (95% CI 1.23, 1.81), but this trend did not result in a significantly higher overall incidence (IRR 1.15; 95% CI 0.90, 1.48) compared with the predicted incidence for 2020 based on annual estimates from 2011 to 2019 (1.29 per 100,000 PYs; 95% CI 1.05, 1.59). Similarly, the observed incidence in 2020 increased in both age groups but was not statistically different from the respective predicted estimates (Table 1). Similarly, the substantial increase in the raw case number in boys in 2020 did not result in an incidence that significantly exceeded the predicted rate (IRR 1.29; 95% CI 0.91, 1.81) (Table 1). In girls, the observed incidence in 2020 (1.37; 95% CI 1.02, 1.83) matched the predicted incidence for that year (IRR 1.00; 95% CI 0.70, 1.43). The IRR in boys was not significantly different from the IRR in girls (ratio of sex-specific IRRs in boys vs. girls 1.28; 95% CI 0.78, 2.11).

In 2021, the observed type 2 diabetes incidence of 1.95 per 100,000 PYs (95% CI 1.65, 2.31) in the total population of children and adolescents was significantly higher than predicted (1.38 per 100,000 PYs; 95% CI 1.13, 1.69), corresponding to a 41% increase (IRR 1.41; 95% CI 1.12, 1.77) (Table 1 and Fig. 1*A*).

In 2021, there was no statistically significant increase in the observed type 2 diabetes incidence in girls compared with the predicted incidence (IRR 1.22; 95% CI 0.87, 1.70). Therefore, the distinct increment in the overall incidence of type 2 diabetes in this year was attributable to a sharp rise in the incidence among boys (IRR 1.55; 95% CI 1.14, 2.12). Again, the IRR in boys was not significantly higher than that in girls (ratio of sex-specific IRRs in boys vs. girls 1.28; 95% CI 0.81, 2.02). Trend analysis of the proportion of boys among the total number of incident type 2 diabetes cases, based on data from 2011 to 2019, showed that the observed proportions of boys in 2020 and 2021 were not significantly higher than expected (2020 rate ratio 1.13; 95% CI 0.91, 1.42; 2021 rate ratio 1.12; 95% CI 0.93, 1.36) (Table 2).

Subanalysis by age group revealed an increase in type 2 diabetes diagnoses in those aged 6 to $<$12 years in both 2020 and 2021 (2020 IRR 1.49; 95% CI 0.72, 3.09; 2021 IRR 1.84; 95% CI 0.94, 3.61), but this trend did not reach statistical significance (Table 1 and Fig. 1*D*). In contrast, the significant increase in incidence in adolescents aged 12 to $<$18 years compared with the predicted incidence (2021 IRR 1.36; 95% CI 1.07, 1.74) contributed significantly to the increase in diabetes incidence in the total population (Table 1 and Fig. 1*E*). IRRs in the age groups 6 to $<$12 and 12 to $<$18 years were not significantly different from each other in 2020 and 2021 (2020 rate ratio 1.34; 95% CI 0.62, 2.90; 2021 rate ratio 1.35; 95% CI 0.66, 2.77).

Patient Characteristics at Type 2 Diabetes Diagnosis

Comparing anthropometric and metabolic characteristics at diabetes diagnosis between the 2 prepandemic years 2018 and 2019 and the pandemic years 2020 and 2021 revealed no significant changes (Table 3); there was a slightly

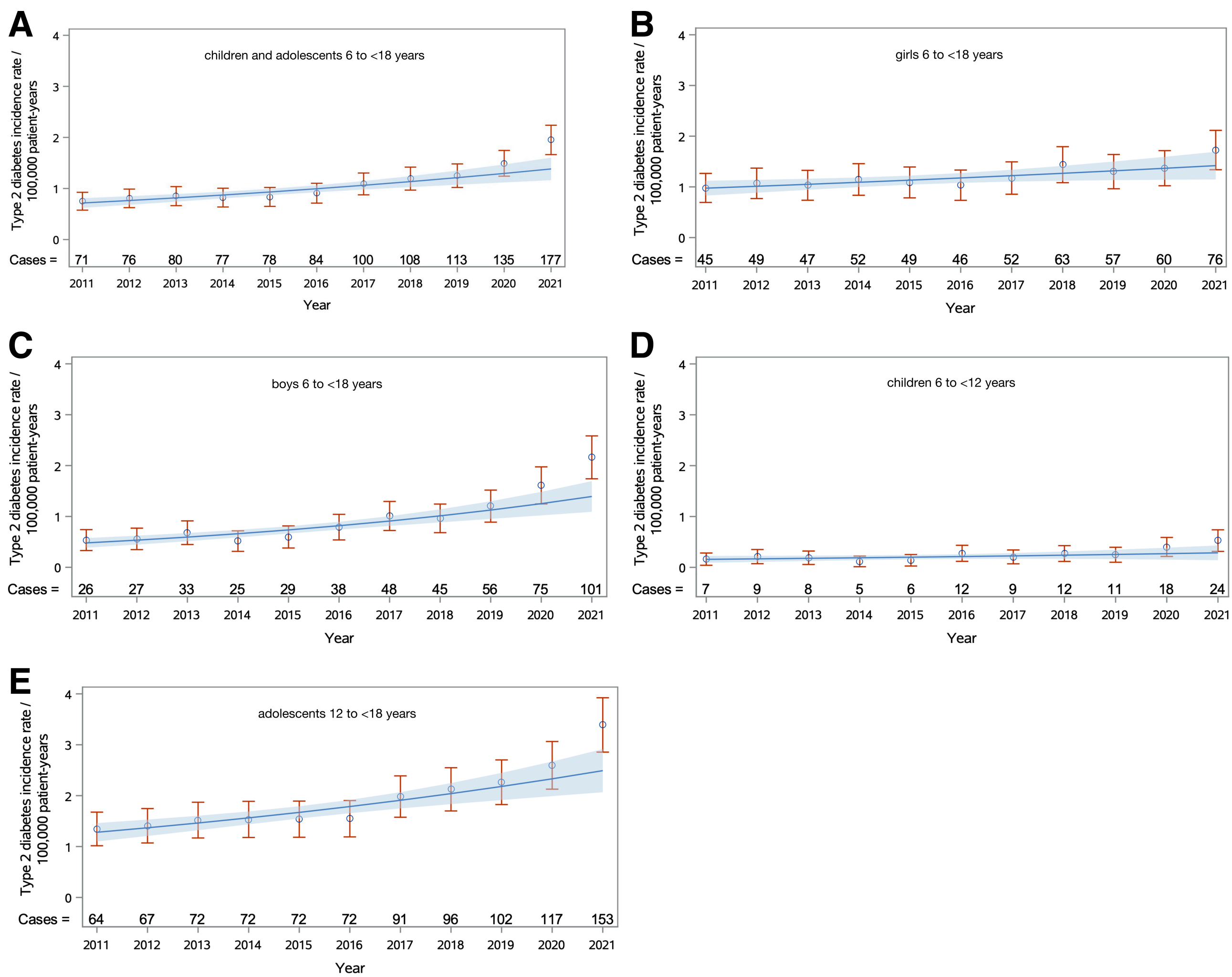

Figure 1—*A*–*E*: Annual incidences of type 2 diabetes from 2011 to 2021 in children and adolescents aged 6 to <18 years (*A*), in girls (*B*), in boys (*C*), in children aged 6 to <12 years (*D*), and in adolescents aged 12 to <18 years (*E*) living in Germany. Annual incidences (blue circles) were standardized for age and/or sex using the 2021 population as reference. Error bars represent the corresponding 95% CIs of the observed incidences. Absolute case numbers of new-onset type 2 diabetes registered in the DPV database are detailed for each year from 2011 to 2021 separately. The predicted type 2 diabetes incidence (dark blue line) and the corresponding 95% CIs (light blue–shaded area) were estimated using a multivariable Poisson trend regression model based on age- and/or sex-standardized incidence data from 2011 to 2019.

higher frequency of DKA compared with the 2 prepandemic years.

Observed and Predicted BMI *z* Scores and HbA_{1c} Levels in 2020 and 2021

The trend model for BMI *z* score at diabetes onset revealed that observed values were not significantly different from predicted values for the entire study population in 2020 (adjusted difference −0.02; 95% CI −0.17, 0.14) and 2021 (adjusted difference 0.03; 95% CI −0.11, 0.16). Additionally, no significant deviations from predicted BMI *z* score in 2020 or 2021 were observed in subanalyses stratified by sex and age group (Table 2).

Accordingly, HbA_{1c} at diabetes diagnosis in the total population did not deviate from predicted values in 2020 and 2021. Similarly, no significant changes in HbA_{1c} were observed in the subgroup analyses for girls, boys, or the group of adolescents aged 12 to <18 years. Of note, in 2021, the observed mean HbA_{1c} at diagnosis was significantly higher than that predicted in the group aged 6 to <12 years (Table 2).

CONCLUSIONS

The present population-representative analysis shows that the incidence of youth-onset type 2 diabetes increased significantly during the COVID-19 pandemic in Germany. The observed increase was mainly driven by adolescent boys, resulting in a reversal of the previous sex ratio because for the first time more boys than girls developed type 2 diabetes.

Significant Rise in Incidence of Youth-Onset Type 2 Diabetes

We delineate for the first time a significant increase in youth-onset type 2 diabetes in Germany from 2011 to 2019. The observed annual incidence increase of 6.8% during these prepandemic years seems to be consistent with reported annual changes in the prevalence of youth-onset type 2 diabetes in the German NRW Diabetes Registry (28,29). Importantly, we detected significant changes in the rate of change in type 2 diabetes incidence in the years before 2020, namely, in 2015, for the total population and in 2016 for boys.

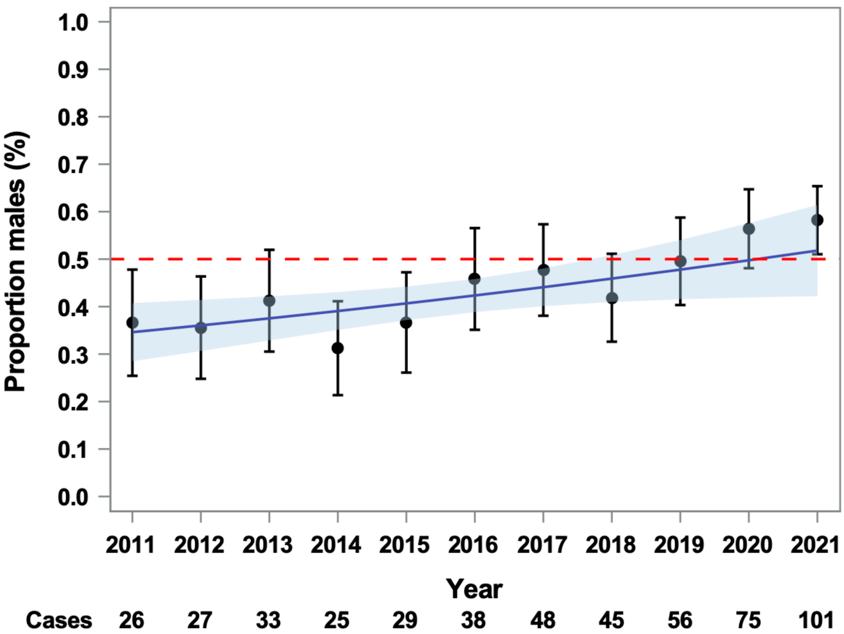

Figure 2—Proportion of boys with incident type 2 diabetes (aged 6 to <18 years) per year of diabetes diagnosis from 2011 to 2021 in Germany. Annual proportions of boys (black dots) were standardized for age using the 2021 population as reference. Error bars represent the corresponding 95% CIs of the observed proportion of boys. Absolute case numbers of boys with new-onset type 2 diabetes registered in the DPV database are detailed for each year from 2011 to 2021 separately. The predicted proportion of boys (dark blue line) and the corresponding 95% CIs (light blue–shaded area) were estimated using a multivariable Poisson trend regression model based on age-standardized incidence data from 2011 to 2019. For illustrative purposes, the horizontal red dashed line indicates equal proportions of girls and boys with type 2 diabetes.

In 2020 and 2021, the preexisting upward trajectory in youth-onset type 2 diabetes incidence strengthened considerably, with 19 and 30% increases in the total population compared with the previous year. Available data on potential changes in the epidemiology of pediatric type 2 diabetes during the COVID-19 pandemic come primarily from the U.S. (6,8–12). In Florida, based on analysis of ICD codes and medication prescriptions in the population-representative OneFlorida+ Network, quarterly type 2 diabetes incidences in children were observed to fluctuate from 2020 to mid 2021, but they consistently exceeded those predicted by 10 to 25% (range of type 2 diabetes incidences from first quarter [Q1] 2017 to Q4 2019 10.6–14.6 per 100,000 PYs; range from Q1 2020 to Q2 2021 13.1–16.9 per 100,000 PYs) (6). Therefore, in the context of substantially higher population incidence rates, the observed increases in youth-onset type 2 diabetes incidence in Florida during the COVID-19 pandemic seem to range below those observed in our population-representative study. However, comparability of the data may be limited, not only because of differences in data acquisition methodology (e.g., ICD-based vs. health care provider–verified diagnoses), but also because of the different ethnic and sociodemographic compositions of the populations, structural differences in the health care systems, and different temporal dynamics of the COVID-19 pandemic and the heterogeneity of the containment measures implemented.

Direct comparisons of the significantly increased standardized incidence rates of type 2 diabetes in our population-based study with respective case numbers of new type 2 diabetes diagnoses in recently published case series from single tertiary care centers in the U.S. do not seem feasible.

Table 1—Observed versus predicted annual incidences of type 2 diabetes (per 100,000 PYs) in children and adolescents (aged 6 to <18 years) during pandemic years 2020 and 2021 in Germany

	Incidence		IRR for observed vs. predicted incidence (95% CI)
	Observed (95% CI)	Predicted (95% CI)	
2020			
All	1.49 (1.23, 1.81)	1.29 (1.05, 1.59)	1.15 (0.90, 1.48)
Boys	1.61 (1.24, 2.09)	1.25 (0.93, 1.68)	1.29 (0.91, 1.81)
Girls	1.37 (1.02, 1.83)	1.37 (1.02, 1.83)	1.00 (0.70, 1.43)
Aged 6–12 years	0.40 (0.24, 0.68)	0.27 (0.14, 0.51)	1.49 (0.72, 3.09)
Aged 12–18 years	2.60 (2.11, 3.19)	2.33 (1.87, 2.90)	1.11 (0.86, 1.45)
2021			
All	1.95 (1.65, 2.31)	1.38 (1.13, 1.69)	1.41 (1.12, 1.77)
Boys	2.16 (1.73, 2.70)	1.39 (1.05, 1.84)	1.55 (1.14, 2.12)
Girls	1.73 (1.34, 2.23)	1.42 (1.07, 1.88)	1.22 (0.87, 1.70)
Aged 6 to <12 years	0.53 (0.33, 0.83)	0.29 (0.15, 0.53)	1.84 (0.94, 3.61)
Aged 12 to <18 years	3.39 (2.83, 4.06)	2.49 (2.02, 3.08)	1.36 (1.07, 1.74)

Poisson regression models were used to estimate predicted incidences for 2020 and 2021 based on annual increases in incidence from 2011 to 2019. For comparison of observed vs. predicted incidences, IRRs with 95% CIs were estimated. CIs of the observed and predicted incidence rates were adjusted for multiple inference using the Bonferroni method.

Reversal of the Sex Ratio in Youth-Onset Type 2 Diabetes

A novel finding is the observation of higher type 2 diabetes incidence in boys than in girls for 2020 and 2021 in Germany. This remarkable reversal of the prior female predominance in youth-onset type 2 diabetes became more consolidated in the second year of the pandemic (28). A similar reversal of the previous prepandemic sex ratio was recently documented in a retrospective multicenter case series study in the U.S. from March 2020 to March 2021 (2 years prepandemic in girls 55%; pandemic years in girls 45%) (14). Furthermore, a statistically significant increase in the proportion of boys with incident type 2 diabetes (4 years prepandemic in boys 34.1%; pandemic years in boys 46.2%) was recently reported in a pediatric cohort in Alabama between April 2020 and March 2021 (12). In contrast, comparable studies at other U.S. centers

Table 2—Observed versus predicted values of proportion of boys (%), HbA_{1c}, and BMI *z* score at type 2 diabetes diagnosis in children and adolescents (aged 6 to <18 years) during pandemic years 2020 and 2021 in Germany

	Observed values (95% CI)	Predicted values (95% CI)	IRR for observed vs. predicted incidence (95% CI)
Sex ratio			
2020			
Boys, %	56.4 (47.6, 66.8)	49.8 (41.0, 60.4)	1.13 (0.91, 1.42)
2021			
Boys, %	58.2 (50.5, 67.1)	51.8 (44.0, 60.9)	1.12 (0.93, 1.36)
BMI *z* score at type 2 diabetes diagnosis			
2020			
All	2.11 (1.97, 2.25)	2.13 (1.99, 2.27)	−0.02 (−0.17, 0.14)
Boys	2.16 (1.95, 2.36)	2.14 (1.94, 2.34)	0.02 (−0.21, 0.24)
Girls	2.09 (1.89, 2.28)	2.13 (1.93, 2.33)	−0.04 (−0.26, 0.18)
Aged 6 to <12 years	2.09 (1.66, 2.51)	2.34 (1.91, 2.76)	−0.25 (−0.72, 0.22)
Aged 12 to <18 years	2.12 (1.97, 2.27)	2.11 (1.96, 2.25)	0.01 (−0.15, 0.18)
2021			
All	2.17 (2.04, 2.29)	2.14 (2.02, 2.26)	0.03 (−0.11, 0.16)
Boys	2.16 (1.99, 2.33)	2.13 (1.96, 2.30)	0.03 (−0.16, 0.22)
Girls	2.21 (2.03, 2.38)	2.15 (1.97, 2.33)	0.06 (−0.14, 0.25)
Aged 6 to <12 years	2.41 (2.07, 2.76)	2.41 (2.06, 2.75)	0.01 (−0.38, 0.39)
Aged 12 to <18 years	2.12 (1.99, 2.25)	2.11 (1.98, 2.24)	0.01 (−0.13, 0.16)
HbA_{1c} at type 2 diabetes diagnosis			
2020			
All, %	8.48 (7.89, 9.08)	8.47 (7.88, 9.07)	0.01 (−0.65, 0.67)
mmol/mol	69 (63, 76)	69 (63, 76)	0 (−7, 7)
Boys, %	8.78 (7.94, 9.62)	8.82 (7.98, 9.66)	−0.04 (−0.97, −0.89)
mmol/mol	72 (63, 82)	73 (64, 82)	0 (−11, 10)
Girls, %	8.24 (7.40, 9.08)	8.21 (7.37, 9.05)	0.03 (−0.90, 0.97)
mmol/mol	67 (57, 76)	66 (57, 75)	0 (−10, 11)
Aged 6 to <12 years, %	8.25 (6.40, 10.1)	6.74 (4.89, 8.59)	1.50 (−0.55, 3.55)
mmol/mol	67 (46, 87)	50 (30, 70)	16 (−6, 39)
Aged 12 to <18 years, %	8.51 (7.88, 9.13)	8.66 (8.04, 9.29)	−0.16 (−0.85, 0.54)
mmol/mol	69 (63, 76)	71 (64, 78)	−2 (−9, 6)
2021			
All, %	8.77 (8.26, 9.29)	8.50 (7.99, 9.02)	0.27 (−0.30, 0.84)
mmol/mol	72 (67, 78)	69 (64, 75)	3 (−3, 9)
Boys, %	9.08 (8.36, 9.80)	8.88 (8.16, 9.60)	0.20 (−0.60, 1.00)
mmol/mol	76 (68, 84)	74 (66, 81)	2 (−8, 11)
Girls, %	8.51 (7.77, 9.25)	8.22 (7.48, 8.96)	0.29 (−0.53, 1.11)
mmol/mol	69 (61, 78)	66 (58, 74)	3 (−6, 12)
Aged 6 to <12 years, %	8.58 (7.09, 10.07)	6.46 (4.97, 7.95)	2.12 (0.47, 3.77)
mmol/mol	70 (54, 86)	47 (31, 63)	23 (5, 41)
Aged 12 to <18 years, %	8.79 (8.24, 9.34)	8.73 (8.18, 9.28)	0.06 (−0.55, 0.67)
mmol/mol	73 (67, 79)	72 (66, 78)	1 (−6, 7)

Regression models were used to estimate predicted values for 2020 and 2021 for all parameters based on trend analysis data from 2011 to 2019. For comparison of observed vs. predicted values, rate ratios with 95% CIs were calculated. CIs of the observed and predicted HbA_{1c} and BMI *z* score levels were adjusted for multiple inference using the Bonferroni method.

showed no clear trend toward a disproportionate increase in diabetes incidence among boys in 2020 and 2021 (9–11).

During the 9-year prepandemic observation period in our study, the annual increase in type 2 diabetes incidence was almost three times higher in boys than in girls. Thus, the trend toward a change in sex ratio was already detectable in the pre-COVID era. This finding is partly supported by a recent analysis of annual percent changes in type 2 diabetes prevalence in the regional NRW Diabetes Registry. Baechle et al. (29) reported a consistently larger annual increase in type 2 diabetes prevalence in boys than in girls from 2002 to 2016 (boys 8.0%; 95% CI 6.8, 9.3; girls 5.4%; 95% CI 4.0, 6.4), although this trend lost statistical significance from 2017 to 2020 in the context of an overall flattening of the increase in type 2 diabetes prevalence. In the U.S., data from the SEARCH for Diabetes in Youth study comparing the years 2002, 2008, and 2016 showed a continuous and significant increase in incident type 2 diabetes in boys but not in girls. Thus, these data also suggest a longer-term trend of narrowing of the sex gap in type 2 diabetes incidence (30). Consistent with previous findings (29,30), in our study, the increase in incident diabetes cases in those aged 12 to <18 years contributed significantly to the overall increase in type 2 diabetes incidence over the entire observation period.

Table 3—Comparison of demographic, anthropometric, and metabolic characteristics of children and adolescents (aged 6 to <18 years) with new-onset type 2 diabetes in 2018/2019 and 2020/2021 in Germany

	2018/2019 (n = 221)	2020/2021 (n = 312)
Median age, years (IQR)	14.7 (13.9–16.2)	14.5 (13.2–16.4)
Median BMI z score, (IQR)	2.25 (1.84–2.55)[a]	2.19 (1.88–2.52)[b]
Median HbA_{1c}, mmol/mol (IQR)	64 (45–90)[c]	61 (46–94)[d]
Median HbA_{1c}, % (IQR)	8.0 (6.3–10.4)[c]	7.7 (6.4–10.8)[d]
Migration background, % (95% CI)	37.1 (30.7, 43.5)	40.4 (34.9, 45.9)
DKA, % (95% CI)	1.8 (0.04, 3.60)	2.9 (1.02, 4.75)

Median with IQR for continuous variables, and mean with 95% CI for binary data. P values derived from Kruskal-Wallis test for continuous variables and χ^2 test for dichotomous parameters. [a]n = 210. [b]n = 287. [c]n = 212. [d]n = 291.

Patient Characteristics at Type 2 Diabetes Diagnosis: DKA, HbA_{1c}, and BMI

Recent publications from U.S. diabetes centers uniformly reported a doubling or even tripling of the rate of DKA at the time of type 2 diabetes diagnosis during the COVID-19 pandemic (8,9,11). In contrast, no significant increase in DKA was observed in our study. Increasing rates of DKA, as well as increasing HbA_{1c} levels (7), seem to reflect delays in diagnosis and have been attributed to possible changes in population health behaviors or a pandemic-related reduction in the availability of primary health care. Available data on HbA_{1c} in youth with incident type 2 diabetes reveal a heterogeneous pattern, with three studies supporting notable increases in initial HbA_{1c} (8,9,14); however, three others and our own study provide no evidence of a similar trend (11–13).

Given the actual increase in obesity prevalence in Germany and the U.S. during the course of the pandemic (17), it is notable that, in agreement with several single-center studies, we did not find an increase in BMI z score in children with incident type 2 diabetes (8,10–12), whereas the aforementioned U.S. multicenter study revealed significantly higher BMI at presentation during the first year of the pandemic (14). In our study, it can be assumed that this observation was not biased by weight loss associated with delayed diagnosis because neither the initial HbA_{1c} nor the frequency of DKA increased. However, whether youth with newly diagnosed type 2 diabetes were possibly affected by particularly dynamic weight gain during the pandemic months cannot be deduced from the available data.

Potential Pathophysiological Mechanisms Linking the Increasing Type 2 Diabetes Incidence and COVID-19

Hypotheses about pathophysiological mechanisms linking COVID-19 to increased diabetes risk range from virus-mediated impairment of β-cell function to systemic deterioration of insulin sensitivity (e.g., by persistent low-grade inflammation) (15,16). In addition, the drastic changes in the social environment associated with the pandemic may have had a decisive influence on diabetes risk (19,21,22). The effects of the COVID-19 pandemic seem to have had a particularly unfavorable impact on the population of vulnerable children at high risk of diabetes because nonobese or moderately obese children may have gained weight. Similarly, a loss of regular physical activity might have led to a critical increase in insulin resistance in predisposed individuals and especially in male teenagers (31–33). Against the background of a steady increase in the number of male adolescents at high risk of early-onset type 2 diabetes already in the prepandemic years, the pandemic control measures may have contributed directly to the reversal of the sex ratio in type 2 diabetes incidence now observed in Germany.

A direct effect of SARS-CoV-2 infections on diabetes incidence also seems conceivable. An analysis of two medical claims databases in the U.S. recently showed significantly increased hazard ratios for diabetes development in children within 30 days after acute COVID-19 (4). Unfortunately, this analysis does not allow conclusions to be drawn about the type of diabetes. Interestingly, a recent retrospective analysis of Veterans Health Administration data on adults showed a significantly increased risk of incident diabetes in the 120-day period after acute COVID-19 in men but not in women (34). However, whether these epidemiological observations are indicative of the pathophysiological cause of the excessive amplification of the preexisting trend toward a higher type 2 diabetes incidence in boys remains unresolved at this time.

Strengths and Limitations

A strength of our study is the use of population-based data on German children and adolescents. In addition, data from 2 complete years during the course of the COVID-19 pandemic were analyzed. For comparison with observed incidence rates, estimates of expected incidence rates in 2020 and 2021 were obtained using appropriate statistical approaches, taking into account the observed trend in type 2 diabetes incidence over the past decade. The same statistical approach allowed us to assess the degree of obesity and HbA_{1c} in youth with new-onset type 2 diabetes during the COVID-19 pandemic. Limitations of our study include that the multivariable Poisson regression models accounted for only a limited number of possible confounding factors. Therefore, residual confounding at the patient or population level cannot be ruled out. Specifically, an analysis of the association of incident type 2 diabetes with COVID-19 could not be performed, because only incomplete data on the COVID-19 status of the investigated children were available. Furthermore, we did not have sufficient information on the possible use of diabetes-causing drugs or on the results of possibly initiated but not yet completed molecular genetic investigations to exclude monogenetic forms of diabetes. Therefore, it seems possible that despite the application of guideline-based diagnostic criteria for type 2 diabetes (23), reclassifications of the diagnosis may occur in some cases in the future. Conversely, it seems possible that in the pandemic years of 2020 and 2021, overall reduced health care use also resulted in less frequent screening for type 2 diabetes and thus an underestimation of the number of incident cases. Inevitable variations in the coverage of a real-world data registry such as the DPV Registry may also have influenced the incidence estimates, most likely in the direction of an underestimation of the IRRs for 2020 and 2021. Furthermore, it must be considered that possibly the choice of age groups could have influenced the results, and we cannot exclude bias resulting from residual confounding or effect modification, because information on possibly relevant variables (e.g., ethnicity or socioeconomic status) was not available in a sufficiently large number of children. We also did not perform regional analyses, because the small number of pediatric type 2 diabetes cases in Germany does not allow valid conclusions to be drawn. Finally, the data available to us so far do not allow us to draw conclusions about how the incidence of youth-onset type 2 diabetes will evolve as the pandemic progresses.

Implications/Research Needs

Our study results underscore the urgent need for further investigation of the association of the COVID-19 pandemic and accompanying policies and environmental changes with the increasing incidence of type 2 diabetes in children and adolescents. Given the substantial morbidity associated with youth-onset type 2 diabetes, a better understanding of the underlying pathophysiological mechanisms and better calibrated and targeted pandemic interventions are critical for all children and adolescents at high risk of type 2 diabetes.

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