



Invited Commentary | Pediatrics

Elucidating the Underlying Mechanisms of the Marked Increase in Childhood Type 1 Diabetes During the COVID-19 Pandemic—The Diabetes Pandemic

Clemens Kamath, MD; Reinhard W. Holl, MD; Joachim Rosenbauer, MD

In a systematic review and meta-analysis in *JAMA Network Open*, D'Souza et al¹ compared changes in the incidence of diabetes (type 1 and type 2) and the proportion of diabetic ketoacidosis (DKA) in children and adolescents during the COVID-19 pandemic with the prepandemic year. This meta-analysis included 17 studies with 38 149 children with newly diagnosed type 1 diabetes and 15 studies with 4324 children presenting with DKA. Few studies have examined the incidence of type 2 diabetes, and the available data has been inconclusive.

The authors found a 16% (95% CI, 10%-23%) higher incidence rate of childhood type 1 diabetes during the first 12 months and a 28% (95% CI, 18%-39%) higher incidence rate during the subsequent 12 months of the pandemic compared with the year before the COVID-19 pandemic. This increase is significantly higher than the prepandemic increase of 2% to 3% in the annual incidence rate of type 1 diabetes.²

Theoretically, there could be a transient period of lower incidence at the beginning of the pandemic due to delays in diabetes diagnosis, followed by a period of increased incidence of type 1 diabetes as a catch-up effect. A strength of the study by D'Souza et al¹ is that only studies with at least 12 months before and during the COVID-19 pandemic were included to avoid bias from short-term and seasonal effects. Furthermore, the study by D'Souza et al¹ has shown a significant increase in the incidence of type 1 diabetes even throughout the second year of the pandemic.

How can this increase in childhood type 1 diabetes during the COVID-19 pandemic be explained? Studies using large health service data sets have suggested a direct effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the development of type 1 diabetes. However, these studies do not adequately account for the high proportion of asymptomatic children. This shortcoming may have led to an overestimation of the risk of diabetes after COVID-19.^{3,4}

Second, the increase in childhood type 1 diabetes during the COVID-19 pandemic may be due to autoimmunity,^{2,5} and direct cytotoxicity of β cells in children seem rather unlikely. Recent data from Finland showed an increased incidence rate ratio of 1.16 (95% CI, 1.06-1.25) of childhood type 1 diabetes during the first 18 months of the pandemic compared with a prepandemic period. Importantly, of 583 children with newly diagnosed type 1 diabetes who were tested for SARS-CoV-2 antibodies, only 5 (0.9%) were positive.⁶ Furthermore, a study using data from 51 970 children and adolescents of 2 large registries in Colorado, US, and Bavaria, Germany, found no significant association between antibodies against SARS-CoV-2 and the development of multiple type 1 diabetes-associated autoantibodies (odds ratio, 1.06 [95% CI, 0.59-1.08]) or singular high-affinity islet autoantibodies (odds ratio, 1.34 [0.70-2.44]).⁷

Third, environmental changes that occurred during the COVID-19 pandemic may explain the observed increase in the incidence rate of type 1 diabetes in children. The COVID-19 pandemic has led to a reduction in the biodiversity of exposures. Although common infections in childhood are a risk factor for developing type 1 diabetes, the hygiene hypothesis states that infections may also protect against autoimmune diseases. Therefore, one theory suggests that changes in the overall environmental exposures of young children during the pandemic may be involved in the increase in type 1 diabetes by shifting the balance of environmental factors from protective to inducing islet

+ Related article

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

autoimmunity. Finally, weight gain seen in young children during the pandemic may be associated with an increased risk of islet autoimmunity.⁸

Regardless, the substantial increase in the incidence of type 1 diabetes in children during the COVID-19 pandemic provides an opportunity to learn more about the causes of the rising incidence of type 1 diabetes in children that was observed well before the SARS-CoV-2 outbreak, albeit at a much slower rate.² One area of interest may be the impact of the pandemic on the gut microbiome in young children. In a series of longitudinal studies, the fecal microbiota of individuals with islet autoimmunity seroconversion or new-onset type 1 diabetes was found to be less diverse than that of healthy controls.⁹ Even if the microbiome has changed again during the ongoing pandemic, its effects on islet autoimmunity could be further analyzed using biobanks that store blood, stool, and other samples. It is possible that the factors leading to the increase in diabetes incidence before and during the pandemic are the same, with a more pronounced effect during the pandemic.

The article by D'Souza et al¹ also found a 26% (95% CI 17%-36%) higher rate of DKA at type 1 diabetes diagnosis during the first 12 months of the pandemic compared with the previous year. DKA is an acute life-threatening complication of a delayed diagnosis of new onset type 1 diabetes. During the pandemic, several studies demonstrated an increase in the prevalence of DKA but also of the HbA1c level at the time of diabetes diagnosis.² Because the HbA1c level at the time of diabetes diagnosis is lower when β cell destruction is more rapid, as is often the case in very young children, and higher when diagnosis is delayed, this suggests that delayed diagnosis of diabetes was the main cause of the increased rate of DKA during the pandemic. D'Souza et al¹ proposed that delays in diabetes diagnosis resulting in DKA may reflect hesitancy to seek or barriers to access emergency care. This is certainly a plausible explanation for the early phase of the pandemic. However, it is unclear why the increased prevalence of DKA persisted throughout the second year of the pandemic, even though the lockdown in most countries had ended, normal life had indeed resumed, and the vast majority of people had become accustomed to living with a pandemic. In addition, a recent study reported that the frequency of DKA at diagnosis of type 1 diabetes was increasing even before the pandemic.¹⁰ Again, the pandemic could accelerate—and possibly unravel—a long-term development in the pathophysiology of type 1 diabetes.

Both the increased incidence of pediatric type 1 diabetes and the higher prevalence of DKA at diagnosis led to a massive rise in the number of children with DKA during the pandemic needing intensive care. With limited personnel resources, this increase can lead to overload and bottlenecks in care—currently in acute care, but also in the long-term care of children with type 1 diabetes. Epidemiologic studies during the last decades, including during the COVID-19 pandemic, indicate that the incidence of type 1 diabetes continues to rise.

ARTICLE INFORMATION

Published: June 30, 2023. doi:10.1001/jamanetworkopen.2023.21231

Open Access: This is an open access article distributed under the terms of the [CC-BY License](#). © 2023 Kamath C et al. *JAMA Network Open*.

Corresponding Author: Clemens Kamrath, MD, Center of Child and Adolescent Medicine, Justus Liebig University, Feulgenstr. 12, 35385 Giessen, Germany (clemens.kamrath@paediat.med.uni-giessen.de).

Author Affiliations: Centre of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany (Kamath); Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany (Holl); German Centre for Diabetes Research (DZD), Munich-Neuherberg, Germany (Holl, Rosenbauer); Institute for Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany (Rosenbauer).

Conflict of Interest Disclosures: None reported.

REFERENCES

1. D'Souza D, Empringham J, Pechlivanoglou P, Uleryk EM, Cohen E, Shulman R. Incidence of diabetes in children and adolescents during the COVID-19 pandemic: a systematic review and meta-analysis. *JAMA Netw Open*. 2023; 6(6):e2321281. doi:10.1001/jamanetworkopen.2023.21281
2. Baechle C, Eckert A, Kamrath C, et al. Incidence and presentation of new-onset type 1 diabetes in children and adolescents from Germany during the COVID-19 pandemic 2020 and 2021: current data from the DPV registry. *Diabetes Res Clin Pract*. 2023;197:110559. doi:10.1016/j.diabres.2023.110559
3. Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Association of SARS-CoV-2 infection with new-onset type 1 diabetes among pediatric patients from 2020 to 2021. *JAMA Netw Open*. 2022;5(9):e2233014. doi:10.1001/jamanetworkopen.2022.33014
4. Hippich M, Holthaus L, Assfalg R, et al. A public health antibody screening indicates a 6-fold higher SARS-CoV-2 exposure rate than reported cases in children. *Med*. 2021;2(2):149-163.e4. doi:10.1016/j.medj.2020.10.003
5. Kamrath C, Rosenbauer J, Tittel SR, et al. Frequency of autoantibody-negative type 1 diabetes in children, adolescents, and young adults during the first wave of the COVID-19 pandemic in Germany. *Diabetes Care*. 2021; 44(7):1540-1546. doi:10.2337/dc20-2791
6. Knip M, Parviainen A, Turtinen M, et al; Finnish Pediatric Diabetes Register. SARS-CoV-2 and type 1 diabetes in children in Finland: an observational study. *Lancet Diabetes Endocrinol*. 2023;11(4):251-260. doi:10.1016/S2213-8587(23)00041-4
7. Rewers M, Bonifacio E, Ewald D, et al; ASK Study Group and Fr1da Study Group. SARS-CoV-2 infections and presymptomatic type 1 diabetes autoimmunity in children and adolescents from Colorado, USA, and Bavaria, Germany. *JAMA*. 2022;328(12):1252-1255. doi:10.1001/jama.2022.14092
8. Liu X, Vehik K, Huang Y, et al; TEDDY Study Group. Distinct growth phases in early life associated with the risk of type 1 diabetes: the TEDDY study. *Diabetes Care*. 2020;43(3):556-562. doi:10.2337/dc19-1670
9. Dedrick S, Sundaresh B, Huang Q, et al. The role of gut microbiota and environmental factors in type 1 diabetes pathogenesis. *Front Endocrinol (Lausanne)*. 2020;11:78. doi:10.3389/fendo.2020.00078
10. Birkebaek NH, Kamrath C, Grimsman JM, et al. Impact of the COVID-19 pandemic on long-term trends in the prevalence of diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes: an international multicentre study based on data from 13 national diabetes registries. *Lancet Diabetes Endocrinol*. 2022;10(11):786-794. doi:10.1016/S2213-8587(22)00246-7