Journal Pre-proof

The COVID-19 pandemic is associated with a substantial rise in frequency and severity of presentation of youth-onset type 2 diabetes

Sheela N. Magge, MD, MSCE, Risa M. Wolf, MD, Laura Pyle, PhD, Elizabeth A. Brown, MPH, Valeria C. Benavides, MD, MPH, Monica E. Bianco, MD, Lily C. Chao, MD, Anna Cymbaluk, MD, Pinar Gumus Balikcioglu, MD, Kelsee Halpin, MD, MPH, Daniel S. Hsia, MD, Lina Huerta-Saenz, MD, Jane J. Kim, MD, Seema Kumar, MD, Lorraine E. Levitt Katz, MD, Brynn E. Marks, MD, MSHPEd, Anna Neyman, MD, Katie L. O'Sullivan, MD, Sabitha Sasidharan Pillai, MD, Amy S. Shah, MD, MS, Ashley H. Shoemaker, MD, MSCI, Juwairriyyah A.W. Siddiqui, MD, Shylaja Srinivasan, MD, Inas H. Thomas, MD, Jeanie B. Tryggestad, MD, Maha F. Yousif, MD, Megan M. Kelsey, MD, MS, on behalf of the COVID-19 and Type 2 Diabetes Consortium

PII: S0022-3476(22)00719-3

DOI: https://doi.org/10.1016/j.jpeds.2022.08.010

Reference: YMPD 13121

To appear in: *The Journal of Pediatrics*

Received Date: 10 May 2022

Revised Date: 31 July 2022

Accepted Date: 10 August 2022

Please cite this article as: Magge SN, Wolf RM, Pyle L, Brown EA, Benavides VC, Bianco ME, Chao LC, Cymbaluk A, Gumus Balikcioglu P, Halpin K, Hsia DS, Huerta-Saenz L, Kim JJ, Kumar S, Levitt Katz LE, Marks BE, Neyman A, O'Sullivan KL, Sasidharan Pillai S, Shah AS, Shoemaker AH, Siddiqui JAW, Srinivasan S, Thomas IH, Tryggestad JB, Yousif MF, Kelsey MM, on behalf of the COVID-19 and Type 2 Diabetes Consortium, The COVID-19 pandemic is associated with a substantial rise in frequency and severity of presentation of youth-onset type 2 diabetes, *The Journal of Pediatrics* (2022), doi: https://doi.org/10.1016/j.jpeds.2022.08.010.

during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: The COVID-19 pandemic is associated with a substantial rise in frequency and severity of presentation of youth-onset type 2 diabetes

**Authors: ***Sheela N. Magge, MD, MSCE[a], *Risa M. Wolf, MD[a], Laura Pyle, PhD[b], Elizabeth A. Brown, MPH[a], Valeria C. Benavides, MD, MPH[c], Monica E. Bianco, MD[d], Lily C. Chao, MD[e], Anna Cymbaluk, MD[f], Pinar Gumus Balikcioglu, MD[g], Kelsee Halpin, MD, MPH[h], Daniel S. Hsia, MD[i], Lina Huerta-Saenz, MD[j], Jane J. Kim, MD[k], Seema Kumar, MD[l], Lorraine E Levitt Katz, MD[m], Brynn E. Marks, MD, MSHPEd[n], Anna Neyman, MD[o], Katie L. O'Sullivan, MD[p], Sabitha Sasidharan Pillai, MD[q], Amy S. Shah, MD, MS[r], Ashley H. Shoemaker, MD, MSCI[s], Juwairriyyah A. W. Siddiqui, MD[t], Shylaja Srinivasan, MD[u], Inas H Thomas, MD[v], Jeanie B. Tryggestad, MD[w], Maha F. Yousif, MD[x], Megan M. Kelsey, MD, MS[b] on behalf of the COVID-19 and Type 2 Diabetes Consortium^

[a]Johns Hopkins Hospital/Johns Hopkins University School of Medicine, Division of Pediatric Endocrinology and Diabetes, Baltimore, MD
[b]University of Colorado Anschutz Medical Campus/Children's Hospital Colorado, Department of Pediatrics, Aurora, CO
[c]University of Illinois, College of Medicine of Peoria/Children's Hospital of Illinois, Department of Pediatrics, Division of Endocrinology, Peoria, IL
[d]Northwestern University/Ann and Robert H Lurie Children's Hospital, Department of Pediatrics, Division of Pediatric Endocrinology, Chicago, IL
[e]Children's Hospital Los Angeles, Center for Endocrinology, Diabetes, and Metabolism, Los Angeles, CA
[f]Texas Children's Hospital/Baylor College of Medicine, Department of Pediatric Diabetes and Endocrinology, Houston, TX
[g]Duke University Medical Center, Division of Pediatric Endocrinology and Diabetes and Duke Molecular Physiology Institute, Durham, NC
[h]University of Missouri-Kansas City School of Medicine, Children's Mercy Kansas City, Division of Endocrinology and Diabetes, Kansas City, MO
[i]Our Lady of the Lake Children's Hospital/Pennington Biomedical Research Center, Baton Rouge, LA
[j]Penn State Health Children's Hospital/Penn State College of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Hershey, PA
[k]University of California San Diego/Rady Children's Hospital San Diego, Department of Pediatrics, Division of Pediatric Endocrinology, San Diego, CA
[l]Mayo Clinic, Department of Pediatrics, Division of Pediatric Endocrinology, Rochester, MN
[m]Children's Hospital of Philadelphia, Division of Endocrinology and Diabetes, Philadelphia, PA
[n]Children's National Hospital, Division of Endocrinology and Diabetes, Washington DC
[o]Indiana University School of Medicine/Riley Hospital for Children, Department of Pediatrics, Indianoplis, IN
[p]University of Chicago Medical Center, Section of Adult & Pediatric Endocrinology, Diabetes & Metabolism, Chicago, IL
[q]Warren Alpert Medical School of Brown University/Hasbro Children's Hospital, Division of Pediatric Endocrinology, Providence, RI
[r]Cincinnati Children's Hospital Medical Center & The University of Cincinnati, Division of Pediatric Endocrinology, Cincinnati, OH

[s]Vanderbilt University Medical Center, Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Nashville, TN
[t]Columbia University Irving Medical Center, Harlem Hospital, Department of Pediatrics, New York, NY
[u]University of California, San Francisco, Department of Pediatrics, Division of Endocrinology, San Francisco, CA
[v]University of Michigan, Department of Pediatrics, Pediatric Endocrinology, Ann Arbor, MI
[w]University of Oklahoma Health Sciences Center, Department of Pediatrics, Section of Diabetes/Endocrinology, Oklahoma City, OK
[x]University of Texas Southwestern, Department of Pediatrics, Pediatric Endocrinology, Dallas, TX

*Contributed equally
^ List of additional members of the COVID-19 and Type 2 Diabetes Consortium is available at www.jpeds.com (Appendix).

Corresponding author:
Megan M. Kelsey, MD, MS
13123 E 16th Ave, B265
Aurora, CO 80045
Tel: 720-777-6128
E-mail: megan.kelsey@childrenscolorado.org

Conflict of Interest Disclosures: Dr Huera-Saenz is a site investigator for a type 2 diabetes treatment trial sponsored by Boehringer-Ingelheim; Dr Kelsey is a site investigator for type 2 diabetes treatment trials sponsored by Boehringer-Ingelheim and Janssen; Dr Marks has received investigator-initiated funding from Tandem Diabetes Care and Dexcome; Dr Shoemaker is site PI for trials sponsored by AstraZeneca, NovoNordisk, and Boehringer-Ingelheim; Dr Wolf has received investigator-initiated funding from Dexcom; the other authors declare no conflicts of interest.

Funding: No specific support was received for this project.

Abbreviations: T1D=type 1 diabetes; **BMI**= body mass index; **DKA**=diabetic ketoacidosis

Abstract

Objectives: To evaluate the frequency and severity of new cases of youth-onset type 2 diabetes in the United States during the first year of the pandemic compared with the mean of the prior two years.

Study Design: Multicenter (n=24 centers), hospital-based, retrospective chart review. Youth aged ≤ 21 years with newly-diagnosed TYPE 2 DIABETES between March 2018 and February 2021, body mass index ≥ 85th%ile, and negative pancreatic autoantibodies were included. Demographic and clinical data, including case numbers and frequency of metabolic decompensation, were compared between groups.

Results: A total of 3113 youth (mean [SD] 14.4 [2.4] years, 50.5% female, 40.4% Hispanic, 32.7% Black, 14.5% non-Hispanic White) were assessed. New cases of TYPE 2 DIABETES increased by 77.2% in the year during the pandemic (n=1463) compared with the mean of the previous 2 years, 2019 (n=886) and 2018 (n=765). Likelihood of presenting with metabolic decompensation and severe diabetic ketoacidosis also increased significantly during the pandemic.

Conclusions: The burden of newly diagnosed youth-onset type 2 diabetes increased significantly during the COVID-19 pandemic, resulting in enormous strain on pediatric diabetes health care providers, patients, and families. Whether the increase was caused by COVID-19 infection, or just associated with environmental changes and stressors during the pandemic is unclear. Further studies are needed to determine whether this rise is limited to the United States and whether it will persist over time.

Introduction

The incidence of youth-onset type 2 diabetes is rising worldwide. The SEARCH for Diabetes in Youth Study showed an increase in incidence of 5% per year in the United States from 2002 to 2012[1], such that prevalence nearly doubled between 2001 and 2017[2]. This has significant long-term implications, given observations from the Treatment Options for Type 2 Diabetes in Youth (TODAY) study showing rapid β-cell failure[3] and early onset of complications[4] in least half of US youth with type 2 diabetes.

A recent CDC study[5] demonstrated increased diabetes incidence in youth following COVID-19 infection, but did not differentiate diabetes type. Moreover, irrespective of concomitant COVID-19 infection, since the onset of the pandemic, pediatric endocrinologists have anecdotally experienced an unprecedented acute burden of newly-diagnosed type 2 diabetes. Multicenter and/or population-based studies in the US and Europe suggest that the proportion of youth with T1D presenting in diabetic ketoacidosis (DKA) rose early in the pandemic, but the impact on the overall incidence of T1D is still unclear[6-10]. Several U.S. individual institutions showed an increase in both rates and severity of presentation of youth-onset type 2 diabetes during the pandemic[11-15]. However, multicenter/population-based data regarding effects of the COVID-19 pandemic on youth-onset type 2 diabetes have not yet been published.

This study was designed to compile retrospective data from electronic medical records (EMRs) from institutions across the U.S. to assess the national impact of the COVID-19 pandemic on rates of youth-onset type 2 diabetes. Specifically, the aims were to compare the total number of new cases of youth-onset type 2 diabetes and the proportion of those youth presenting with

metabolic decompensation (DKA and/or hyperosmolar hyperglycemic syndrome [HHS]) from March 2020 – February 2021 to the prior 2 years.

Research Design and Methods

This retrospective, multi-center study examined trends in youth-onset type 2 diabetes diagnosis and incidence of metabolic decompensation at presentation during the first year of the COVID-19 pandemic (March 1, 2020 - February 28, 2021) compared with the prior two years (March 1, 2018 – Feb 29, 2020). This collaborative effort was organized by the Children's Hospital Colorado/University of Colorado School of Medicine and the Johns Hopkins Hospital/Johns Hopkins University School of Medicine, with 24 contributing diabetes clinics in the United States (Acknowledgements). IRB approval was obtained by each contributing site, with a waiver of consent. Deidentified data were submitted to the coordinating center.

Patients ≤ 21 years old diagnosed with type 2 diabetes from March 1, 2018 – March 1, 2021 were included. Diagnosis of type 2 diabetes, in accordance with American Diabetes Association (ADA) guidelines, required ≥ 2 negative diabetes-associated antibodies (glutamic acid decarboxylase-65 [GAD-65], insulin antibodies, zinc transporter 8 [ZnT8], and/or islet antibodies [islet antigen-2 (IA-2) or islet cell antibodies]), and no positive antibodies [16]. Medication-induced diabetes, pre-diabetes, post-transplant diabetes, and body mass index (BMI) <85%ile were exclusionary. Patients were included if BMI was ≥85%ile was confirmed before onset of type 2 diabetes, but acute weight loss resulted in BMI <85%ile at diagnosis. Inclusion criteria were designed to ensure participants had type 2 diabetes while being kept broad enough to ensure generalizability and reduce bias. Eligibility was adjudicated at each site based on these

criteria. Of note, history of overweight/obesity was confirmed in 112 participants who do not have BMI at diagnosis due to missing height.

EMR-extracted data included: diabetes-related clinical variables, sex, race/ethnicity, insurance type, age at diagnosis, BMI, hemoglobin A1c (HbA1c) and initial random blood sugar at diagnosis; for those with metabolic decompensation (DKA or HHS, or mixed DKA/HHS) at presentation, initial pH, bicarbonate and serum osmolarity were recorded. At 23/24 instutitions race and ethnicity were determined by two separate questions; in addition to these self-report questions, the University of Columbia uses Spanish language to help determine Hispanic/LatinX ethnicity if a family reports "other or unknown". Data extraction from EMR allowed for options of "other" and "unknown" for race, and thus some of these data are incomplete. Laboratory values reported as either above or below the limit of detection were set to the limit of detection. DKA was defined as either pH<7.3 or bicarbonate≤15. DKA severity was categorized using the International Society for Pediatric and Adolescent Diabetes 2018 guidelines: mild DKA=pH 7.2 -7.29 and/or bicarbonate 11-15 mmol/L, moderate DKA=pH 7.1-7.19 and/or bicarbonate 6-10 mmol/L, and severe DKA=pH<7.1 and/or bicarbonate ≤5 mmol/L[17]. HHS was defined as serum osmolality ≥330 mOsm/kg and serum glucose >600mg/dL. If data regarding pH or osmolality were missing, it was presumed that they did not present in DKA or HHS, respectively.

The primary outcome was the absolute case number of new-onset type 2 diabetes diagnosed in the first year of the COVID-19 pandemic, compared with the mean of the prior 2 years. The secondary outcome was the percentage of these patients presenting with metabolic decompensation (DKA, HHS, or mixed DKA/HHS) compared with the prior 2 years.

Statistical Analysis

Descriptive statistics reported include mean ± standard deviation (SD) for normally distributed continuous variables, median (25^{th}, 75^{th} percentile) for skewed continuous variables, and frequency and percentage for categorical variables. Groups were compared using either a t-test or ANOVA for normally distributed continuous variables, the Kruskal Wallis test for non-normally distributed variables, and the chi-square test for categorical variables.

A negative binomial time series model was used to model the count of youth-onset type 2 diabetes diagnoses per month. A background linear trend of 5% increase per year was assumed. Seasonality was assessed by allowing the number of diagnoses in a particular month to depend on the number in the prior month, and the number 12 months prior. A test of intervention was performed to determine whether the onset of the pandemic in March 1, 2020, had a significant effect on the count of diagnoses[18, 19].

The year from 3/1/18 - 2/28/19 is referred to as pre-pandemic year 18-19 (PPY18-19), from 3/1/19 - 2/29/20 as pre-pandemic year 19-20 (PPY19-20), and from 3/1/20 - 2/28/21 as the pandemic year.

Results

A total of 3,459 patients with new-onset type 2 diabetes were identified from 24 centers across the U.S. Of these, 312 were excluded due to inadequate antibody data, 32 were excluded due to BMI <85%ile, one was excluded due to suspicion for monogenic diabetes, and onewas excluded due to young age, atypical of type 2 diabetes. Thus, the final analysis included3,113 participants (Table I). The average number of new diagnoses per year in the two pre-pandemic years was

825, compared with 1463 diagnosed during the first pandemic year, an increase of 77.3% (Figure 1). The increase in new presentation was seen across almost all sites (Table II; available at www.jpeds.com). The largest contributing site reported 426 new cases (13.7% of the total sample). The South and West regions were over-represented, particularly compared with the Northeast (Table I, p=0.11). The mean age at presentation did not change over the 3-year period.

Because of an apparent peak of diagnoses in August, a covariate corresponding to August vs. other months was tested but was not significant. Thus, the final model did not include any effect of seasonality. There was a difference in racial/ethnic distribution over the 3 years, p=0.004 (Table I, Figure 2), with post-hoc analyses demonstrating increased diagnoses among Black youth (p= 0.002) and decreased diagnoses among White youth (p=0.039) during the pandemic year. The vast majority of new type 2 diabetes diagnoses occurred in those with public insurance during all three years. There was a reversal in the proportion of male vs female new diagnoses—55% female/45% male in PPY18-19 and PPY19-20 compared with 45% female/55% male during the pandemic year (p<0.001, Figure 2). There was no difference in association of sex by race/ethnicity pre- and post- pandemic.

BMI was statistically higher on presentation in the pandemic year compared with PPY1 and PPY2. Patients with new-onset type 2 diabetes presented with higher HbA1c (median 10.4% vs 9.3% (PPY1) and 9.7% (PPY2), p<0.001) and higher blood glucose during the pandemic compared with the two previous years (median 286 mg/dL vs 240 mg/dL (PPY18-19) and 246 mg/dl (PPY19-20), p<0.001). In the pre-pandemic years, more patients with new-onset type 2 diabetes were diagnosed as outpatients; there was a reversal during the pandemic year such that

more patients were diagnosed and managed as inpatients (43% inpatient vs 57% outpatient during PPY18-19 and PPY19-20, as opposed to 57% inpatient and 43% outpatient during the pandemic). Further, 21% of youth presented with metabolic decompensation (DKA and/or HHS) at diagnosis of type 2 diabetes during the first year of the pandemic compared with 9.4% and 9.0% in PPY1 and PPY2, respectively ($p<0.001$) (Table I, Figure 1). Few patients in this cohort had a concurrent COVID-19 infection detected at presentation of type 2 diabetes (Table I).

A negative binomial time series model showed that pandemic onset (March 1, 2020) had a significant effect on the number of type 2 diabetes diagnoses, with a parameter estimate of 15.2, $p<0.0001$. This estimate represents an increase of 15.2 type 2 diabetes cases per month, although the effect is not strictly additive because the background linear trend of 5% increase per year is applied to the increased number of cases per month. Another negative binomial time series model demonstrated a significant effect of the pandemic on the number of patients presenting with metabolic decompensation, with a parameter estimate of 7.0, $p= 0.002$.

Discussion

This first multicenter report from 24 U.S. diabetes centers, including more than 3,100 youth diagnosed with new-onset type 2 diabetes over 3 years, shows an unprecedented impact of the COVID-19 pandemic on the frequency of diagnosis of youth-onset type 2 diabetes, increasing by 77.3% compared with the average in the 2 prior years. Moreover, severity of initial presentation rose, based on proportion presenting with metabolic decompensation, which more than doubled, and median HbA1c at diagnosis. This confirms the findings of three single-center studies, all of

which contributed data to this analysis, suggesting that rates of type 2 diabetes and presentation in DKA rose during the COVID-19 pandemic[11, 14, 15].

Although the incidence of type 2 diabetes was already on the rise, the increase seen in the past year significantly outpaces recently published epidemiologic data, which demonstrated an annual increase in incidence of approximately 5% between 2002 and 2012[1]. Interestingly, the rise in youth-onset type 2 diabetes between PPY18-19 and PPY19-20, at 15.8%, was also greater than previously reported. However, data presented here are derived from subspecialty diabetes care centers, and are not population-based data, so trends seen in this study may not be generalizable. Historically, type 2 diabetes has been described as almost twice as common among females in U.S. youth[1, 20], but during the pandemic this trend changed, with an increase in the relative proportion of adolescent males diagnosed. There was also an increase in proportion of cases diagnosed in Black youth and a decrease in White youth during the pandemic. The sex differences seen do not appear to be driven by racial or ethnic differences. However, the increase in proportion of Black youth diagnosed with type 2 diabetes is consistent with recent U.S. population data[2].

Potential explanations for the pandemic-associated rise in youth-onset type 2 diabetes are broad and likely multi-factorial. Pediatric weight gain tends to increase during summer months, when school is out[21, 22]. Indeed, there are regional[23, 24] and national[25, 26] database reports of a rising trajectory of BMI during the pandemic, when most youth were out of school, and BMI increases were greatest in youth with prior overweight or obesity. However, the rise in BMI appears to have had the most significantly affected younger children (5-11 years)[25], whereas the onset of type 2 diabetes seldom occurs prior to puberty. We noted an increase in BMI of youth at diabetes diagnosis in the pandemic year compared with the prior 2 years. The reasons for

pandemic gains in BMI have yet to be elucidated, but presumably are in part related to increases in sedentary behavior and changes in eating behaviors. During the pandemic, families reported changes in the home food environment, purchasing more shelf-stable foods that are ultra-processed and calorie-dense, which could contribute to weight gain[27]. Sedentary behavior changes included increased screen time related to online school, lack of physical education, cancellation of organized sports and other activities, and people being more confined to their homes[28]. One group specifically reported an increase in screen time during the pandemic in youth with previously diagnosed type 2 diabetes [29]. However, most of available data regarding pandemic-related behavior changes are based on self-report, relying on recall for report of prepandemic behaviors; thus, these are likely to be inaccurate[28-30]. Accelerometry-based data from TODAY and NHANES suggested that greater sedentary behavior distinguishes youth with type 2 diabetes from youth with obesity but without diabetes[31]. Furthermore, boys are known to be more physically active than girls during adolescence[32, 33], thus may have been affected in terms of BMI gains and metabolic risk by increases in sedentary behavior than girls. This may, in part explain, the reversal in sex differences in incident type 2 diabetes in youth during the pandemic. Although there is some evidence that boys experience greater weight gain during the pandemic[34], the largest studies did not break results down by sex[24, 25, 35], so it is unclear if boys had more significant weight gain than girls. However, data from the TODAY study supports the hypothesis lifestyle change may more significantly affect type 2 diabetes in adolescent males, as males in TODAY responded more favorably to lifestyle intervention than females[3]. Although this evidence is certainly not adequate to prove that lifestyle behavior changes are the sole cause of rising cases of youth-onset type 2 diabetes during the pandemic, they certainly may contribute to its onset in those at increased risk.

Another potential contributor to the pandemic-related increase in type 2 diabetes presentation is an increase in psychosocial stress[36]. Youth with type 2 diabetes are known to be exposed to significant environmental stressors, as evidenced by a high proportion coming from single-caregiver and low-income households, with low parental education attainment[37]. Furthermore, mental health disorders are common in youth with obesity and diabetes[38, 39]. It is possible that elements of this underlying stress could contribute to the pathophysiology of diabetes. Shomaker et al demonstrated that treatment of depression with cognitive behavioral therapy in girls at risk for type 2 diabetes improved insulin sensitivity compared with health education-controls one year after the treatment, and independent of BMI change[40]. Furthermore, in SEARCH, depression was associated with higher metabolic and inflammatory markers[41]. The COVID-19 pandemic has resulted in a significant mental health crisis in youth, with rates of depression and anxiety among youth that have doubled compared with prepandemic years[42]. In addition, screens assessing suicide risk have shown increasing rates of positivity during the COVID-19 pandemic in both the pediatric emergency department[43] and primary care setting[44]. In addition to potentially affecting stress physiology, social determinants of health also impact access to healthy food, access to health care, and safe outdoor environments. The pandemic may have disproportionately affected Black youth, who already are at higher risk for health disparities[45]. This may in part explain the racial differences in newly diagnosed diabetes associated with the pandemic. Whether there is a direct or indirect relationship between psychosocial stress and incident youth-onset type 2 diabetes, this coincident increase during the pandemic warrants further investigation.

Finally, there is a possibility that COVID-19 infection itself may have caused a non-autoimmune destruction of β cells, resulting in declines in β-cell function in adolescents already predisposed

to develop diabetes. There is *in vitro* evidence that the β-cell expresses the ACE2-receptor—the receptor that the SARS-CoV-2 virus binds to to gain entry into the cell and, further, that COVID-19 infection in the β-cell can result in decreased insulin secretion[46, 47]. Some have argued that this might explain high rates of DKA in adults with COVID-19 infection and coincident diabetes. However, the evidence is conflicting and purely *in vitro* in nature[48]. A recent CDC publication using retrospective claims data in thousands of youth found a significant increase in diabetes incidence at least 30 days after COVID-19 infection, both compared with a control population without COVID-19 infection and compared with a pre-pandemic control group with non-COVID-19 respiratory infection[5]. However, the study did not differentiate diabetes type. COVID-19 infection has been associated with an increase in type 2 diabetes onset among adults[49, 50]. Currently, an international group has designed a registry (CoviDIAB) to better evaluate the clinical impact of COVID-19 on incident type 2 diabetes[50]. In those hospitalized from our cohort, very few had coincident COVID-19 infection. Because symptomatic COVID-19 infections are low in youth, and antibody testing was very limited at our sites, our study lacks evidence for whether these youth with newly diagnosed type 2 diabetes had a previous COVID-19 infection.

Our results also demonstrated increased severity of presentation of youth-onset type 2 diabetes during the pandemic, with increased HbA1c on presentation and increased presentation with metabolic decompensation. Although criteria for inpatient admission of youth with new-onset type 2 diabetes varies by institution, and these criteria may have been impacted by the COVID-19 pandemic, inpatient admission generally suggests a more severe presentation at diagnosis. A pandemic-associated increase in severity of presentation has also been reported in youth with T1D[7, 8, 14, 50]. It is also likely that patients and families may have delayed seeking care due to

concerns about being exposed to COVID-19; delayed presentation with other diseases has been reported in the literature[51, 52]. Whereas the adult literature reports increased DKA rates in those with a previous diabetes diagnosis associated with concurrent COVID-19 infection, as well as hyperglycemia associated with COVID-19 infection in patients without diabetes, detected rates of COVID-19 positivity were low in our patients presenting with metabolic decompensation.

This study has the known limitations of retrospective chart review data, which include inconsistency of reported data and missing information. In addition, incidence data cannot be derived due to lack of an appropriate denominator. Thus, the findings need to be validated in population-based cohorts. One of the strengths is the use of a rigorous type 2 diabetes definition, requiring at least two pancreatic autoantibodies tested and negative, without positive detected antibodies. This, combined with the pediatric endocrinology provider-based diagnosis, ensures that patients with type 2 diabetes were captured in this analysis. Another strength is the racial/ethnic and geographic heterogeneity of the study population, which is possible only with multicenter data from centers throughout the U.S. In addition, the findings confirm what single sites have previously reported.

The results of this study of more than 3100 patients with newly diagnosed diabetes demonstrate a dramatic impact of the COVID-19 pandemic on the presentation of type 2 diabetes in youth, which was already rising in incidence and prevalence prior to the pandemic. This has created a significant strain on pediatric endocrinology, general practioner and obesity providers, who have been managing this growing population with limited resources. Moreover, marginalized and under-resourced families already impacted by high rates of unemployment, food and housing insecurity during the pandemic, have been disproportionately affected. The long-term implications of this rapid rise in youth-onset type 2 diabetes case numbers are important in the

context of the final outcome analysis of the TODAY study, which demonstrated an alarming incidence of complications— 60% of youth experienced at least one complication after a mean follow-up of 13.3 years[4]. It is important to note that the TODAY study participants were treated and followed rigorously as part of a clinical trial and, thus, results may understestimate the burden of complications in youth-onset type 2 diabetes. Follow-up studies will need to assess durability of the trend of increasing type 2 diabetes case numbers and severity, and to further explore potential underlying causes and outcomes.

REFERENCES:

[1] Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med. 2017;376:1419-29.

[2] Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, Pihoker C, et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. JAMA. 2021;326:717-27.

[3] Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366:2247-56.

[4] Group TS, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021;385:416-26.

[5] Barrett CE, Koyama AK, Alvarez P, Chow W, Lundeen EA, Perrine CG, et al. Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years - United States, March 1, 2020-June 28, 2021. MMWR Morb Mortal Wkly Rep. 2022;71:59-65.

[6] Beliard K, Ebekozien O, Demeterco-Berggren C, Alonso GT, Gallagher MP, Clements M, et al. Increased DKA at presentation among newly diagnosed type 1 diabetes patients with or without COVID-19: Data from a multi-site surveillance registry. J Diabetes. 2021;13:270-2.

[7] Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J, et al. Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. JAMA. 2020;324:801-4.

[8] Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 Delayed the Diagnosis and Worsened the Presentation of Type 1 Diabetes in Children? Diabetes Care. 2020;43:2870-2.

[9] Tittel SR, Rosenbauer J, Kamrath C, Ziegler J, Reschke F, Hammersen J, et al. Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? Diabetes Care. 2020;43:e172-e3.

[10] Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, et al. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. Diabetes Care. 2020;43:e170-e1.

[11] Chao LC, Vidmar AP, Georgia S. Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes During the COVID-19 Pandemic. Diabetes Care. 2021;44:1451-3.

[12] Modarelli R, Sarah S, Ramaker ME, Bolobiongo M, Benjamin R, Gumus Balikcioglu P. Pediatric Diabetes on the Rise: Trends in Incident Diabetes During the COVID-19 Pandemic. J Endocr Soc. 2022;6:bvac024.

[13] Schmitt JA, Ashraf AP, Becker DJ, Sen B. Changes in Type 2 diabetes trends in Children and Adolescents during the COVID-19 Pandemic. J Clin Endocrinol Metab. 2022.

[14] Marks BE, Khilnani A, Meyers A, Flokas ME, Gai J, Monaghan M, et al. Increase in the Diagnosis and Severity of Presentation of Pediatric Type 1 and Type 2 Diabetes During the COVID-19 Pandemic. Horm Res Paediatr. 2021.

[15] Neyman A, Nabhan Z, Woerner S, Hannon T. Pediatric Type 2 Diabetes Presentation During the COVID-19 Pandemic. Clin Pediatr (Phila). 2021:99228211064030.

[16] 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021;44:S15-S33.

[17] Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018;19 Suppl 27:155-77.

[18] Fokianos K, Fried R. Interventions in INGARCH processes. Journal of Time Series Analysis. 2010;31:210-25.

[19] Fokianos K, Fried R. Interventions in log-linear Poisson autoregression. Statistical Modelling. 2012;12:299-322.

[20] Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab. 2011;96:159-67.

[21] Franckle R, Adler R, Davison K. Accelerated weight gain among children during summer versus school year and related racial/ethnic disparities: a systematic review. Prev Chronic Dis. 2014;11:E101.

[22] Moreno JP, Johnston CA, Woehler D. Changes in weight over the school year and summer vacation: results of a 5-year longitudinal study. J Sch Health. 2013;83:473-7.

[23] Jenssen BP, Kelly MK, Powell M, Bouchelle Z, Mayne SL, Fiks AG. COVID-19 and Changes in Child Obesity. Pediatrics. 2021;147.

[24] Woolford SJ, Sidell M, Li X, Else V, Young DR, Resnicow K, et al. Changes in Body Mass Index Among Children and Adolescents During the COVID-19 Pandemic. JAMA. 2021;326:1434-6.

[25] Lange SJ, Kompaniyets L, Freedman DS, Kraus EM, Porter R, Blanck HM, et al. Longitudinal Trends in Body Mass Index Before and During the COVID-19 Pandemic Among

Persons Aged 2–19 Years — United States, 2018–2020. MMWR Morbidity and Mortality Weekly Report. 2021;70:1278-83.

[26] Weaver RG, Hunt ET, Armstrong B, Beets MW, Brazendale K, Turner-McGrievy G, et al. COVID-19 Leads to Accelerated Increases in Children's BMI z-Score Gain: An Interrupted Time-Series Study. Am J Prev Med. 2021.

[27] Adams EL, Caccavale LJ, Smith D, Bean MK. Food Insecurity, the Home Food Environment, and Parent Feeding Practices in the Era of COVID-19. Obesity. 2020;28:2056-63.

[28] Pietrobelli A, Pecoraro L, Ferruzzi A, Heo M, Faith M, Zoller T, et al. Effects of COVID-19 Lockdown on Lifestyle Behaviors in Children with Obesity Living in Verona, Italy: A Longitudinal Study. Obesity. 2020;28:1382-5.

[29] Cheng HP, Wong JSL, Selveindran NM, Hong JYH. Impact of COVID-19 lockdown on glycaemic control and lifestyle changes in children and adolescents with type 1 and type 2 diabetes mellitus. Endocrine. 2021;73:499-506.

[30] Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. BMC Public Health. 2020;20:1351.

[31] Kriska A, Delahanty L, Edelstein S, Amodei N, Chadwick J, Copeland K, et al. Sedentary behavior and physical activity in youth with recent onset of type 2 diabetes. Pediatrics. 2013;131:e850-6.

[32] Basterfield L, Adamson AJ, Frary JK, Parkinson KN, Pearce MS, Reilly JJ. Longitudinal study of physical activity and sedentary behavior in children. Pediatrics. 2011;127:e24-30.

[33] Nader PR, Bradley RH, Houts RM, McRitchie SL, O'Brien M. Moderate-to-vigorous physical activity from ages 9 to 15 years. JAMA. 2008;300:295-305.

[34] Maltoni G, Zioutas M, Deiana G, Biserni GB, Pession A, Zucchini S. Gender differences in weight gain during lockdown due to COVID-19 pandemic in adolescents with obesity. Nutr Metab Cardiovasc Dis. 2021;31:2181-5.

[35] Brooks CG, Spencer JR, Sprafka JM, Roehl KA, Ma J, Londhe AA, et al. Pediatric BMI changes during COVID-19 pandemic: An electronic health record-based retrospective cohort study. EClinicalMedicine. 2021;38:101026.

[36] Patrick SW, Henkhaus LE, Zickafoose JS, Lovell K, Halvorson A, Loch S, et al. Well-being of Parents and Children During the COVID-19 Pandemic: A National Survey. Pediatrics. 2020;146.

[37] Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab. 2011;96:159-67.

[38] Gulley LD, Shomaker LB. Depression in Youth-Onset Type 2 Diabetes. Curr Diab Rep. 2020;20:51.

[39] Rankin J, Matthews L, Cobley S, Han A, Sanders R, Wiltshire HD, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolesc Health Med Ther. 2016;7:125-46.

[40] Shomaker LB, Tanofsky-Kraff M, Stern EA, Miller R, Zocca JM, Field SE, et al. Longitudinal study of depressive symptoms and progression of insulin resistance in youth at risk for adult obesity. Diabetes Care. 2011;34:2458-63.

[41] Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, Daniels S, et al. Metabolic and Inflammatory Links to Depression in Youth With Diabetes. Diabetes Care. 2012;35:2443-6.

[42] Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global Prevalence of Depressive and Anxiety Symptoms in Children and Adolescents During COVID-19: A Meta-analysis. JAMA Pediatr. 2021;175:1142-50.

[43] Hill RM, Rufino K, Kurian S, Saxena J, Saxena K, Williams L. Suicide Ideation and Attempts in a Pediatric Emergency Department Before and During COVID-19. Pediatrics. 2021;147.

[44] Mayne SL, Hannan C, Davis M, Young JF, Kelly MK, Powell M, et al. COVID-19 and Adolescent Depression and Suicide Risk Screening Outcomes. Pediatrics. 2021;148.

[45] Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care. 2021;44:258-79.

[46] Tang X, Uhl S, Zhang T, Xue D, Li B, Vandana JJ, et al. SARS-CoV-2 infection induces beta cell transdifferentiation. Cell Metab. 2021;33:1577-91.e7.

[47] Wu C-T, Lidsky PV, Xiao Y, Lee IT, Cheng R, Nakayama T, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. Cell Metab. 2021;33:1565-76.e5.

[48] Accili D. Can COVID-19 cause diabetes? Nature Metabolism. 2021;3:123-5.

[49] Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594:259-64.

[50] Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. N Engl J Med. 2020;383:789-90.

[51] Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health. 2020;4:e10-e1.

[52] Rosenberg Danziger C, Krause I, Scheuerman O, Luder A, Yulevich A, Dalal I, et al. Pediatrician, watch out for corona-phobia. Eur J Pediatr. 2021;180:201-6.

FIGURE 1: New youth-onset type 2 diabetes diagnosis by month and year

Legend: 1a) Number of new type 2 diabetes cases by month, including the proportion presenting with metabolic decompensation. The dotted vertical line demarcated onset of the COVID-19 pandemic. 1b) Total number of new diagnoses by year.

FIGURE 2: New youth-onset type 2 diabetes diagnosis by sex and race/ethnicity

Legend: 2a) Number of new cases each month broken down by sex, with the dotted line representing onset of the pandemic. This depicts the rise in proportion of male cases during the pandemic. 2b) Number of new cases each month broken down by race and ethnicity, with the dotted line representing onset of the pandemic. This depicts the relative rise in type 2 diabetes diagnoses in Black youth during the pandemic.

TABLE 1: Demographic, Anthropometric and Clinical Characteristics of Study Participants

		PPY 18-19	PPY 19-20	Pandemic	p-value
Total new-onset T2DM (n)		765	886	1463	0.005
Region (%)	Midwest	201 (26.3)	214 (24.2)	342 (23.4)	0.114
	Northeast	64 (8.4)	93 (10.5)	168 (11.5)	
	South	265 (34.7)	277 (31.3)	458 (31.3)	
	West	234 (30.6)	302 (34.1)	495 (33.8)	
Age at Diagnosis (years) (mean (SD)) n=22 missing		14.3 (2.3)	14.5 (2.4)	14.4 (2.3)	0.226
Race/Ethnicity (%)	Asian	20 (2.6)	24 (2.7)	40 (2.7)	0.004
	Black	231 (30.2)	267 (30.1)	519 (35.5)	
	Hispanic	323 (42.3)	356 (40.2)	577 (39.4)	
	White	121 (15.8)	143 (16.1)	187 (12.8)	
	Other	49 (6.4)	45 (5.1)	88 (6.0)	
	Unknown	20 (2.6)	51 (5.8)	52 (3.6)	
Sex (%)	Female	421 (55.1)	488 (55.1)	663 (45.3)	<0.001
	Male	343 (44.9)	398 (44.9)	800 (54.7)	
Insurance (%)	Private	182 (23.8)	207 (23.4)	305 (20.8)	0.009
	Public	556 (72.8)	647 (73.0)	1110 (75.9)	
	Other	4 (0.5)	9 (1.0)	5 (0.3)	
	Uninsured	20 (2.6)	22 (2.5)	27 (1.8)	
	Unknown	2 (0.3)	1 (0.1)	16 (1.1)	

Location at Diagnosis (%)	Inpatient	329 (43.1)	382 (43.1)	836 (57.1)	<0.001
	Outpatient	434 (56.8)	502 (56.7)	626 (42.8)	
	Unknown	1 (0.1)	2 (0.2)	1 (0.1)	
COVID-19 at diagnosis (%)	No	529 (82.4)	625 (82.3)	954 (66.0)	<0.001
n=266 missing	Unknown	113 (17.6)	133 (17.5)	456 (31.5)	
	Yes	0 (0.0)	0 (0.0)	36 (2.5)	
BMI (kg/m^2) (Median [IQR])		34.6 [29.6,	34.3 [30.0,	35.1 [30.9,	0.001
n=112 missing		39.2]	39.3]	40.9]	
BMI % of 95%ile (Mean [SD])		133.88	132.41	137.04	0.001
		(31.11)	(30.17)	(30.09)	
HbA1c (%) (Median [IQR])		9.3 [7.3,	9.7 [7.1,	10.4 [7.9,	<0.001
n=14 missing		11.9]	12.1]	12.4]	
Serum glucose (random) (mg/dl) (median		241 [142,	246 [146,	286 [171,	<0.001
[IQR])		360]	361]	414]	
pH (median [IQR])[a]		7.37 [7.30,	7.36 [7.31,	7.34 [7.21,	<0.001
n=1837 missing		7.40]	7.39]	7.39]	
		n=261	n=320	n=695	
Bicarbonate (mmol/L) (median [IQR])[a]		23.0 [20.0,	24.0 [19.0,	21.0 [12.0,	<0.001
n=1530 missing		26.0]	26.0]	25.0]	
		n=355	n=401	n=827	

Serum osmolality (mOsm/kg) (median [IQR]) [a] n=2657 missing		298.0 [292.0, 307.0] n=122	297.0 [293.0, 304.5] n=87	306.0 [293.0, 333.5] n=247	0.002
Diabetic ketoacidosis (%)		70 (9.2)	79 (8.9)	304 (20.8)	<0.001
Hyperglycemic Hyperosmolar Syndrome (%)		7 (0.9)	6 (0.7)	56 (3.8)	<0.001
Metabolic Decompensation (%)		72 (9.4)	80 (9.0)	307 (21.0)	<0.001
DKA Severity (%)	Mild	25 (35.7)	33 (41.8)	121 (39.8)	0.35
	Moderate	30 (42.9)	25 (31.6)	93 (30.6)	
	Severe	15 (21.4)	21 (26.6)	90 (29.6)	

[a]Data only included for subset of patients with data available

Abbreviations: Pre-Pandemic Yr1 (PPY1) = 3/1/18 - 2/28/19, Pre-Pandemic Yr2 (PPY2) = 3/1/19 - 2/29/20, Pandemic = 3/1/20 - 2/28/21

SI conversion factors: To convert HbA1c to mmol/mol, multiply by 0.01, to convert serum osmolality to mmol/kg, multiply by 1

INSTITUTION	3/1/2018-2/28/2019 N=764	3/1/2019-2/28/2020 N=886	3/1/2020-2/28/2021 N=1463
CHILDREN'S HOSPITAL COLORADO	59 (7.7)	61 (6.9)	95 (6.5)
CHILDREN'S HOSPITAL ILLINOIS	2 (0.3)	4 (0.5)	4 (0.3)
CHILDREN'S HOSPITAL LOS ANGELES	86 (11.3)	130 (14.7)	210 (14.4)
CHILDREN'S HOSPITAL PHILADELPHIA	21 (2.7)	42 (4.7)	72 (4.9)
CHILDREN'S MERCY	35 (4.6)	59 (6.7)	69 (4.7)
CHILDREN'S NATIONAL HOSPITAL	39 (5.1)	30 (3.4)	86 (5.9)
CINCINNATI CHILDREN'S HOSPITAL	38 (5.0)	41 (4.6)	45 (3.1)
COLUMBIA UNIVERSITY IRVING MEDICAL CENTER, HARLEM HOSPITAL	8 (1.0)	13 (1.5)	27 (1.8)
DUKE UNIVERSITY MEDICAL CENTER	3 (0.4)	3 (0.3)	20 (1.4)
HASBRO CHILDREN'S HOSPITAL	18 (2.4)	19 (2.1)	37 (2.5)
JOHN HOPKINS HOSPITAL	25 (3.3)	24 (2.7)	57 (3.9)
LURIE CHILDREN'S HOSPITAL	52 (6.8)	33 (3.7)	101 (6.9)
MAYO CLINIC	5 (0.7)	5 (0.6)	9 (0.6)
OUR LADY OF THE LAKE CHILDREN'S HOSPITAL	17 (2.2)	20 (2.3)	23 (1.6)
PENN STATE HEALTH CHILDREN'S HOSPITAL	17 (2.2)	19 (2.1)	32 (2.2)
RADY CHILDREN'S HOSPITAL	43 (5.6)	47 (5.3)	98 (6.7)
RILEY CHILDREN'S HOSPITAL	35 (4.6)	42 (4.7)	62 (4.2)
TEXAS CHILDREN'S HOSPITAL	31 (4.1)	32 (3.6)	43 (2.9)
UNIVERSITY OF CALIFORNIA SAN FRANCISCO	46 (6.0)	64 (7.2)	92 (6.3)
UNIVERSITY OF CHICAGO MEDICAL CENTER	20 (2.6)	20 (2.3)	41 (2.8)
UNIVERSITY OF MICHIGAN	14 (1.8)	10 (1.1)	11 (0.8)
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER	42 (5.5)	55 (6.2)	67 (4.6)
UNIVERSITY OF TEXAS SOUTHWESTERN	91 (11.9)	95 (10.7)	132 (9.0)
VANDERBILT UNIVERSITY MEDICAL CENTER	17 (2.2)	18 (2.0)	30 (2.1)

Supplementary table: Number of new cases by year at each site (%of total for that year).