DiSH Session
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COVID-19 and Children with Type 1 Diabetes

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Conflicts of interest

- None

Learning objectives

01

Contrast the known risks for COVID-19 in adults vs. children with type 1 diabetes

02

Describe factors that appear to increase risk for children with type 1 diabetes when they experience COVID-19

03

Contribute to plans to reduce risk for children with type 1 diabetes during the pandemic

What do we know?

- Adults with T1D are more likely than those without diabetes to have infections of the urinary tract, skin, lower resp tract, and serious bacterial infections.
- Children and adolescents with A1c at/near target range do not appear to have increased risk of infections.
- Healthy children are susceptible to COVID-19, but usually have a milder course than adults.

- Muller LM a. J, Gorter KJ, Hak E, et al. Increased Risk of Common Infections in Patients with Type 1 and Type 2 Diabetes Mellitus. *Clin Infect Dis*. 2005;41(3):281-288. doi:10.1086/431587
- Shah BR, Hux JE. Quantifying the Risk of Infectious Diseases for People With Diabetes. *Diabetes Care*. 2003;26(2):510-513. doi:10.2337/diacare.26.2.510
- Laffel LM, Limbert C, Phelan H, Virmani A, Wood J, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018: Sick day management in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19:193-204. doi:10.1111/pedi.12741
- CDCMMWR. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69. doi:10.15585/mmwr.mm6914e4
- Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *New England Journal of Medicine*. 2020;382(17):1663-1665. doi:10.1056/NEJMc2005073
- Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020;145(6). doi:10.1542/peds.2020-0702

What do we know?

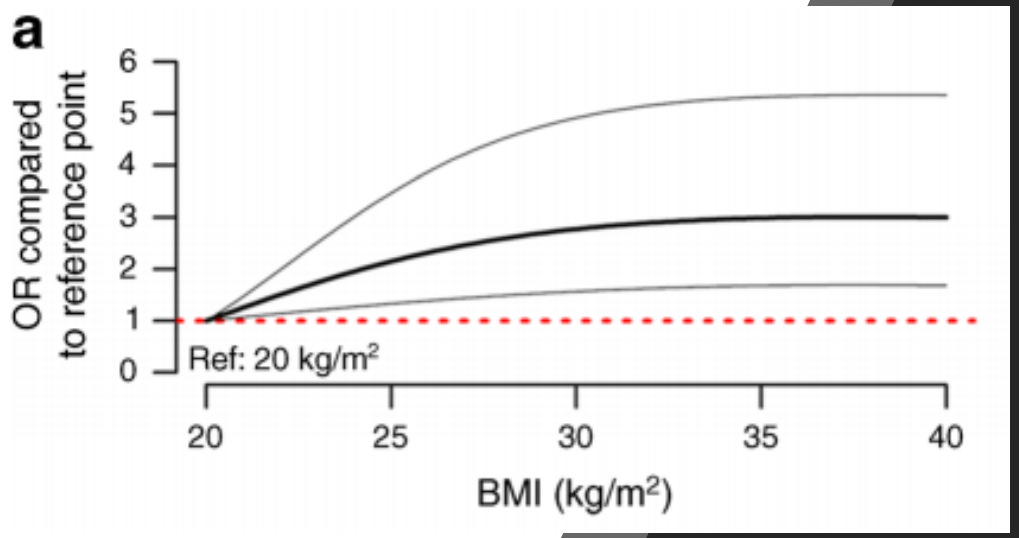
- Infectious diseases in people with T1D may trigger DKA.
- High A1c and minority race/ethnicity are risk factors for DKA.
- COVID-19 hit minority communities harder.

➢ Do kids with T1D get sicker with COVID-19 than other kids?

➢ Are some kids with T1D at higher risk?

- Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. *Pediatric Diabetes*. 2013;14(6):447-454. doi:10.1111/pedi.12030
- Kahkoska AR, Shay CM, Crandell J, et al. Association of Race and Ethnicity With Glycemic Control and Hemoglobin A1c Levels in Youth With Type 1 Diabetes. *JAMA Netw Open*. 2018;1(5). doi:10.1001/jamanetworkopen.2018.1851
- Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States. *Clin Infect Dis*. Published online June 20, 2020. doi:10.1093/cid/ciaa815

A little COVID-19 data on type 1



- Nationwide (France), multicenter, observational study in people with diabetes hospitalized for COVID-19 in 53 centers
- March 10-31, 2020
- 1,317 patients with diabetes
  - 29% intubated
  - 10.6% death
  - 18% discharged on day 7
- Multivariable analysis
  - Only BMI associated with intubation (OR 1.28 [1.1-1.47])
- Only 39 with T1D
  - ETT 0.73 (0.35-1.56)
  - Death 0.44 (0.11-1.86)
  - No deaths under 65 years of age

Cariou B, Wargny M, Pichelin M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. Published online May 29, 2020.

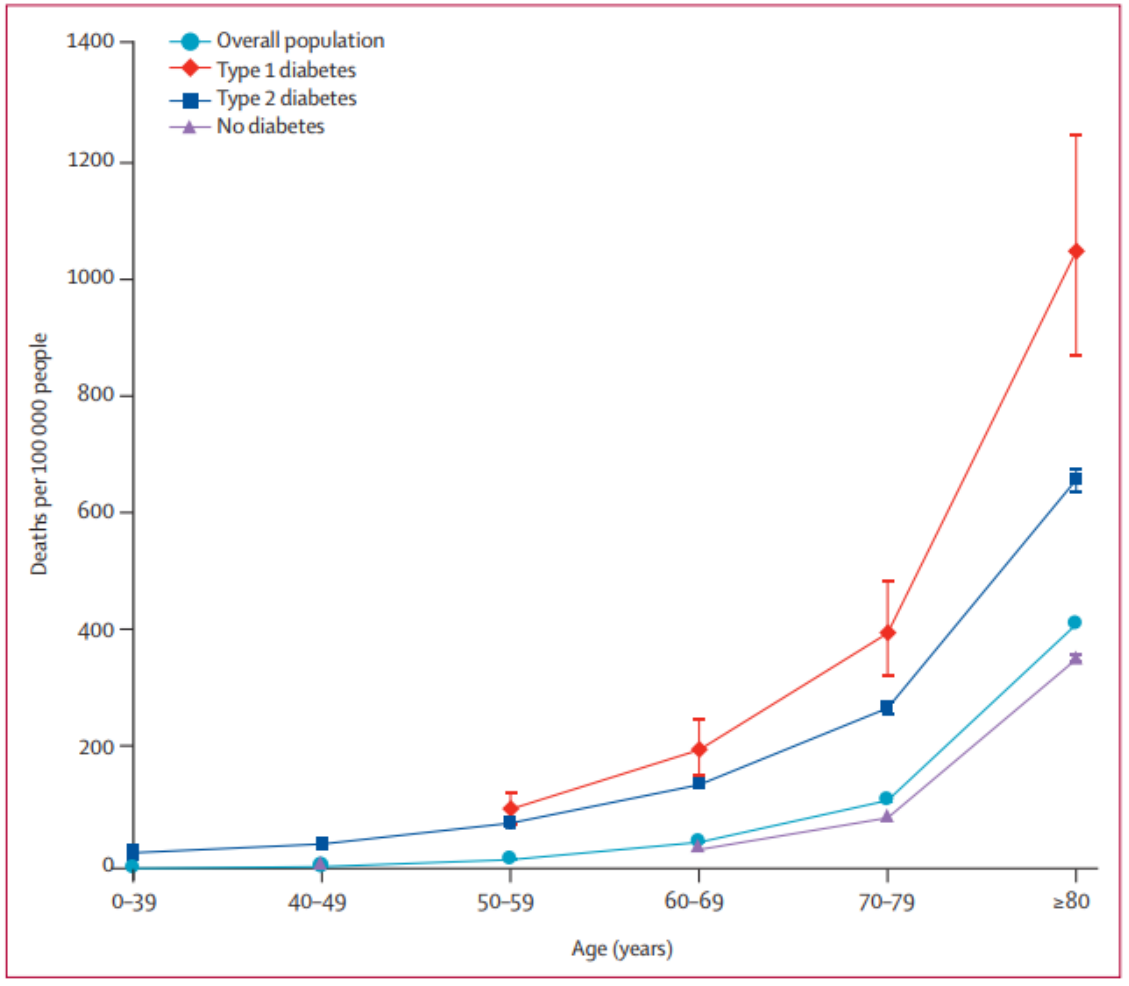
A little COVID-19 data on type 1

- National (UK) study with 98% of general practices reporting to the National Diabetes Audit. Population 61 million.
- In-hospital death for people with diabetes from 3/1/20-5/11/20.
- T1D: 263,830 people (no deaths < age 50)
- T2D: 2,864,670 people

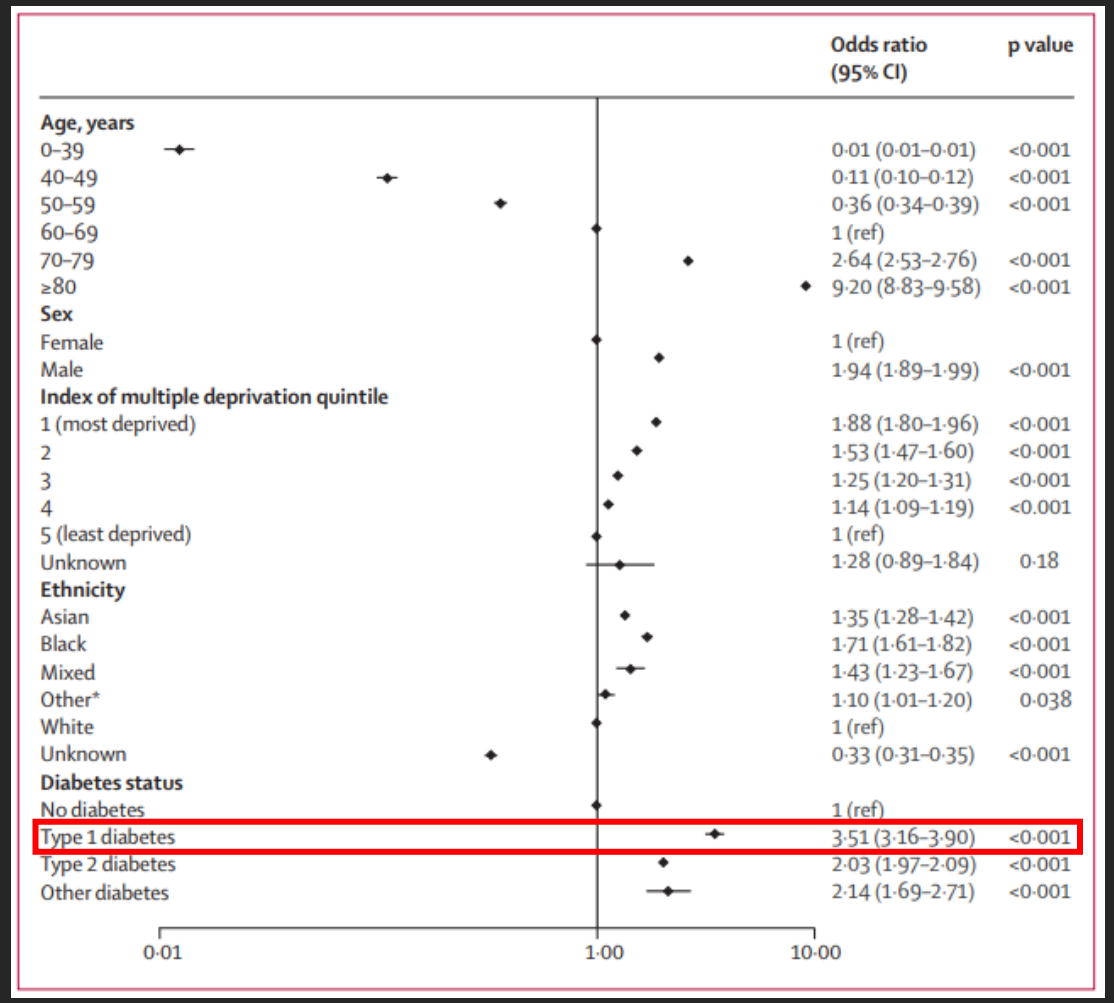
	COVID-19-related deaths		
	Overall population	Type 1 diabetes	Type 2 diabetes
Total	23 698	364	7434
Age, years			
0–39	160 (0·7%)	..	18 (0·2%)
40–49	384 (1·6%)	..	89 (1·2%)
50–59	1313 (5·5%)	49 (13·5%)	399 (5·4%)
60–69	2865 (12·1%)	73 (20·1%)	1042 (14·0%)
70–79	5904 (24·9%)	97 (26·6%)	2096 (28·2%)
≥80	13 072 (55·2%)	125 (34·3%)	3790 (51·0%)

Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *The Lancet Diabetes & Endocrinology*. 2020;8(10).

Unadjusted in-hospital COVID-19 mortality



Adjusted OR for in-hospital deaths with COVID-19



	Odds ratio (95% CI)	p value
Age, years		
0–39	0·01 (0·01–0·01)	<0·001
40–49	0·11 (0·10–0·12)	<0·001
50–59	0·36 (0·34–0·39)	<0·001
60–69	1 (ref)	
70–79	2·64 (2·53–2·76)	<0·001
≥80	9·20 (8·83–9·58)	<0·001
Sex		
Female	1 (ref)	
Male	1·94 (1·89–1·99)	<0·001
Index of multiple deprivation quintile		
1 (most deprived)	1·88 (1·80–1·96)	<0·001
2	1·53 (1·47–1·60)	<0·001
3	1·25 (1·20–1·31)	<0·001
4	1·14 (1·09–1·19)	<0·001
5 (least deprived)	1 (ref)	
Unknown	1·28 (0·89–1·84)	0·18
Ethnicity		
Asian	1·35 (1·28–1·42)	<0·001
Black	1·71 (1·61–1·82)	<0·001
Mixed	1·43 (1·23–1·67)	<0·001
Other*	1·10 (1·01–1·20)	0·038
White	1 (ref)	
Unknown	0·33 (0·31–0·35)	<0·001
Diabetes status		
No diabetes	1 (ref)	
Type 1 diabetes	3·51 (3·16–3·90)	<0·001
Type 2 diabetes	2·03 (1·97–2·09)	<0·001
Other diabetes	2·14 (1·69–2·71)	<0·001

Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *The Lancet Diabetes & Endocrinology*. 2020;8(10).

Barbara Davis Center data through 12/16/20

- **68** pediatric T1D patients with COVID+ cases
- 1 new onset, had DKA
- 5 established patients with DKA
  - 3 patients with A1c >14%,
  - 1 patient with A1c >10% 2 mo prior to DKA
  - 1 patient with A1c 8.3%, stopped CGM?
- No other hospitalizations
- Mostly URI symptoms (cough, congestion, fever, runny nose, headache)
- No one needing O_2 treatment

	Hospitalized N=35	Non-Hospitalized N=58	p value
Age			.31
0 to 5	2 (6)	1 (2)	
6 to 10	4 (11)	6 (10)	
11 to 15	12 (34)	30 (52)	
16 to 19	17 (49)	21 (36)	
Female	16 (46)	32 (55)	.39
Race/Ethnicity			<.001
NHW	6 (17)	30 (52)	
NHB	18 (51)	9 (16)	
H	8 (23)	15 (25)	
Other	3 (9)	4 (7)	
Insurance Type			.02
Public	26 (74)	29 (50)	
Private	9 (26)	29 (50)	
A1c %	11.7 [3.8]	8.8 [2.4]	<.001
Last A1c Group			<.001
<7%	0 (0)	5 (9)	
7%-9%	4 (11)	27 (46)	
>9%	31 (89)	26 (45)	
Insulin Pump Use	6 (17)	29 (50)	.001
CGM Use	10 (29)	36 (62)	.002

Alonso GT, et al. Diabetic ketoacidosis drives COVID-19 related hospitalizations in children with type 1 diabetes. In review.

T1D Exchange COVID-19 registry

- 46 diabetes centers submitted cases of T1D patients who had COVID-19 (n=110)
- No deaths*
- No multisystem inflammatory disease of childhood (MIS-C)

Logistic regression for hospitalization among COVID-19+ patients with established T1D

n = 93	Unadjusted	Adjusted
A1c	1.60 (1.30, 2.04) *	1.49 (1.20, 1.94) *
Age	-	0.97 (0.84, 1.11)
Female gender	-	0.54 (0.18, 1.53)
Public insurance	-	1.26 (0.30, 5.02)
Minority Race/ethnicity	-	2.75 (0.71, 11.74)

*1 death in patient who was not tested for COVID-19. Out of hospital death from apparent pulmonary embolus. NY area in spring 2020.

Hypercoagulation and COVID-19

- COVID-19 causes a coagulopathy
  - Mild laboratory alterations
  - Disseminated intravascular coagulation (DIC) with thrombotic/multiple organ failure
- Hypercoagulability:
  - ATIII deficiency (1:500)
  - Protein C or S deficiency (inherited or inducible – liver disease, vit K antagonists, renal failure)
  - Hyperhomocysteinemia
  - Elevated factor VIII (higher in African Americans, lower in type O blood)
  - Malignancy
  - Smoking
  - Estrogen, testosterone
  - Trauma
  - **Dehydration**

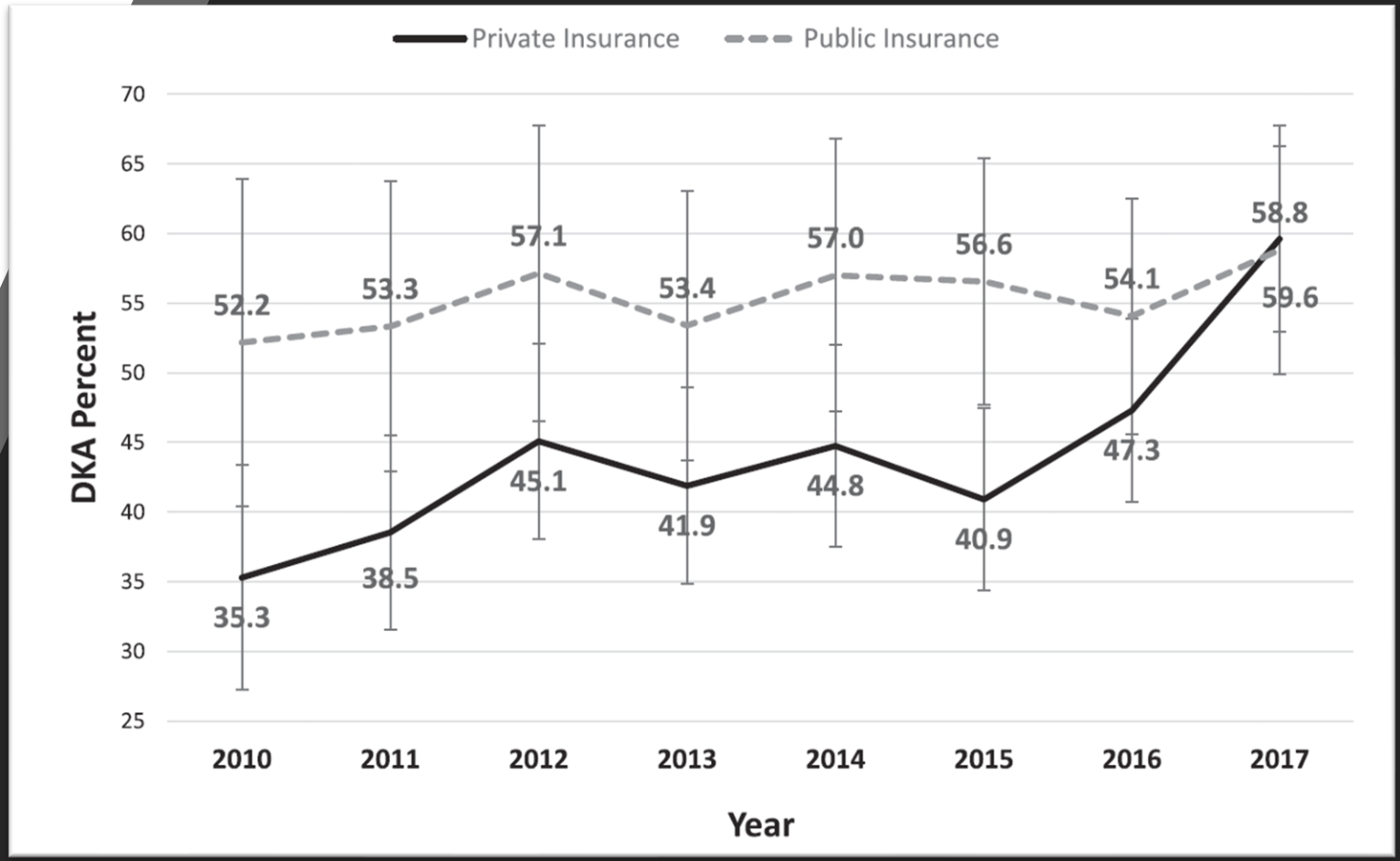
Akel T, Qaqa F, Abuarqoub A, Shamoon F. Pulmonary embolism: A complication of COVID 19 infection. *Thromb Res*. 2020;193:79-82.

Fei Y, Tang N, Liu H, Cao W. Coagulation dysfunction: A hallmark in COVID-19. *Arch Pathol Lab Med*. Published online June 18, 2020.

Senst B, Tadi P, Goyal A, Jan A. Hypercoagulability. In: *StatPearls*. StatPearls Publishing; 2020. Accessed September 24, 2020. http://www.ncbi.nlm.nih.gov/books/NBK538251/

DKA at diagnosis of type 1 diabetes in Colorado

Could the pandemic increase incidence of DKA at T1D onset?



Alonso GT, Coakley A, Pyle L, Manseau K, Thomas S, Rewers A. Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Colorado Children, 2010-2017. *Diabetes Care*. 2020;43(1):117-121.

New onset type 1 diabetes during the pandemic

Could SARS-CoV-2 increase the incidence of type 1 diabetes?

- Virus binds to ACE2, enters endocrine cells
- SARS epidemic: high incidence of hyperglycemia
- Viral infections appear to trigger autoimmune diseases

https://www.endocrineweb.com/news/diabetes/-covid-19-may-trigger-new-onset-diabetes

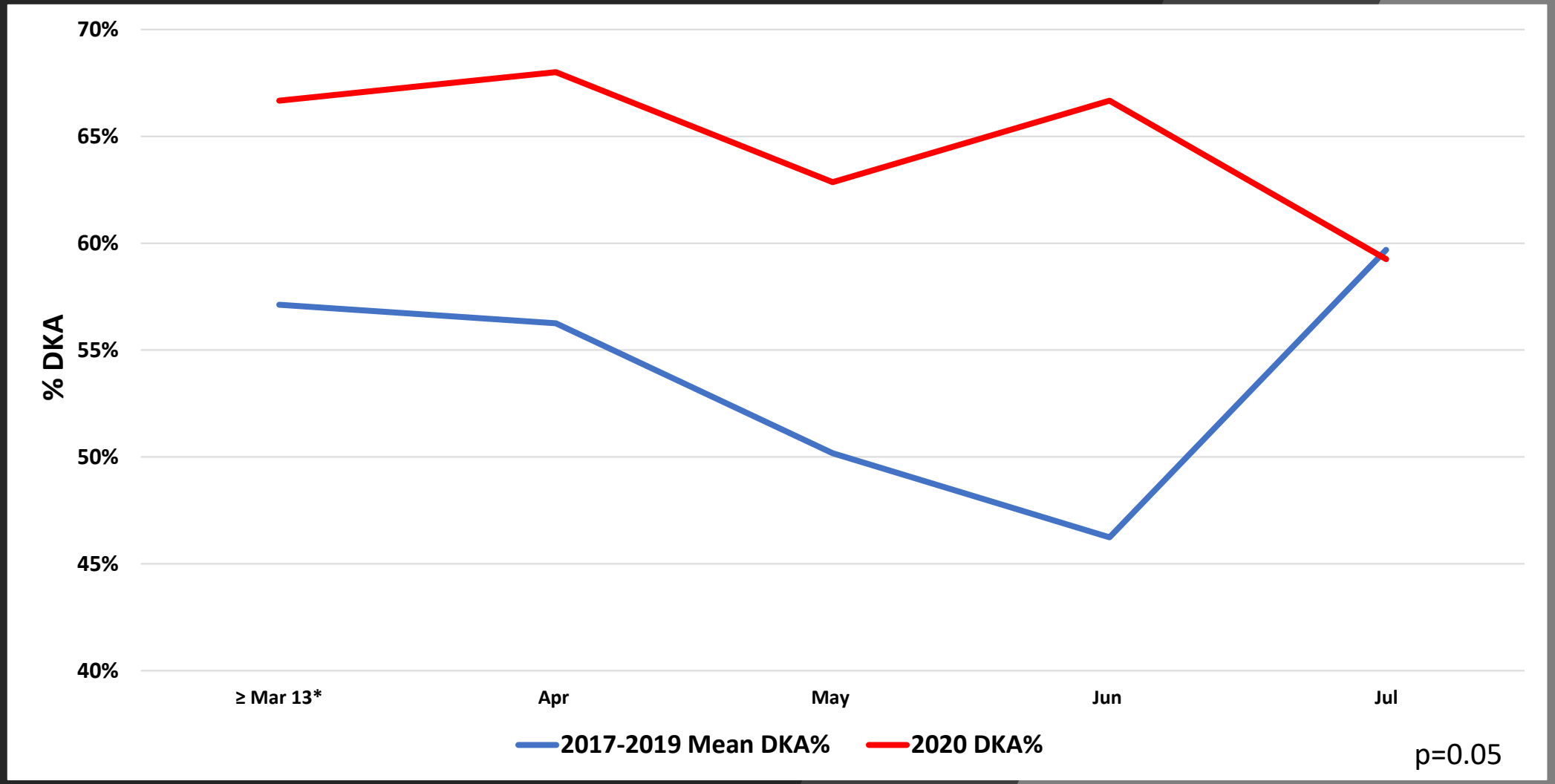
New onset type 1 diabetes during the pandemic

- Italy: 23% fewer new onset T1D cases in Feb-Apr. More severe DKA.
- UK: Increased T1D? High rates of severe DKA in Mar-June.
- Germany: T1D incidence as predicted
- Australia: No increase in incidence or severity

- Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A, Diabetes* the DSG of the IS for PE and. Has COVID-19 Delayed the Diagnosis and Worsened the Presentation of Type 1 Diabetes in Children? *Diabetes Care*. Published online August 10, 2020. doi:10.2337/dc20-1321
- Unsworth R, Wallace S, Oliver NS, et al. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. *Diabetes Care*. Published online August 13, 2020. doi:10.2337/dc20-1551
- Tittel SR, Rosenbauer J, Kamrath C, et al. Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? *Diabetes Care*. Published online August 21, 2020. doi:10.2337/dc20-1633
- Atlas G, Rodrigues F, Moshage Y, Welch J, White M, O'Connell MA. Presentation of Paediatric Type 1 Diabetes in Melbourne, Australia During the Initial Stages of the Covid-19 Pandemic. *Journal of Paediatrics and Child Health*.

DKA at diagnosis of T1D – BDC data

2017-2019 vs 2020



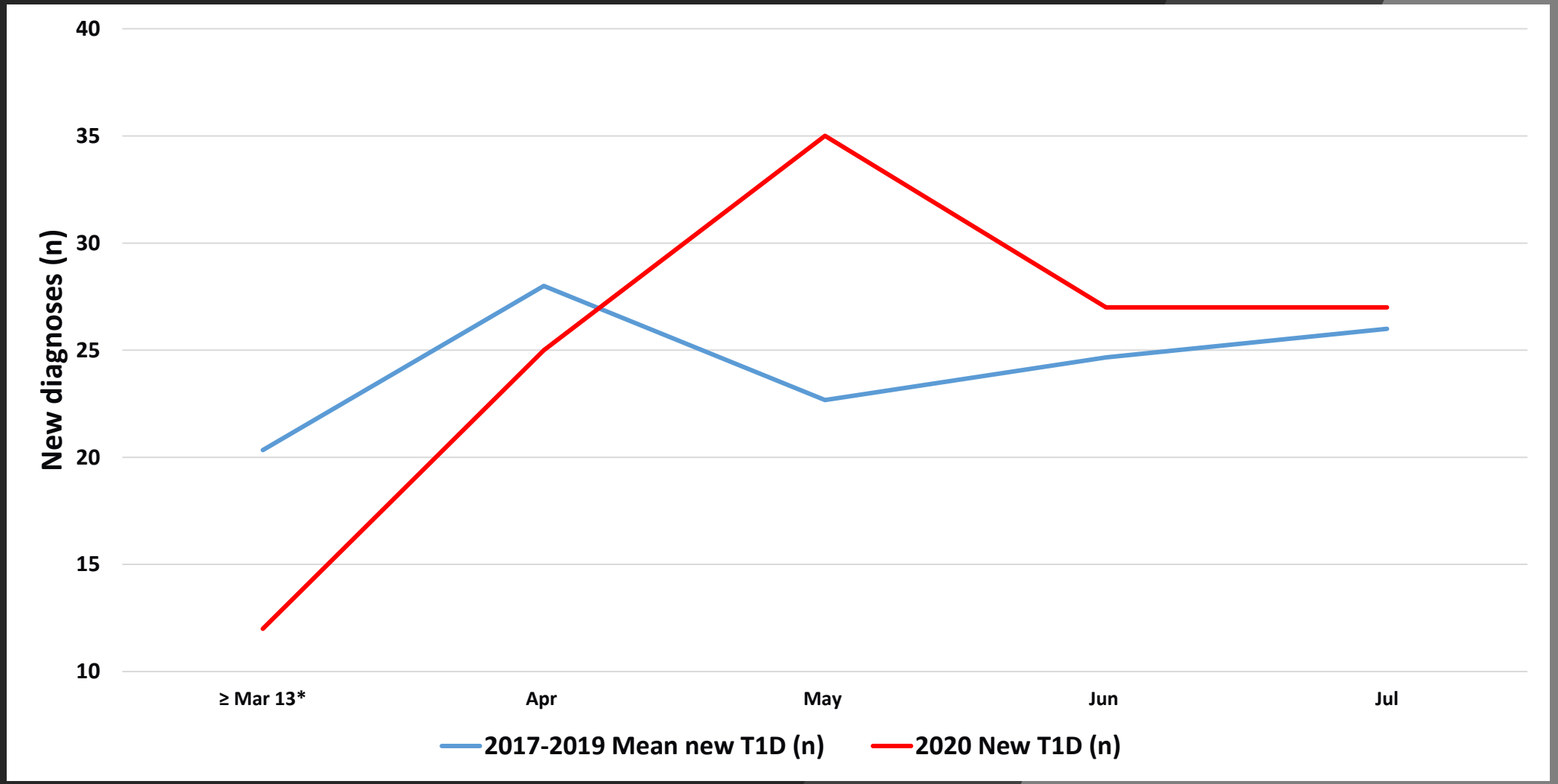
*partial month

(Severe DKA: 17.3% vs. 28.6%)

Alonso, et al. Increasing diabetic ketoacidosis among children with new diagnosis of type 1 diabetes during the COVID-19 pandemic. In preparation.

New diagnosis of T1D – BDC data

2017-2019 vs 2020



*partial month

Alonso, et al. Increasing diabetic ketoacidosis among children with new diagnosis of type 1 diabetes during the COVID-19 pandemic. In preparation.

Newly diagnosed T1D, COVID-19+

	N = 17
Age	
0 to 5	1 (6)
6 to 10	4 (24)
11 to 15	11 (64)
16 to 19	1 (6)
Female	10 (67)
Race/Ethnicity	
Non-Hispanic White	1 (6)
Non-Hispanic Black	6 (35)
Hispanic	6 (35)
Other	4 (24)
Insurance Type	
Public	13 (76)
Private	4 (24)
A1c %	12.4 [2.7]
Primary reason for Hospitalization	
DKA	12 (71)
Diabetes education	3 (18)
N/A	2 (12)

T1D Exchange QI Collaborative COVID-19 registry

New diagnosis of T1D

- 17 cases who were COVID+ at the time of T1D diagnosis
- DKA rate 71%

Alonso GT, et al. Diabetic ketoacidosis drives COVID-19 related hospitalizations in children with type 1 diabetes. In review.

Summary: Hospitalization

- DKA is the leading cause of hospitalization in children with T1D who get COVID-19.
- A1c >9% is the single greatest risk factor for DKA. COVID-19 is almost incidental in many cases.
- Racial/ethnic minority patients are much more likely to get COVID-19.
- Non-Hispanic White patients with mild symptoms of COVID-19 are much more likely to come to our attention than their minority counterparts.
- Compared to adults, children appear to have better outcomes.

Summary: New diagnosis of T1D

- We are not seeing increases in T1D incidence. Yet.
- DKA rates skyrocketed during lockdowns.
  - Clinics were closed.
  - People were afraid to venture out.
- DKA rates may be normalizing now (but they're still too high).