

THE LANCET

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Supplementary appendix

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Supplemental Material

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

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Methods: (a) Joinpoint regression analysis

To analyse differences in the increasing trend of DKA prevalence over time, joinpoint regression (segmented regression) was applied to the logarithmically transformed directly age- and sex-standardized prevalence taking account of their standard errors. This allowed to make inferences about changes in trends over time. The underlying assumption is that the observation period can be divided into subperiods with specific loglinear trend. Joinpoints represent the time points when the trends change. In each case, the best model among models allowing 0 and 5 joinpoints was selected according to a permutation test approach. Segmental trends were described by the annual percent change (APC) with corresponding 95% CIs.

Analyses were performed using the Joinpoint Regression Program (Version 4.9.0.1, February 2022, Statistical Research and Applications Branch, National Cancer Institute, Bethesda, Maryland, USA).

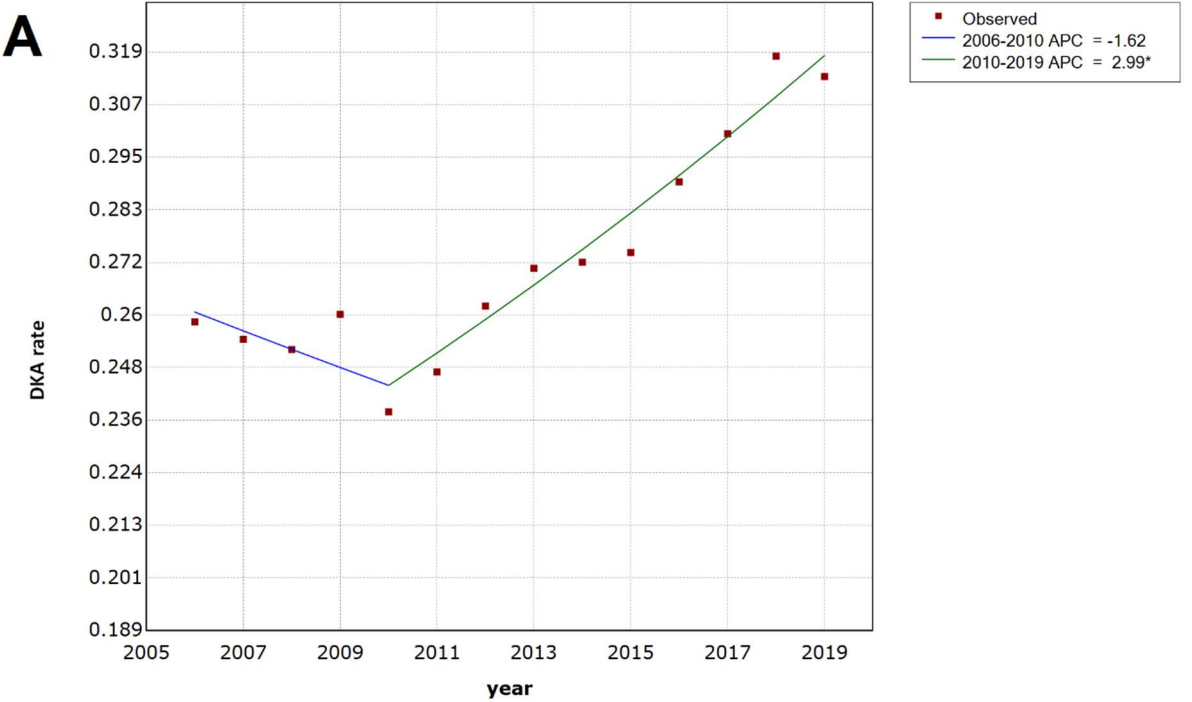
References:

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2. Baechle C, Stahl-Pehe A, Prinz N, et al. Prevalence trends of type 1 and type 2 diabetes in children and adolescents in North Rhine-Westphalia, the most populous federal state in Germany, 2002-2020 [published online ahead of print, 2022 Jul 16]. *Diabetes Res Clin Pract.* 2022;109995. doi:10.1016/j.diabres.2022.109995

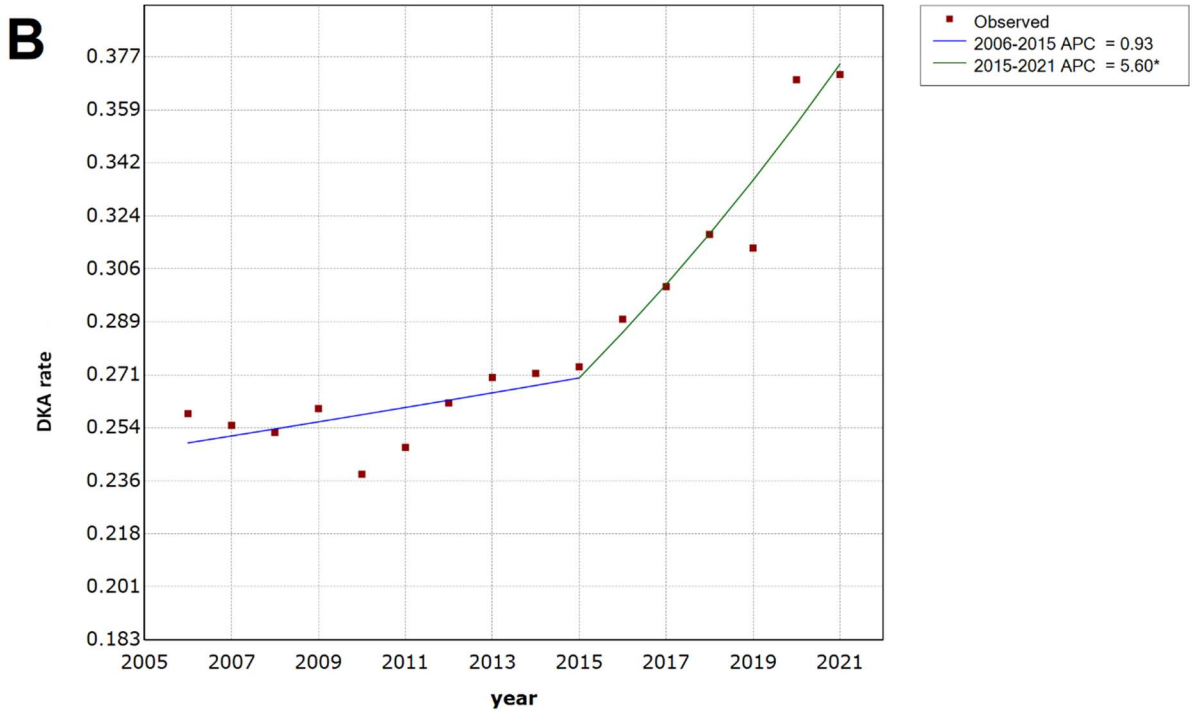
Methods: (b) Participating registers

Register	Reference
Australasian Diabetes Data Network (ADDN), Australia	https://www.addn.org.au
Two regions of New Zealand (Auckland and Christchurch)	Clapin H, Phelan H, Bruns L, Jr., et al. Australasian Diabetes Data Network: Building a Collaborative Resource. <i>J Diabetes Sci Technol</i> 2016; 10 (5):1015-26.
The state of Colorado, USA	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. <i>Diabetes Care</i> 2020; 43 (1):117-121.
Austria, Germany and Luxembourg; Diabetes Patient Follow-Up registry (DPV)	Hofer SE, Schwandt A, Holl RW. Standardized Documentation in Pediatric Diabetology: Experience from Austria and Germany. <i>J Diabetes Sci Technol</i> 2016; 10 (5):1042-9.
Czech Republic; Czech National Childhood Diabetes Register (ČENDA)	Šumník Z, Venháčová J, Škvor J, et al. Five years of improving diabetes control in Czech children after the establishment of the population-based childhood diabetes register ČENDA. <i>Pediatr Diabetes</i> 2020; 21 (1):77-87.
Denmark; Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids)	Svensson J, Cerqueira C, Kjærsgaard P, et al. Danish Registry of Childhood and Adolescent Diabetes. <i>Clin Epidemiol</i> 2016; 8 :679-683.
Italy; Study Group for diabetes of the Italian Society for Paediatric Endocrinology and Diabetes	Cherubini V, Skrami E, Ferrito L, et al. High frequency of diabetic ketoacidosis at diagnosis of type 1 diabetes in Italian children: a nationwide longitudinal study, 2004-2013. <i>Sci Rep</i> 2016; 6 :38844.
Norway; Norwegian Childhood Diabetes Registry (NCDR)	Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. <i>Diabetologia</i> 2014; 57 (1):57-62.
Slovenia; Slovenian national childhood type 1 diabetes registry	Dovc K, Telic SS, Lusa L, et al. Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. <i>Diabetes Technol Ther</i> 2014; 16 (1):33-40.
Sweden; The Swedish Paediatric Diabetes Quality Registry (SWEDIABKIDS)	Hanberger L, Samuelsson U, Lindblad B, Ludvigsson J. A1C in children and adolescents with diabetes in relation to certain clinical parameters: the Swedish Childhood Diabetes Registry SWEDIABKIDS. <i>Diabetes Care</i> 2008; 31 (5):927-929.
Wales; Children and Young People's Wales Diabetes Network (and Brecon Group)	https://www.welshpaediatrics.org.uk/link/children-and-young-people%E2%80%99s-wales-diabetes-network-and-brecon-group

Figure S1. Joinpoint regression analysis for the prevalence of diabetic ketoacidosis between 2006–2019 and 2006–2021.



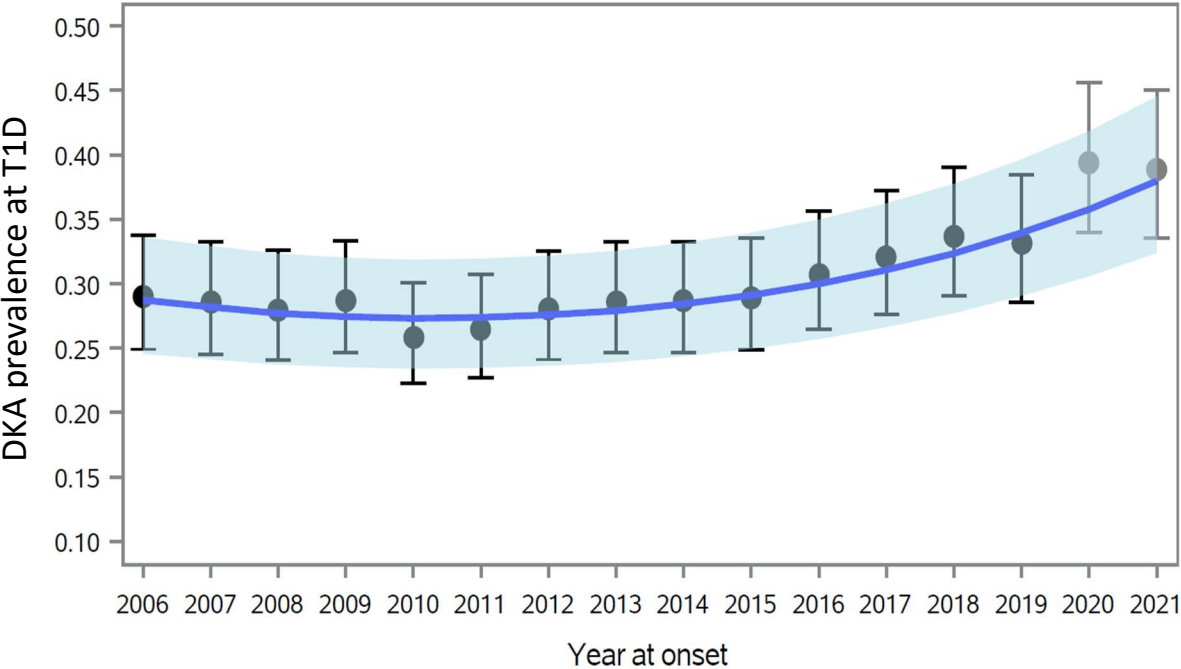
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 1 Joinpoint.



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
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Mean prevalence of diabetic ketoacidosis (DKA) at diagnosis of paediatric type-1-diabetes in 13 registries and segmental trend curves estimated by joinpoint regression for the period 2006 to 2019 (A) and from 2006 to 2021 (B). APC: annual percent change.

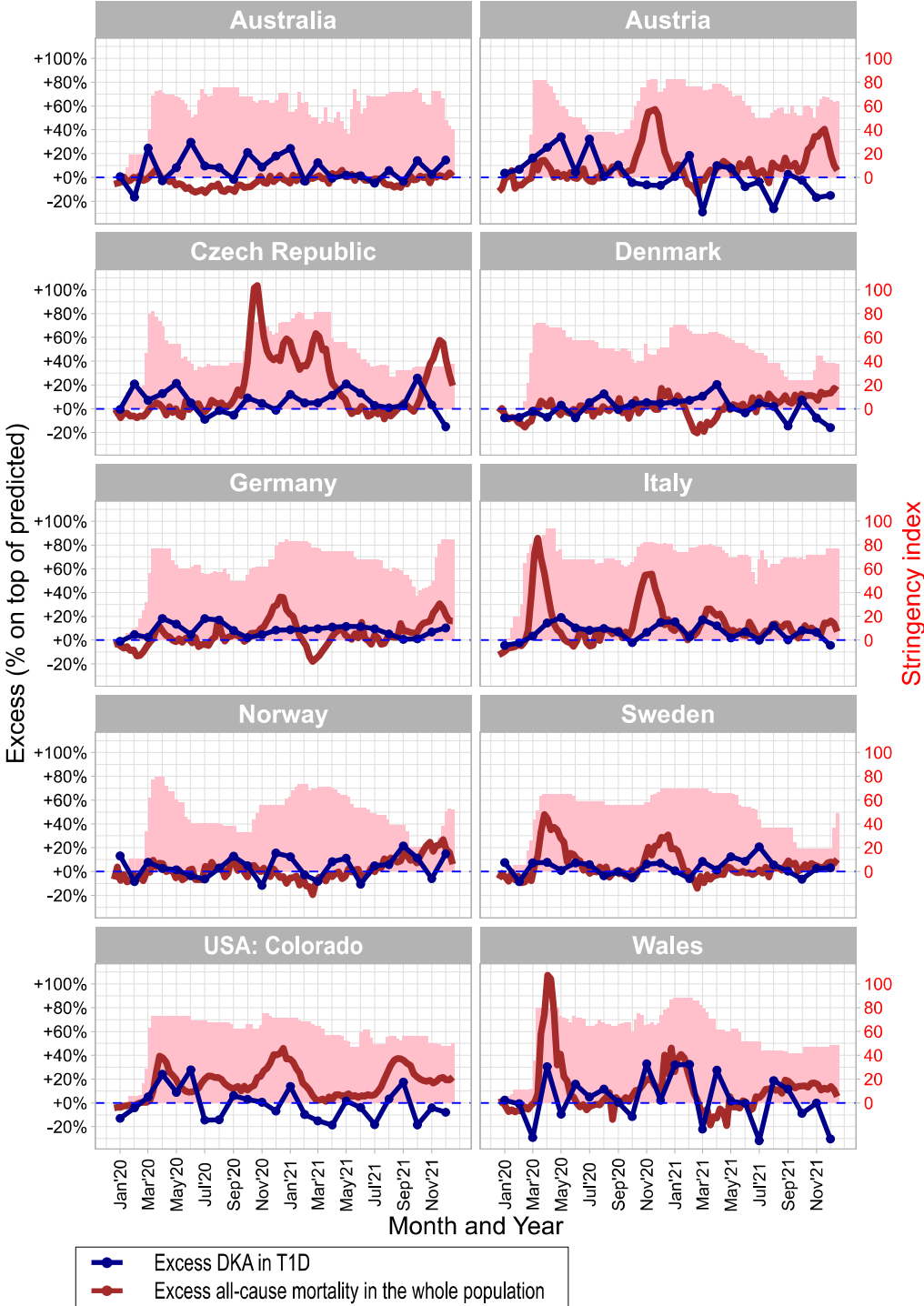
Figure S2. Prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in children in the years 2020 and 2021 compared to predicted prevalence estimated from non-linear (linear + quadratic) temporal trend from 2006 to 2019.



To analyse predictors for diabetic ketoacidosis (DKA) at diagnosis of paediatric type 1 diabetes in 2020 and 2021, we used a log-binomial model based on data from 2006-2019 with age groups, sex, country, and year as predictors, including countries as random intercepts. In this model we included year and year² as predictors of DKA prevalence. The estimated trend line is shown in dark blue with the corresponding 95% confidence interval (light blue area). The black dots show the observed age- and sex-adjusted DKA prevalence at T1D onset from 2006 to 2019, which was used to calculate the trend until 2021. The grey dots show the observed age- and sex-adjusted DKA prevalence for 2020 and 2021. The vertical bars indicate the corresponding 95% confidence interval of the observed DKA prevalence.

According to the model, the adjusted observed prevalence of DKA was 39.4% (95% CI, 34.0–45.6%) in 2020 and 38.9% (95% CI, 33.6–45.0%) in 2021, and the adjusted predicted prevalence were 35.8% (95% CI, 30.6–41.8%) and 38.0% (95% CI, 32.4–44.5%), respectively. The adjusted absolute percentage differences were 3.6% (95% CI, 2.1–5.1; P<0.0001) and 0.9 (95% CI, -0.5–2.3%; P=0.21) for 2020 and 2021, respectively.

Figure S3. Excess in the prevalence of diabetic ketoacidosis vs excess all-cause mortality and the Stringency Index.



The percent excess in the diabetic ketoacidosis (DKA) prevalence (observed in 2020 and 2021 vs the predicted prevalence) is plotted along the excess all-cause mortality (labelling left), and the Stringency Index (labelling right) is plotted as a pink shaded area being indicators describing the perception of the pandemic severity by the government. Only the 10 registers with more than 100 new cases each year in 2020 and 2021 are plotted to minimise random noise. The figure illustrates that the governmental responses to the spring and autumn waves were nearly similar (the Stringency Index levels were comparable in most countries), whereas the objective measure of the pandemic severity expressed as excess all-cause mortality differed among countries both in size and timing.

Table S1: Documented cases of new-onset paediatric type 1 diabetes in the 13 registries from 2006 to 2021 according to the status of diabetic ketoacidosis.

Year of diabetes onset		Australia	Austria	Czech Republic	Denmark	Germany	Italy	Luxemburg	New Zealand	Norway	Slovenia	Sweden	USA	Wales	Total
2006	all	245	101	167	284	1730	807	13	23	234	54	738	-	189	4585
	DKA (%)	88 (35.9)	34 (33.7)	34 (20.4)	48 (16.9)	328 (19.0)	350 (43.4)	4 (30.8)	9 (39.1)	60 (25.6)	16 (29.6)	163 (22.1)	-	43 (22.8)	1177 (25.7)
	no DKA	157	67	133	236	1402	457	9	14	174	38	575	-	146	3408
2007	all	344	112	209	276	1947	801	23	20	227	55	715	-	162	4891
	DKA (%)	101 (29.4)	35 (31.3)	53 (25.4)	51 (18.5)	371 (19.1)	357 (44.6)	10 (43.5)	7 (35.0)	49 (21.6)	22 (40.0)	140 (19.6)	-	42 (25.9)	1238 (25.3)
	no DKA	243	77	156	225	1576	444	13	13	178	33	575	-	120	3653
2008	all	370	116	215	276	1999	884	11	18	256	40	651	-	161	4997
	DKA (%)	113 (30.5)	33 (28.4)	45 (20.9)	55 (19.9)	385 (19.3)	374 (42.3)	5 (45.5)	3 (16.7)	72 (28.1)	11 (27.5)	116 (17.8)	-	40 (24.8)	1252 (25.1)
	no DKA	257	83	170	221	1614	510	6	15	184	29	535	-	121	3745
2009	all	342	130	227	296	2071	1049	16	27	328	46	720	-	158	5410
	DKA (%)	102 (29.8)	56 (43.1)	49 (21.6)	56 (18.9)	426 (20.6)	429 (40.9)	6 (37.5)	9 (33.3)	85 (25.9)	11 (23.9)	133 (18.5)	-	35 (22.2)	1397 (25.8)
	no DKA	240	74	178	240	1645	620	10	18	243	35	587	-	123	4013
2010	all	412	143	256	320	2143	950	18	77	302	58	679	222	186	5766
	DKA (%)	128 (31.1)	40 (28.0)	60 (23.4)	76 (23.8)	248 (11.6)	418 (44.0)	3 (16.7)	19 (24.7)	71 (23.5)	15 (25.9)	133 (19.6)	93 (41.9)	59 (31.7)	1363 (23.6)
	no DKA	284	103	196	244	1895	532	15	58	231	43	546	129	127	4403
2011	all	484	181	338	296	2243	1054	27	75	302	50	696	299	164	6209
	DKA (%)	163 (33.7)	58 (32.0)	72 (21.3)	62 (20.9)	325 (14.5)	457 (43.4)	3 (11.1)	18 (24.0)	61 (20.2)	19 (38.0)	129 (18.5)	128 (42.8)	29 (17.7)	1524 (24.5)
	no DKA	321	123	266	234	1918	597	24	57	241	31	567	171	135	4685
2012	all	542	221	341	276	2497	1014	21	72	303	50	683	289	185	6494
	DKA (%)	181 (33.4)	77 (34.8)	68 (19.9)	50 (18.1)	447 (17.9)	408 (40.2)	9 (42.9)	20 (27.8)	80 (26.4)	28 (56.0)	132 (19.3)	137 (47.4)	52 (28.1)	1689 (26.0)
	no DKA	361	144	273	226	2050	606	12	52	223	22	551	152	133	4805
2013	all	663	179	315	331	2438	1028	31	81	331	64	697	316	170	6644
	DKA (%)	215 (32.4)	75 (41.9)	67 (21.3)	60 (18.1)	465 (19.1)	444 (43.2)	7 (22.6)	26 (32.1)	89 (26.9)	27 (42.2)	124 (17.8)	141 (44.6)	41 (24.1)	1781 (26.8)
	no DKA	448	104	248	271	1973	584	24	55	242	37	573	175	129	4863
2014	all	733	211	302	328	2469	915	34	77	335	54	720	304	143	6625
	DKA (%)	264 (36.0)	73 (34.6)	74 (24.5)	70 (21.3)	520 (21.1)	318 (34.8)	10 (29.4)	23 (29.9)	83 (24.8)	25 (46.3)	149 (20.7)	145 (47.7)	33 (23.1)	1787 (27.0)
	no DKA	469	138	228	258	1949	597	24	54	252	29	571	159	110	4838

2015	all	742	190	367	340	2558	904	25	103	316	50	706	355	175	6831
	DKA (%)	276 (37.2)	80 (42.1)	88 (24.0)	83 (24.4)	533 (20.8)	320 (35.4)	10 (40.0)	30 (29.1)	79 (25.0)	13 (26.0)	139 (19.7)	164 (46.2)	40 (22.9)	1855 (27.2)
	no DKA	466	110	279	257	2025	584	15	73	237	37	567	191	135	4976
2016	all	672	210	368	342	2760	984	33	93	251	69	743	368	163	7056
	DKA (%)	265 (39.4)	70 (33.3)	89 (24.2)	78 (22.8)	599 (21.7)	393 (39.9)	10 (30.3)	26 (28.0)	56 (22.3)	25 (36.2)	186 (25.0)	185 (50.3)	45 (27.6)	2027 (28.7)
	no DKA	407	140	279	264	2161	591	23	67	195	44	557	183	118	5029
2017	all	711	211	358	400	2671	970	15	76	355	65	720	316	167	7035
	DKA (%)	298 (41.9)	72 (34.1)	81 (22.6)	83 (20.8)	620 (23.2)	370 (38.1)	1 (6.7)	23 (30.3)	88 (24.8)	29 (44.6)	170 (23.6)	191 (60.4)	67 (40.1)	2093 (29.8)
	no DKA	413	139	277	317	2051	600	14	53	267	36	550	125	100	4942
2018	all	702	218	348	353	2760	990	28	76	377	73	736	333	167	7161
	DKA (%)	326 (43.4)	71 (32.6)	87 (25.0)	84 (23.8)	687 (24.9)	404 (40.8)	9 (32.1)	28 (36.8)	110 (29.2)	32 (43.8)	184 (25.0)	172 (51.7)	60 (35.9)	2254 (31.5)
	no DKA	376	147	261	269	2073	586	19	48	267	41	552	161	107	4907
2019	all	686	245	386	307	2935	1094	31	98	394	68	792	309	179	7524
	DKA (%)	305 (44.5)	96 (39.2)	106 (27.5)	71 (23.1)	781 (26.6)	416 (38.0)	8 (25.8)	36 (36.7)	103 (26.1)	31 (45.6)	173 (21.8)	151 (48.9)	61 (34.1)	2338 (31.1)
	no DKA	381	149	280	236	2154	678	23	62	291	37	619	158	118	5186
2020	all	644	268	461	330	3379	1162	26	99	453	77	835	290	185	8209
	DKA (%)	357 (55.4)	126 (47.0)	138 (29.9)	79 (23.9)	1133 (33.5)	509 (43.8)	9 (34.6)	38 (38.4)	130 (28.7)	36 (46.8)	220 (26.3)	156 (53.8)	74 (40.0)	3005 (36.6)
	no DKA	287	142	323	251	2246	653	17	61	323	41	615	134	111	5204
2021	all	545	288	490	330	3672	1521	35	112	396	79	865	315	205	8853
	DKA (%)	287 (52.7)	96 (33.3)	163 (33.3)	91 (27.6)	1261 (34.3)	657 (43.2)	17 (48.6)	52 (46.4)	126 (31.8)	35 (44.3)	239 (27.6)	163 (51.7)	79 (38.5)	3266 (36.9)
	no DKA	258	192	237	239	2411	864	18	60	270	44	626	152	126	5587
Total	all	8837	3024	5148	5085	40272	16127	387	1127	5160	952	11696	3716	2759	104290
	DKA (%)	3469 (39.3)	1092 (36.1)	1274 (24.7)	1097 (21.6)	9129 (22.7)	6624 (41.1)	121 (31.3)	367 (32.6)	1342 (26.0)	375 (39.4)	2530 (21.6)	1826 (49.1)	800 (29.0)	30046 (28.8)
	no DKA	5368	1932	3874	3988	31143	9503	266	760	3818	577	9166	1890	1959	74244

DKA: diabetic ketoacidosis.