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REVIEW

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The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis

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Abstract

Viral infections may increase the risk of developing type 1 diabetes (T1D), and recent reports suggest that Coronavirus Disease 2019 (COVID-19) might have increased the incidence of pediatric T1D and/or diabetic ketoacidosis (DKA). Therefore, this meta-analysis aims to estimate the risk of global pediatric new-onset T1D, DKA, and severe DKA before and after the COVID-19 pandemic. A systematic search of MEDLINE/PubMed, CINAHL, Scopus, and EMBASE was conducted for articles published up to March 2022. A random-effects meta-analysis was performed to compare the relative risk of T1D and DKA among pediatric patients with T1D between the COVID-19 pre-pandemic and pandemic periods. We also compared glucose and HbA1c values in children who were newly diagnosed with T1D before and after the COVID-19 pandemic. The global incidence rate of T1D in the 2019 period was 19.73 per 100 000 children and 32.39 per 100 000 in the 2020 period. Compared with pre-COVID-19 pandemic, the number of worldwide pediatric new-onset T1D, DKA, and severe DKA during the first year of the COVID-19 pandemic increased by 9.5%, 25%, and 19.5%, respectively. Compared with pre-COVID-19 pandemic levels, the median glucose, and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic increased by 6.43% and 6.42%, respectively. The COVID-19 pandemic has significantly increased the risk of global pediatric new-onset T1D, DKA, and severe DKA. Moreover, higher glucose and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic mandates targeted measures to raise public and physician awareness.

KEYWORDS

COVID-19, exercise, meta-analysis, physical activity

Abbreviations: ACE2, angiotensin converting enzyme 2; CI, confidence interval; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; ER, event rate; HbA1c, glycosylated hemoglobin; NOS, Newcastle–Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standard mean difference; T1D, type 1 diabetes.

1 | INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disorder with a permissive genetic background that various environmental factors such as food chemicals, viral infections, and so forth act as autoimmune stimuli and eventually lead to the partial or complete destruction of pancreatic b-cells as a result of insulin deficiency.[1] Numerous studies have reported the involvement of various viruses such as enteroviruses, Coxsackie B, Coxsackie A, Echo, cytomegalovirus, rotaviruses, retroviruses, and so forth in the pathogenesis of T1D.[2–4] The causative agent of the current epidemic, coronavirus disease 2019 (COVID-19), is a positive-sense single-stranded RNA virus that acts on various organs in the body after entering human cells by binding to the angiotensin-converting enzyme 2 (ACE2). ACE2 binds to the membranes of various cells in the body, such as islets of Langerhans [5]

Numerous types of diabetes including new-onset diabetes and metabolic complications such as diabetic ketoacidosis (DKA) and hyperosmolarity have been observed in patients with COVID-19.[6] DKA is one of the most common and life-threatening acute complications of T1D. Ketoacidosis is the first manifestation of T1D or occurs when the need for insulin increases during illness or stress as well as when insulin intake decreases.[7] Psychiatric disorders, stress, lower socioeconomic status, and elevated glycosylated hemoglobin (HbA1C) levels increase the risk of DKA.[8] Infection is one of the most important predisposing factors for DKA in diabetic patients. Insufficiency of insulin injection also leads these patients to ketoacidosis.[9] Diabetic ketoacidosis and its associated cerebral edema are the leading cause of hospitalization and mortality in diabetic children and adolescents and children under the age of 5 years are at higher risk for developing DKA.[10] Despite the association between T1D and DKA with infection during COVID-19 epidemics, different findings have been reported. Gottesman et al. reported an increase in the incidence of new-onset T1D among US children during the COVID-19 pandemic.[11] In contrast, Ho et al.[12] reported no change and Rabbone et al.[13] reported a decrease in T1D frequency. Despite different outcomes in the development of new-onset T1D, these studies have shown a significant increase in DKA and severe DKA in the diagnosis of diabetes in children and adolescents during the COVID-19 pandemic.[11–14] Alfayez el al. recently published a systematic review and meta-analysis reported the risk of DKA and severe DKA during the COVID-19 pandemic versus the prior-to-COVID-19 period among pediatric patients with T1D and showed that risk of DKA and severe DKA increased significantly during the pandemic.[15] Although, they did not perform any analysis on the number and rate of newly diagnosed children with T1D and the levels of glucose and HbA1c before and after the COVID-19 pandemic. Additionally, they did not identify all relevant studies in their search strategy and five relevant reports [16–20] were missed in their analyses. Moreover, they included a study by Danne et al. which does not report the risk of DKA and severe DKA among newly diagnosed patients.[21] To date, several studies have reported childhood T1D as a new beginning in the COVID-19 pandemic. Given the dire consequences of childhood T1D, this study reviews and summarizes studies on the prevalence of childhood T1D during COVID-19.

2 | METHODS

The present systematic review and meta-analysis were carried out in accordance with methodological guidelines from the Cochrane Handbook for Systematic Reviews.[22] The findings of the present study were reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Online Supporting Material S1). [23]

2.1 | Search strategy

Relevant studies were systematically searched in electronic databases including MEDLINE/PubMed, CINAHL, Scopus, and EMBASE by two researchers (MA and MK) up to March 2022. The search strategy was as follows: ("severe acute respiratory syndrome coronavirus 2" or "novel coronavirus" or "COVID-19" or "2019-nCoV" or "SARS-CoV-2") and ("type 1 diabetes mellitus" or "diabetes mellitus" or "juvenile onset diabetes" or "insulin-dependent diabetes" or "T1D" or "diabetic ketoacidosis" or "diabetic acidosis" or "acidosis") (Online Supporting Material S2). Further, to find any other eligible articles, we searched all reference lists of included studies. Additionally, language restriction was not considered.

2.2 | Eligibility criteria

The Eligibility criteria followed the PICOs question in the present systematic review and meta-analysis.[24] We included studies that evaluated pediatrics' new-onset T1D during the COVID-19 pandemic in 2020 and during the same periods in 2019 which have reported at least one of the following outcomes: the number of children with new-onset T1D, the number of DKA among newly diagnosed children with T1D, and the number of severe DKA among newly diagnosed children with T1D. We also included studies that evaluated the level of hyperglycemia and HbA1c at T1D diagnosis before and after COVID-19 in newly identified children. Moreover, abstracts with insufficient data and studies with no reported sample size were excluded from the present meta-analysis.

2.3 | Data extraction and quality assessment

First, all retrieved articles were screened by two investigators (M.A. and M.K.) in multiple levels of title, abstract, and full-text, and final studies that met the inclusion criteria were included. Second, the following data were extracted from eligible studies, where available: study design, country, age and gender, T1D diagnosis criteria, and relative outcomes. The quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS).[25] In all stages, discrepancies were solved by consensus with a third investigator (Sh.M.) before conducting a meta-analysis.

2.4 | Statistical analyses

All meta-analyses were conducted using Comprehensive Meta-Analysis Software, version v. 2.0 (CMA, Biostat), and p value less than 0.05 was considered as significant. Dichotomous outcomes were pooled and expressed as logit event rate (ER), risk ratio (RR), and standard mean difference (SMD) with 95% confidence interval (CI).[26] The pooled analysis results were classified based on study types into two categories, cohorts and cross-sectional and the pooled effect sizes were estimated using the random-effect model.[27] Moreover, heterogeneity was calculated using Cochran's Q statistics and I^2. Funnel plots with Egger weighted regression test were used for assessing the potential for publication bias. Finally, the overall pooled effect size of the respective outcomes was re-estimated by the one study that removed methods to perform sensitivity analysis.[28]

3 | RESULTS

3.1 | Study identification and characteristics

A total of 4344 potentially relevant articles were identified in our literature search. Five hundred and eighty-nine studies remained after removing duplicates. After screening titles and abstracts, 448 research articles were excluded. Of 41 obtained research articles, another 15 articles were excluded. Finally, 26 qualified articles met the eligibility criteria and were included in the meta-analysis (Figure 1). The characteristics of the included studies for meta-analysis are listed in Table 1. Data on newly diagnosed T1D among children during the COVID-19 pandemic period in all included studies were compared with those diagnosed during the same period in the previous year. The COVID-19 year in all included studies was defined as finding the first case of COVID-19 infected patient in the country. Publication ranged from 2020 to 2022 in most European countries, Saudi Arabia, Kuwait, Turkey, US, UK, Australia, Israel, Korea, and Canada. Data regarding the number of children infected by COVID-19 among all new-onset T1D were limited as 10 studies did not report any information about the number of diagnosed COVID-19 patients.[12,14,18,20,30,32,37,38,40,46] The number of COVID-19-positive cases in 16 remaining studies was as follows: one case in three studies,[33,35,42] two cases in two studies,[29,36] four cases in two studies,[17,45] eight cases in four studies,[13,19,31,41] and no case in five studies.[16,34,39,43,44] The worldwide incidence rate of diagnosis of T1D in the 2019 period was 19.73 per 100 000 children (18 years and younger) and 32.39 per 100 000 in the 2020 period. Compare with pre-COVID-19 pandemic, the number of worldwide pediatric new-onset T1D, DKA, and severe DKA during the first year of COVID-19 pandemic increased by 9.5%, 25%, and 19.5%, respectively. Compare with pre-COVID-19 pandemic, the median glucose (423.5 mg/dL vs. 397.9 mg/dL) and HbA1c values

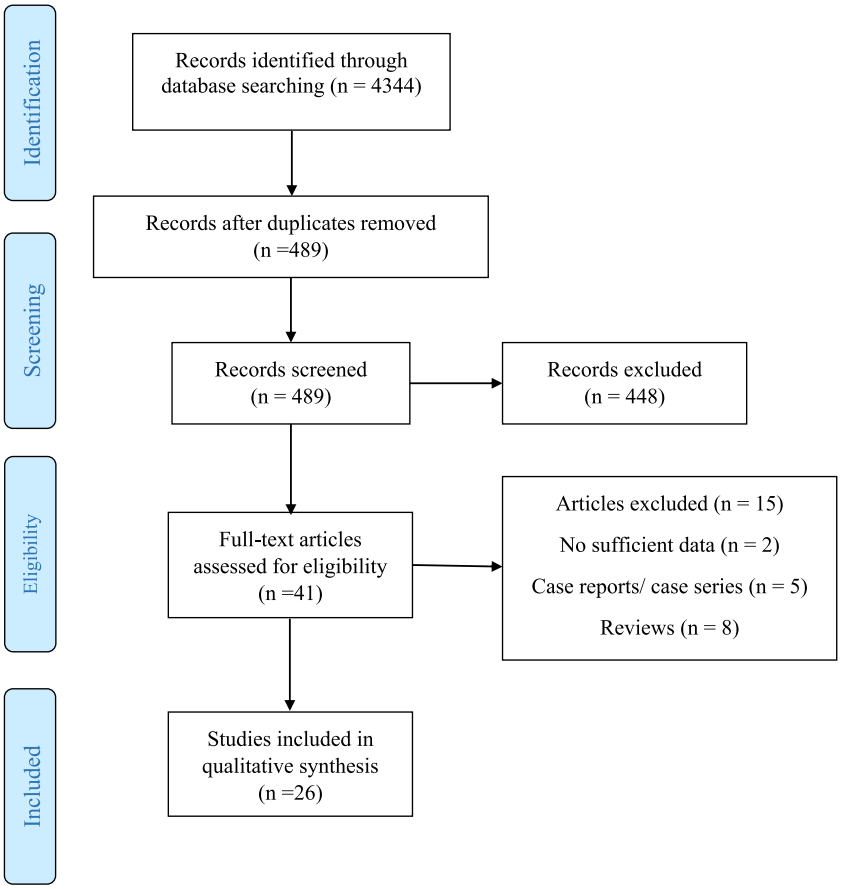


FIGURE 1 PRISMA flow diagram of study selection.

TABLE 1 General characteristics of included studies

Study	Design	Country	Age (year)	Gender, *n* (F)	Analyzed periods during the pandemic*	T1D diagnosis criteria	DKA diagnosis	Severe DKA diagnosis	Outcome		
									Group	2019, *n*	2020, *n*
Alaqeel et al. 2021[29]	Cohort	Saudi Arabia	9.8 ± 0.2	154 (85)	March to June in 2020	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	57	41
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	15	23
									Severe DKA	4	7
Al-Abdulrazzaq et al. 2021[30]	Cohort	Kuwait	8 ± 2.3	303 (153)	February to February of 2020 and 2021	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	303	324
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	113	166
									Severe DKA	33	60
Atlas et al. 2021[16]	Cohort	Australia	NR	58 (26)	February and May in 2020	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	89	58
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	41	30
									Severe DKA	13	13
Boboc et al. 2021[31]	Cohort	Romania	7.2 ± 0.2	147 (72)	March to February of 2020 and 2021	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	113	147
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	97	123
									Severe DKA	33	41
Bogale et al. 2021[32]	Cohort	US	9.2 ± 4.5	42 (19)	January to September in 2020	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	NR	42
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	172	20
									Severe DKA	123	13
Dilek et al. 2021[33]	Cross-sectional	Turkey	10 ± 7.4	74 (39)	March to March of 2020 and 2021	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	46	74
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	27	68
									Severe DKA	4	15

(Continues)

TABLE 1 (Continued)

Study	Design	Country	Age (year)	Gender, *n* (F)	Analyzed periods during the pandemic*	T1D diagnosis criteria	DKA diagnosis	Severe DKA diagnosis	Outcome		
									Group	2019, *n*	2020, *n*
Dżygało et al. 2020[34]	Cohort	Poland	9.9 ± 4.9	34 (12)	March to May in 2020	WHO	pH level < 7.3	pH level < 7.1	New-onset T1D	52	34
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	29	18
									Severe DKA	6	11
Goldman et al. 2022[35]	Cohort	Israel	9.9 ± 2.8	146 (59)	March to June in 2020	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	113	146
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	44	85
									Severe DKA	6	11
Gottesman et al. 2022 [17]	Cross-sectional	US	9.8 ± 0.2	187 (NR)	March to March of 2020 and 2021	NR	NR	NR	New-onset T1D	119	187
									DKA	47	93
									Severe DKA	NR	NR
Hawkes et al. 2021[36]	Cohort	US	<18	73 (NR)	March to July in 2020	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	92	73
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	33	35
									Severe DKA	11	11
Herrero et al. 2022[18]	Cohort	Spain	9.8 ± 1.4	37 (17)	January to January of 2020 and 2021	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	23	37
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	13	12
									Severe DKA	5	2
Ho et al. 2021[12]	Cohort	Canada	6–18	107 (61)	March to August in 2020	DCCP	pH level < 7.3	pH level < 7.1	New-onset T1D	114	107
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	52	73
									Severe DKA	3	8

TABLE 1 (Continued)

Study	Design	Country	Age (year)	Gender, *n* (F)	Analyzed periods during the pandemic*	T1D diagnosis criteria	DKA diagnosis	Severe DKA diagnosis	Outcome		
									Group	2019, *n*	2020, *n*
Jacob et al. 2021[37]	Cross-sectional	Israel	12 ± 2.7	86 (NR)	March to May in 2020	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	80	86
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	31	46
									Severe DKA	14	16
Kamrath et al. 2020[14]	Cohort	Germany	6–18	532 (205)	March to May in 2020	NR	NR	NR	New-onset T1D	503	532
									DKA	123	238
									Severe DKA	70	103
Kostopoulou et al. 2021[38]	Cohort	Greece	8.3 ± 0.9	21 (12)	March to February of 2020 and 2021	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	17	21
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	6	14
									Severe DKA	1	9
Lawrence et al. 2021[39]	Cohort	Australia	8 ± 4.3	11 (8)	March to May in 2020	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	9	11
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	2	8
									Severe DKA	1	5
Lee et al. 2021[40]	Cross-sectional	Korea	12 ± 6.5	10 (9)	February to February of 2020 and 2021	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	10	10
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	4	6
									Severe DKA	0	1
Mameli et al. 2021[41]	Cohort	Italy	8.5 ± 4.2	256 (110)	March to December in 2020	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	231	256
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	65	91
									Severe DKA	24	39

(Continues)

TABLE 1 (Continued)

Study	Design	Country	Age (year)	Gender, *n* (F)	Analyzed periods during the pandemic*	T1D diagnosis criteria	DKA diagnosis	Severe DKA diagnosis	Outcome		
									Group	2019, *n*	2020, *n*
Marks et al. 2021[19]	Cohort	US	10 ± 4.3	182 (81)	March to March of 2020 and 2021	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	158	182
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	82	105
									Severe DKA	27	51
McGlacken-Byrne et al. 2021[42]	Cross-sectional	UK	10.3 ± 6.5	17 (8)	March to June in 2020	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	30	17
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	9	13
									Severe DKA	3	8
Modarelli et al. 2022[43]	Cohort	US	9.8 ± 0.2	46 (16)	April to March of 2020 and 2021	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	31	46
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	NR	NR
									Severe DKA	NR	NR
Rabbone et al. 2020[13]	Cross-sectional	Italy	0–14	160 (NR)	February to April in 2020	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	208	160
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	86	61
									Severe DKA	31	27
Salmi et al. 2022[44]	Cross-sectional	Finland	10 ± 2.3	20 (9)	April to October in 2020	NR	NR	NR	New-onset T1D	57	84
									DKA	NR	NR
									Severe DKA	5	13
Sellers et al. 2021[20]	Cohort	Canada	9.8 ± 0.2	260 (NR)	March to July in 2020	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	236	260
							Bicarbonate level <15 mmol/L	Bicarbonate level <5 mmol/L	DKA	86	143
									Severe DKA	29	69

TABLE 1 (Continued)

Study	Design	Country	Age (year)	Gender, *n* (F)	Analyzed periods during the pandemic*	T1D diagnosis criteria	DKA diagnosis	Severe DKA diagnosis	Outcome Group	2019, *n*	2020, *n*
Unsworth et al. 2020[45]	Cohort	UK	12 ± 6	30 (8)	March to June in 2020	ISPAD	pH level < 7.3 Bicarbonate level <15 mmol/L	pH level < 7.1 Bicarbonate level <5 mmol/L	New-onset T1D DKA Severe DKA	15 NR NR	30 NR NR
Vlad et al. 2021[46]	Cross-sectional	Romania	0–14	NR	January to June in 2020	NR	NR	NR	New-onset T1D DKA Severe DKA	11.4** NR NR	13.3** NR NR

Abbreviations: ADA, American Diabetes Association; COVID-19, coronavirus disease 2019; DCCP, Diabetes Canada Clinical Practice; ISPAD, International Society of Paediatric and Adolescent diabetes; NR, Not reported; T1D, type 1 diabetes; WHO, World Health Organization.

*The COVID-19 pandemic period in all included studies was compared with those diagnosed during the same period in the previous year.

**This study only reported the rate of incidence.

(12.26 ± 1.9% vs. 11.52 ± 2.3%) in newly diagnosed pediatric T1D children after COVID-19 pandemic were increased by 6.43% and 6.42%, respectively. All included studies were of moderate or high quality with NOS scores equal to or greater than 6 (Table 2). The designs of the included studies were cohort ($n = 18$) and cross-sectional ($n = 8$) and we performed a subgroup analysis based on different study types.

3.2 | The worldwide impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes

Twenty-four studies[12–14,16–20,29–31,33–45] involving 5671 new T1D patients (2706 new T1D patients in 2019 and 2965 new T1D patients in 2020) reported numbers of pediatric new-onset T1D before and after the COVID-19 pandemic. Overall, the COVID-19 pandemic was significantly associated with an increase in the number of worldwide pediatric newly diagnosed T1D (logit ER = 0.080, 95% confidence interval [CI] 0.028–0.133, $p = 0.003$; Figure 2A). Significant heterogeneity was observed among the included studies ($I^2 = 66\%$, $p = 0.0001$). According to the study types, the pooled main effect of COVID-19 pandemic in the number of worldwide pediatric newly diagnosed T1D in cohort and cross-sectional studies were logit ER, 0.076 (95% CI: 0.018–0.135; $p = 0.010$), and logit ER, 0.097 (95% CI: −0.026 to 0.221; $p = 0.123$), respectively. Additionally, eight studies[12,14,18,30,33,41,44,46] reported incidence rate of T1D before and after the COVID-19 pandemic. Overall pooled analysis showed that COVID-19 pandemic was significantly associated with an increase in incidence rate of diagnosis of T1D in children (overall: logit ER = 0.493, 95% CI 0.289–0.697, $p = 0.001$; cohorts: logit ER = 0.494, 95% CI 0.279–0.709, $p = 0.0001$; cross-sectionals: logit ER = 0.482, 95% CI −0.166 to 0.129, $p = 0.145$; Figure 2B).

3.3 | The worldwide impact of COVID-19 pandemic on the risk incidence of pediatric diabetic ketoacidosis

Twenty-one studies[12–14,16,18–20,29–42] involving 2648 new T1D patients with DKA and 979 new T1D patients with severe DKA (DKA: 1177 new cases in 2019 and 1471 new cases in 2020; severe DKA: 446 new cases in 2019 and 533 new cases in 2020) were included. The random-effect model showed that COVID-19 pandemic was associated with an elevation in the risk incidence of worldwide pediatric DKA and severe DKA compared with pre-COVID-19 period (RR = 0.064, 95% CI 0.043– 0.084, $p = 0.0001$, and RR, 0.049 (95% CI: 0.029–0.066; $p = 0.0001$, respectively; Figure 3). The values of $I^2 = 3\%$ ($p = 0.412$) and $I^2 = 14\%$ ($p = 0.26$) indicated that no significant heterogeneity exist in the included studies evaluating DKA and severe DKA. The pooled main effects were comparable for the different study designs: RR = 0.068, 95% CI: 0.045–0.091; $p = 0.0001$ (DKA in cohort studies), RR = 0.049, 95% CI: 0.028–0.070; $p = 0.0001$ (severe DKA in cohort studies), RR = 0.048,

TABLE 2 Summary of the Newcastle–Ottawa scale for bias assessment of included studies

Cohort study	Selection (4)				Comparability (2)		Outcome (3)			
Author	Representativeness of exposed cohort	Selection based on national registry data	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	Study control for diabetic risk factors	Adjustment of incidence rate for age	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Alaqeel et al.[29]	1	1	1	1	1	0	1	1	1	8
Al-Abdulrazzaq et al.[30]	1	1	1	1	1	1	1	1	1	9
Atlas et al.[16]	1	0	0	1	0	0	1	1	1	5
Boboc et al.[31]	1	0	1	1	1	0	1	1	1	7
Bogale et al.[32]	1	1	0	1	1	0	1	1	1	7
Dżygało et al.[34]	1	0	1	1	1	0	1	1	1	7
Goldman et al.[35]	1	1	1	1	0	0	1	1	1	7
Hawkes et al.[36]	1	0	1	1	0	0	1	1	1	6
Herrero et al.[18]	1	0	1	1	0	1	1	1	1	7
Ho et al.[12]	1	1	1	1	0	1	1	1	1	8
Kamrath et al.[14]	1	1	0	1	0	1	1	1	1	7
Kostopoulou et al.[38]	1	0	0	1	1	0	1	1	1	6
Lawrence et al.[39]	1	0	1	1	1	0	1	1	1	7
Mameli et al.[41]	1	1	1	1	0	1	1	1	1	8
Marks et al.[19]	1	1	1	1	1	0	1	1	1	8
Modarelli et al.[43]	1	1	1	1	1	0	1	1	1	8
Sellers et al.[20]	1	1	0	1	0	0	1	1	1	6
Unsworth et al. [45]	1	1	1	1	0	0	1	1	1	7

Cross-sectional study	Selection (5)				Comparability (2)	Outcome (3)		
Author	Representativeness of the sample	Sample size	Selection based on national registry data	Ascertainment of exposure	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	Assessment of the outcome	Statistical test	Total
Dilek et al.[33]	1	1	0	2	2	1	1	8
Gottesman et al.[17]	1	1	1	1	1	1	1	7

TABLE 2 (Continued)

Cross-sectional study	Selection (5)					Comparability (2)	Outcome (3)		
Author	Representativeness of the sample	Sample size	Selection based on national registry data	Ascertainment of exposure		The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	Assessment of the outcome	Statistical test	Total
Jacob et al.[37]	1	1	1	2		0	1	1	7
Lee et al.[40]	1	1	0	2		1	1	1	7
McGlacken-Byrne et al.[42]	1	1	1	2		1	1	1	8
Rabbone et al.[13]	1	1	1	2		1	1	1	8
Salmi et al.[44]	1	1	1	1		2	1	1	8
Vlad et al.[46]	1	1	1	1		1	1	1	7

95% CI: −0.002 to 0.093; $p = 0.059$ (DKA in cross-sectional studies), and RR = 0.049, 95% CI: −0.009 to 0.106; $p = 0.096$ (severe DKA in cross-sectional studies).

3.4 | The worldwide impact of COVID-19 pandemic on the risk of increased hyperglycemia and HbA1c at T1D diagnosis

In total, six studies[19,32,34,39,40,43] included within this meta-analysis, which reported blood glucose and HbA1c levels in children who were newly diagnosed with T1D in 2019 and 2020. There were statistically significant associations between COVID-19 pandemic with elevation in blood glucose and HbA1c levels in pediatric newly diagnosed T1D compared with pre-COVID-19 period (SMD = 0.336, 95% CI 0.074–0.598, $p = 0.012$, and SMD = 0.173, 95% CI 0.022–0.323, $p = 0.024$, respectively; Figure 4). The SMDs observed for blood glucose in the cohort and cross-sectional studies were 0.169 (95% CI: 0.017–0.322, $p = 0.030$), and 0.286 (95% CI: −0.595 to 1.688, $p = 0.524$), respectively. Additionally, the SMDs observed for HbA1c in the cohort and cross-sectional studies were 0.378 (95% CI: 0.030–0.725, $p = 0.033$), and 0.282 (95% CI: −0.117 to 0.681, $p = 0.167$), respectively.

3.5 | Sensitivity analysis and publication bias

The results of sensitivity analysis showed that the overall pooled estimates of the respective outcomes in all analyses obtained closely resembled preliminary associations. To further clarify the publication bias for the included studies, funnel plots suggested no noticeable bias in the studies of the present meta-analysis (Online Supporting Material S3). Further, *Begg's* correlation rank and *Egger's* regression did not show significant publication bias (Table 3)

4 | DISCUSSION

In the present systematic review and meta-analysis, we performed a pooled analysis to evaluate and compare the effects of the first year of COVID-19 pandemic on the global incidence of T1D, DKA, hyperglycemia, and mean HbA1c levels in children. Based on the results of 26 eligible articles, the present meta-analysis shows that the global new-onset of childhood T1D rate and number have increased in 2020 compared with 2019. In addition, compared with pre-pandemic COVID-19 period, significant increases were observed in global DKA, severe DKA, blood glucose levels, and HbA1c levels in children.

Long-term complications of childhood-onset T1D have been considered as a main cause of death and cardiovascular-associated disease.[47] More importantly, even before the onset of diabetes-related complications, young people with T1D are still at a higher risk of mortality.[48] A systematic review of 13 articles assessing structural

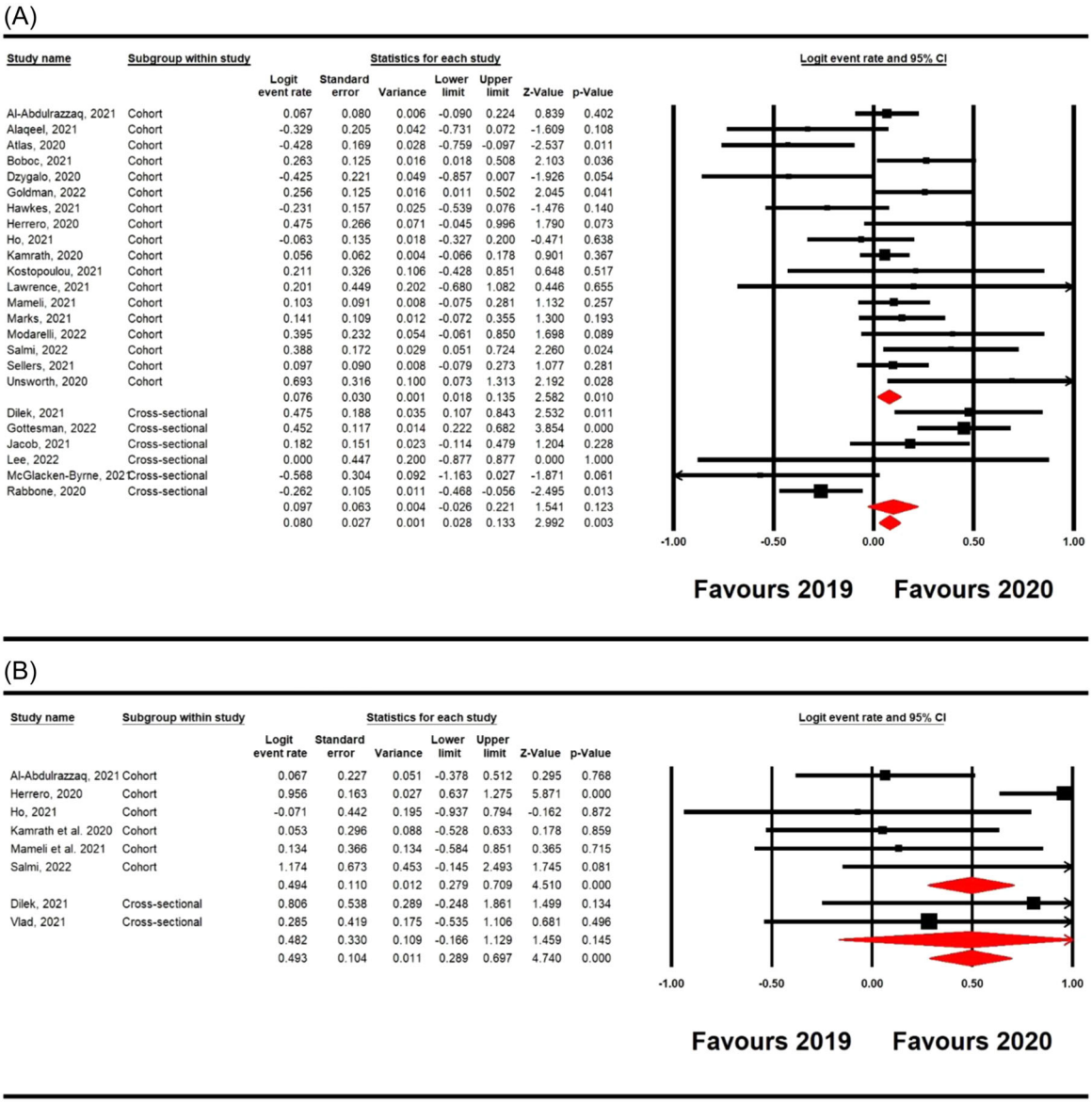


FIGURE 2 Forest plot of the logit event rates of numbers (A) and incidence (B) of pediatric new-onset T1D before and after the COVID-19 pandemic. CI, confidence interval; COVID-19, coronavirus disease-2019; T1D, type 1 diabetes

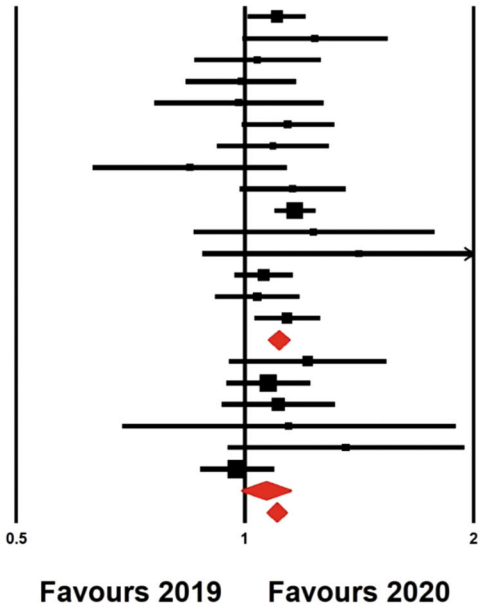
changes in the central nervous system in children and adolescents with diabetes concluded that repeated episodes of acute hyperglycemia, for example, DKA, are associated with detrimental structural changes in the brain.[49] Additionally, acute diabetic complications including DKA and hyperglycemia were identified as leading causes of death before the age of 30 in a cohort study of 7871 childhood-onset T1D in Norway.[50] Moreover, the Brecon cohort study of 3642 individuals in Wales showed that a near threefold excess mortality before age 30 which persists in individuals with young onset T1D occurred before age 15 years, and ketoacidosis was the most common cause of death in these patients.[51] Further, a nationwide cohort study of 12 652 individuals in the Swedish pediatric diabetes quality registry from 2006 to 2014 showed that higher mean HbA1c during childhood was associated with higher diabetes-related premature mortality in young people (<30 years of age).[52] Overall, these studies indicate that hyperglycemia, higher mean HbA1c, and DKA are associated with an increased risk of mortality in individuals with young onset T1D before the age of 30 years.

Given the accepted theory of the pathogenesis of T1D[1] and the global increasing incidence of severe T1D, DKA, and severe DKA in children during the recent pandemic, it can be hypothesized that SARS-CoV-2 is probably a stimulus for the autoimmune system, especially for pancreatic autoimmunity, and the initiation of T1D. Therefore, this hypothesis can be a common cause between these two diseases, and raising awareness about this issue is recommended. Although, further research is needed to demonstrate this hypothesis

T1D is a multifactorial disease and in addition to environmental stimuli (food, stress, etc.), exposure to infectious agents such as

(A)

Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Al-Abdulrazzaq, 2021	Cohort	1.102	1.010	1.201	2.194	0.028
Alaqeel, 2021	Cohort	1.236	0.993	1.537	1.900	0.057
Atlas, 2020	Cohort	1.039	0.859	1.256	0.391	0.695
Boboc, 2021	Cohort	0.988	0.837	1.167	-0.138	0.890
Dzygalo, 2020	Cohort	0.982	0.760	1.268	-0.140	0.888
Goldman, 2022	Cohort	1.139	0.991	1.308	1.838	0.066
Hawkes, 2021	Cohort	1.089	0.921	1.288	0.996	0.319
Herrero, 2020	Cohort	0.846	0.631	1.134	-1.119	0.263
Ho, 2021	Cohort	1.155	0.986	1.354	1.785	0.074
Kamrath, 2020	Cohort	1.163	1.094	1.236	4.844	0.000
Kostopoulou, 2021	Cohort	1.232	0.856	1.772	1.125	0.261
Lawrence, 2021	Cohort	1.413	0.880	2.270	1.430	0.153
Mameli, 2021	Cohort	1.058	0.970	1.154	1.265	0.206
Marks, 2021	Cohort	1.038	0.915	1.178	0.579	0.562
Sellers, 2021	Cohort	1.136	1.030	1.253	2.553	0.011
		1.108	1.073	1.145	6.223	0.000
Dilek, 2021	Cross-sectional	1.209	0.955	1.531	1.577	0.115
Gottesman, 2022	Cross-sectional	1.073	0.946	1.218	1.099	0.272
Jacob, 2021	Cross-sectional	1.106	0.933	1.312	1.162	0.245
Lee, 2022	Cross-sectional	1.143	0.691	1.891	0.519	0.603
McGlacken-Byrne, 2021	Cross-sectional	1.357	0.950	1.940	1.678	0.093
Rabbone, 2020	Cross-sectional	0.977	0.876	1.090	-0.412	0.680
		1.067	0.989	1.150	1.677	0.093
		1.102	1.069	1.135	6.380	0.000



(B)

Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Al-Abdulrazzaq, 2021	Cohort	1.069	1.011	1.130	2.343	0.019
Alaqeel, 2021	Cohort	1.030	0.759	1.397	0.189	0.850
Atlas, 2020	Cohort	1.068	0.935	1.220	0.973	0.331
Boboc, 2021	Cohort	0.990	0.882	1.111	-0.173	0.863
Dzygalo, 2020	Cohort	1.187	0.983	1.432	1.786	0.074
Goldman, 2022	Cohort	1.021	0.962	1.084	0.687	0.492
Hawkes, 2021	Cohort	1.028	0.924	1.143	0.504	0.614
Herrero, 2020	Cohort	0.866	0.718	1.044	-1.506	0.132
Ho, 2021	Cohort	1.047	0.988	1.110	1.559	0.119
Kamrath, 2020	Cohort	1.048	1.001	1.097	1.995	0.046
Kostopoulou, 2021	Cohort	1.349	1.041	1.749	2.261	0.024
Lawrence, 2021	Cohort	1.309	0.887	1.933	1.355	0.175
Mameli, 2021	Cohort	1.044	0.984	1.108	1.413	0.158
Marks, 2021	Cohort	1.093	0.999	1.197	1.936	0.053
Salmi, 2022	Cohort	1.062	0.953	1.182	1.090	0.276
Sellers, 2021	Cohort	1.127	1.051	1.208	3.352	0.001
		1.056	1.032	1.081	4.567	0.000
Dilek, 2021	Cross-sectional	1.106	0.977	1.253	1.597	0.110
Jacob, 2021	Cross-sectional	1.009	0.896	1.137	0.154	0.878
Lee, 2022	Cross-sectional	1.091	0.850	1.400	0.683	0.495
McGlacken-Byrne, 2021	Cross-sectional	1.337	1.001	1.786	1.964	0.050
Rabbone, 2020	Cross-sectional	1.017	0.942	1.098	0.435	0.663
		1.050	0.988	1.117	1.568	0.117
		1.055	1.033	1.079	4.825	0.000

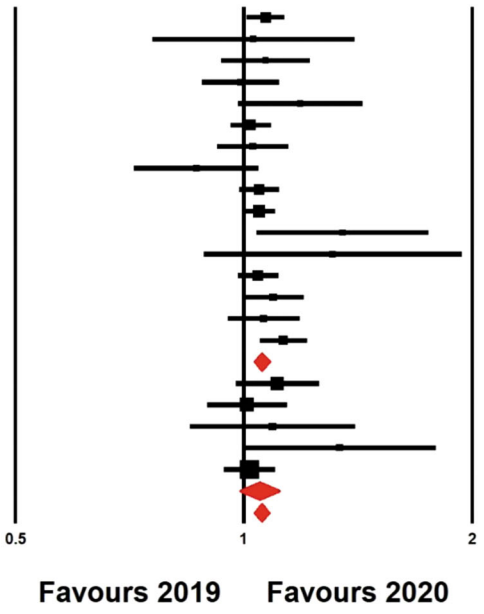
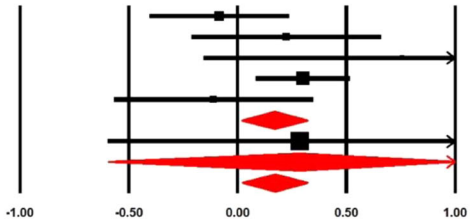


FIGURE 3 Forest plot of the risk of global pediatric DKA (A) and severe DKA (B) before and after the COVID-19 pandemic. CI, confidence interval; COVID-19, coronavirus disease-2019; DKA, diabetic ketoacidosis

(A)

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bogale, 2021	Cohort	-0.084	0.162	0.026	-0.401	0.234	-0.518	0.605
Dzygalo, 2020	Cohort	0.224	0.221	0.049	-0.209	0.658	1.013	0.311
Lawrence, 2021	Cohort	0.756	0.465	0.216	-0.155	1.668	1.626	0.104
Marks, 2021	Cohort	0.301	0.109	0.012	0.086	0.515	2.750	0.006
Modarelli, 2022	Cohort	-0.111	0.233	0.054	-0.567	0.345	-0.478	0.632
		0.169	0.078	0.006	0.017	0.322	2.176	0.030
Lee, 2022	Cross-sectional	0.286	0.450	0.202	-0.595	1.168	0.637	0.524
		0.286	0.450	0.202	-0.595	1.168	0.637	0.524
		0.173	0.077	0.006	0.022	0.323	2.253	0.024



(B)

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Al-Abdulrazzaq, 2021	Cohort	0.227	0.080	0.006	0.069	0.384	2.825	0.005
Alaqeel el al. 2021	Cohort	0.250	0.206	0.042	-0.153	0.653	1.217	0.224
Boboc, 2021	Cohort	0.769	0.130	0.017	0.515	1.023	5.932	0.000
Bogale, 2021	Cohort	0.084	0.162	0.026	-0.234	0.401	0.517	0.605
Dzygalo, 2020	Cohort	0.219	0.221	0.049	-0.214	0.653	0.991	0.322
Kostopoulou, 2021	Cohort	4.118	0.574	0.330	2.993	5.244	7.173	0.000
Lawrence, 2021	Cohort	0.068	0.450	0.202	-0.813	0.949	0.152	0.879
Marks, 2021	Cohort	-0.250	0.109	0.012	-0.464	-0.036	-2.290	0.022
Modarelli, 2022	Cohort	-0.250	0.233	0.054	-0.707	0.207	-1.072	0.284
Salmi, 2022	Cohort	0.335	0.468	0.219	-0.582	1.252	0.716	0.474
		0.378	0.177	0.031	0.030	0.725	2.131	0.033
Dilek, 2021	Cross-sectional	0.183	0.188	0.035	-0.186	0.552	0.972	0.331
Gottesman et al. 2022	Cross-sectional	-0.054	0.117	0.014	-0.284	0.176	-0.464	0.643
Lee, 2022	Cross-sectional	0.398	0.452	0.204	-0.487	1.284	0.882	0.378
McGlacken-Byrne, 2021	Cross-sectional	0.941	0.319	0.102	0.317	1.566	2.954	0.003
		0.282	0.204	0.041	-0.117	0.681	1.383	0.167
		0.336	0.134	0.018	0.074	0.598	2.515	0.012

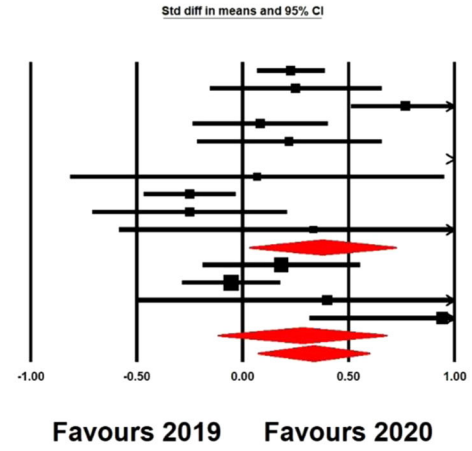


FIGURE 4 Forest plot of risk of pediatric hyperglycemia (A) and elevated HbA1c (B) before and after the COVID-19 pandemic. CI, confidence interval; COVID-19, coronavirus disease-2019; HbA1c, glycosylated hemoglobin

viruses in genetically predisposed individuals can trigger the disease.[53,54] It has been shown that the RNA virus carrying COVID-19 may damage pancreatic β-cells.[33,55] Several hypotheses have been proposed for the association between COVID-19 and the higher incidence rate of T1D. Diabetes increases the risk of infections, including viral infections, due to its innate immuno-deficiency on neutrophil chemotaxis phagocytosis and cellular immunity.[56] Inflammatory markers of COVID-19 enter the cell through the binding of the COVID-19 spike protein using the enzyme ACE2. The mechanism of this process is a decrease in the expression of ACE2 induced by COVID-19, which eventually leads to cell damage, inflammation, and respiratory failure. Pancreatic β-cells are affected by the enzyme ACE2, and this direct link puts diabetics at greater risk for COVID-19 and finally the infection can cause new diabetes [57]

It is essential that all nondiabetic patients (especially those at high risk for metabolic disease) be evaluated for the possibility of developing new-onset diabetes. Other factors such as unknown biological factors, avoidance, limited access or delay in seeking medical care, fear of seeing a doctor because of the risk of infection, and failure to recognize DKA symptoms, and stress may be involved in combating the COVID-19 pandemic. It is clearly worrying that T1D and DKA remain undiagnosed during the limited interaction of patients referred to healthcare centers. Another interesting finding in the data collected in this study was the higher HbA1c during the pandemic among the new T1D, which could be due to delays and limitations in medical care etc. Owing to rising T1D and DKA rates, public awareness of the symptoms of the disease in the public, improvement of telemedicine technology due to concerns about COVID-19 in hospitals and quarantine, warning to take the milder symptoms of the onset of new diabetes seriously is warranted

Results of the present meta-analysis must be interpreted in light of its limitations. First, the present systematic review and meta-analysis only covered the first wave of the COVID-19 pandemic and future studies should evaluate the number of childhood new-onset

TABLE 3 Results of the subgroup analysis based on study design

Risk factors	Effect measures	Number of study	Z-Value	*p*-Value	Effect size (95% CI)	Heterogeneity I^2	Heterogeneity *p* value	*Begg's* test *p*-value	*Egger's* test *p*-value
New-onset T1D									
Cohorts	Event rate	18	2.582	0.010	0.076 (0.018–0.135)	56%	0.002	0.235	0.414
Cross-sectionals	Event rate	6	1.541	0.123	0.097 (−0.026 to 0.221)	83%	0.0001	0.425	0.468
Overall	Event rate	24	2.992	0.003	0.080 (0.028–0.133)	66%	0.0001	0.327	0.443
T1D incidence rate									
Cohorts	Event rate	6	4.510	0.0001	0.494 (0.279–0.709)	71%	0.004	0.286	0.198
Cross-sectionals	Event rate	2	1.459	0.145	0.482 (−0.166 to 0.129)	0%	0.444	NA	NA
Overall	Event rate	8	4.740	0.0001	0.493 (0.289–0.697)	61%	0.012	0.211	0.108
Risk of DKA									
Cohorts	Risk ratio	15	6.223	0.0001	1.108 (1.073–1.145)	0%	0.456	0.480	0.915
Cross-sectionals	Risk ratio	6	1.677	0.093	1.067 (0.989–1.150)	9%	0.356	0.132	0.112
Overall	Risk ratio	21	6.380	0.0001	1.102 (1.069–1.135)	3%	0.414	0.216	0.437
Risk of Severe DKA									
Cohorts	Risk ratio	16	4.567	0.0001	1.056 (1.032–1.081)	14%	0.289	0.471	0.449
Cross-sectionals	Risk ratio	5	1.568	0.117	1.050 (0.988–1.117)	11%	0.342	0.052	0.117
Overall	Risk ratio	21	4.825	0.0001	1.055 (0.033–1.079)	9%	0.334	0.183	0.209
Risk of higher glucose									
Cohorts	SMD	5	2.176	0.030	0.169 (0.017–0.322)	42%	0.136	1	0.970
Cross-sectionals	SMD	1	0.637	0.524	0.282 (−0.595 to 1.188)	0%	1	NA	NA
Overall	SMD	6	2.253	0.024	0.173 (0.022–0.323)	29%	0.216	0.573	0.945
Risk of higher HbA1c									
Cohorts	SMD	10	2.131	0.033	0.378 (0.030–0.725)	89%	0.0001	0.531	0.350
Cross-sectionals	SMD	4	1.383	0.167	0.282 (−0.117 to 0.681)	67%	0.025	0.174	0.172
Overall	SMD	14	2.515	0.012	0.336 (0.074–0.598)	86%	0.0001	0.139	0.182

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; HbA1c, Glycosylated hemoglobin; SMD, standard mean difference; T1D, Type 1 diabetes.

T1D in 2021 and 2022. Second, data regarding the number of children infected by COVID-19 among all new-onset T1D are limited and this make it difficult to attribute such an increase in T1D, DKA, and severe DKA to COVID-19 infection. Third, our findings should be interpreted with caution since our meta-analysis did not capture the unexpected confounders, time-varying exposure such as multifactorial environmental stimuli (i.e., food, stress, and outdoor environmental factor), and different ethnic effect. Finally, the criteria used for the T1D diagnosis varied between studies and should be consistent in future studies

5 | CONCLUSION

The results of the present meta-analysis demonstrate a global significant increase in the incidence of childhood new-onset T1D, DKA, and severe DKA with elevated hyperglycemia and mean HbA1c levels at T1D diagnosis in the first year of the COVID-19 pandemic compared to pre-COVID-19 period. Due to this fact, physicians should consider this issue in all nondiabetic children and monitor their blood sugar and HbA1C when accepting them for proper and early management. Based on these findings, continuous and repeated

educational diabetes awareness should be delivered to physicians, caregivers, and the public to improve health outcomes in the world and change trends in childhood T1D and DKA

AUTHOR CONTRIBUTIONS

Masoud Rahmati and Jae Il Shin developed the idea and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Masoud Rahmati and Maryam Keshvari ran the search strategy; Masoud Rahmati and Maryam Keshvari selected articles and extracted data. Masoud Rahmati evaluated the quality of the literature. Masoud Rahmati, Maryam Keshvari, Shahrzad Mirnasuri, Dong K Yon, Seung Won Lee, Jae Il Shin, and Lee Smith wrote the manuscript. All listed authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in Table 1.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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