Incidence and prevalence of type 1 diabetes and diabetic ketoacidosis in children and adolescents (0−19 years) in Thailand (2015−2020): A nationwide population-based study

Thanitsara Rittiphairoj,[a,b] Maira Owais,[a,c] Zachary J. Ward,[d] Ché L. Reddy,[a] Jennifer M. Yeh,[e] and Rifat Atun[a,f]*

[a]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA
[b]Division of Health Systems Management, Department of Community Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[c]Amherst College, Amherst, USA
[d]Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, USA
[e]Division of General Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA
[f]Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA

The Lancet Regional Health - Western Pacific 2022;21: 100392
Published online xxx
https://doi.org/10.1016/j.lanwpc.2022.100392

Summary

Background There is a lack of published studies on incidence of type 1 diabetes (T1D) and diabetic ketoacidosis (DKA) in Thailand. We aimed to estimate the national prevalence and incidence of T1D and DKA.

Methods Using Thailand's nationwide population-based longitudinal data covering 69 million individuals, we included the entire children and adolescents recorded in the database. Diseases were identified using ICD-10 codes. We investigated the prevalence of T1D and cumulative incidence of T1D, T1D referral, DKA, and mortality risk of DKA in five years from 2015 to 2020. T1D and DKA annual incidence were also estimated. We present findings for the total population and by sex, age, and urban-rural residencies.

Findings A total of 19,784,781 individuals aged less than 20 years were identified in 2015. The crude T1D prevalence in 2015 was 17·6 per 100,000 and crude T1D incidence rate was 5·0 per 100,000. T1D prevalence and cumulative incidence were significantly higher in older children ($p < 0·001$) and females ($p < 0·001$) than their counterparts. Among those with T1D, cumulative incidence of T1D referral was 42·4%. It was highest amongst children aged 5−14 years and was significantly higher among females (all $p < 0·05$). The crude DKA incidence rate at any point after diagnosis was 10·8%. The cumulative incidence of DKA was significantly higher in females and peaked in individuals aged 5−14 years (all $p < 0·001$). The DKA mortality risk was 258·2 per 100,000.

Interpretation Older children and females had higher T1D prevalence. The DKA cumulative incidence and mortality risk were relatively low, and such incidence was peak in individuals aged 5−14 years.

Funding Harvard University.

Keywords: Type 1 diabetes; Diabetic ketoacidosis; Incidence; Prevalence; Thailand

Introduction

Type 1 Diabetes (T1D) is a chronic disease characterised by minimal insulin production due to autoimmune-mediated destruction of pancreatic beta cells,[1] leading to elevated blood glucose levels. Individuals with T1D require lifelong exogenous insulin supplementation, regular health care, and behavioral lifestyle changes to control their blood glucose.[2] Failure to access treatment and care can lead to the development of life-threatening complications.[3] Providing such care is fundamental to promoting healthy growth of children and adolescents, a key driver of the United Nations Sustainable Development Goals (SDGs) and human capital development.[4]

Several studies have suggested that T1D incidence is underestimated globally, particularly in low-income and middle-income countries,[5−7] leading to

*Corresponding author at: Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA.
E-mail address: trittiphairoj@hsph.harvard.edu (T. Rittiphairoj).

Research in context

Evidence before this study

There is a lack of published studies on national incidence of type 1 diabetes (T1D) and diabetic ketoacidosis (DKA) in Thailand. We searched MEDLINE via PubMed and Embase from inception to December 19, 2020, using Medical Subject Headings and keywords related to "diabetes mellitus", "type 1 diabetes", and "diabetic ketoacidosis", in combination with the term "Thailand". We did not apply any language restriction. We found that all published studies investigating incidence of T1D in Thailand were conducted in 1990s, and they revealed only some localised incidence patterns in some regions of the country. Likewise, a study investigating incidence of DKA in Thailand were conducted only in a tertiary care setting. Therefore, it is not known to what extent the incidence of T1D and DKA in Thailand compare with current international trends, and whether their epidemiological characteristics differ. Such a lack of evidence creates challenges in health system planning to provide an appropriate and equitable level of screening, diagnosis, treatment and effective care of children and adolescents with T1D.

Added value of this study

To our knowledge, this is the first nationwide population-based investigation to examine prevalence and incidence trends and patterns of T1D and DKA amongst children and adolescents in Thailand. Using population-based longitudinal data covering 69 million individuals, we captured most, if not all, patients seen at all hospital levels and in all provinces in Thailand. Our results show that the T1D prevalence and annual incidence rate in Thailand were relatively low as compared to the levels observed globally, possibly due to differences in genetic susceptibility, and the trend showed an increase over time. We found that older children and females had higher level of T1D. Females and children aged 5 to 14 years were more likely to be referred to other hospitals for T1D management. Among children and adolescents with T1D, the annual incidence rate of DKA was relatively low and its trend over time declined. The five-year cumulative incidence of DKA was higher in females and older children with a peak amongst children aged 5 to 14 years. The mortality risk of DKA was low. The evidence of low DKA incidence and mortality risk of DKA suggests benefits of Thailand's Universal Health Coverage (UHC) that improve access to care both in aspects of affordability and timeliness.

Implication of all the available evidence

Incidence of T1D amongst children and adolescent is increasing globally, even in countries with low T1D incidence, such as Thailand. In addition, policy makers should give careful consideration to allocating low-cost affordable or free T1D care interventions, such as self-management support, community involvement, and decision support systems, to target children aged 5 to 14 years as they have a higher risk of DKA and are more vulnerable to poor compliance with medical and self-care as compared to other age groups. Finally, our findings inform important implications of UHC's benefits to enhanced T1D care in terms of improving access to care, especially in low- and middle-income countries.

potentially inefficient health system planning to provide an appropriate and equitable level of screening, diagnosis, treatment and effective care of children and adolescents with T1D.

T1D has varying incidence worldwide,[8] and global trends suggest an increasing incidence for the past three decades.[9] When inadequately managed, T1D can lead to several serious complications, such as diabetic ketoacidosis (DKA).[10] DKA, in particular, which is characterised by excess ketone production, is one of the most common causes of mortality, morbidity, and hospitalization in T1D children and adolescents.[11] It is therefore critically important to measure true levels of the incidence and prevalence of T1D and its complications in order to provide an appropriate level of care to reduce avertable disability and mortality from the disease.

It is not known to what extent the incidence of T1D and DKA in Thailand compare with international trends, and whether their epidemiological characteristics differ. A study conducted from 1991 to 1995 suggested that north-eastern Thailand had one of the lowest incidence rates in the world.[12] Other studies have assessed disease patterns in Thailand, showing that the average age of onset was 11 years with a higher incidence occurring in females.[13–17] A further study reported on the social determinants found a higher incidence of T1D in families with lower socioeconomic levels.[14] There is sparse evidence on the incidence of DKA amongst children and adolescents with T1D in Thailand, possibly due to challenge of obtaining reliable data. A study conducted in a tertiary care center in Thailand found that the DKA incidence in the study's setting increased to 6·2% in 2010.[18] While these studies reveal localised incidence patterns to help inform T1D care in some regions of the country, there is a need for national population-level research to inform national policies and healthcare delivery for enhanced T1D care.

This study utilised a nationwide population-based database, which covers the whole Thai population (69 million) sourced from individual-level longitudinal data reported by public health care facilities across Thailand from December 1, 2015 to December 1, 2020.[19] Focusing on approximately 19 million individuals aged less than 20 years, this study comprised three main study objectives: (1) to determine national estimates of the incidence and prevalence of T1D among children and adolescents in Thailand; (2) to establish the incidence of DKA; and (3) to better understand their epidemiological patterns in terms of sex, age, and geographic setting.

Methods

Data source

We used a nationally representative population-based database that provides de-identified individual-level longitudinal data, called "43 Folders".[19] The database captures data from registrations and health records of all patients seen at all public hospital levels in all provinces. It is owned by the Ministry of Public Health and was launched in 2013. All patient registrations and health information reported by public health facilities across Thailand are recorded monthly in the database. General patient information is annually updated to the main database system. The data quality is reviewed at the hospital and provincial levels to ensure the accuracy of data. As 70% of health facilities are public and are accessible by all due to Thailand's universal health coverage (UHC), this database captures the vast majority, if not all, of the Thai population.

For this study, we retrieved data for all children and adolescents available in the database, which were approximately 19 million unique patients' data in 2015 and 17 million in 2020. The data used for this study contain registration and health data, including personal information, service and medical records of both out-patient visits and in-patient admissions, drug prescription, and death records. Disease diagnoses are classified using the International Classification of Disease, Tenth Edition, Clinical Modification (ICD-10-CM) according to the World Health Organization Guidelines. Since data are de-identified, personal consents were not needed.

To assess the completeness of ascertainment, we used a two-sample capture-recapture method.[20] The primary source of ascertainment was hospital records of T1D, and the secondary source of ascertainment was prescription data of insulin. The database had the completeness of ascertainment of 100%.

Study population

The study used a nationwide population-based database, covering all 13 regional health service areas across Thailand and captured data on patients seen at all hospital levels, including primary health centers, district hospitals, general hospitals, and regional hospitals.

Our population of interest was children and adolescents in Thailand, which was defined as all individuals aged less than 20 years whose data were available in the database. As we focused on outcomes measured in 2015, 2020 and from 2015 to 2020, individuals were included in our study if they were born from December 2, 1995, to December 1, 2015 (for outcomes measured in 2015), from December 2, 2000, to December 1, 2020 (for outcomes measured in 2020), or from December 2, 1995 to December 1, 2020 (for outcomes measure from 2015 to 2020). According to the National Statistical Office, Thailand is an aging society and thus the population aged 0 to 19 is declining over time.[21]

Outcome and explanatory variables

Outcome variables. Our analysis focused on the following outcome variables:

- Prevalence of T1D among children and adolescents in 2020;
- Prevalence of T1D among children and adolescents in 2015;
- Five-year cumulative incidence of T1D among children and adolescents from 2015 to 2020;
- Five-year cumulative incidence of referral to other hospitals for T1D management (T1D referral) among children and adolescents with T1D from 2015 to 2020;
- Five-year cumulative incidence of DKA at any point after T1D diagnosis among children and adolescents with T1D from 2015 to 2020;
- Five-year mortality risk of DKA among children and adolescents with T1D from 2015 to 2020;
- Annual incidence rate of T1D among children and adolescents from 2015 to 2020;
- Annual incidence rate of DKA at any point after T1D diagnosis among and adolescents with T1D from 2015 to 2020.

For prevalence outcomes, we use the index date of December 1, 2015 for an outcome measured in 2015 and December 1, 2020 for an outcome measured in 2020. For cumulative incidence outcomes, using the index date of December 1, 2015, we counted episodes of events of interest from December 1, 2015, to December 1, 2020. Likewise, for annual incidence rate outcomes, episodes of events of interest were counted for each year period (December 1 to November 30) from 2015 to 2020. Following the annual data update period of the database, we used the index date of December 1 to reduce the likelihood of missing data. For simplicity, only 1 episode of such events per individual was considered (i.e., for incidence outcomes, individuals were removed from the study cohort after they developed an event of interest).

Case definition. Individuals with T1D were identified from out-patient visit records using any of the ICD10-CM codes for T1D at a specific time point (for prevalence outcomes) or within a study time frame (for incidence outcomes). The ICD10-CM codes for T1D included E10·0, E10·1, E10·2, E10·3, E10·4, E10·5, E10·6, E10·7, E10·8, and E10·9. T1D individuals being referred to other hospitals for T1D management were identified from hospital service records if they had a

record showing a post-service status as being referred to other hospitals within the study time frame. Similarly, hospitalizations for DKA were identified using the ICD10-CM code E10·9, and deaths from DKA were identified from death records using the same code.

Explanatory variables. Children and adolescents were categorised according to (1) sex: male versus female; (2) age group: ages 0–4, 5–9, 10–14, and 15–19 years; and (3) urban versus rural residencies. Urban versus rural residencies were classified based on subdistricts. Subdistricts that were upgraded to "Subdistrict Municipality" were classified as "Urban". Otherwise, subdistricts were classified as "Rural".

Statistical analysis

For prevalence, we calculated crude prevalence of T1D in 2015 and 2020. The denominator for the prevalence of T1D included the entire living children and adolescent population in Thailand. The numerator included those classified as T1D at the index dates.

For cumulative incidence, we calculated crude five-year cumulative incidences of T1D, T1D referral, DKA, and five-year mortality risk of DKA. The denominator (at-risk population) for the cumulative incidence of T1D included living individuals without T1D at the index date. Its numerator included those who developed T1D during the 5-year follow-up period. For the cumulative incidence of T1D referral and DKA as well as the mortality risk of DKA, their denominator included living individuals with T1D at the index date. The numerator for these three outcome variables included those being referred to other hospitals for T1D management, those developing DKA, and those dying from DKA during the 5-year follow-up period, respectively.

We also estimated crude annual incidence rates of T1D and DKA for each year period from 2015 to 2020. The direct method of age standardisation was performed for prevalence of T1D and annual incidence rates of T1D and DKA using 2009 Thai standard population, for T1D outcomes, and 2015 Thai calculated T1D population, for DKA outcomes.

Individuals with missing data for each selected characteristic were excluded from their corresponding stratified analyses. We reported each outcome as an estimate and its 95% confidence interval (CI). All outcomes were estimated for the overall population and stratified by sex, age group, and urban versus rural residencies. Associations between each explanatory variable and outcomes were determined by *p*-values obtained from chi-squared tests using StataMP 15. We considered *p*-values less than 0·05 as statistically significant.

Role of the funding source

The funders did not have any role in study design, data collection, data analysis, interpretation, and writing of the report.

Results

The demographic characteristics of the study population in 2015 and 2020 were presented in Table 1. Of the study population in 2015, 48% were females and 52% were males. 23% were in the 0–4 age group, while 23·4%, 24%, and 29·6% were in the 5–9, 10–14, and 15–19 age groups, respectively. In terms of urban versus rural locations, 39·6% were in urban areas while 60·4% were in rural areas. The demographic patterns of the study population in 2020 were similar to those in 2015.

Prevalence of T1D among children and adolescents in 2015 and 2020 (Table 2)

In 2015, of the 19,784,781 individuals aged less than 20 years in Thailand, 3,486 (17·6 per 100,000; 95% CI:

Demographic characteristics	2015	2020
Sex		
Female (*n*, %)	9,496,695; 48·0	8,320,599; 48·0
Male (*n*, %)	10,288,086; 52·0	9,013,982; 52·0
Age group (year)		
0 to 4 (*n*, %)	4,550,500; 23·0	3,089,022; 17·8
5 to 9 (*n*, %)	4,629,639; 23·4	4,373,515; 25·2
10 to 14 (*n*, %)	4,748,347; 24·0	4,773,944; 27·6
15 to 19 (*n*, %)	5,856,295; 29·6	5,098,100; 29·4
Urban versus rural locations[a]		
Urban (*n*, %)	6,335,063; 39·6	5,476,072; 39·1
Rural (*n*, %)	9,644,696; 60·4	8,534,635; 60·9

***Table 1*: Demographic characteristics of children and adolescents in Thailand in 2015 and 2020.**

[a] Approximately 19% of individuals with missing data for address were excluded from the study.

17·0/100,000 to 18·2/100,000) were classified as having T1D. In 2020, of the 17,334,581 individuals aged less than 20 years, 5,117 (29·5 per 100,000; 95% CI 28·7/100,000 to 30·3/100,000) were classified as having T1D. The crude prevalence was significantly higher in 2020 than that in 2015 ($p < 0·001$). The same pattern was observed in age-standardised prevalence ($p < 0·001$; Supplementary Table 3). Also, we observed similar trends of variations between these two years. Older children were associated with a higher T1D prevalence. Compared with children aged 0–4 years, adolescents aged 15–19 years had 15 and 9 times higher in T1D prevalence in 2015 and 2020, respectively (both $p < 0·001$). We found that females had a higher prevalence of T1D. When compared with males, females had approximately 1·3 times higher in T1D prevalence both in 2015 and 2020 (both $p < 0·001$). However, there was no difference in the prevalence of T1D among those living in urban versus rural residence in both years.

Five-year cumulative incidence of T1D among children and adolescents (Table 2)

Of the 19,781,230 individuals without T1D aged less than 20 years who were identified at the index date, 3410 (17·2 per 100,000; 95% CI 16·7/100,000 to 17·8/100,000) developed T1D in five years of follow-up period. We observed similar trends of variations in this outcome as those in T1D prevalence. Older children were associated with higher T1D five-year cumulative incidence. Compared with children aged 0–4 years, adolescents aged 15–19 years had five times higher risks of developing T1D in five years ($p < 0·001$). Also, we found that females were associated with a higher T1D five-year cumulative incidence. When compared with males, females had 1·4 times higher risk of T1D incidence in five years ($p < 0·001$). However, there was no difference in the five-year cumulative incidence of T1D among those living in urban versus rural residencies in both years.

Five-year cumulative incidence of T1D referral among children and adolescents with T1D (Table 3)

Overall, 3486 individuals diagnosed with T1D at age less than 20 years were identified at the index date. There were 1,477 (42·4%; 95% CI 40·7% to 44·0%) unique individuals who were referred to other hospitals for T1D management in five years of follow-up period. The five-year cumulative incidence of T1D referral was lowest among individuals aged 15–19 years (34·7%), followed by individuals aged 0–4 years (39·1%), 5–9 years (53·0%), and 10–14 years (56·2%). While the higher cumulative incidence in the 5–9 and 10–14 age groups were both statistically significant when compared with individuals aged 0–4 years ($p = 0·011$ and 0·001, respectively), there was no significant difference observed between the 15–19 and 0–4 age groups. Females had 1·2 times higher five-year cumulative incidence of T1D referral compared with their counterparts ($p < 0·0001$). There was no difference in the five-year cumulative incidence of T1D among those living in urban versus rural residence.

Five-year cumulative incidence of DKA at any point after T1D diagnosis among children and adolescents with T1D (Table 4)

Of the 3486 individuals diagnosed with T1D at age less than 20 years who were identified at the index date, 802 (23·0%; 95% CI 21·6% to 24·4%) developed a new onset

Characteristic	Prevalence per 100,000 in 2015	95% CI		*P*-value[a]	Prevalence per 100,000 in 2020	95% CI		*P*-value[a]	Five-year cumulative incidence of T1D per 100,000	95% CI		*P*-value[a]
Total	17·6[b]	(17·0,	18·2)	-	29·5[b]	(28·7,	30·3)	-	17·2	(16·7,	17·8)	-
Age group (years)												
0 to 4	2·4	(2·0,	2·9)	Ref	5·3	(4·5,	6·0)	Ref	5·3	(4·7,	6·0)	Ref
5 to 9	7·7	(6·9,	8·5)	<0·001	11·6	(10·7,	12·6)	<0·001	12·4	(11·4,	13·4)	<0·001
10 to 14	19·4	(18·1,	20·6)	<0·001	26·4	(25·1,	27·8)	<0·001	22·0	(20·6,	23·3)	<0·001
15 to 19	35·9	(34·3,	37·4)	<0·001	47·7	(45·9,	49·4)	<0·001	26·5	(25·2,	27·9)	<0·001
Sex												
Male	14·9	(14·2,	15·7)	Ref	25·3	(24·2,	26·3)	Ref	14·5	(13·8,	15·2)	Ref
Female	20·0	(19·1,	20·9)	<0·001	32·9	(31·7,	34·1)	<0·001	19·7	(18·8,	20·6)	<0·001
Urban versus rural residencies[c]												
Urban	17·6	(16·5,	18·6)	Ref	32·1	(30·6,	33·6)	Ref	17·0	(16·0,	18·1)	Ref
Rural	18·7	(17·8,	19·5)	0·113	31·7	(30·5,	32·9)	0·671	17·2	(16·4,	18·1)	0·771

***Table 2*: Crude prevalence and crude five-year cumulative incidence of diagnosed type 1 diabetes among children and adolescents in Thailand for the total population and by selected characteristics.**

Ref: reference group; T1D: Type 1 Diabetes; 95% CI: 95% confidence interval.

[a] *P*-value indicated the statistical significance of the differences of an outcome (e.g., T1D prevalence in 2015) compared with the reference group.

[b] *P*-value for a difference of the T1D prevalence between in 2015 and 2020 is <0.001 (reference group: T1D prevalence in 2015).

[c] Approximately 19% of individuals with missing data for address were excluded from the stratified analyses by urban versus rural residencies.

Characteristic	Five-year cumulative incidence of T1D referral per 100	95% CI		*P*-value[a]
Total	42·4	(40·7,	44·0)	-
Age group (years)				
0 to 4	39·1	(30·0,	48·2)	Ref
5 to 9	53·0	(47·8,	58·2)	0·011
10 to 14	56·2	(52·9,	59·4)	0·001
15 to 19	34·7	(32·7,	36·8)	0·35
Sex				
Male	38·1	(35·7,	40·6)	Ref
Female	45·8	(43·6,	48·0)	<0·0001
Urban versus rural residencies[b]				
Urban	48·9	(45·9,	51·8)	Ref
Rural	46·9	(44·6,	49·2)	0·297

***Table 3*: Crude five-year cumulative incidence of being referred to other hospitals for management of type 1 diabetes (T1D) among children and adolescents with T1D in Thailand for the total population and by selected characteristics.**
Ref: reference group; T1D referral: being referred to other hospitals for management of Type 1 Diabetes; 95% CI: 95% confidence interval.
[a] *P*-value indicated the statistical significance of the differences of cumulative incidence of T1D referral compared with the reference group.
[b] 14% of individuals with missing data for address were excluded from stratified analyses by urban versus rural residencies.

of DKA at any point after T1D diagnosis in five years of follow-up period. Females had a higher risk of DKA. The five-year cumulative incidence of DKA peaked in the 5–9 and 10–14 age groups. Compared with children aged 0–4 years, children aged 5–9 years and 10–14 years both had approximately four times higher in the risk of DKA ($p < 0{\cdot}001$), while adolescents aged 15–19 years had double the risk of DKA in five years ($p = 0{\cdot}006$). No urban versus rural residencies difference was observed in the five-year cumulative incidence of DKA.

Five-year mortality risk of DKA among children and adolescents with T1D (Table 4)

Of the 3486 individuals diagnosed with T1D at age less than 20 years who were identified at the index date, only nine (258·2 per 100,000; 95% CI 89·7/100,000 to 426·6/100,000) died from DKA in five years of follow-up period. There were no T1D cases aged 0–9 years who died from DKA observed during the five-year follow-up period. The risk of dying from DKA was highest in the 10–14 age group. However, this difference was not statistically significant. Similarly, no sex nor urban

Characteristic	Five-year cumulative incidence of DKA per 100	95% CI		*P*-value[a]	Five-year mortality risk of DKA per 100,000	95% CI		*P*-value[a]
Total	23·0	(21·6,	24·4)	-	258·2	(89·7,	426·6)	-
Age group (years)								
0 to 4	8·2	(3·1,	13·3)	Ref	0·0	n/a	n/a	Ref
5 to 9	31·0	(26·2,	35·8)	<0·001	0·0	n/a	n/a	n/a
10 to 14	32·0	(29·0,	35·0)	<0·001	326·4	(0·0,	695·2)	1
15 to 19	18·5	(16·9,	20·2)	0·006	285·4	(57·4,	513·5)	1
Sex								
Male	19·4	(17·4,	21·3)	Ref	320·5	(40·0,	601·0)	Ref
Female	26·0	(24·0,	27·9)	<0·0001	207·7	(4·4,	411·0)	0·514
Urban versus rural residencies[b]								
Urban	26·5	(23·9,	29·1)	Ref	449·2	(56·4,	842·1)	Ref
Rural	25·8	(23·8,	27·9)	0·688	166·7	(0·0,	355·1)	0·273

***Table 4*: Crude five-year cumulative incidence of diabetic ketoacidosis (DKA) and crude five-year mortality risk of DKA among children and adolescents with type 1 diabetes in Thailand for the total population and by selected characteristics.**
DKA: diabetic ketoacidosis; Ref: reference group; 95% CI: 95% confidence interval.
[a] *P*-value indicated the statistical significance of the differences of an outcome (e.g., cumulative incidence of DKA) compared with the reference group.
[b] 14% of individuals with missing data for address were excluded from stratified analyses by urban versus rural residencies.

versus rural differences were observed in the five-year mortality risk of DKA.

Annual incidence rate of T1D among children and adolescents and annual incidence rate of DKA any point after T1D diagnosis among children and adolescents with T1D from 2015 to 2020 (Supplementary Tables 2 and 4)

Of 22,748,162 children and adolescents identified from 2015 to 2020, a total of 4628 individuals developed T1D. The crude annual incidence rate of T1D increased over time. A 12·5% increase (from 4·8/100,000 to 5·4/100,000) in the crude annual incidence rate of T1D was observed from year period 2015 to 2020 (Figure 1 and Supplementary Table 2). The trend over time observed in the age-standardised incidence rate of T1D was relatively steady (Figure 1 and Supplementary Table 4).

Of 7185 children and adolescents with T1D identified from 2015 to 2020, a total of 2222 individuals developed a new onset of DKA at any point after T1D diagnosis. The crude annual incidence rate of DKA had a declining trend over time. From year period 2015 to 2020, there is a 44·7% decrease (from 15·9 per 100 to 8·8 per 100) in the crude annual incidence of DKA (Figure 2 and Supplementary Table 2). The similar trend was observed in the age-standardised incidence rate of DKA (Figure 2 and Supplementary Table 4).

We provided numbers of prevalent T1D cases from 2015 to 2020 for total population and annual incidence rates of T1D and DKA from 2015 to 2020 by sex, urban versus rural, and age group in the supplementary information.

Discussion

This study is the first nationwide population-based investigation to examine national estimates of the prevalence and incidence trends and patterns of T1D and DKA amongst children and adolescents, with data across all hospital levels and provinces in Thailand. We further investigated the incidence of referral to other hospitals for T1D management and the mortality risk of DKA to understand the performance of T1D

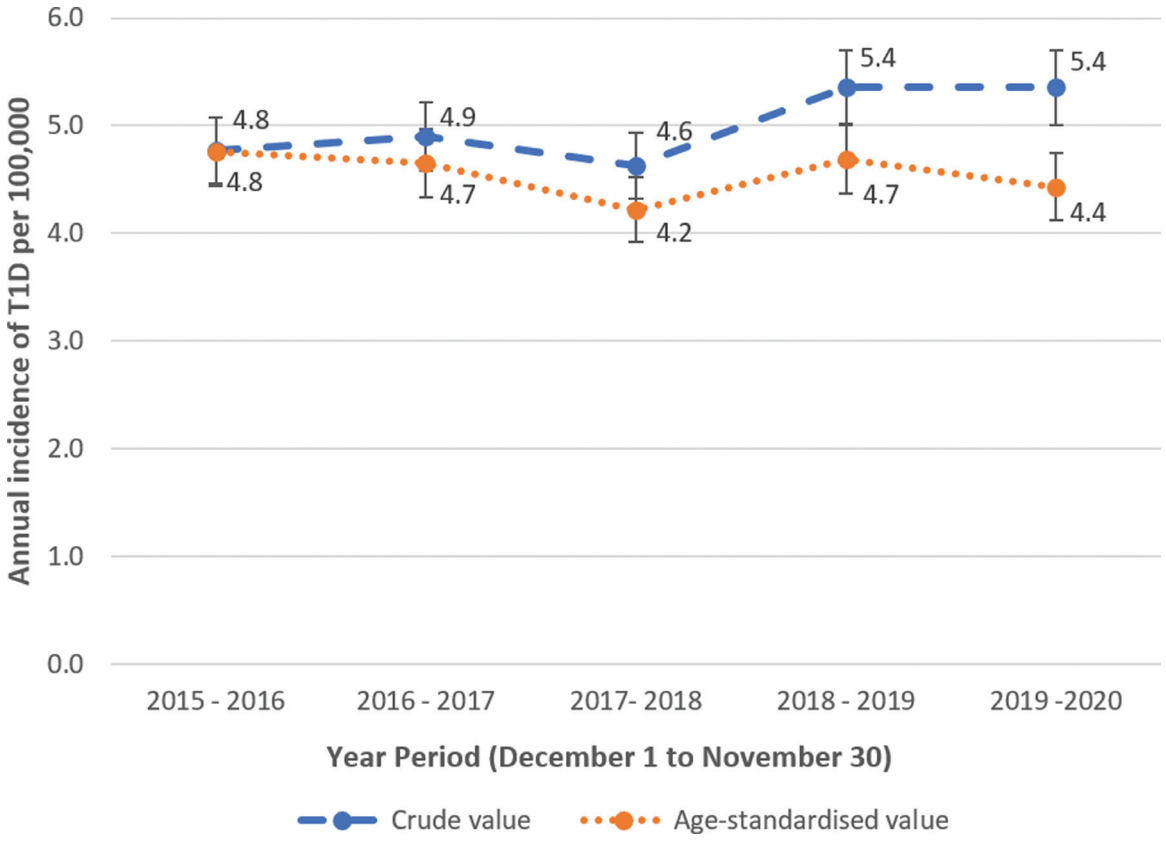

Figure 1. Trend in the crude and age-standardised annual incidence rates of type 1 diabetes among children and adolescents in Thailand from 2015 to 2020.

• The data labels correspond to crude and age-standardised values. The bars correspond to 95% confidence intervals. For age-standardised values, the direct method of age standardization was performed using 2009 Thai standard population.

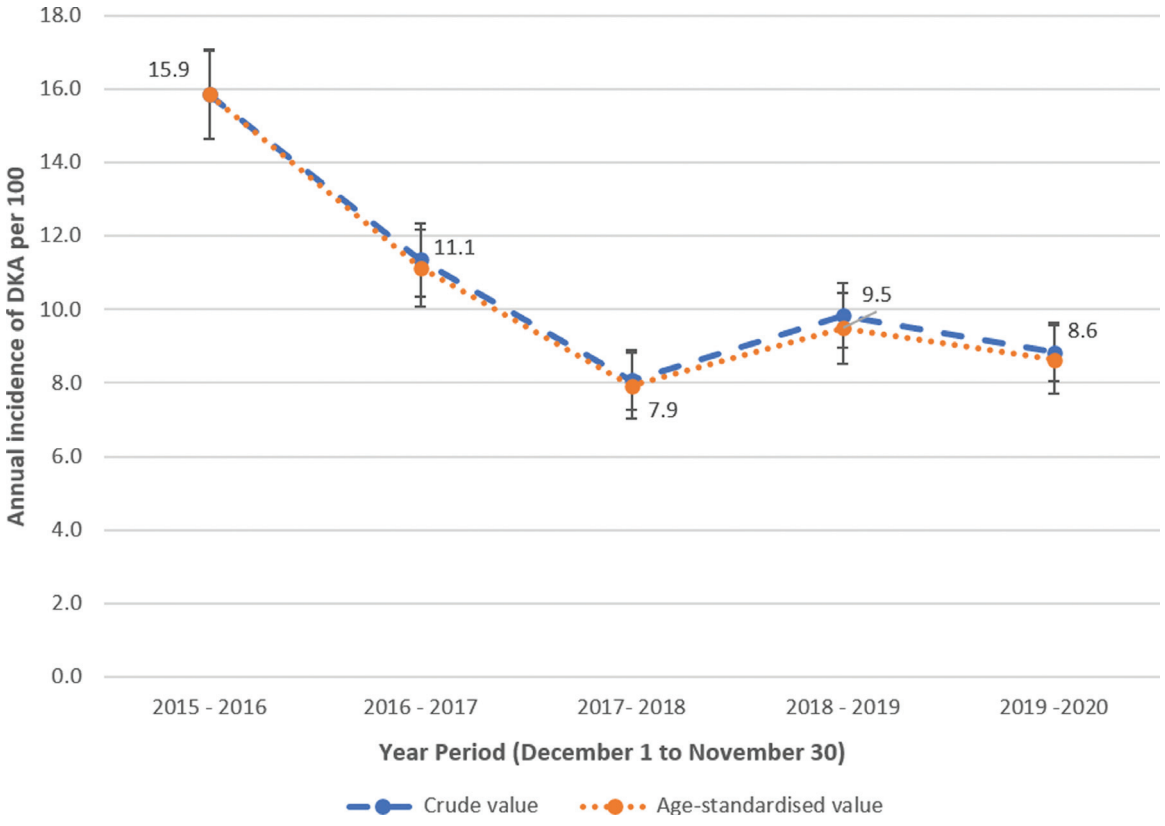

Figure 2. Trend in the crude and age-standardised annual incidence rates of diabetic ketoacidosis among children and adolescents with type 1 diabetes in Thailand from 2015 to 2020.

• The data labels correspond to age-standardised values. The bars correspond to 95% confidence intervals. For age-standardised values, the direct method of age standardization was performed using 2015 Thai calculated T1D population.

management. All outcomes were determined for the total population and analysed by sex, age, and urban versus rural residencies.

The T1D prevalence in 2015 and five-year cumulative incidence of T1D among children and adolescents in Thailand were 17·6 and 17·2 per 100,000, respectively. Both levels were significantly higher in older children and females than their counterparts. The prevalence and annual incidence rate of T1D increased over time. Among those with T1D, the five-year cumulative incidence of being referred to other hospitals for T1D management was 42·4%. Such an incidence was lowest amongst children aged 15–19 years and peaked in children aged 5–14 years. It significantly increased in females. Interestingly, no difference by urban/rural location was observed in this outcome. We found that the annual incidence rate of DKA among individuals with T1D had a decreasing trend over time. The five-year cumulative incidence of DKA among children and adolescents with T1D was 23·0%, with a significantly higher risk in females and older children, especially those in 5–14 age group. The five-year mortality risk of DKA was relatively low at 258·2 per 100,000. Although there was a pattern of an increasing risk of dying from DKA in older children, we did not find any significant differences in age, sex, or urban versus rural residencies.

Our findings of T1D incidence patterns are consistent with prior studies, although with difference in the magnitude of the T1D incidence due to differences in timing and setting.[12–17] Unlike a finding from a prior study in 2006,[18] our study found a higher level of DKA incidence rate, suggesting either an increased trend of DKA incidence or improvement in DKA detection and reports over the last few decades.

Compared to the earlier published studies on T1D in children and adolescents in Thailand, we used a nationwide population-based database that provided individual-level longitudinal data for the entire population of Thailand, which covers all hospital levels in all provinces. The availability of such a nationwide database improved comprehensiveness of the results and helped reflect current national patterns and trends of the disease to inform health burden at the aggregate national

Region	Country	Parameter of primary data	Primary result
Incidence rates (per 100,000) of type 1 diabetes in children and adolescents			
North America	Canada and USA	Age-sex standardised incidence rate	20 to <30 per 100,000
	Mexico	Age-sex standardised incidence rate	5 to <10 per 100,000
Western Europe	Belgium, France, Luxembourg	Age-sex standardised incidence rate	10 to <20 per 100,000
	Germany, Ireland, Netherlands, UK	Age-sex standardised incidence rate	20 to <30 per 100,000
SEA	Other SEA countries	n/a	n/a
	Thailand	Age-sex standardised incidence rate[a]	4·3 per 100,000
Incidence rates (per 100) of diabetic ketoacidosis in children and adolescents with type 1 diabetes			
North America	Canada	Crude incidence rate[b]	22·1 per 100
	USA	Crude incidence rate[b]	38·9 per 100
Western Europe	Belgium	Crude incidence rate[b]	25·6 per 100
	France	Crude incidence rate[b]	43·9 per 100
	Germany	Crude incidence rate[b]	20·8 per 100
	UK	Crude incidence rate[b]	40·2 per 100
SEA	Other SEA countries	n/a	n/a
	Thailand	Crude incidence rate[c]	10·8 per 100

***Table 5*: Comparisons of incidence rates of type 1 diabetes and diabetic ketoacidosis in children and adolescents by country in three regions (North America, Western Europe, and Southeast Asia).**

Incidence data of type 1 diabetes were acquired from Patterson et al.[22] and incidence data of diabetic ketoacidosis were acquired from Grosse et al.[28]

SEA: Southeast Asia; n/a: data not available.

[a] The direct method of age-sex standardisation was performed using the standard population mentioned in Patterson et al. The age-sex standardised incidence rate of T1D of Thailand was an average of the age-sex standardised annual incidence rates of T1D from 2015 to 2020 Year Periods (i.e., 4.5, 4.4, 4.0, 4.4, and 4.2 per 100,000, respectively).

[b] The standardised rates were not able to be obtained from the primary sources.

[c] The crude incidence rate of DKA was estimated from an average of the crude annual incidence rates of DKA from 2015 to 2020 Year Periods (Supplementary Table 2).

level. Therefore, we further estimated the incidence trends of T1D and DKA from 2015 to 2020 and investigated the variation of all outcomes by age, sex, and geographic setting to understand key demographic and geographic trends and patterns of T1D and DKA.

Compared with the global trend, the standardised incidence rate of T1D among children and adolescents in Thailand was relatively low (4·3 per 100,000).[8,22] While evidence on the incidence rate of T1D in other Southeast Asian (SEA) countries is scant, the standardised rates of T1D range from 10 to 30 per 100,000 in Western Europe and 5 to 30 per 100,000 in North America (20 to 30 per 100,000 in Canada and the USA, and 5 to 10 per 100,000 in Mexico; Table 5 and Figure 3).[22] This variation in reported incidence among different countries might be due to differences in genetic susceptibility (e.g., frequency of certain T1D-associated HLA alleles) or genetic–environmental interactions.[23] Evidence suggests the disequilibrium of the DRB1 and DQB1 alleles in a population, which varies by geographic and ethnicity, may explain the low incidence of T1D in some countries, as well as Thailand.[23,24] Similar to the international trends,[8] we found evidence of increasing annual incidence rate of T1D in Thailand from 2015 to 2020.

Although the underlying mechanisms explaining the relationship between T1D and sex are unknown, the heightened risk of T1D amongst females might be explained by the fact that its pathophysiology involves autoimmune mechanisms.[25] For the five-year cumulative incidence of being referred to other hospitals for T1D management, we found it was low (42·4%), in light of the fact that Thailand established a multilevel health system to enhance proper referral systems and that T1D is a condition required long-term care coordination between primary and secondary care. However, given the Thai health system context, this finding may not reflect the capacity of referral system nor the health system performance in managing T1D in Thailand since Thai health system does not have a formal gatekeeper.[26] Indeed, it is common that patients bypass primary care units and directly visit general or regional hospitals with which they are registered due to their trusts in secondary or tertiary hospitals.[27] The T1D referral five-year cumulative incidence was higher in children aged 5–14 years, possibly due to their high incidence of DKA. In addition, we found there was no significant variation by urban versus rural residencies on T1D referral cumulative incidence in five years, suggesting benefits of UHC.

The DKA incidence rate in Thailand was lower than the levels observed in other countries (Table 5 and Figure 4),[28] although its sociodemographic variations are consistent with prior studies in other countries.[29] While the DKA incidence trends vary across countries, similar to studies conducted in Australia, India, Kuwait,

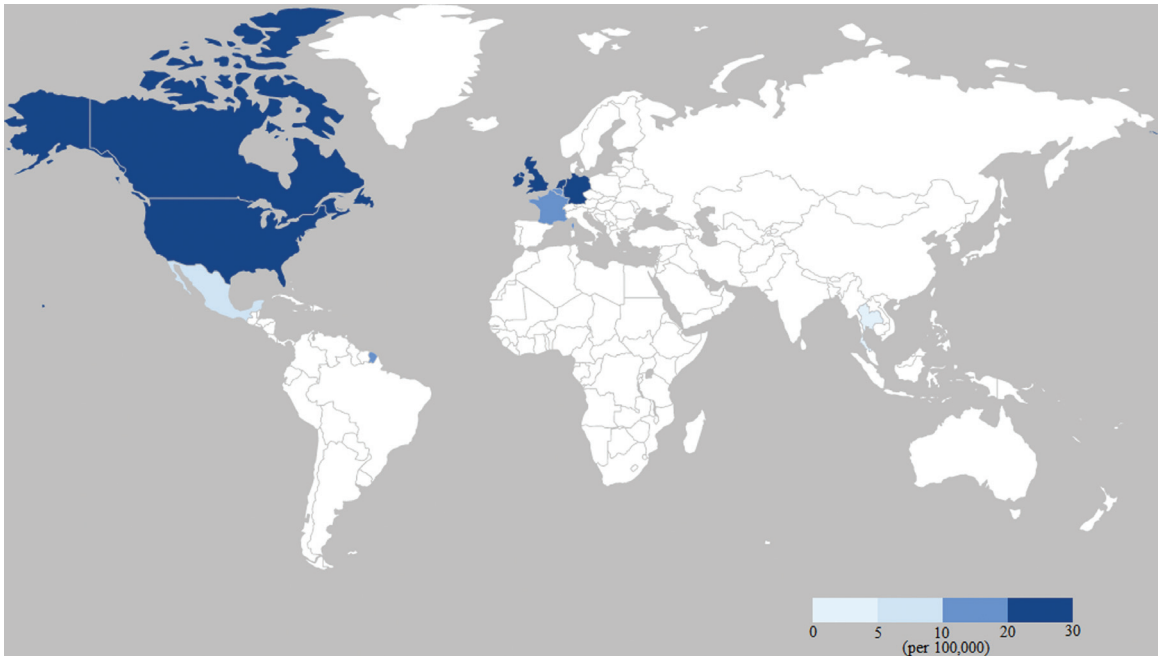

Figure 3. Map of age-sex standardised incidence rates (per 100,000) of type 1 diabetes in children and adolescents aged less than 20 years in three regions (North America, Western Europe, and Southeast Asia).

• Incidence data of type 1 diabetes of other countries, apart from Thailand, were acquired from Patterson et al.[22] Data in other Southeast Asian countries were scant. The direct method of age-sex standardization was performed using the standard population mentioned in Patterson et al.[22]

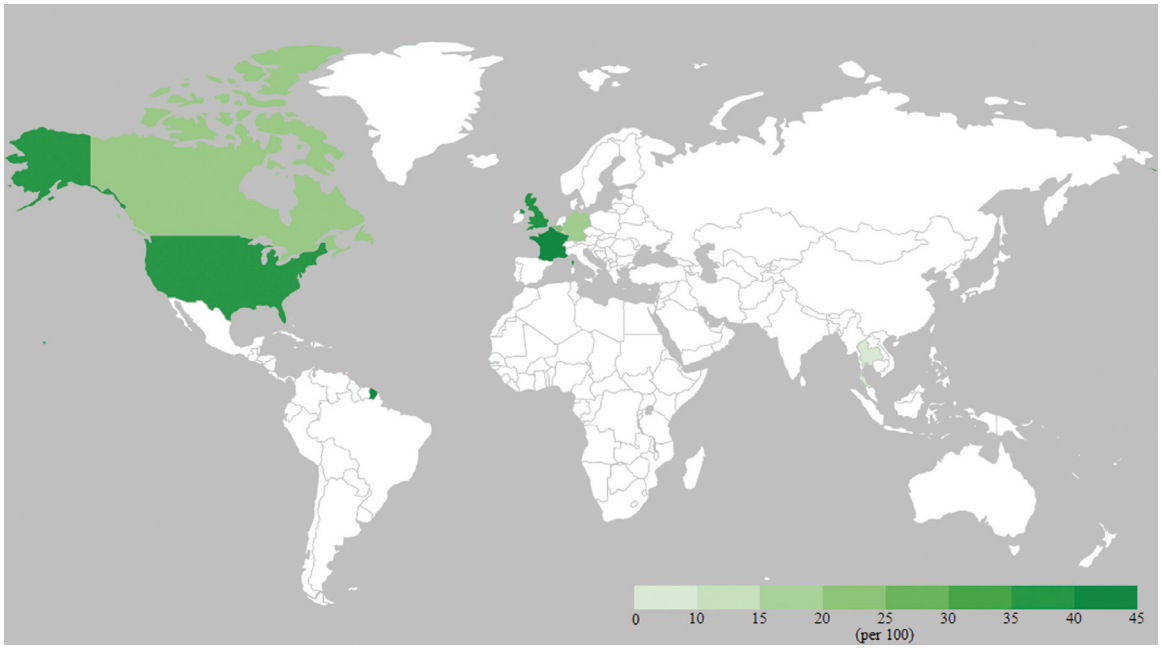

Figure 4. Map of crude incidence rates (per 100) of diabetic ketoacidosis in children and adolescents with type 1 diabetes aged less than 20 years in three regions (North America, Western Europe, and Southeast Asia).

• Incidence data of diabetic ketoacidosis of other countries, apart from Thailand, were acquired from Grosse et al.[28] Data in other Southeast Asian countries were scant. The standardised rates were not able to be obtained from the primary sources.[28]

and Northern Finland,[30–33] the annual incidence rate of DKA among children and adolescents in Thailand had a declining trend over time.

The finding of the high DKA incidence among individuals aged 5 to 14 years can be attributable to many factors. Some possible explanations include delayed treatment and poor compliance to medical treatment and self-care among children and adolescents in these age groups. However, it is worth noting that we found no association between geographic setting and the heightened risk of DKA. One possible explanation is the equal access to health care due to Thailand's UHC.[27] The mortality risk of DKA in Thailand is relatively low when compared with other countries, potentially reflecting well-performing DKA management of Thai health system. Studies found that the five-year mortality risks of DKA range from 995 to 11,750 per 100,000 in other low- and middle-income countries and 1980 per 100,000 in the USA.[34,35]

Our findings suggest that policy makers should give careful consideration to (i) allocating affordable or free T1D care interventions, such as self-management support, community involvement, and decision support systems, to target children aged 5 to 14 years as they have a high risk of DKA and are more vulnerable to poor compliance with medical and self-care as compared to other age groups, (ii) promoting early detection of diabetic symptoms among healthcare providers and parents to prevent delayed T1D diagnosis and prolonged illness duration, which could trigger life-threatening DKA, and (iii) improving vertical referral systems of Thailand to be well-organised to expand early detection of T1D and access to long-term T1D care, where primary care units in each district have clear responsibilities of providing basic consultations of T1D to community members, self-management supports, and coordinating transitional and long-term care for T1D individuals. We further highlight the need for future research to (i) investigate relationships between multiple sociodemographic factors and T1D outcomes in Thailand using multivariate analysis to understand factors associated with T1D burden and (ii) investigate why incidence of T1D referral in Thailand is lower in adolescents aged 15–19 years than those in other age groups and its impact on patient outcomes. In the global aspect, our finding emphasized the rising incidence of T1D amongst children and adolescents globally, even in countries with low T1D incidence, such as Thailand. Our study also informs important implications of UHC's benefits as a way to enhanced T1D management in terms of improving access to care, especially in low- and middle-income countries.

We acknowledge limitations of this study that relate to the use of this large national database. Firstly, as diagnostic coding is assigned by physicians and then verified and coded by hospitals, insulin-dependent diabetes mellitus and DKA episodes may have been unintentionally included, missed, or incorrectly coded. However, there is a two-step coding validation system performed by hospital administrative personnel at a hospital level, and subsequently by the health data center of the Ministry of Public Health at a provincial level, minimizing the risk of incorrect or missing data. Secondly, we were not able to obtain information regarding the socioeconomic status of the parents of children with T1D (e.g., income or education level and occupational status) due to the incompleteness of data on these variables. Instead, we used urban versus rural residencies as a proxy for socioeconomic status of children and adolescents in this study. Also, querying massive data from the database caused the limitation in obtaining specific information of individual-level data to allow multivariate analyses. Thirdly, the strictness of criteria for T1D diagnosis may slightly vary across practices. Lastly, it should be noted that the database solely captures health information reported by public health facilities in Thailand, which account for approximately 70% of all health facilities that provide most of the care.[19] However, as Thailand has UHC that allows all Thais to receive services at public health facilities free of charge,[36] we believe that our database has captured most, if not all, children and adolescents in Thailand.

This study also has several strengths. Firstly, our study used a nationwide population-based database that captured the entire population of children and adolescents seen at all hospital levels and in all provinces of Thailand, ensuring comprehensiveness, generalization, and validity of the results. Secondly, for each incidence outcome, we used a unified population throughout the study span of five-year follow-up time to avoid nonresponse bias. Thirdly, we were able to differentiate paediatric type 1 and type 2 diabetes using diagnostic coding recorded in the database. Although we were not able to distinguish children or adolescents with monogenic diabetes treated with insulin from T1D individuals, those patients are rare and therefore should not significantly impact our findings.[37,38]

In conclusion, the T1D prevalence and incidence in Thailand were relatively low as compared to the levels observed globally, possibly due to differences in genetic susceptibility, and the trends show an increase over time. We found that older children and females had higher level of T1D. Females and children aged 5 to 14 years were more likely to be referred to other hospitals for T1D management. Among children and adolescents with T1D, the incidence of DKA was relatively low, and it was higher in females and older children with a peak amongst children aged 5 to 14 years. Its trend over time declined. The mortality risk of DKA was low, and there were no significant variations observed by age, sex, and urban versus rural residencies. The evidence of low DKA incidence and mortality risk of DKA suggests benefits of Thailand's UHC that improve access to care both in aspects of affordability and

timeliness. Health service systems research is needed to explore why incidence of T1D referral is relatively low in adolescents aged 15–19 years, who have a higher incidence of T1D, when compared with children in other age groups.

Author contributions

Study concept and design: TR, ZJW, CR, JY, RA
Acquisition of data: TR
Analysis and interpretation of data: TR
Drafting of the manuscript: TR, MO
Critical revision of the manuscript for important intellectual content: TR, ZJW, CR, JY, RA
Statistical analysis: TR
Obtained funding: Not applicable
Administrative, technical, or material support: TR
Study supervision: RA
All authors gave final approval of the version to be published.

Data sharing statement

Data used in this study are not publicly available because of restrictions involving confidentiality of nationwide individual-level data. Requests for data access would be subject to scrutiny by the Health Data Center, Ministry of Public Health of Thailand. Access to data will only be granted after agreement from Ministry of Public Health of Thailand. For further inquiries, please contact Dr. Thanitsara Rittiphairoj (trittiphairoj@hsph.harvard.edu).

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations

Declaration of interests

The authors declare that they have no competing interests.

Funding/support

Harvard University. The authors declare that they have no financial relationships relevant to this article to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100392.

References

1 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl 1):S81–S90.
2 Pathak V, Pathak NM, O'Neill CL, Guduric-Fuchs J, Medina RJ. Therapies for type 1 diabetes: current scenario and future perspectives. *Clin Med Insights Endocrinol Diabetes*. 2019;12:1179551419844521.
3 Gale EA. How to survive diabetes. *Diabetologia*. 2009;52(4):559–567.
4 Racioppi F, Martuzzi M, Matić S, et al. Reaching the sustainable development goals through healthy environments: are we on track? *Eur J Public Health*. 2020;30(Suppl_1):i14–i18.
5 Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383(9911):69–82. (London, England).
6 Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. *BMC Med*. 2017;15(1):199.
7 Bruno G, Runzo C, Cavallo-Perin P, et al. Incidence of type 1 and type 2 diabetes in adults aged 30–49 years: the population-based registry in the province of Turin, Italy. *Diabetes Care*. 2005;28(11):2613–2619.
8 Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. *Health Promot Perspect*. 2020;10(2):98–115.
9 Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care*. 2000;23(10):1516–1526.
10 Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the pittsburgh epidemiology of diabetes complications study experience. *Diabetes*. 2006;55(5):1463–1469.
11 Realsen J, Goettle H, Chase HP. Morbidity and mortality of diabetic ketoacidosis with and without insulin pump care. *Diabetes Technol Ther*. 2012;14(12):1149–1154.
12 Panamonta O, Thamjaroen J, Panamonta M, Panamonta N, Suesirisawat C. The rising incidence of type 1 diabetes in the northeastern part of Thailand. *J Med Assoc Thai*. 2011;94(12):1447–1450.
13 Unachak K, Tuchinda C. Incidence of type 1 diabetes in children under 15 years in northern Thailand, from 1991 to 1997. *J Med Assoc Thai*. 2001;84(7):923–928.
14 Tuchinda C, Angsusingha K, Chaichanwalanakul K, Likitmaskul S, Vannasaeng S. The epidemiology of insulin-dependent diabetes mellitus (IDDM): report from Thailand. *J Med Assoc Thai*. 1992;75(4):217–222.
15 Panamonta O, Laopaiboon M, Tuchinda C. Incidence of childhood type 1 (insulin dependent) diabetes mellitus in northeastern Thailand. *J Med Assoc Thai*. 2000;83(8):821–824.
16 Patarakijvanich N, Tuchinda C. Incidence of diabetes mellitus type 1 in children of southern Thailand. *J Med Assoc Thai*. 2001;84(8):1071–1074.
17 Jaruratanasirikul S, Thammaratchuchai S, Sriplung H. Trends of childhood diabetes in Southern Thailand: 20-year experience in a tertiary medical center. *World J Pediatr*. 2017;13(6):566–570.
18 Anthanont P, Khawcharoenporn T, Tharavanij T. Incidences and outcomes of hyperglycemic crises: a 5-year study in a tertiary care center in Thailand. *J Med Assoc Thai*. 2012;95(8):995–1002.
19 Health Data Center. Thai health promotion foundation big data: primary care related big data analysis manual [in Thai]. 2018.
20 Bishop YMM, Fienberg SE, Holland PW. *Discrete Multivariate Analysis: Theory and Practice*. Cambridge, MA: MIT Press; 1974.
21 National Satistical Office. Number of population from registration by age group province and region: 2011–2020. 2021. http://statbbi.nso.go.th/staticreport/Page/sector/EN/report/sector_01_11102_EN_.xlsx Accessed 22 August 2021.
22 Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107842.
23 Park Y. Why is type 1 diabetes uncommon in Asia? *Ann N Y Acad Sci*. 2006;1079:31–40.
24 Park Y, Eisenbarth GS. Genetic susceptibility factors of Type 1 diabetes in Asians. *Diabetes Metab Res Rev*. 2001;17(1):2–11.
25 Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. *Endocr Connect*. 2018;7(1):R38–R46.
26 Towse A, Mills A, Tangcharoensathien V. Learning from Thailand's health reforms. *BMJ*. 2004;328(7431):103–105.

27 World Health Organization. Regional office for the Western P. The Kingdom of Thailand health system review: Manila: WHO regional office for the Western Pacific; 2015.
28 Grosse J, Hornstein H, Manuwald U, Kugler J, Glauche I, Rothe U. Incidence of diabetic ketoacidosis of new-onset type 1 diabetes in children and adolescents in different countries correlates with Human Development Index (HDI): an updated systematic review, meta-analysis, and meta-regression. *Horm Metab Res*. 2018;50(3):209–222.
29 Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. *BMJ*. 2011;343:d4092.
30 Bui TP, Werther GA, Cameron FJ. Trends in diabetic ketoacidosis in childhood and adolescence: a 15-yr experience. *Pediatr Diabetes*. 2002;3(2):82–88.
31 Praveen PA, Hockett CW, Ong TC, et al. Diabetic ketoacidosis at diagnosis among youth with type 1 and type 2 diabetes: results from SEARCH (United States) and YDR (India) registries. *Pediatr Diabetes*. 2021;22(1):40–46.
32 Abdul-Rasoul M, Al-Mahdi M, Al-Qattan H, et al. Ketoacidosis at presentation of type 1 diabetes in children in Kuwait: frequency and clinical characteristics. *Pediatr Diabetes*. 2010;11(5):351–356.
33 Hekkala A, Knip M, Veijola R. Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. *Diabetes Care*. 2007;30(4):861–866.
34 Saperstein Y, Park J, McFarlane SI. Closing the mortality gap in diabetic ketoacidosis and hyperosmolar hyperglycemic state: implications of a clinical decision support app. *Int J Clin Endocrinol Metab*. 2018;4(1):8–11.
35 Lizzo J, Goyal A, Gupta V. *Adult Diabetic Ketoacidosis*. Treasure Island (FL): StatPearls Publishing; 2021.
36 Tangcharoensathien V, Witthayapipopsakul W, Panichkriangkrai W, Patcharanarumol W, Mills A. Health systems development in Thailand: a solid platform for successful implementation of universal health coverage. *Lancet*. 2018;391(10126):1205–1223.
37 Plengvidhya N, Tangjittipokin W, Teerawattanapong N, Narkdontri T, Yenchitsomanus PT. HNF1A mutation in a Thai patient with maturity-onset diabetes of the young: a case report. *World J Diabetes*. 2019;10(7):414–420.
38 Unnikrishnan R, Shah VN, Mohan V. Challenges in diagnosis and management of diabetes in the young. *Clin Diabetes Endocrinol*. 2016;2:18.