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# Epidemiology and phenotypes of diabetes in children and adolescents in non-European-origin populations in or from Western Pacific region

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## Abstract

### BACKGROUND

Type 1 diabetes (T1D) incidence varies substantially between countries/territories, with most studies indicating increasing incidence. In Western Pacific region (WPR), reported rates are much lower than European-origin populations. In contrast, there are reports of substantial numbers of young people with type 2 diabetes (T2D). A deeper understanding of T1D and T2D in the WPR may illuminate factors important in pathogenesis of these conditions. Furthermore, with varying resources and funding for diabetes treatment in this region, there is a need to more clearly determine the current burden of disease and also any gaps in knowledge.

### AIM

To compile and summarise published epidemiologic and phenotypic data on

childhood diabetes in non-European populations in and from WPR.

### METHODS

Research articles were systematically searched from PubMed (MEDLINE), Embase, Cochrane library, and gray literature. Primary outcome measures were incidence and prevalence, with secondary measures including phenotypic descriptions of diabetes, including diabetes type categorization, presence of diabetic ketoacidosis (DKA) at onset, autoantibody positivity, C-peptide levels, and human leucocyte antigen phenotype. Extracted data were collected using a customized template. Three hundred and thirty relevant records were identified from 16 countries/territories, with analysis conducted on 265 (80.3%) records published from the year 2000.

### RESULTS

T1D incidence ranged from < 1-7.3/100000 individuals/year, rates were highest in emigrant/mixed populations and lowest in South-East Asia, with most countries/territories (71.4%) having no data since 1999. Incidence was increasing in all six countries/territories with data (annual increases 0.5%-14.2%, highest in China). Peak age-of-onset was 10-14 years, with a female case excess. Rate of DKA at onset varied from 19.3%-70%. Pancreatic autoantibodies at diagnosis were similar to European-origin populations, with glutamic acid decarboxylase-65 autoantibody frequency of 44.1%-64.5%, insulinoma-associated 2 autoantibody 43.5%-70.7%, and zinc transporter-8 autoantibody frequency 54.3% (one study). Fulminant T1D also occurs. T2D was not uncommon, with incidence in Japan and one Chinese study exceeding T1D rates. Monogenic forms also occurred in a number of countries.

### CONCLUSION

T1D is less common, but generally has a classic phenotype. Some countries/ territories have rapidly increasing incidence. T2D is relatively common. Registries and studies are needed to fill many information gaps.

**Key Words:** Epidemiology; Phenotypes; Diabetes; Children; Adolescents; Western Pacific

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**Core Tip:** This systematic review found type 1 diabetes (T1D) incidence was generally low in countries/territories in the Western Pacific region. However, incidence is rising in most countries where this has been studied. Many countries do not have data or data are quite old. Peak age-of-onset was in later childhood. Rates of diabetic ketoacidosis vary but can be quite high (up to 70%). Autoantibody status is generally like European-origin populations. Fulminant and slowly progressive forms of T1D also occur in the region. Of note, type 2 diabetes was sometimes more common in countries than T1D. Establishment of registers will facilitate incidence studies and also define prevalence and mortality, and assist in outcome assessment. Such data will inform quality of care improvements, health professional training, and assist advocacy.

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## INTRODUCTION

A diagnosis of diabetes is particularly challenging in young people. An estimated 1.1 million children and adolescents aged < 20 years are estimated to have type 1 diabetes (T1D) globally, with the number with type 2 diabetes (T2D) unknown[1]. Published information on diabetes in this age group is from European origin populations, and yet over half of the global burden is from non-European origin populations.

The commonest form of diabetes in this age group is T1D but other forms do occur[2]. T1D incidence and prevalence varies substantially between countries/territories, with most studies indicating that incidence is increasing at an average of 3%-4% [3], but this appears to be tailoring off in some high-

income nations/territories[1].

Increasing incidence in countries/territories with previously low rates offer a chance to better understand the link between genetics and environment in T1D development, especially in countries/territories with little population admixture[1,4]. Additionally, some studies have shown differences in diabetes incidence among migrant populations relative to the native population, which gives further support to the role of environment in T1D causation[5,6].

In the Western Pacific region (WPR), early studies had reported T1D being very rare in young people [4,7], and subsequent reports have shown incidence rates much lower than most European-origin populations[4,8-10]. In contrast, there are reports of substantial numbers of young people with T2D in some countries in the WPR[11,12].

A deeper understanding of both the epidemiology and phenotypes/endotypes of T1D and T2D in non-European populations such as those in WPR may illuminate factors important in pathogenesis of these conditions. Furthermore, with varying resources and funding for diabetes treatment in this region, there is a need to more clearly determine the current burden of disease and also any gaps in knowledge in related epidemiology and phenotypes/endotypes[1].

The objective of this systematic review is to compile and summarise current published epidemiologic and phenotypic data on childhood diabetes in non-European populations in and from the Western Pacific. Primary outcome measures were incidence and prevalence of diabetes in people < 20 years of age. Secondary measures included diabetes type categorisation and phenotype/endotype features including presence of diabetic ketoacidosis (DKA) at diagnosis, pancreatic autoantibody positivity rates, C-peptide levels, and human leucocyte antigen (HLA) phenotypes.

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## MATERIALS AND METHODS

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### **Population**

Non-European populations in and recently emigrated from the WPR.

### **Inclusion/exclusion criteria**

Any relevant published study conducted in one or more of the 37 countries/territories of the Western Pacific, as determined by the World Health Organization[13], extending from the Mongolian steppes in central Asia, east to the Pitcairn Islands in the Pacific Ocean and south to New Zealand. The included countries/territories were Australia, Brunei, Cambodia, Cook Islands, Democratic People's Republic of Korea, Federated States of Micronesia, Fiji, Guam, Hong Kong, Indonesia, Japan, Kiribati, Laos, Macau, Malaysia, Marshall Islands, Mongolia, Myanmar, Nauru, New Caledonia, New Zealand, Niue, North Korea, Palau, Papua New Guinea, South Korea, Samoa, Singapore, Solomon Islands, Taiwan, Thailand, Timor-Leste, Philippines, Tonga, Tuvalu, Vanuatu and Vietnam. Studies on recent emigrant populations from these countries/territories to others were also included.

Publications were included if they focused on incidence, prevalence, diabetes type, clinical presentation (presence/rate of DKA), pancreatic autoantibody status, and HLA phenotype. Studies that did not include data on at least one of these factors were excluded.

Data from Australia and New Zealand exclusively were only included if children and adolescents < 20 years of age identified as being an Aboriginal and/or Torres Strait Islander, or Maori, respectively.

Studies were of any study design and in any language. There was no restriction on publication date or type.

### **Types of outcome measures (primary and secondary)**

**Primary outcomes:** Incidence and prevalence of T1D, T2D and other forms in children and youth < 20 years in and from the WPR.

**Secondary outcomes:** Phenotypic descriptions of childhood- and youth-onset diabetes, including diabetes type categorization, the presence of DKA at onset, autoantibody positivity, C-peptide levels, and HLA phenotype.

### **Search strategy for identification of studies**

Research articles were systematically searched in the following databases: PubMed (MEDLINE), Embase, and the Cochrane library. The search terms below were developed for PubMed and then adapted for other databases. The MeSH terminologies include Diabetes Mellitus, Epidemiology, Diagnosis, Symptoms, and Clinical Chemistry. The search strategy was: (Diabetes Mellitus) AND (Epidemiology OR Diagnosis OR symptom OR antibod\* OR autoantibod\* OR Ketoacidosis OR clinical chemistry OR HLA) AND (Country) AND (child\* OR adolesc\*).

For Embase database, the search terminology for "Diabetes Mellitus" was replaced with "insulin dependent diabetes mellitus".

To search the gray literature, we searched the following: (1) ProQuest Dissertations and Theses Global for theses; (2) Citation searching, including reference list searching and forward citation searching in Google Scholar, Scopus and Web of Science Core Collection; and (3) Hand-searched paediatric diabetes conference abstracts not indexed in the above databases: International Society for Pediatric and Adolescent Diabetes (ISPAD, available in Pediatric Diabetes); Pediatric Endocrine Society (PES, available in Hormone Research in Children); European Society for Pediatric Endocrinology (ESPE, available in Hormone Research in Children); Asia Pacific Paediatric Endocrine Society (APPES, abstracts available in member's area).

For each database, the years searched included the earliest available online year of indexing up to December 2019.

### Data extraction and synthesis

The Covidence systematic review platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at [www.covidence.org](http://www.covidence.org)) was used to assist with data management. Two independent reviewers reviewed the titles and abstract of the identified studies for relevance. The same reviewers independently reviewed the full text of these studies in a first screen to assess if they met inclusion and exclusion criteria. The reasons for excluding articles were recorded in Covidence. Any disagreements or queries were discussed until a consensus was reached. Thereafter, a final list of studies was produced.

The extracted data was collected using a customized template in Microsoft Excel (Microsoft, Redmond, United States). The extracted data included the following: Country/territory, city/region, type of study, year of publication, time period of study, diagnosis criteria used, T1D incidence and/or prevalence, T2D studies, other forms of diabetes, age range distribution, sex distribution, DKA at diagnosis, pancreatic autoantibody test results, and HLA phenotype. Additional information about the derivation of each value was collected to help qualify the data. Descriptive analyses were performed using Excel. A qualitative comparison of the results across the collected variables is the main focus of this review.

A total of 14252 records were identified, downloaded to EndNote version X9 and screened by reading titles and abstracts. Of these, 2924 records were excluded based upon duplication, language, and contents of titles/abstracts indicating they did not meet inclusion criteria. The remaining 11328 full-text articles were assessed for eligibility; their reference lists and citations were searched, and an additional 105 papers identified. Of these records, 11104 did not meet review inclusion criteria, leaving 330 relevant records. The search process and outcomes are summarised in [Figure 1](#).

The 330 papers were from 16 WPR countries/territories ([Table 1](#)), with 204 (62.1%) papers from three countries/territories only. These were from China ( $n = 72$ ), Japan ( $n = 94$ ) and South Korea ( $n = 38$ ). Two-hundred and sixty-five (80.3%) of the 330 studies were published in or after the year 2000. [Table 1](#) summarises the number of papers for each variable and other characteristics of the included studies.

## RESULTS

### T1D

**Incidence:** [Table 2](#) summarises the 25 studies from ten WPR countries/territories that had information about T1D incidence with data from 2000 or afterwards. Six studies were from China, five from South Korea, two from Thailand and Taiwan, and one each from four other countries/territories. Most studies ( $n = 18$ ) reported data for youth aged < 15 years, and only 16 had been published within the past decade.

Incidence ranged from < 1 to 7.3 *per* 100000 individuals per year. An incidence of < 1 *per* 100000 were reported in four countries: Fiji[14], Indonesia[15], Thailand[16,17] and Papua New Guinea[18]. However in Fiji, the rate in Indo-Fijians was 9.3 times higher than the rate in Native Fijians[14].

T1D rates of approximately two *per* 100000 were observed in Japan[19], three in South Korea[20,21], four in Hong Kong[22], five in Taiwan[23,24] and seven in mixed population immigrants in the United States[25]. In China, average T1D rates were variable, with rates ranging from 0.7 to 3.1[26-31].

Single-study data looking at changes in incidence rates over time was available from six countries/territories. In China, rates rose 7.4% *per* annum (pa) in Harbin from 1990-2000[26], 12.0% pa in Zhejiang from 2007-2013[32], 4.4% pa in Beijing from 1995-2010[28], and 14.2% pa in Shanghai from 1997-2011[31]. In South Korea, rates rose by 7.6% pa from 2001-2010[33]. In Hong Kong, data was presented from 2008-2017 in an abstract published in 2018[22], with full data published in 2020[34]. The annual increment between 2008-2017 was 3.5% pa, with authors noting that this was less than the increment of 4.3% in the period 1997-2007. In Taiwan, rates rose 8.7% every two years from 1999-2000 to 2009-2010[23]. In Thailand, incidence almost quadrupled between 1996 and 2005, however, the authors commented that increased diagnosis likely contributed to this[16]. However, in Japan, incidence barely changed from 2005-2010 with a 0.5% pa increase[19].

**Table 1** Overview of the included studies (excluding publications with all data before 2000) (*n* = 265)

Country/territory	Total records	
	<i>n</i>	Proportion of total
Australia	10	3.8%
China	67	25.3%
Fiji	1	0.4%
Hong Kong, China	6	2.3%
Indonesia	5	1.9%
Japan	66	24.9%
Malaysia	5	1.9%
New Zealand	6	2.3%
Papua New Guinea	1	0.4%
Philippines	2	0.8%
Singapore	5	1.9%
South Korea	35	13.2%
Taiwan, China	20	7.5%
Thailand	21	7.9%
Tonga	1	0.4%
Vietnam	11	4.2%
Multiple countries/territories	3	1.1%

**Subtypes of T1D:** In Japan, three sub-groups of T1D have been identified: “abrupt-onset” form (65%), “slowly-progressive” form (30%) and “fulminant” form (5%)[35]. Childhood-onset slowly-progressive T1D is usually detected by urine-glucose screening at schools, or testing by chance, and has minimum symptoms of diabetes without showing ketosis. This type of diabetes is commonest in adolescent females, and has positive beta-cell associated antibodies in approximately 70% of the cases[35]. Fulminant T1D is more common in adults with T1D where it represents around 20% of Japanese cases [36], although in children, age-of-onset has been reported as biphasic with one peak < 5 years[37]. Aside from other Japanese reports[38-40], fulminant T1D has also been reported in China[41-43] and South Korea[44].

**Prevalence:** Five countries reported prevalence of T1D, with two papers from South Korea[20,45], and one each from Fiji[14], Japan[19] and Papua New Guinea[18]. There was a wide variation in rates, from South Korea with 52 (< 25 years)[45] and 21 (< 20 years)[20] *per* 100000, Japan 13.5 (< 15 years)[19], Fiji 5.9 (< 15 years)[14], and Papua New Guinea 0.28 (< 15 years)[18]. The Fiji study[14] reported rates by ethnicity, with T1D prevalence in Indo-Fijians being almost 10 times higher than the rate in native-Fijians (13.6 *vs* 1.4).

**Age at diagnosis:** Table 3 summarises the 20 studies from seven WPR countries that had information about either mean/median or peak age of diagnosis. Only eight studies reported peak age of diagnosis. One study from Japan[19] reported peak age of onset in girls at 10 years and boys at 13 years. The remaining nine papers reported five-year interval data with peak 10-14 years.

**Gender ratio:** Twenty-two papers from eight countries reported new-onset T1D cases by gender (Table 4). Ten of these reported rates according to respective population sizes and the remaining 12 just presented numbers for each gender. There was a female excess in almost all studies, with the male:female ratio ranging from 0.58-1.13. The mean ratio across the 22 papers was 0.81.

**DKA at diagnosis:** Twenty papers from seven countries reported on the rate of DKA at onset (Table 5). The rates varied from 19.3% in one Taiwanese study[46] to 75.3% in one study from Malaysia[47]. Only three studies had rates below 33%.

**Autoantibodies at diagnosis:** Table 6 lists the 15 studies from four countries that reported autoantibody testing. All studies had glutamic acid decarboxylase 65 autoantibody (GAD65) data, with average frequencies of 51.3% (China), 58.1% (Japan), 64.5% (Taiwan), and 62.7% (Thailand). The frequencies in

**Table 2 Type 1 diabetes incidence under 20 years of age in/from Western Pacific region (excluding publications with all data before 2000)**

Ref.	Country/territory	Study period	Incidence/100000	n (%)	Age range (yr)
Zhang <i>et al</i> [26], 2008	Harbin, China	1990-2000	0.7 (average)	103	< 15
Gong <i>et al</i> [28], 2015 <sup>1</sup>	Beijing, China	1995-2010	1.7 <sup>2</sup>	485	< 15
Shen <i>et al</i> [29], 2002	Shanghai, China	1997-2000	1.6	103	< 15
Gong <i>et al</i> [30], 2004	Beijing, China	1997-2000	1.0 (annual): 1997 (0.76); 2000 (1.21)	71	< 15
Zhao <i>et al</i> [31], 2014	Shanghai, China	1997-2011	3.1 <sup>2</sup> (annual): 1997-2001 (1.5); 2007-2011 (5.5)	622	< 15
Wu <i>et al</i> [32], 2016	Zhejiang, China	2007-2013	2.0 <sup>2</sup> (annual): 2007 (1.2); 2013 (2.5)	611	< 20
Ogle <i>et al</i> [14], 2016	Fiji	2001-2012	0.9 (overall); 2.1 (Indo-Fijian); 0.2 (Native-Fijian)	28	< 15
Huen <i>et al</i> [154], 2009	Hong Kong, China	1997-2007	2.4 <sup>2</sup> < 15 yr, 2.0 <sup>2</sup> < 19 yr	335	< 19
Tung <i>et al</i> [22], 2018	Hong Kong, China	2008-2017	2.4 (annual)	498	< 18
Tung <i>et al</i> [34], 2020	Hong Kong, China	1997-2007; 2008-2017	2.1 <sup>2</sup> (annual): 1997 (1.6); 2007 (2.3). 3.5 <sup>2</sup> (annual): 2008 (4.0); 2017 (4.5)	498	< 18
Pulungan[15], 2013	Indonesia	2010	0.03 <sup>3</sup>	825	NS
Urakami <i>et al</i> [35], 2008	Japan	1974-2004	0.6 <sup>4</sup>	54	< 15
Onda <i>et al</i> [19], 2017	Japan	2005-2010	2.3 (annual): 2005 (2.17); 2010 (2.23)	2326	< 15
Campbell-Stokes and Taylor [138], 2005	New Zealand	1999-2000	5.6 (Māori)	22	< 15
Ogle <i>et al</i> [18], 2001	Papua, New Guinea	1996-2000	0.1	8	< 15
Lee[141], 2014	South Korea	1995-2000 and 2012	1995-2000 (1.4); 2012 (2.9)	217	< 15
Lee <i>et al</i> [33], 2015	South Korea	2001-2010	2.0 (annual): 2001 (1.3); 2010 (2.7)	239	< 15
Song <i>et al</i> [20], 2016	South Korea	2011-2013	3.3	2346	< 20
Kim <i>et al</i> [21], 2015	South Korea	1995-2000 and 2012-2014	1995-2000 (1.4); 2012-2014 (3.2)	706	< 15
Hong <i>et al</i> [149], 2013	South Korea	2001-2010	2.0 (annual)	239	< 15
Lin <i>et al</i> [23], 2014	Taiwan, China	1999-2010	4.6 (annual): 1999-2000 (3.6); 2009-2010 (5.9)	1280	< 15
Lu <i>et al</i> [24], 2014	Taiwan, China	2003-2008	5.3	1306	< 15
Panamonta <i>et al</i> [16], 2011	Thailand	1996-2005	0.6	340	< 15
Patarakijvanich <i>et al</i> [17], 2008	Thailand	1997-2005	0.7	116	< 15
The Writing Group for SEARCH[25]	United States-Asian and Pacific Islander immigrants	2002-2003	7.3	56	< 20

<sup>1</sup>These data were partially published in 2013 also (Gong *et al*[27]).

<sup>2</sup>Standardised rate.

<sup>3</sup>Degree of ascertainment not stated.

<sup>4</sup>Urine glucose screening test.

NS: Not stated.

South Korea, Philippines and Singapore were 53.0%, 44.1%, and 41.5%, respectively. Nine studies reported on insulinoma-associated 2 autoantibody (IA-2), with average prevalence of 43.5% (China), 70.7% (Taiwan) and 54.9% (Thailand). However, rates for islet autoantibody (ICA) were variable, ranging from 4 to 68.8%. Only one study (from Thailand[48]) reported zinc transporter 8 autoantibody (ZnT8) results, with 54.3% of cases positive.

**C-peptide at diagnosis:** Nineteen studies (from China, India, Japan, South Korea, Singapore, Taiwan and Thailand)[37,41,44,46,48-62], reported C-peptide results. C-peptide levels were generally low, consistent with classic T1D. Kim *et al*[44] in South Korea found that C-peptide values were lower in

**Table 3** Age of diagnosis of type 1 diabetes patients in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	n	Mean $\pm$ SD/median (IQR) age of diagnosis (yr)	Age range (yr)	Peak age of diagnosis (yr)
Gong <i>et al</i> [28], 2015	Beijing, China	485	NS	< 15	10-14
Huo <i>et al</i> [155], 2018	Beijing, China and Shantou, China	515	11 (7-14)	< 21	10-14
Weng <i>et al</i> [156], 2018	China (13 areas) <sup>1</sup>	1239	NS	< 15	10-14
Huen <i>et al</i> [154], 2009	Hong Kong, China	335 (< 19); 293 (< 15)	NS	< 19	10-14
Tung <i>et al</i> [22], 2018	Hong Kong, China	498	10.5 ( $\pm$ 4.2)	< 18	NS
Onda <i>et al</i> [19], 2017	Japan	2326	NS	< 15	13 (boys); 10 (girls)
Lee <i>et al</i> [157], 2006	Singapore	211	7.9 ( $\pm$ 4.0)	< 17	NS
Kim <i>et al</i> [21], 2012	South Korea	110	10.6 ( $\pm$ 0.9)	< 18	NS
Kim and Kim[158], 2012	South Korea	113	9.26 ( $\pm$ 0.99)	< 18	NS
Hong <i>et al</i> [149], 2013	South Korea	239	NS	< 15	10-14
Lee <i>et al</i> [141], 2014	South Korea	217	NS	< 15	10-14
Kim <i>et al</i> [159], 2016	South Korea	706	NS	< 15	10-14
Lee <i>et al</i> [160], 2017	South Korea	361	8.9 ( $\pm$ 4.0)	< 20	NS
Lo <i>et al</i> [46], 2004	Taiwan, China	165	7.3 ( $\pm$ 4.1)	< 18	NS
Ting <i>et al</i> [61], 2007	Taiwan, China	304	7.9 ( $\pm$ 3.8)	< 20	NS
Panamonta <i>et al</i> [161], 2000	Thailand	77	NS	< 15	10-14
Likitmaskul <i>et al</i> [79], 2006	Thailand	195	9.2 ( $\pm$ 2.5)	< 19	NS
Patarakijvanich <i>et al</i> [17], 2008	Thailand	116	NS	< 15	11-14
Panamonta <i>et al</i> [16], 2011	Thailand	340	NS	< 15	10-14
Khwanhatai <i>et al</i> [162], 2018	Thailand	229	7.71 ( $\pm$ 3.3)	< 18	NS

<sup>1</sup>Harbin, Shenyang, Beijing, Shanghai, Nanjing, Jinan, Wuhan, Changsha, Guangzhou, Chengdu, Xi'an, Lanzhou and Yinchuan.  
NS: Not stated.

fulminant versus autoimmune and idiopathic T1D. Lo *et al*[46] in Taiwan found that C-peptide levels were lower in subjects diagnosed younger. Finally, also in Taiwan, Ting *et al*[61] reported lower C-peptide levels in subjects who had DKA at diagnosis.

**HLA status:** Twelve studies reported HLA phenotype data, from China[49,63-67], Japan[68,69], South Korea[70,71], Taiwan[72] and Thailand[73]. Nine papers found an association between T1D and HLA-DRB1[49,63,67,69-72,74]. However, alleles contributing to T1D association differ among WPR countries. In China, several studies reported DRB1\*0301[49,63,64] conferred the strongest risk for T1D, whereas in Japan, risk is conferred mainly from DRB1\*0901 and \*0802[69,74], with a contribution also from DRB1\*0405[74] and \*0404[69]. DRB1\*0901 was strongly associated with early onset in preschool children in Japan with type 1A diabetes[68]. One study in a Japanese population reported that DRB1\*0301 and \*0302 were absent in T1D patients[74]. In South Korea, T1D risk was strongly associated with DRB1\*0301,\*0405 and \*09012 alleles[70].

There were also significant findings for DQB1, with unique alleles contributing to T1D risk in various countries[49,65,66,69,73] and within different parts of China[49,66]. DQB1\*0201 conferred the strongest risk and DQB1\*0601 and \*0602 were protective specifically amongst the Chinese Han population[66]. In Guangdong, T1D risk was linked with higher frequencies of DQB1\*0303, \*0401 and \*0402 but DQB1\*0301 was found to be protective[49]. DQB1\*0601 and \*0602 were associated with risk of type 1B in Japan [69]. In Thailand, higher frequencies of DQB1\*0201,\*0202 and \*0302 were found in children with T1D.

**Table 4 Gender ratio of type 1 diabetes patients in/from the Western Pacific region (excluding publications with all data before 2000)**

Ref.	Country/territory	Ratio (M:F)	Age range (yr)
Xin <i>et al</i> [163], 2010	Shenyang, China	0.77	< 15
Gong <i>et al</i> [27], 2013	Beijing, China	0.58 <sup>1</sup> (1995-2002); 0.74 <sup>1</sup> (2003-2010)	< 15
Zhao <i>et al</i> [31], 2014	Shanghai, China	0.97 <sup>1</sup>	< 15
Gong <i>et al</i> [28], 2015	Beijing, China	0.70 <sup>1</sup>	< 15
Wu <i>et al</i> [32], 2016	Zhejiang, China	0.78 <sup>1</sup>	< 20
Tao <i>et al</i> [164], 2017	Kunming, China	1.13	< 15
Huo <i>et al</i> [155], 2018	Beijing, China and Shantou, China	0.77	< 21
Weng <i>et al</i> [156], 2018	China (13 areas) <sup>2</sup>	0.78 <sup>1</sup>	< 15
Huen <i>et al</i> [154], 2009	Hong Kong, China	0.76	< 19
Tung <i>et al</i> [22], 2018	Hong Kong, China	0.75	< 18
Onda <i>et al</i> [19], 2017	Japan	0.76 <sup>1</sup>	< 15
Lee <i>et al</i> [157], 2006	Singapore	0.77	< 17
Hong <i>et al</i> [149], 2012	South Korea	0.86 <sup>1</sup>	< 15
Lee <i>et al</i> [141], 2014	South Korea	0.84 <sup>1</sup>	< 15
Kim <i>et al</i> [159], 2016	South Korea	0.80 <sup>1</sup>	< 15
Song <i>et al</i> [20], 2016	South Korea	0.89	< 20
Lee <i>et al</i> [160], 2017	South Korea	0.86	< 20
Lo <i>et al</i> [46], 2004	Taiwan, China	0.70	< 18
Ting <i>et al</i> [61], 2007	Taiwan, China	0.94	< 20
Lu <i>et al</i> [24], 2014	Taiwan, China	0.78 <sup>1</sup>	< 15
Patarakujvanich <i>et al</i> [165], 2001	Thailand	1.0	< 15
Panamonta <i>et al</i> [16], 2011	Thailand	0.65	< 15

<sup>1</sup>Ratio of T1D incidence.

<sup>2</sup>Harbin, Shenyang, Beijing, Shanghai, Nanjing, Jinan, Wuhan, Changsha, Guangzhou, Chengdu, Xi'an, Lanzhou and Yinchuan.

M: Male; F: Female.

There are also some reports of DQA alleles susceptible to T1D in China[49,64].

## T2D

**Incidence:** Table 7 summarises the 14 studies from seven WPR countries that had information about T2D incidence. The studies from Australia and New Zealand on indigenous/regional origin populations, and also Asian/Pacific emigrants to the United States, showed high rates. The rates from four other countries/territories including China, Hong Kong, Japan and South Korea ranged from 0.43 to 2.63 *per* 100000 individuals. Rapid increases in incidence were seen in China[75] and Hong Kong[22], with data being published in 2021 showing a rate of 3.42[76]. In Fiji, the rate for Indo-Fijians was 20 times higher than the rate for Native Fijians[14]. The mixed population of Asian and Pacific Islanders emigrants to the United States recorded the highest T2D incidence rate (12.2 *per* 100000)[77].

**Prevalence:** Four countries reported population prevalence of T2D, with one paper each from China [11], Fiji[14], South Korea[45] and Taiwan[78]. There was a wide variation in rates, from South Korea with 249 *per* 100000 < 24 years[45], China 96.8 *per* 100000 < 18 years[11], Taiwan with 70 (males) and 80 (females) *per* 100000 (0-19 years)[78], and Fiji 2.4 *per* 100000 (< 15 years)[14]. The South Korea study[45] reported that between 2002 to 2013, T2D prevalence increased 2.35 fold; the 5-9 and 10-14 year age groups showed remarkable increases (2.59 and 2.54 fold respectively), although the age group 20-24 years had the highest prevalence. Similarly, the Taiwan study[78] reported a 33% increase from 2000 to 2008.

In Thailand, a multi-centre report in 2006 found that 18.6% of diabetes cases < 18 years were T2D[79]. A more recent report from Thailand showed clinic prevalence increasing from 10%-15% in 1995-2003 to 35%-40% in 2009-2014[80].

**Table 5 Diabetic ketoacidosis at diagnosis with type 1 diabetes in/from the Western Pacific region (excluding publications with all data before 2000)**

Ref.	Country/territory	% with DKA	n	Age range (yr)
Huen <i>et al</i> [154], 2009	Hong Kong, China	60.0	335	< 19
Tung <i>et al</i> [22], 2018	Hong Kong, China	41.0	498	< 18
Jalaludin and Harun[47], 2005	Malaysia	75.3	55	< 13
Fuziah <i>et al</i> [166], 2008	Malaysia	57.1	166	< 20
Gunn <i>et al</i> [167], 2017	New Zealand	28.7 (overall); 23.7 <sup>1</sup> ; 34.3 <sup>2</sup>	38 <sup>1</sup> ; 35 <sup>2</sup>	< 15
Lee <i>et al</i> [157], 2006	Singapore	53.0	211	< 17
Park <i>et al</i> [168], 2011	South Korea	55.0	23	NS
Kim <i>et al</i> [158], 2012	South Korea	36.4	110	< 18
Kim <i>et al</i> [169], 2013	South Korea	32.0	100	< 18
Kim and Kim[170], 2014	South Korea	39.0	113	< 18
Kim <i>et al</i> [21], 2015	South Korea	39.7	706	< 15
Lee <i>et al</i> [160], 2017	South Korea	56.5	361	< 13
Lo <i>et al</i> [46], 2004	Taiwan, China	19.3	165	< 17
Ting <i>et al</i> [61], 2007	Taiwan, China	65.1	304	< 19
Tung <i>et al</i> [62], 2009	Taiwan, China	67.0	157	< 19
Chen <i>et al</i> [171], 2017	Taiwan, China	66.2 (overall): 87.0; 55.0	52; 94	< 6; 6-18
Likitmaskul <i>et al</i> [172], 2003	Thailand	55.0; 78.0	94; 28	6-18; < 15
Patjamontri and Santiprabjob[173], 2012	Thailand	40.8	49	< 15
Jaruratanasirikul <i>et al</i> [80], 2017	Thailand	70.0	99	< 15
Trisorus <i>et al</i> [48], 2018	Thailand	63.0	81	< 15

<sup>1</sup>Māori.<sup>2</sup>Pacific Islanders.

DKA: Diabetic ketoacidosis.

### Other types of diabetes

**Monogenic causes:** There are numerous reports of single gene defects causing diabetes in China, Japan, Vietnam, Thailand, Singapore, South Korea and Fiji. These include reports of gene mutations resulting in permanent and transient neonatal diabetes mellitus and diabetes with onset later in childhood.

Most reports were case studies[81-102]. Larger studies that conducted genetic testing on neonatal diabetes cases were undertaken in China[103] and Vietnam[104-106]. Cao *et al*[103] reported a total of 25 cases with neonatal period onset. 72.0% cases ( $n = 18$ ) were permanent (five with *KCNJ11* gene mutations, one *ABCC8* mutation, two *EIF2AK3*, one each with *INS*, *GLIS3* and *SLC19A* and seven without any known mutation) and seven cases (28%) with transient diabetes (two with *ABCC8* mutation, one paternal UPD6q24, and four without mutations). In Vietnam, Craig *et al*[104] identified 13 neonatal cases that had gene mutations of *KCNJ11* ( $n = 3$ ), *ABCC8* ( $n = 4$ ), *INS* ( $n = 2$ ) and uniparental disomy of chromosome 6q24 ( $n = 1$ ) and three others without any mutations. Also in Vietnam, Can *et al*[105] genetically confirmed 16 neonatal cases with gene mutations of *KCNJ11* ( $n = 6$ ), *ABCC8* ( $n = 5$ ), *INS* ( $n = 2$ ) and abnormality in chromosome 6q24 ( $n = 3$ ). Finally, Ngoc *et al*[106] reported 38 cases (28 permanent and 10 transient) with monogenic diabetes, 31% with mutations of *ABCC8*, 29% *KCNJ11*, 16% *INS*, 16% chromosome 6q24, 3% *FOXP3*, 3% *EIF2B1*, and 2% *EIF2AK3*.

Successful switching from insulin to sulfonylurea treatment was observed in cases with *KCNJ11* V59M/C42R and *ABCC8* mutations[82,83,88,102,107,108].

In addition, there are various reports of diabetes occurring as part of a known syndrome: DEND syndrome (developmental delay, epilepsy, and neonatal diabetes syndrome)[82,90,109], Wolfram syndrome[110-113], Prader-Willi syndrome[114], Wolcott-Rallison syndrome[81] and Kearns-Sayre syndrome[115].

There were reports of maturity-onset diabetes of the young (MODY) among children and adolescents < 20 years from China[116-122] and Japan[123-131], with this condition also seen in Hong Kong[120, 132].

**Table 6 Autoantibodies studies in children and youth with type 1 diabetes in/from the Western Pacific region (excluding publications with all data before 2000)**

Ref.	Country/territory	n	Age range (yr)	% positive for GAD65	% positive for IA-2	% positive for IAA	% positive for ZnT8A	% positive for ICA
Huang[174], 2004	Guangdong, China	34	7-12	44.1	35.3			17.6
Li <i>et al</i> [175], 2008	Changsha, China	35; 51	0-9; 10-14	60.0; 64.7	62.8; 33.3			
Baoerhan and Maimaiti [176], 2015	Urumqi, China.	94	< 15	45.0	62.0			76.0
Urakami <i>et al</i> [35], 2008	Japan	48	6-15	70.8				68.8
Iwabuchi <i>et al</i> [177], 2013	Japan	43	Children	44.0				
Habu <i>et al</i> [134], 2013	Japan	48	< 19	59.5	68.1			
Mabulac[178], 2013	Philippines	68	Paediatric	44.1				
Lee <i>et al</i> [59], 2001	Singapore	41	< 15	41.5				41.5
Kim and Kim[170], 2014	South Korea	113	< 18	53.0		26.0		4.0
Chen <i>et al</i> [179], 2001	Taiwan, China	70	< 17	54.3				
Tung <i>et al</i> [62], 2009	Taiwan, China	157	12-18	73.0	76.0	21.0		
Cheng <i>et al</i> [146], 2018	Taiwan, China	750	< 20	66.3	65.3	35.7		
Santiprabhob <i>et al</i> [180], 2007	Thailand	51	< 15	63.0	61.0			
Patjamontri <i>et al</i> [173], 2012	Thailand	90	< 20	50.0	58.0			
Trisorus <i>et al</i> [48], 2018	Thailand	81	< 15	75.3	45.7		54.3	

GAD65: Glutamic acid decarboxylase 65 autoantibody; IA-2: Insulinoma-associated 2 autoantibody; IAA: Insulin autoantibody; ZnT8A: Zinc transporter 8 autoantibodies; ICA: Islet autoantibody.

## DISCUSSION

This systematic review examined all published information on diabetes in young people in and from the 37 countries/territories in the WPR, excluding European-origin populations. Three hundred and thirty papers were relevant for the review. The analysis demonstrates both differences and commonality compared to observations in European-origin populations.

### T1D

T1D incidence is dependent on both genetic and environmental factors[2,133]. HLA haplotype variations are the main genetic driver, although some other genes also play significant roles[2,133]. The specific environmental factors are less well understood[2,134].

T1D is most common in European-origin and some Arab-origin populations, with annual incidences ranging from 13-60 *per* 100000 population < 15 years[1,135]. In contrast, this systematic review demonstrates that all published WPR rates are much lower, although data since 2000 are available for only ten countries as well as one migrant population. A review by Park[136] in 2006 proposed a lower incidence of high-risk HLA alleles as with respect to identical DR-DQ haplotypes, the association and transmission to diabetic offspring were similar for Asians and Caucasians.

Reported incidence is even lower in non-Chinese-origin South-East Asian and Pacific countries (Thailand, Indonesia, Papua New Guinea, and Fiji), than in Eastern Asian nations (China, Hong Kong, Japan, South Korea and Taiwan), although lack of ascertainment may underestimate the true incidence rate in Thailand, Indonesia and Papua New Guinea, as some cases may die at onset misdiagnosed with another condition[16,18,137]. However, it must be noted that in Fiji, incidence < 15 years was nine times higher in Indo-Fijians compared to Native Fijians[14] and the incidence in New Zealand Maori was 4.5 times lower than in European-origin children[138]. In addition, incidence is similarly low in Bangladesh which is adjacent to South East Asia[139].

The highest incidence seen was in South- and Western-Asian- and Pacific Island-origin children who had emigrated to the United States, although the rate remained less than a third of that in non-Hispanic white children[25]. Finally, in a study of all-age T1D incidence in Australia in 2013, incidence in the

**Table 7 Type 2 diabetes incidence in non-European populations in/from the Western Pacific region (excluding publications with all data before 2000)**

Ref.	Country/territory	Study period	n	Incidence/100000	Age range (yr)
Craig <i>et al</i> [181], 2007	Australia Torres Straits Islands	2001-2006	23	12.7	< 19
Tran <i>et al</i> [182], 2014	Australia, Torres Straits Islands	2001-2008	31	20.7	< 19
Haynes <i>et al</i> [183], 2016	Australia, Torres Straits Islands	1990-2012	76	12.6	< 17
Wu <i>et al</i> [75], 2017	Zhejiang, China	2007-2013	392	1.73 (overall); 0.62 (2007); 3.62 (2013)	< 20
Ogle <i>et al</i> [14], 2016	Fiji	2001-2012	13; 11; 1; 1	0.43 (overall); 1.17 <sup>1</sup> ; 0.06 <sup>2</sup> ; 0.70 <sup>3</sup>	< 15
Huen <i>et al</i> [154], 2009	Hong Kong, China	1997-2007	198	1.2	< 19
Tung <i>et al</i> [22], 2018; Tung <i>et al</i> [76], 2021	Hong Kong, China	2008-2017; 2008-2017	391; 391	1.9 (3.42)	< 18
Urakami <i>et al</i> [184], 2005	Japan	1974-2002	232	2.63 (overall); 1.73 (< 1980); 2.76 (> 1981)	< 16
Urakami <i>et al</i> [148], 2018	Japan	1975-2015	301	2.6	< 16
Campbell-Stokes and Taylor [138], 2005	New Zealand	1999-2000	7 <sup>4</sup>	1.78	< 15
Jefferies <i>et al</i> [185], 2012	New Zealand	1995-2007	43 <sup>4,5</sup>	3.4	< 15
Sjardin <i>et al</i> [186], 2018	New Zealand	1995-2015	34 <sup>4</sup> 47 <sup>5</sup>	3.3 (overall); 3.4 (1995-2007); 4.0 (2008-2015) 3.6 (overall); 3.4 (1995-2007); 4.0 (2008-2015)	< 15
Hong <i>et al</i> [149], 2013	South Korea	2001-2010	89	0.76	< 15
Liu <i>et al</i> [77], 2009	United States-Asian and Pacific Islander immigrants	2002-2003	73	12.2	< 15

<sup>1</sup>Indo-Fijian.<sup>2</sup>Native-Fijian.<sup>3</sup>Fijian of European descent.<sup>4</sup>Māori.<sup>5</sup>Pacific Islanders.

Aboriginal population was only 70% of that in the non-indigenous population[140], despite the extensive admixture between the two populations. Therefore, in these populations, changes in environment that could potentially increase incidence do not appear to fully overcome the impact of varying genetic susceptibility.

In the absence of large-scale immigration, genetic factors will remain essentially constant. Therefore, any changes in incidence will be due to changing environmental factors. Incidence in European-origin populations has increased by 3%-4% pa in many European-origin populations[135], although this is tailing off now in some countries[3]. There is some evidence that the rate of increase is higher in some lower-incidence countries[3].

The four studies from China[26,30-32] show that T1D incidence is rising quickly (from 4.4%-14.2% pa). South Korea[141] and Taiwan[23] also had high rates of increase at 7.6% and 8.7% pa respectively. However, the rate of rise was slowing in Hong Kong[22] and was virtually zero in Japan[19]. This may be due to evolving environmental factors which then approach a peak effect, as has been seen with slowing or peaking rates in some high-incidence countries[3].

Slowly-progressive diabetes that is clearly T1D is well described from Japan[35], and fulminant T1D (which occurs more in adults and in younger children) is well reported from Japan[36-40], China[41-43] and South Korea[44].

These distinct subtypes, as opposed to acute-onset T1D, do not have exact correlates in European-origin populations, although it is possible that to some extent these represent the more general heterogeneity of T1D, which is being increasingly recognised[142]. For instance, onset is more rapid in younger European-origin populations[143]. A study done in Western Asia and also in a European-origin population that used identical methodology to assess genotype, phenotype and endotype could help illuminate this and add to global knowledge of T1D pathogenesis.

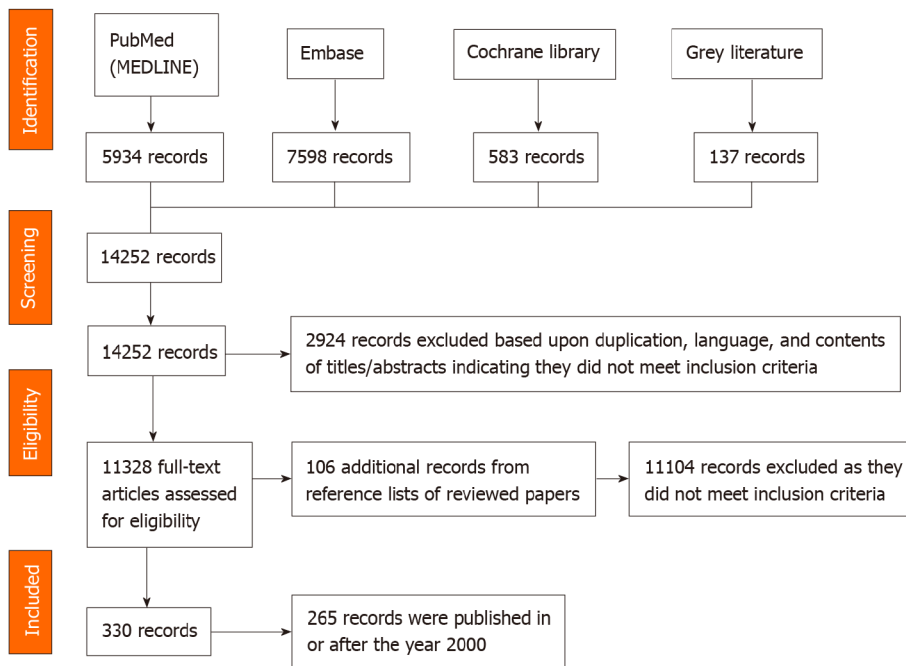


Figure 1 PRISMA flow diagram for searches and screening of articles included in the systematic review.

Prevalence data from non-European origin populations in WPR are limited to five countries. Prevalence is dependent upon past incidence and mortality. We did not find any publications on mortality in these populations.

The age of onset of T1D cases, with peak age 10-14 years, is consistent with European-origin populations.

Nearly all studies found a female excess of cases. In high-incidence countries, T1D is slightly more common in males[2]. In contrast, as in this review, a female excess is more common in lower-incidence countries[144].

Pancreatic autoantibody rates varied across studies. This could be due to various factors including study group age, duration of diabetes at the time of measurement, assay variations, and diagnostic uncertainty. Most GAD-65 and IA2 autoantibody rates were consistent with European-origin data. Only one study in this review, from Thailand[48] measured ZnT8 autoantibodies. Positivity was high at 54.3% in new-onset cases, with 16% of all new-onset cases having ZnT8 but not GAD-65 or IA2 autoantibodies. A recent study from Japan found that ZnT8 positivity was most common < 10 years[145]. With respect to change in autoantibodies over time, Cheng *et al*[146] found that in Taiwan, the rate of GAD-65 and/or IA-2 autoantibodies were 89.4% in the first year after diagnosis but fell to 36.7% after nine years.

The rate of DKA at diagnosis in most studies was higher than in high-incidence countries[147]. Usher-Smith *et al*[147] found that lower-incidence countries generally had higher DKA rates, presumably due to decreased awareness. Less-resourced health systems also had higher DKA rates, and this factor may also be impacting rates in some WPR countries.

T1D HLA associations showed some variation compared to European-origin populations, with also some differences across the region.

## T2D

Our review underscores the limited data on T2D in non-European youth from the WPR region, with six studies in indigenous populations conducted in Australia and New Zealand, and single studies from China, Hong Kong, Japan, South Korea and Fiji, as well as one study on emigrant Asian/Pacific youth to the United States. However, a clear finding is that T2D incidence exceeded the T1D rates in some countries, and unlike T1D were comparable to rates in European-origin populations. For instance, the incidence of T2D, detected by urine-glucose screening at schools in Tokyo, was higher compared with that of T1D (2.5-3.0/100000/year vs 2-2.5/100000/year, particularly among junior high school children aged 13-15 years (6.5/100000/year)[148]. On the other hand, the incidence of T2D in school children was increasing during 1975-1982, but there was decreased tendency in recent years. Lifestyle changes might contribute to improved incidence of T2D in Japanese school children. In contrast to this, the most recent data from South Korea[149], China[75] and Hong Kong[22,76] showed that incidence was increasing sharply.

While not addressed in detail in this review, several studies noted the phenotypic heterogeneity of T2D when compared to European-origin populations. While obesity or morbid obesity are a

**Table 8 Recommendations for further research and interventions**

No.	
1	Establishment registers of diabetes in young people in all countries, and, where necessary, in distinct geographic/ethnic regions within countries
2	Ongoing incidence, prevalence, and mortality studies for both T1D and T2D in all countries
3	Phenotype, endotype and genotype studies in youth with any type of diabetes
4	Education campaigns aimed at increasing awareness of the signs and symptoms of T1D and reducing rates of DKA at onset
5	Public health measures aimed at reducing incidence of T2D in young people
6	In-country/territory advocacy efforts, informed by updated and new epidemiological research, aimed at improving quality of care
7	Regional coordination and dissemination of data and research skills

DKA: Diabetic ketoacidosis; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

predominant feature in European origin youth with T2D, in Japan, for example, 10%-15% of youth with T2D are non-obese, with milder insulin resistance and substantial insulin secretion failure, in the absence of autoimmunity[148]. The genetic background likely plays a role[148], although more HLA and non-HLA genetic data are needed to further explore and support this hypothesis.

Overall, the high and, in some countries, increasing rates of T2D in the WPR region are concerning given their known and substantial risk of long-term complications and premature morbidity and mortality[150]. There is an urgent need for more and complete epidemiologic and phenotype data in youth with T2D from across the entire WPR in order to better understand and subsequently develop adequate and effective strategies that address T2D in youth as a public health concern.

### Other types

Monogenic forms of diabetes were reported from various countries. Such disorders can present in the neonatal period or later in life. Genetic testing confirms diagnosis and helps identify selective forms responsive to alternate treatment: Most KCNJ11 and some ABCC8 mutations respond to oral sulphonylureas and so insulin can be discontinued, and also thiamine treatment is of benefit in SLC19A mutations (thiamine-resistant megaloblastic anaemia)[151]. In all monogenic cases, genetic counselling is indicated if desired by the family.

## CONCLUSIONS

Given the population and number of countries in this region, many gaps in knowledge remain. A number of countries in WPR, including populous nations such as Indonesia, Philippines, and Vietnam, as well as a number of others, have no or minimal information published. Keeping this in mind as a major limitation, T1D with onset in childhood and adolescence is substantially less common in WPR than in European-origin populations, and incidence appears to be lower in South-East Asia than in Eastern Asia. The female preponderance differs from European-origin populations but is in line with the lower incidence rates. As incidence is rapidly increasing across the region, sex distribution will be informative to monitor. Age-of-onset, pancreatic autoantibody positivity rates and, at least across a large part of the WPR region HLA risk associations are similar to European-origin populations. Rates of DKA at onset are concerningly high across the region, consistent with published risk factors.

Data on youth-onset T2D are limited across WPR, with representations from only a handful of countries. Incidences are concerningly high and exceed those of T1D in some countries. Furthermore, rates are increasing.

Other forms of diabetes occur including various monogenic forms that also occur in European-origin and other populations.

Incidence studies are needed from all countries. A high ascertainment is needed, and it is preferable to have at least two overlapping data sources so a 'capture-recapture' method can be used[152]. Given the geographic size and ethnic diversity in some WPR countries, it is quite possible that T1D and T2D rates vary within countries as well. Establishment of registers will facilitate such incidence studies and also define prevalence and mortality, and assist in assessment of outcomes. These data will then inform quality of care improvements and health professional training, and assist in advocacy to improve provision of care by the respective government health system. An example of such a register is the "Thai Type 1 Diabetes and Diabetes Diagnosed Before Age 30 Years Registry, Care and Network"[153]. Table 8 gives recommendations for further research and interventions.

## ARTICLE HIGHLIGHTS

### **Research background**

Type 1 diabetes (T1D) incidence varies, with most studies indicating increasing incidence. Reported rates are much lower in the Western Pacific region (WPR), than European-origin populations. Conversely, there are reports of substantial numbers of young people with type 2 diabetes (T2D).

### **Research motivation**

A greater understanding of T1D and T2D in the WPR may highlight factors important in pathogenesis of these conditions. There is a need to determine the current burden of disease more clearly and also any gaps in knowledge, in view of varying funding and resources for diabetes treatment in this region.

### **Research objectives**

To gather and summarise epidemiologic and phenotypic data on childhood diabetes in non-European populations in and from WPR.

### **Research methods**

A comprehensive systematic search of available literature was undertaken.

### **Research results**

There are both differences and similarities compared to observations in European-origin populations. T1D was found to be less common, but generally has a classic phenotype. Some countries/territories have rapidly increasing incidence. T2D is relatively common. There are, however, many information gaps.

### **Research conclusions**

Given the population and number of countries in this region, many gaps in knowledge remain.

### **Research perspectives**

Registries and studies are needed to fill many information gaps. Establishment of registers will facilitate incidence studies and also define prevalence and mortality, and assist in outcome assessment. Such data will inform quality of care improvements, health professional training, and assist advocacy.

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## FOOTNOTES

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