The Incidence of Adult-Onset Type 1 Diabetes: A Systematic Review From 32 Countries and Regions

Diabetes Care 2022;45:994–1006 | https://doi.org/10.2337/dc21-1752

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BACKGROUND

The epidemiology of adult-onset type 1 diabetes (T1D) incidence is not well-characterized due to the historic focus on T1D as a childhood-onset disease.

PURPOSE

We assess the incidence of adult-onset (≥20 years) T1D, by country, from available data.

DATA SOURCES

A systematic review of MEDLINE, Embase, and the gray literature, through 11 May 2021, was undertaken.

STUDY SELECTION

We included all population-based studies reporting on adult-onset T1D incidence and published from 1990 onward in English.

DATA EXTRACTION

With the search we identified 1,374 references of which 46 were included for data extraction. Estimates of annual T1D incidence were allocated into broad age categories (20–39, 40–59, ≥60, or ≥20 years) as appropriate.

DATA SYNTHESIS

Overall, we observed the following patterns: *1*) there is a paucity of data, particularly in low- and middle-income countries; *2*) the incidence of adult-onset T1D is lowest in Asian and highest in Nordic countries; *3*) adult-onset T1D is higher in men versus women; *4*) it is unclear whether adult-onset T1D incidence declines with increasing age; and *5*) it is unclear whether incidence of adult-onset T1D has changed over time.

LIMITATIONS

Results are generalizable to high-income countries, and misclassification of diabetes type cannot be ruled out.

CONCLUSIONS

From available data, this systematic review suggests that the incidence of T1D in adulthood is substantial and highlights the pressing need to better distinguish T1D from T2D in adults so that we may better assess and respond to the true burden of T1D in adults.

SYSTEMATIC REVIEW

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Received 20 August 2021 and accepted 10 January 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.18409844.

The incidence of type 1 diabetes (T1D) is highest in children, though T1D onset can occur at any age (1,2). The global epidemiology of childhood-onset T1D is well characterized, with estimates updated biannually in the International Diabetes Federation (IDF) Diabetes Atlas (3). The epidemiology of adult-onset T1D incidence is, in contrast, less well characterized due to the historic focus on T1D as a common childhood-onset disease (2), challenges in distinguishing adult-onset T1D from type 2 diabetes (T2D), and a lack of national diabetes registries that include T1D incidence across the life span. Recognition of adult-onset T1D, and assessment of trends in its incidence, is important, as this incurable condition is commonly misclassified as T2D (4) and often requires treatment very different from that for T2D (5).

In an earlier systematic review (6) investigators reported on the epidemiology of T1D incidence in young adults (age >15 years) as compared with childhood-onset T1D (age <15 years). Key findings of this earlier review included the following: *1*) there is a general paucity of data on adult-onset T1D incidence; *2*) country-to-country variations in incidence in those aged >15 years paralleled those of children, with highest estimates in Nordic countries (e.g., Finland); *3*) T1D incidence was higher in male (vs. female) young adults; and *4*) T1D incidence decreased after the age of 14 years (6).

In the current Systematic Review, our primary objective is to complement and extend the earlier work by Diaz-Valencia et al. (6) by exclusively examining population-based studies reporting on T1D incidence among adults aged ≥20 years and incorporating data from the gray literature (e.g., registries, national health surveys) in an attempt to better capture the epidemiology of adult-onset T1D by country. Our secondary objective is to assess the quality of the epidemiological evidence pertaining to adult-onset T1D incidence, including diagnostic methods.

METHODS

This Systematic Review adheres to the Preferring Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This Systematic Review has been registered with the PROSPERO International prospective register of systematic reviews (reg. no. CRD42021238967).

Data Sources and Searches

A literature search was performed in MEDLINE and Embase on 11 May 2021 without any restrictions of time. We used Medical Subject Headings (MeSH) related to "type 1 diabetes," "incidence," and "study design" combined with the operator "AND" and restricted the search strategy to studies published in English. A description of the final search strategies for MEDLINE and Embase are can be found in Supplementary Tables 1 and 2, respectively. To identify additional studies or data sources not captured in the traditional literature search, we also searched the gray literature including national health and diabetes registry websites (see Supplementary Table 3 for a full list of the 54 countries searched), contacted experts and IDF Diabetes Atlas collaborators to identify country-specific estimates of adult-onset T1D incidence, and screened the reference lists of included studies.

Study Selection

We included all full-text research articles in which investigators reported on the incidence of adult-onset T1D (aged ≥20 years) in population-based studies, including occupation- and insurance-based populations, published from 1990 onward. We considered latent autoimmune diabetes in adults as a subtype of T1D and included studies in which incidence of latent autoimmune diabetes in adults was reported. We excluded the following: *1*) articles where described T1D incidence was among a non-population-based sample (e.g., a trial or hospital-based population); *2*) editorials/commentaries, case studies, or abstracts; *3*) articles where investigators described prevalence of T1D; *4*) articles where investigators reported on the incidence of maturity-onset diabetes of the young; and *5*) studies with a focus on specific populations such as T1D post-pancreatectomy. For some studies, the age range included adolescents (i.e., 15–34 years). In these instances, and where data were not reported in age-specific groups ≥20 years, we contacted authors of the original studies to provide age-specific estimates. Where age-specific estimates were not provided, the broader age range including adolescents was reported.

All identified articles from the literature search were entered into Covidence for screening. Each article was title and abstract screened by two reviewers (any combination of J.L.H., P.L.W., X.Z., X.L., and R.C.W.M.), and conflicts were resolved by a third reviewer. Studies subsequently included in the full-text screen were also screened by two reviewers (J.L.H., X.Z., R.C.W.M.), and conflicts were resolved by a third reviewer. In the event that conflicts could not be resolved by a third reviewer, a discussion by the full team was conducted until a final disposition was reached. Where multiple studies reported on the same data source, we included the most recently published study only.

Data Extraction and Quality Assessment

Microsoft Excel was used to extract the following data from included articles: publication characteristics (i.e., year of publication, author names, PubMed identifier [PMID], journal, data source), study characteristics (i.e., study design [cohort, cross-sectional], country/region/territory, study year), sample characteristics (i.e., sample size, description of the sample, age range), and diabetes definition and incidence (overall, sex-stratified, age-stratified, and calendar year stratified where appropriate, with 95% CIs and unit of measurement, i.e., person-years). Data extraction was performed by J.L.H.

The methodological quality of each study was critically appraised by two authors (P.L.W. and X.Z.) using a modified version of the Newcastle-Ottawa Scale (7), and conflicts were resolved by a third reviewer (J.L.H.). This modified tool, previously used in studies of T2D incidence (8), includes items to assess the representativeness of the study population, the sample size, and the method of assessing diabetes status. For the current review, we further tailored the scale of outcome assessment for T1D. Specifically, we scored the quality of the diagnostic criteria using the following algorithm where a higher score indicates higher quality: no description (score 0), patient self-report (score 1), record linkage (clinical diagnosis or ICD code) (score 2), administrative algorithm including where two or more clinical criteria are used (score 3), and use of one or more biomarkers (e.g., anti-GAD, other antibodies, C-peptide, genetic scores) supplemented with clinical criteria (score 4) (Supplementary Table 4). We acknowledge that for earlier studies, the use of biomarker data was not standard practice,

and thus these studies may score lower based on current quality metrics. The maximum score was 11, and final scores were categorized as low (score 0–4), medium (score 5–7), or high (score 8–11) quality.

Data Synthesis and Analysis

Estimates of adult-onset T1D are provided per study and overall patterns across studies described. To present results graphically, we allocated T1D incidence estimates, per data source, into broad age categories (20–39, 40–59, ≥60, or ≥20 years) as appropriate. Where one study reported on more than one age-group per category (i.e., 25–29 and 30–34 years), we took the unweighted average of these two estimates and ascribed this to the 20–39 years category. This same approach was used where incidence was reported by sex. The majority of studies (*n* = 35 [76%]) reported T1D incidence per 100,000 persons per year, while 11 (24%) reported T1D incidence per 100,000 PY. For this review, we have assumed that PY approximates per person per year and have reported this across all studies. Last, the reporting of geographical regions (e.g., Europe, Western Pacific) in this review is in accordance with standard guidelines used for the IDF Diabetes Atlas and does not reflect the views of the authors regarding geographical boundaries or legal status of territories.

RESULTS

The literature search yielded 1,354 articles (658 from MEDLINE and 696 from Embase). Sixteen additional articles were identified from the reference list of included studies, and four reports were identified from the gray literature (three from diabetes registries and one from an organization). Among 86 studies assessed for eligibility, 40 were excluded including 15 that were excluded due to duplicate results reported from the same data source. At the conclusion of the search, 46 articles or reports were included in the final review (see Figs. 1 and 2).

The 46 articles or reports included in this review describe the incidence of adult-onset T1D across 32 countries or regions between 1973 and 2019 (Table 1). The majority (36 of 46 [78%]) of studies were from Europe and the Western Pacific, 3 (7%) were from North America (the U.S. only), 4 (8%) were from Africa (Eritrea, Ethiopia, Mali, and Rwanda), 2 (4%) were from the Middle East and North Africa (Iran and Libya), and 1 (2%) was from Southeast Asia (India).

The incidence of adult-onset T1D varied considerably, and the following general patterns were observed: *1*) the incidence of adult-onset T1D is lowest in predominantly Asian countries, regions, or territories (China, Taiwan, and Hong Kong) and highest in Nordic countries (Sweden, Finland, Norway, and Denmark); *2*) the majority of studies stem from high-income countries in Europe and the Western Pacific, with a clear gap in data from low- and middle-income countries; *3*) among studies with reporting of T1D incidence across all age categories (20–39, 40–59, and ≥60 years), in 7 of 12 (58%) a decrease was reported in T1D incidence with increasing age, and in 5 of 12 (42%) an increase was reported in T1D incidence with increasing age (Supplementary Fig. 1); and *4*) among 26 studies with reporting of sex-specific estimates, in 92% there was a higher incidence of T1D reported among men compared with women, excluding in Iran and in the U.S. Navy study where women had

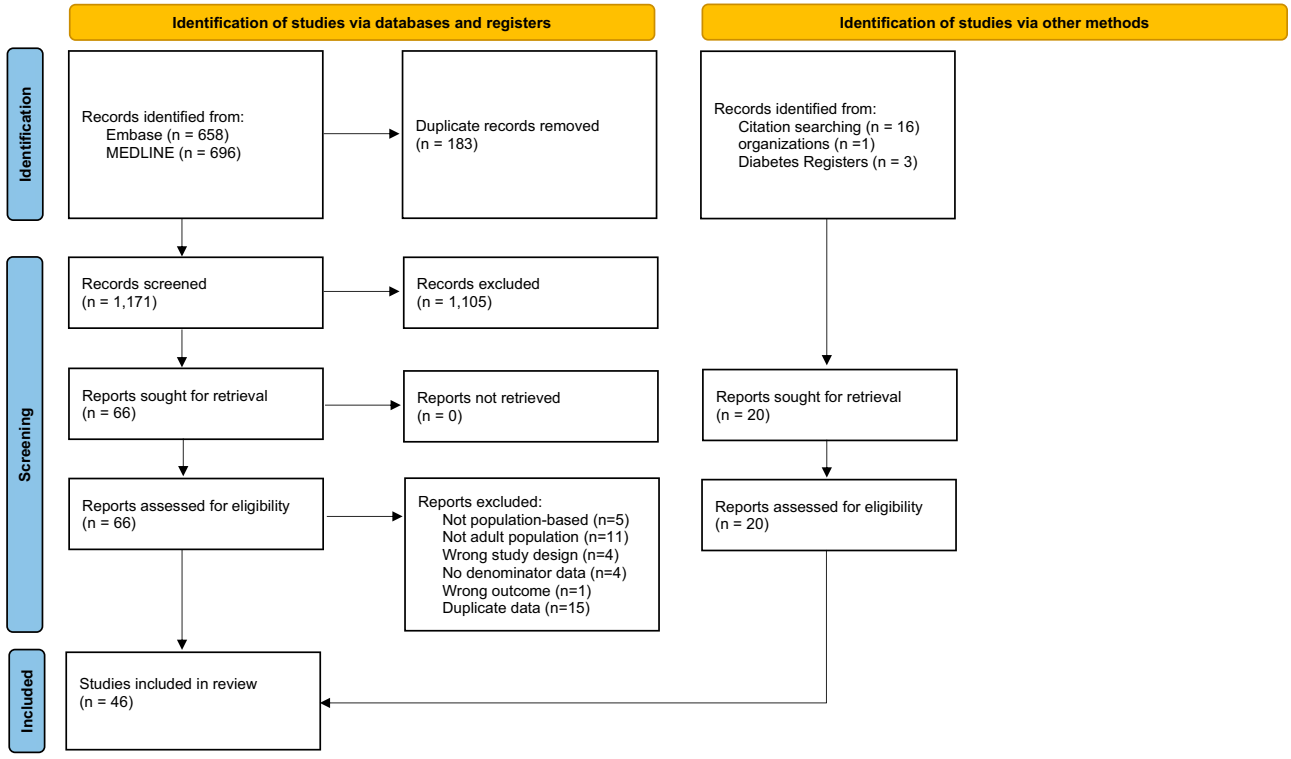

Figure 1—PRISMA 2020 flow diagram for new systematic reviews including searches of databases, registers, and other sources. Adapted from Page et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

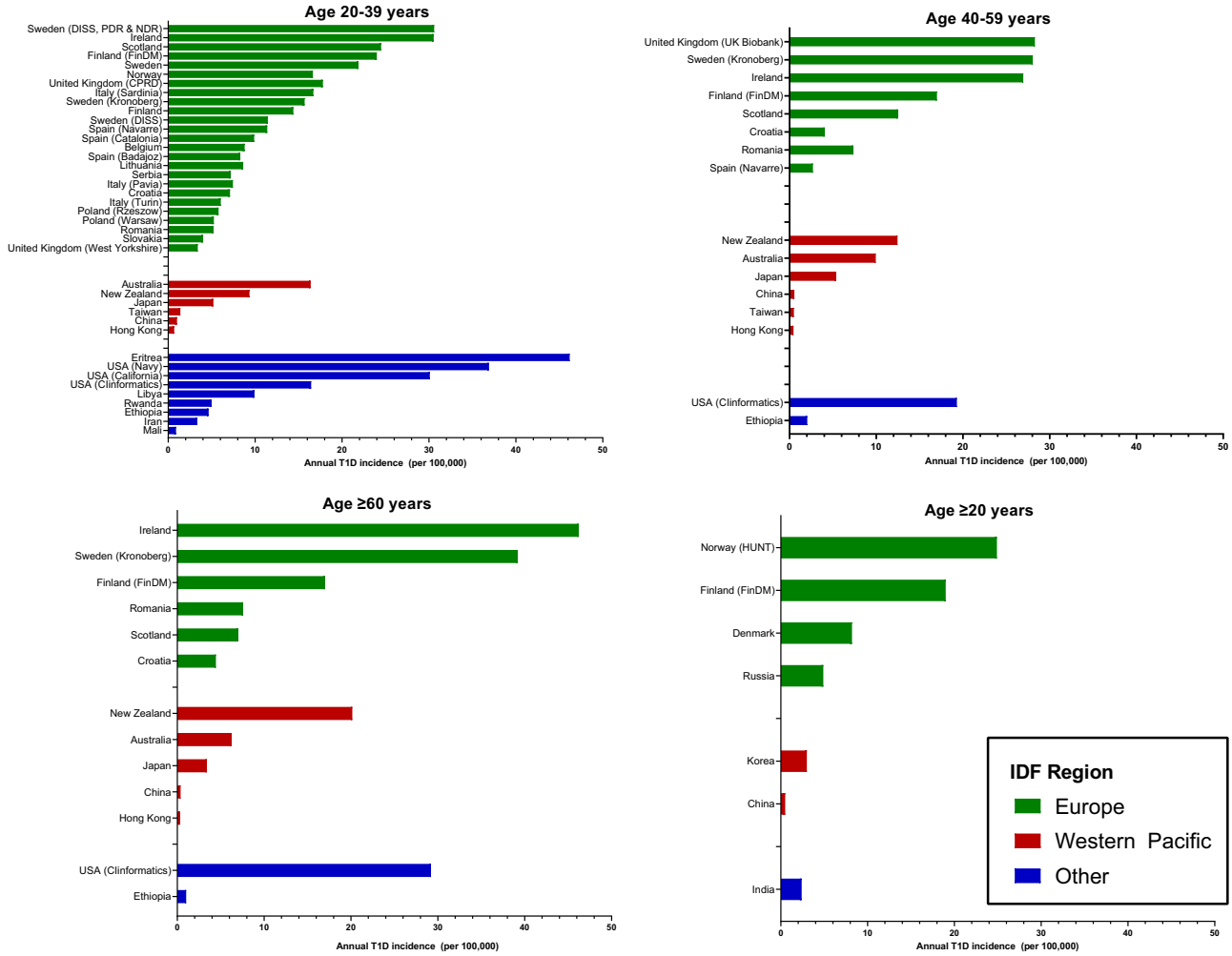

Figure 2—Incidence of adult-onset T1D diabetes by age-group, IDF region, and country. Clinformatics, Clinformatics Data Mart database; HUNT, Nord-Trøndelag Health Study (The HUNT Study).

a similar or higher incidence of T1D relative to men (Supplementary Fig. 2).

Time Trends

In 13 studies investigators reported trends in adult-onset T1D incidence over time (Fig. 3), with mixed findings. For five (38%) studies, including data from Serbia (9), Sweden (Diabetes Incidence Study in Sweden [DISS]) (10), Korea (11), Taiwan (12), and the U.S. (13), a decrease was reported in adult-onset T1D incidence over time, ranging from 1983 to 2017. In contrast, in one study from Mali (14) an increase was reported in adult-onset T1D incidence between 2007 and 2016, while data from Spain (2009–2016) (15), the U.K. (1994–2013) (16), and Hong Kong (2002–2015) (17) showed no change over time. These trends were consistent across age-groups. Four studies did not include formal assessment of changes in incidence over time, though data from Finland (Diabetes in Finland [FinDM]) (18) suggest a decline in adult-onset T1D incidence between 2010 and 2017, data from Poland (1983–1988) (19) and Sweden (DISS, National Diabetes Register [NDR], and Prescribed Drug Register [PDR], from 2007–2009) (20) indicate T1D incidence was stable over time, and data from Scotland (2012–2019) (21) indicate an increase in T1D incidence among the 20–39 and ≥60 years age-groups.

Diagnosis of T1D and Quality Assessment

Among all studies, seven (15%) included use of biomarkers (in conjunction with clinical features) for definition of T1D. These studies were from the U.K. (UK Biobank) (22), Sweden (10,20,23), the U.S. (California) (24), Spain (Navarre) (15), and Norway (Nord-Trøndelag Health Study [The HUNT Study]) (25). (See Supplementary Table 5 for detailed description of T1D definition and Supplementary Table 6 for scores related to diagnosis of T1D.) For the large majority, record linkage (n = 19 [41%]) or an administrative algorithm (n = 20 [43%]) was used to define T1D.

Based on the modified Newcastle-Ottawa Scale, the quality of studies ranged from a score of 5 (Ethiopia) to a perfect score of 11 (Sweden). No studies were deemed low quality (score 0–4), 13 (28%) studies were deemed moderate quality (score 5–7), and 33 studies (72%) were deemed high-quality studies (score 8–11) (Supplementary Table 6).

DISCUSSION

In this Systematic Review, we identified five key messages from 46 studies across 32 countries and regions reporting on adult-onset T1D incidence. First, there is a general paucity of data on adult-onset

Table 1—Summary of studies included in Systematic Review of annual T1D incidence (per 100,000 people) in adults by IDF region

First author (reference no.)	Country (region)	Cohort name	Study year	Population at risk, *n* (age)	Sex	Age at onset, years (#)	Incidence (95% CI)
Europe							
Weets (44)	Belgium (Antwerp)	Belgian Diabetes Registry	1989–2000	488,457 (0–39 years)	M+F	15–39 (1)	8.8 (7.9–9.8)[a]
					M	15–39 (1)	10.6 (9.2–12.2)[a]
					F	15–39 (1)	7.0 (5.9–8.3)[a]
Roglić (45)	Croatia (Zagreb)	N/A	1988–1992	933,914 (all ages)	M	15–24 (1)	9.8 (6.5–14.3)[c]
					M	25–34 (1)	7.8 (5.2–11.2)[c]
					M	35–44 (1)	7.2 (4.7–10.6)[c]
					M	45–54 (2)	3.0 (1.4–5.7)[c]
					M	≥55 (3)	4.4 (2.6–7.0)[c]
					F	15–24 (1)	9.3 (6.1–13.6)[c]
					F	25–34 (1)	5.1 (3.2–7.8)[c]
					F	35–44 (1)	3.8 (2.1–6.3)[c]
					F	45–54 (2)	5.1 (2.9–8.3)[c]
					F	≥55 (3)	4.5 (3.0–6.6)[c]
Mølbak (46)	Denmark (Copenhagen and Freseriskborg)	N/A	1973–1977	457,281 (>29 years)	M+F	>29 (4)	8.2 (7.1–9.4)[c]
					M	>29 (4)	9.1 (7.3–10.8)[c]
					F	>29 (4)	7.5 (6.0–9.0)[c]
Lammi (47)	Finland	N/A	1992–1996	Not reported	M+F	20–24 (1)	16.1 (14.2–18.3)[c]
					M+F	25–29 (1)	16.2 (14.4–18.2)[c]
					M+F	30–34 (1)	15.2 (13.5–17.0)[c]
					M+F	35–39 (1)	10.1 (8.8–11.6)[c]
					M	20–24 (1)	19.9 (16.9–23.2)[c]
					M	25–29 (1)	20.9 (18.0–24.1)[c]
					M	30–34 (1)	19.8 (17.1–22.8)[c]
					M	35–39 (1)	12.6 (10.5–15.0)[c]
					F	20–24 (1)	12.2 (9.8–14.9)[c]
					F	25–29 (1)	11.3 (9.2–13.8)[c]
					F	30–34 (1)	10.3 (8.4–12.6)[c]
					F	35–39 (1)	7.5 (5.9–9.5)[c]
Arffman (18)	Finland	FinDM	2010–2017[T]*	Not reported	M+F	≥20 (4)	19 (18–20)[a]
					M+F	20–29 (1)	25 (21–29)[c]
					M+F	30–39 (1)	23 (20–27)[c]
					M+F	40–49 (2)	17 (14–20)[c]
					M+F	≥50 (3)	17 (15–18)
Gajewska (48)	Ireland	N/A	2011–2016	3.1 million (≥25 years)	M+F	25–34 (1)	29.9 (25.7–34.1)[c]
					M+F	35–44 (1)	31.2 (27.2–35.2)[c]
					M+F	45–54 (2)	24.0 (20.1–27.8)[c]
					M+F	55–64 (2)	29.9 (25.1–34.6)[c]
					M+F	65–74 (3)	41.2 (34.7–47.7)[c]
					M+F	≥75 (3)	51.2 (45.3–63.0)[c]
Tenconi (49)	Italy (Pavia)	N/A	1988–1992	71,974 (20–29 years)	M	20–24 (1)	7.9 (3.2–16.2)[c]
					M	25–29 (1)	8.3 (3.6–16.4)[c]
					F	20–24 (1)	4.8 (1.3–12.2)[c]
					F	25–29 (1)	8.8 (3.8–17.4)[c]
Muntoni (50)	Italy (Sardinia)	N/A	1989–1990	290,334 (20–29 years)	M+F	20–24 (1)	17.0 (12.4–21.6)[c]
					M+F	25–29 (1)	16.4 (11.6–21.3)[c]
					M	20–24 (1)	18.9 (12.2–25.7)[c]
					M	25–29 (1)	25.3 (16.8–33.9)[c]
					F	20–24 (1)	14.9 (8.8–21.0)[c]
					F	25–29 (1)	7.5 (2.8–12.1)[c]
Bruno (51)	Italy (Turin)	Turin type 1 diabetes registry	1984–2000	Not reported	M+F	20–24 (1)	6.6 (5.7–7.6)[c]
					M+F	25–29 (1)	5.5 (4.7–6.5)[c]
					M	20–24 (1)	7.9 (6.6–9.5)[c]
					M	25–29 (1)	6.6 (5.4–8.1)[c]
					F	20–24 (1)	5.3 (4.2–6.6)[c]
					F	25–29 (1)	4.4 (3.4–5.6)[c]
Ostrauskas (52)	Lithuania	N/A	1991–2008	798,367 (20–34 years)	M+F	20–24 (1)	7.1 (6.4–7.9)[c]
					M+F	25–29 (1)	8.9 (8.1–9.8)[c]
					M+F	30–34 (1)	9.9 (9.0–10.7)[c]
					M	20–24 (1)	8.7 (7.6–9.9)[c]
					M	25–29 (1)	11.9 (10.6–13.3)[c]

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Table 1—Continued

First author (reference no.)	Country (region)	Cohort name	Study year	Population at risk, *n* (age)	Sex	Age at onset, years (#)	Incidence (95% CI)
					M	30–34 (1)	13.7 (12.3–15.3)[c]
					F	20–24 (1)	5.5 (4.6–6.5)[c]
					F	25–29 (1)	5.6 (4.7–6.7)[c]
					F	30–34 (1)	5.9 (5.0–6.9)[c]
Joner (53)	Norway	N/A	1978–1982	613,293 (20–29 years)	M+F	20–24 (1)	14.5[c]
					M+F	25–29 (1)	18.8[c]
					M	20–24 (1)	15.7[c]
					M	25–29 (1)	21.1[c]
					F	20–24 (1)	13.2[c]
					F	25–29 (1)	16.4[c]
Olsson (25)	Norway	The HUNT Study 1 and 2	1995–2008	64,264	M+F	≥18 (4)	24.9[c]
Wysocki (19)	Poland (Warsaw)	N/A	1983–1988[T]	623,000 (0–29 years)	M	20–24 (1)	4.2 (1.1–10.2)[c]
					M	25–29 (1)	8.2 (3.5–15.8)[c]
					F	20–24 (1)	3.3 (0.6–8.8)[c]
					F	25–29 (1)	5.3 (1.6–11.7)[c]
Sobel-Maruniak (54)	Poland (Rzeszow)	N/A	1980–1999	167,012 (15–29)	M+F	15–29 (1)	5.8 (5.0–6.6)[a]
					M	15–29 (1)	6.8 (5.6–8.1)[a]
					F	15–29 (1)	4.7 (3.7–5.8)[a]
Ionescu-Tîrgovişte (55)	Romania (Bucharest)	Bucharest Diabetes Registry	1981–1991	1.7 million (20–84 years)	M+F	20–24 (1)	5.1
					M+F	25–29 (1)	7.9
					M+F	30–34 (1)	3.5
					M+F	35–39 (1)	4.4
					M+F	40–44 (2)	5.5
					M+F	45–49 (2)	8.0
					M+F	50–54 (2)	7.8
					M+F	55–59 (2)	7.1
					M+F	60–64 (2)	8.3
					M+F	65–69 (3)	10.1
					M+F	70–74 (3)	8.7
					M+F	75–79 (3)	8.4
					M+F	80–84 (3)	3.1
Dedov (56)	Russia	SRDP	2016	Not reported	M+F	Adults[d] (4)	4.9[c]
Scottish Diabetes Data Group (21)	Scotland	Scottish Diabetes Survey	2012–2019[T]*	4 million (≥20 years)	M+F	20–29 (1)	28.0[c]
					M+F	30–39 (1)	21.0[c]
					M+F	40–49 (2)	15.0[c]
					M+F	50–59 (2)	10.0[c]
					M+F	60–69 (3)	8.0[c]
					M+F	≥70 (3)	6.0[c]
Vojislav (9)	Serbia	Serbian Diabetes Registry	2006–2017[T]*	Not reported	M+F	20–24 (1)	7.5[a]
					M+F	25–29 (1)	6.9[a]
Kyvik (57)	Slovakia	EURODIAB TIGER	1996–1997	Not reported	M	20–24 (1)	5.9 (3.8–8.6)[c]
					M	25–29 (1)	5.0 (3.0–7.8)[c]
					F	20–24 (1)	3.3 (1.8–5.4)[c]
					F	25–29 (1)	1.9 (0.8–4.0)[c]
Goday (58)	Spain (Catalonia)	N/A	1987–1990	1.3 million (15–29 years)	M+F	20–24 (1)	11.3 (9.7–13.0)[c]
					M+F	25–29 (1)	8.5 (7.2–9.9)[c]
Forga (15)	Spain (Navarre)	N/A	2009–2016[T]*	508,601 (≥20 years)	M+F	20–29 (1)	17.3 (8.6–30.9)[c]
					M+F	30–44 (1)	5.5 (2.4–10.8)[c]
					M+F	≥45 (2)	2.7 (1.2–5.3)[c]
					M	20–29 (1)	21.6 (8.7–44.5)[c]
					M	30–45 (1)	5.4 (1.5–13.7)[c]
					M	≥45 (2)	3.5 (1.1–8.2)[c]
					F	20–29 (1)	12.8 (3.5–32.8)[c]
					F	30–45 (1)	5.6 (1.5–14.4)[c]
					F	≥45 (2)	1.9 (0.4–5.6)[c]
Morales-Pérez (59)	Spain (Badajoz)	N/A	1992–1996	107,980 (20–29 years)	M+F	20–24 (1)	10.7 (7.1–15.4)[c]
					M+F	25–29 (1)	5.9 (3.3–9.6)[c]
					M	20–24 (1)	13.0 (7.6–20.5)[c]
					M	25–29 (1)	6.6 (3.0–12.4)[c]
					F	20–24 (1)	8.3 (4.1–14.9)[c]
					F	25–29 (1)	5.2 (1.7–10.8)[c]

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Table 1—Continued

First author (reference no.)	Country (region)	Cohort name	Study year	Population at risk, *n* (age)	Sex	Age at onset, years (#)	Incidence (95% CI)
Crump (60)	Sweden	N/A	1973–2015	4.2 million (all ages)	M+F	18–43 (1)	21.9[c]
					M	18–43 (1)	25.6[c]
					F	18–43 (1)	18.1[c]
Dahlquist (10)	Sweden	DISS	1983–2007[T]*	Not reported	M	20–24 (1)	17.4[c]
					M	25–29 (1)	14.6[c]
					M	30–34 (1)	10.6[c]
					F	20–24 (1)	11.3[c]
					F	25–29 (1)	8.6[c]
					F	30–34 (1)	6.3[c]
Thunander (23)	Sweden (Kronoberg)	N/A	1998–2001	138,000 (≥18 years)	M+F	20–29 (1)	19.7 (18.0–21.7)[c]
					M+F	30–39 (1)	11.7 (10.4–13.2)[c]
					M+F	40–49 (2)	20.0 (18.2–21.9)[c]
					M+F	50–59 (2)	36.1 (33.8–38.6)[c]
					M+F	60–69 (3)	35.3 (32.5–38.1)[c]
					M+F	70–79 (3)	55.0 (51.1–58.7)[c]
					M+F	80–100 (3)	27.3 (24.6–30.7)[c]
					M	20–29 (1)	26.2 (23.3–29.2)[c]
					M	30–39 (1)	16.9 (14.7–19.4)[c]
					M	40–49 (2)	16.9 (14.7–19.4)[c]
					M	50–59 (2)	46.0 (42.3–49.8)[c]
					M	60–69 (3)	32.1 (28.4–36.0)[c]
					M	70–79 (3)	38.3 (33.9–43.0)[c]
					M	80–100 (3)	27.0 (22.0–32.8)[c]
					F	20–29 (1)	12.7 (10.7–15.0)[c]
					F	30–39 (1)	6.1 (4.8–7.7)[c]
					F	40–49 (2)	23.2 (20.5–26.0)[c]
					F	50–59 (2)	25.7 (22.9–28.8)[c]
					F	60–69 (3)	38.3 (34.4–42.5)[c]
					F	70–79 (3)	65.1 (55.9–66.4)[c]
					F	80–100 (3)	27.4 (23.4–31.8)[c]
Rawshani (20)	Sweden	DISS, PDR, and NDR	2007–2009[T]*	Not reported	M+F	20–24 (1)	31.2 (26.7–35.7)[c]
					M+F	25–29 (1)	30.4 (25.8–34.9)[c]
					M+F	30–34 (1)	30.2 (25.7–34.7)[c]
Abbasi (16)	U.K.	CPRD	1994–2013[T]*	369,362 (2–25 years)	M+F	16–25 (1)	17.8 (13.8–22.6)[a]
Thomas (22)	U.K.	UK Biobank	2006–2010	379,511 (37–73 years)	M+F	31–60 (2)	28.3[c]
Feltbower (61)	U.K. (West Yorkshire)	Yorkshire Regional Childhood Diabetes Register	1991–1999	2.1 million (all ages)	M+F	15–29 (1)	3.4[c]
Western Pacific							
Diabetes Australia (62)	Australia	NDSS[b]	2020	18.8 million (≥21 years)	M+F	21–29 (1)	17.7[c]
					M+F	30–39 (1)	15.1[c]
					M+F	40–49 (2)	10.1[c]
					M+F	50–59 (2)	9.8[c]
					M+F	60–69 (3)	7.2[c]
					M+F	70–79 (3)	7.5[c]
					M+F	≥80 (3)	4.0[c]
Weng (63)	China	N/A	2010–2013	133 million PY (≥20 years)	M+F	≥30 (4)	0.51 (0.49–0.53)[c]
					M+F	20–24 (1)	1.11 (1.03–1.19)[c]
					M+F	25–29 (1)	1.19 (1.11–1.29)[c]
					M+F	30–34 (1)	1.02 (0.94–1.12)[c]
					M+F	35–39 (1)	0.73 (0.66–0.81)[c]
					M+F	40–44 (2)	0.54 (0.48–0.61)[c]
					M+F	45–49 (2)	0.54 (0.47–0.61)[c]
					M+F	50–54 (2)	0.60 (0.52–0.69)[c]
					M+F	55–59 (2)	0.54 (0.47–0.62)[c]
					M+F	60–64 (3)	0.44 (0.36–0.53)[c]
					M+F	65–69 (3)	0.38 (0.29–0.49)[c]
					M+F	70–74 (3)	0.32 (0.23–0.43)[c]
					M+F	≥75 (3)	0.37 (0.27–0.51)[c]

Continued on p. 1001

Table 1—Continued

First author (reference no.)	Country (region)	Cohort name	Study year	Population at risk, *n* (age)	Sex	Age at onset, years (#)	Incidence (95% CI)
Luk (17)	Hong Kong	HKDSD	2002–2015[T]*	7.3 million (all ages)	M	20–39 (1)	0.53[c]
					M	40–59 (2)	0.59[c]
					M	≥60 (3)	0.39[c]
					F	20–39 (1)	0.84[c]
					F	40–59 (2)	0.33[c]
					F	≥60 (3)	0.23[c]
Nishioka (64)	Japan	NDB	2014–2017	65.3 million (≥20 years)	M	20–39 (1)	5.6 (5.2–5.9)[c]
					M	40–59 (2)	5.7 (5.4–6.0)[c]
					M	≥60 (3)	3.5 (3.3–3.7)[c]
					F	20–39 (1)	4.8 (4.6–5.1)[c]
					F	40–59 (2)	5.0 (4.8–5.2)[c]
					F	≥60 (3)	3.3 (3.1–3.5)[c]
Lee (11)	Korea	NHIS	2007–2013[T]*	51.3 million (all ages)	M+F	≥20 (4)	3.0[c]
Scott (65)	New Zealand (Canterbury)	Canterbury Diabetes Registry	1981–1986	345,768 (all ages)	M+F	20–29 (1)	8.1 (5.4–11.7)[c]
					M+F	30–39 (1)	10.6 (7.3–14.9)[c]
					M+F	40–49 (2)	11.8 (7.8–17.2)[c]
					M+F	50–59 (2)	13.1 (8.6–19.3)[c]
					M+F	60–69 (3)	18.6 (12.9–26.0)[c]
					M+F	≥70 (3)	21.7 (15.2–30.0)[c]
					M	20–29 (1)	11.1 (6.8–17.1)[c]
					M	30–39 (1)	11.7 (6.9–18.5)[c]
					M	40–49 (2)	16.7 (10.1–26.1)[c]
					M	50–59 (2)	17.0 (9.9–27.2)[c]
					M	60–69 (3)	25.9 (15.2–39.1)[c]
					M	≥70 (3)	25.3 (14.5–41.0)[c]
					F	20–29 (1)	5.1 (2.3–9.7)[c]
					F	30–39 (1)	9.5 (5.3–15.7)[c]
					F	40–49 (2)	7.0 (3.0–13.8)[c]
					F	50–59 (2)	9.1 (4.2–17.3)[c]
					F	60–69 (3)	12.3 (6.4–21.5)[c]
					F	≥70 (3)	19.5 (11.9–30.0)[c]
Sheen (12)	Taiwan	NHIRD	2005–2014[T]*	Not reported	M+F	20–39 (1)	1.4[c]
					M+F	≥40 (2)	0.5
All other regions							
Gorham (66)	U.S.	U.S. Navy[e]	1974–1988	1.6 million (17–34 years)	M (W)	20–24 (1)	18.0 (16.3–20.0)[c]
					M (W)	25–29 (1)	24.1 (20.9–27.7)[c]
					M (W)	30–34 (1)	32.4 (28.0–37.6)[c]
					F (W)	20–24 (1)	26.2 (19.5–34.6)[c]
					F (W)	25–29 (1)	29.8 (19.1–44.4)[c]
					F (W)	30–34 (1)	33.2 (15.9–61.1)[c]
					M (B)	20–24 (1)	17.1 (12.7–22.6)[c]
					M (B)	25–29 (1)	39.4 (30.3–51.2)[c]
					M (B)	30–34 (1)	88.1 (67.9–114.0)[c]
					F (B)	20–24 (1)	25.9 (12.9–46.4)[c]
					F (B)	25–29 (1)	15.9 (3.3–46.3)[c]
					F (B)	30–34 (1)	92.9 (34.1–202.0)[c]
Rogers (13)	U.S.	Clinformatics Data Mart database[e]	2001–2015[T]	61 million (all ages)	M+F	20–24 (1)	18.0 (17.2–18.9)[c]
					M+F	25–29 (1)	16.6 (15.8–17.3)[c]
					M+F	30–34 (1)	15.3 (14.6–16.0)[c]
					M+F	35–39 (1)	15.9 (15.2–16.6)[c]
					M+F	40–44 (2)	16.0 (15.3–16.7)[c]
					M+F	45–49 (2)	17.8 (17.1–18.5)[c]
					M+F	50–54 (2)	20.0 (19.2–20.8)[c]
					M+F	55–59 (2)	23.4 (22.5–24.3)[c]
					M+F	60–64 (3)	29.2 (28.0–30.4)[c]
Lawrence (24)	U.S. (California)	Kaiser Permanente[e]	2017	2.4 million (20–45 years)	M+F	20–45 (1)	30.1 (23.5–36.8)[a]
					M+F	20–29 (1)	15.2 (10.2–20.1)[c]
					M+F	30–45 (1)	38.2 (28.6–47.8)[c]
					M	20–45 (1)	32.5 (22.2–42.8)[a]
					F	20–45 (1)	27.2 (21.0–34.5)[a]

Continued on p. 1002

Table 1—Continued

First author (reference no.)	Country (region)	Cohort name	Study year	Population at risk, *n* (age)	Sex	Age at onset, years (#)	Incidence (95% CI)
Mebrahtu (67)	Eritrea	N/A	2019	316,118 (20–24)	M+F	20–24 (1)	46.2 (39.0–53.3)[c]
					M	20–24 (1)	55.0 (44.1–68.0)[c]
					F	20–24 (1)	37.2 (28.2–48.0)[c]
Alemu (68)	Ethiopia	N/A	1995–2008	2.5 million (all ages)	M	21–25	7.2[c]
					M	26–30	8.9[c]
					M	31–35	6.6[c]
					M	36–40	3.9[c]
					M	41–50	2.8[c]
					M	46–60	1.8[c]
					M	61–70	0.5[c]
					M	71–80	1.3[c]
					F	21–25	2.4[c]
					F	26–30	3.1[c]
					F	31–35	2.9[c]
					F	36–40	2.3[c]
					F	41–50	2.4[c]
					F	46–60	1.2[c]
					F	61–70	1.6[c]
					F	71–80	0.7[c]
Sandy (14)	Mali	N/A	2007–2016[T]*	12.1 million (<25 years)	M+F	20–24 (1)	1.1 (0.6–1.8)[c]
					M+F	20–24 (1)	0.7 (0.5–0.9)[c]
Marshall (69)	Rwanda	LFAC program registry	2007–2011	Not reported	M+F	20–24 (1)	5.0 (2.8–8.6)[c]
Pishdad (70)	Iran (Fars)	N/A	1991–1996	587,000 (20–29 years)	M	20–24 (1)	3.3 (2.0–4.6)[c]
					M	25–29 (1)	3.1 (1.8–4.4)[c]
					F	20–24 (1)	3.4 (2.1–4.7)[c]
					F	25–29 (1)	3.6 (2.1–5.0)[c]
Kadiki (71)	Libya (Benghazi)	N/A	1981–1990	9,635 (20–34 years)	M+F	20–24 (1)	7.0 (4.7–10.2)[c]
					M+F	25–29 (1)	10.4 (7.0–14.8)[c]
					M+F	30–34 (1)	12.4 (8.4–17.7)[c]
					M	20–24 (1)	10.9 (6.8–16.5)[c]
					M	25–29 (1)	11.4 (6.8–18.0)[c]
					M	30–34 (1)	16.7 (10.3–25.6)[c]
					F	20–24 (1)	2.9 (1.1–6.3)[c]
					F	25–29 (1)	9.4 (5.1–15.8)[c]
					F	30–34 (1)	7.7 (3.5–14.6)[c]
Kumar (72)	India	Military personnel[e]	1990–2015	51,217 (≥18 years)	M	≥18 (4)	2.4[c]

B, Black adults; CPRD, Clinical Practice Research Datalink; EURODIAB TIGER, EUROpe and DIABetes Type I Genetic Epidemiology Resource; F, females; HKDSD, The Hong Kong Diabetes Surveillance Database; LFAC, Life For a Child; M, males; N/A, not applicable; NDB, National Database of Health Insurance Claims and Specific Health Checkups of Japan; NDSS, National Diabetes Service Scheme; NHIRD, National Health Insurance Research Database; NHIS, National Health Insurance Service; SRDP, State Registry of DM Patients; W, White adults. [T]Time trends available. *Most recent year/period reported. #Assigned categories for age-specific analysis (1, 20–40 years; 2, 40–60 years; 3, >60 years; 4, ≥20 years). [a]Age-standardized rates. [b]For estimation of Australian rates, the number of new cases of T1D, reported by the National Diabetes Service Scheme, was divided by the 2019 Australian estimated resident population, obtained from the Australian Bureau of Statistics. [c]Crude rates. [d]Age range not defined. [e]Insurance- or occupation-based population.

T1D, particularly from low- and middle-income countries, despite our attempts to include data from the gray literature, limiting our ability to make a truly global assessment on the burden of adult-onset T1D. Second, adult-onset T1D generally reflects patterns seen in childhood-onset T1D in that incidence is higher in men (vs. women) and rates are highest in Nordic populations and lowest in Asian populations. Third, though more data are needed, we found no clear relationship between adult-onset T1D incidence and age, with 42% of studies showing an increase in T1D incidence with increasing age, while the remaining 58% of studies showed a decline in T1D incidence with increasing age. Regardless, we found that the incidence of T1D onset in older adults remained substantial. Fourth, there are no clear trends in adult-onset T1D over time due to a paucity of data. Among 13 studies reporting on trends over time, 46% (*n* = 6), 15% (*n* = 2), and 38% (*n* = 5) reported decreasing, increasing, and stable trends, respectively, over varying time periods between 1983 and 2019. Although various organizations such as the World Health Organization and the American Diabetes Association have provided consensus-based guidelines for the diagnosis and classification of diabetes since 1979 (26), we found varying approaches to defining adult-onset T1D with as yet no internationally adopted consensus. Given that the findings of this Systematic Review highlight a substantial burden of adult-onset T1D, there is a pressing need to define, test, and compare diagnostic criteria in multiple high-quality studies to better distinguish T1D from T2D in adults so that we

may better assess the true burden of T1D in adults.

This is an updated and comprehensive overview of the current knowledge on adult-onset T1D, an area with significant knowledge gaps and seemingly slowly advancing knowledge. In comparison with an earlier systematic review of T1D in young adults >15 years (6), we included fewer studies, given our focus on reporting estimates from population-based studies only and our stricter age criteria (≥20 years). The earlier systematic review by Diaz-Valencia et al. (6) included several data sources that were not population based. Hospital-based or other clinic-based cohorts are more likely to represent severe cases of T1D, a form of selection bias that might lead to underestimates of T1D incidence, hence the alternative approach we have undertaken. Nevertheless, we believe the incidence rates of adult-onset T1D are still likely to be in general underestimates, given the likelihood of missed cases among those presenting with diabetes in adulthood (5).

Similar to findings by Diaz-Valencia et al. (6), patterns of adult-onset T1D generally mirror those of childhood-onset T1D, whereby countries and regions with high incidence of adult-onset T1D are also the areas with high incidence of childhood T1D incidence. This suggests that similar patterns of underlying genetic predisposition and environmental exposures, or the interaction between genes and environment, may operate in increased risk of T1D, regardless of age (27). Similar to Diaz-Valencia et al., we also noted that incidence of adult-onset T1D is in general higher among men as compared with women. As an extension to the study by Diaz-Valencia, we searched the gray literature to identify data on adult-onset T1D that may appear in national diabetes registries, or national health surveys, but not in the published literature. From our search of data from 54 countries, we were able to add information from three countries (Australia, Scotland, and Finland) using this approach. To truly capture the burden of adult-onset T1D, existing diabetes registries, and national health surveys, need to incorporate metrics of adult-onset T1D, and not just childhood-onset T1D, and to make this data publicly available.

In comparison with the analysis of adult-onset T1D in the current study, the results of most studies in children and adolescents suggest a global increase in the incidence of T1D, at a rate of approximately 3–4% per year over past decades, with the increase in general steeper in low-incidence countries (1,27–29). Several studies posit that the increases in childhood-onset T1D may be due to changes in dietary patterns,

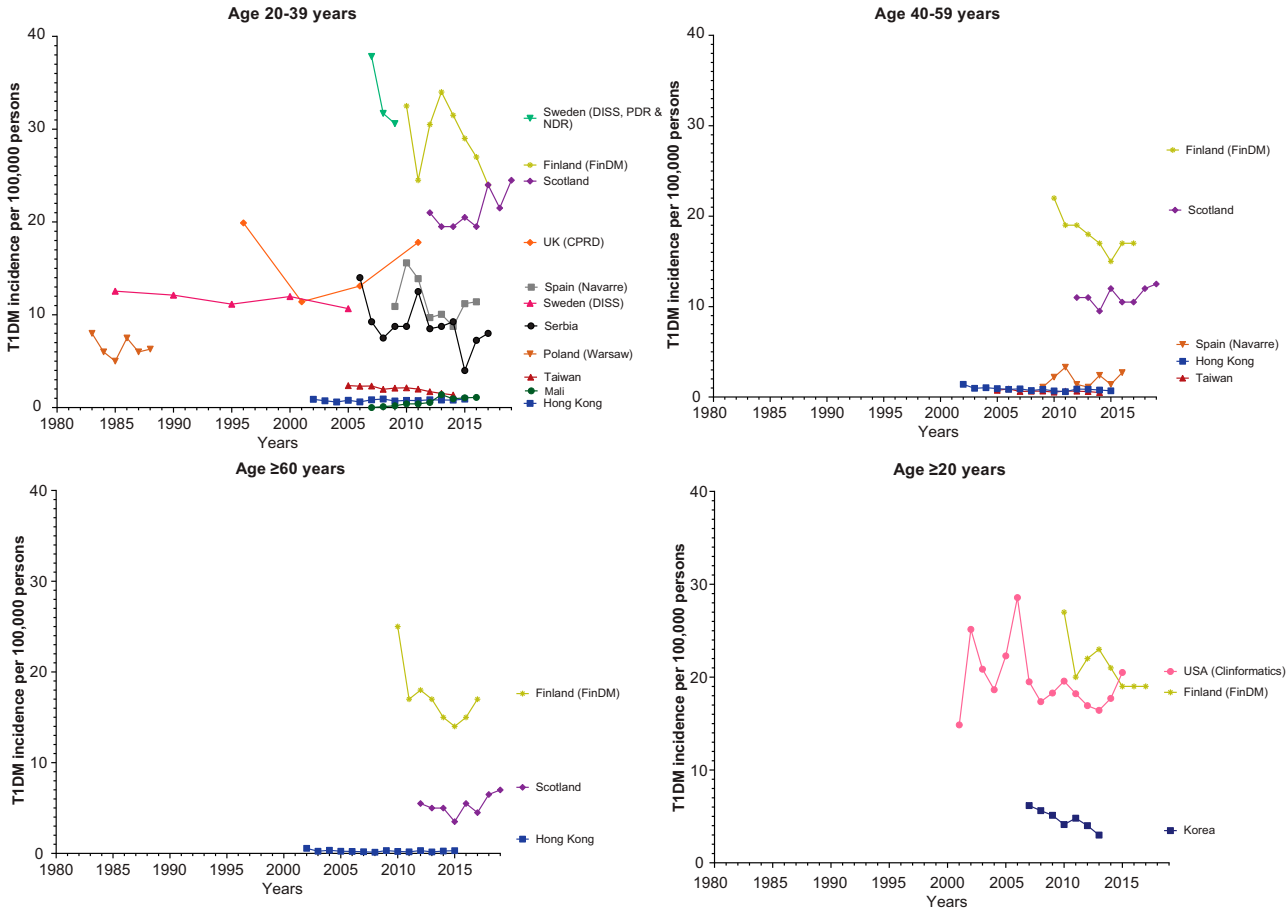

Figure 3—Trends in the incidence of adult-onset T1D by age-group and country/region. Note: U.S. trend data are based on an insurance population. As such, it cannot be determined whether declines in adult-onset T1D are true changes over time or due to changes in the underlying study population. Clinformatics, Clinformatics Data Mart database.

and other environmental factors associated with T1D such as increases in maternal age, obesity, and low vitamin D (27). Whether the incidence of adult-onset T1D is also increasing remains unclear due to a limited number of studies including reports on trends over time. Among these, mixed findings are likely a result of differences in T1D classification as well as different calendar periods. This is coupled with issues relating to missed diagnosis of autoimmune diabetes among those presenting with adult-onset diabetes, and comparatively high and changing background incidence of T2D, which may render any potential increase in adult-onset T1D difficult to detect.

Data from the available studies suggest that T1D incidence in adults does not decline with increasing age. In a U.S. study with use of electronic health records, T1D incidence peaked at age 10–14 years and a stable and gradual increase in T1D incidence was observed throughout adulthood (13). This differs from the common school of thought that T1D is a disease with onset in childhood or adolescence. Results of a recent UK Biobank study with incorporation of genetic markers suggest that the incidence of genetically defined T1D remains stable through different age-groups up to the oldest age-group (51–60 years) studied within the UK Biobank, although T1D cases represent a much smaller proportion of total diabetes cases in the older age-groups, as the number of incident T2D cases increase with age (22). In this same study, patients with genetically identified T1D had clinical features distinct from those with T2D such as being more likely to use insulin within the first year of diagnosis (22).

In most of the studies included in this Systematic Review, physician diagnosis of T1D was used, and some misclassification is likely present. In sub-Saharan African populations where severe undernutrition is prevalent, T1D identified by an administrative algorithm is strongly associated with poverty or markers of undernutrition (30), with a strong male predominance (30). Whether T1D identified in this setting results from β-cell loss due to autoimmunity or other mechanisms remains a topic of inquiry (31). Given the much higher prevalence of T2D in adults, a significant proportion of cases of T1D are likely to be missed and managed as T2D (32–34). Indeed, >40% of those developing T1D after age 30 years are initially treated as having T2D (5,35,36), highlighting the need for assessment of autoimmunity or β-cell function in the evaluation of adult-onset diabetes. In the current Systematic Review, only 15% of included studies had biomarkers incorporated for the diagnosis of T1D, though it should be noted that biomarkers other than blood glucose are often not available, particularly for studies conducted in the 1970–1990s. This is similar to findings from an earlier systematic review, in which only 14 of 70 studies (20%) included measurements of autoantibodies or C-peptide in the assessment of T1D, with most studies relying on clinical symptoms or early initiation of insulin therapy to diagnose T1D (6). Though autoantibody testing among all people with adult-onset diabetes may aid identification of T1D, it is important to remember that in a setting of high prior odds of T2D, and known background population autoantibody positivity, this could also lead to overestimation of T1D in adults. Therefore, combining clinical features that increase odds of T1D, prior to autoantibody measurement, or a combined diagnostic model including clinical features such as low BMI may in the future be the most accurate way to identify and classify individuals with adult-onset T1D (37–39). Indeed, in a 2021 joint consensus statement (published after our Systematic Review was conducted) (40), the American Diabetes Association and the European Association for the Study of Diabetes recommend the use of islet antibodies, in conjunction with clinical features and a C-peptide test (particularly after >3 years' diabetes duration [41]), to distinguish T1D from T2D in adults with suspected T1D.

Our work has highlighted the paucity of data on adult-onset T1D. Given the nature of the disease and the difficulty in establishing an accurate diagnosis, national registries provide an invaluable source of data to chart the burden of adult-onset T1D. National diabetes registries provide population-based data that can offer insights into diagnosis, complications, treatment, and burden of diabetes (42). In this analysis, we have included data from several national registries that provided estimates of incidence of adult-onset T1D. Nevertheless, identifying relevant national registries and extracting the relevant information are not necessarily straightforward. Further, some registries are restricted to childhood-onset T1D only and do not capture data on adult-onset T1D. Development of a globally implemented standard for the implementation and maintenance of national diabetes registries is needed to assess the true burden of adult-onset T1D and to determine where resources and interventions are most needed.

This is a comprehensive Systematic Review of adult-onset T1D with incorporation of both a traditional literature search (e.g., MEDLINE) and an extensive assessment of the available gray literature. There are, however, some limitations. First, with our MEDLINE and Embase search strategies we considered only MeSH terms (not text words) and thus may have missed some studies that had not been indexed accordingly; however, by virtue of searching the reference lists of *1*) included studies and *2*) previous reviews on T1D incidence (6,43), we believe the likelihood that we have missed any relevant studies is low. Second, as discussed above, misclassification of diabetes type cannot be ruled out. Third, given the paucity of data particularly in low- and middle-income countries, our results are generalizable mainly to high-income countries. Last, our data are limited in terms of the time period covered by some data sources.

Conclusion

The findings of this Systematic Review demonstrate a substantial burden of adult-onset T1D incidence and a pressing need to improve the quality and quantity of information on adult-onset T1D, particularly in low- and middle-income countries, through well-designed and maintained diabetes registries with biomarker data. Such data are essential to better understanding of the epidemiology and natural history of adult-onset T1D and, more importantly, ensuring the planning and provision of appropriate clinical care.

Acknowledgments. This work was initiated by the IDF as an extension of the 10th edition of the IDF Diabetes Atlas.

Funding. R.C.W.M. acknowledge support from the Research Grants Council Research Impact Fund (R4012-18) and a Croucher Foundation Senior Medical Research Fellowship. R.A.O. acknowledges support from a Diabetes UK Harry Keen Fellowship (16/0005529). P.L.W.

acknowledges support from VA Puget Sound. A.J.J. acknowledges support from an Australian National Health and Medical Research Council (NHMRC) Practitioner Fellowship. A.J.J. has received research grants from JDRF and the NHMRC.

Duality of Interest. R.A.O. has received consulting fees from Janssen Research & Development (R&D), and funding from Janssen R&D as a co-investigator on the CASCADE Study (Combined Antibody Screening for Celiac and Diabetes Evaluation). R.A.O. has received U.K. Medical Research Council funding to develop a T1D genetic risk score diagnostic test in collaboration with Randox Laboratories R&D. A.J.J. has served on advisory boards for Medtronic Australia, Abbott Diabetes Australia, and Sanofi, has received research grants from Abbott Europe, Mylan, and Sanofi and has received speaker honorarium from Amgen. R.C.W.M. has received research grants for clinical trials from AstraZeneca, Bayer, Merck Sharp & Dohme (MSD), Novo Nordisk, Sanofi, and Tricida, Inc., and honoraria for consultancy or lectures from AstraZeneca and Boehringer Ingelheim. All proceeds were donated to The Chinese University of Hong Kong to support diabetes research. The 10th edition of the IDF Diabetes Atlas was supported by an educational grant from the Pfizer-MSD alliance, with additional support from Sanofi and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.L.H. contributed to study design, conducted the literature search, screened eligible studies, extracted and summarized data, and wrote the manuscript. P.L.W. and X.Z. contributed to study design, screened eligible studies, conducted the quality review, and reviewed and edited the final manuscript. S.K., D.J.M., and A.J.J. contributed to the grey literature search and reviewed and edited the final manuscript. X.L. contributed to screening and reviewed and edited the final manuscript. S.K., H.C., H.S. Y.X., R.A.O., and Z.Z. provided intellectual input and reviewed and edited the final manuscript. R.C.W.M. oversaw the project, contributed to study design, screened eligible studies, and reviewed and edited the final manuscript.

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