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REVIEW

Global trends in diabetes complications: a review of current evidence

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Abstract

In recent decades, large increases in diabetes prevalence have been demonstrated in virtually all regions of the world. The increase in the number of people with diabetes or with a longer duration of diabetes is likely to alter the disease profile in many populations around the globe, particularly due to a higher incidence of diabetes-specific complications, such as kidney failure and peripheral arterial disease. The epidemiology of other conditions frequently associated with diabetes, including infections and cardiovascular disease, may also change, with direct effects on quality of life, demands on health services and economic costs. The current understanding of the international burden of and variation in diabetes-related complications is poor. The available data suggest that rates of myocardial infarction, stroke and amputation are decreasing among people with diabetes, in parallel with declining mortality. However, these data predominantly come from studies in only a few high-income countries. Trends in other complications of diabetes, such as end-stage renal disease, retinopathy and cancer, are less well explored. In this review, we synthesise data from population-based studies on trends in diabetes complications, with the objectives of: (1) characterising recent and long-term trends in diabetes-related complications; (2) describing regional variation in the excess risk of complications, where possible; and (3) identifying and prioritising gaps for future surveillance and study.

Keywords Complications (all) · Epidemiology · Review · Trends

Abbreviations

AMI	Acute myocardial infarction
ASMR	Age-standardised mortality rates
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
ESRD	End-stage renal disease
HHS	Hyperglycaemic hyperosmolar state
IADL	Instrumental activities of daily living
LEA	Lower-extremity amputation
USDSS	United States Diabetes Surveillance System

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Background

In recent decades, large increases in diabetes prevalence have been demonstrated in virtually all regions of the world, with 415 million people worldwide now living with diabetes [1]. This is most concerning because an increase in diabetes prevalence will increase the number of chronic and acute diseases in the general population, with profound effects on quality of life, demand on health services and economic costs. Macrovascular complications of diabetes, including coronary heart disease, stroke and peripheral vascular disease, and microvascular complications, such as end-stage renal disease (ESRD), retinopathy and neuropathy, along with lower-extremity amputations (LEA), are responsible for much of the burden associated with diabetes. There is also growing recognition of a diversifying set of causally-linked conditions, including cancers, ageing-related outcomes (e.g. dementia), infections and liver disease. Since current data suggests that rates of all-cause and cardiovascular disease (CVD) mortality are decreasing in individuals with

diabetes [2], trends in other complications of diabetes may become proportionately more prominent in the future.

Despite widespread international assessment of the growth of diabetes prevalence, quantification of the international burden and variation in the incidence of diabetes-related complications is notably lacking. This stems largely from the fact that data systems and population-based studies assessing diabetes complications are concentrated in Europe, North America and other high-income countries, with little to no availability in low- and middle-income countries, where the absolute increase in diabetes prevalence is largest. The lack of both uniform diagnosis of diabetes and of standardised measurement of diabetes-related complications has caused additional barriers in comparing trends worldwide. In this review, we synthesise data from adult population-based studies on trends in diabetes complications based on original articles, review articles and meta-analyses, with the objectives of: (1) characterising recent and long-term trends in diabetes-related complications; (2) describing regional variation in the excess risk of complications, where possible; and (3) identifying and prioritising gaps for future surveillance and study.

To this end, we conducted an extensive review of the literature in order to identify the majority of relevant publications. However, we did not adopt the formalities of a systematic literature review. Relevant publications were identified through a PubMed and Medline search using the following medical subject heading (MesH) terms: Diabetes Mellitus AND Diabetes Complications OR Mortality; End-Stage Renal Disease; Hyperglycaemia; Amputations; Cardiovascular Disease; Retinopathy; Nephropathy; Infections; Cancer; Dementia AND Epidemiology AND Trend. We also handsearched reference lists of identified publications to determine additional eligible articles. The search was limited to papers in the English language. Throughout this Review, unless otherwise stated, data are reported among populations of people with diabetes, not general populations. All studies included were population-based, not clinic-based. Where more than one study per country (per outcome) existed, we chose the study reporting the most recent trends.

Macrovascular complications

CVD CVD is a major cause of death and disability among people with diabetes. As the number of people with diabetes is predicted to increase, it is expected that the number of people with CVD will also increase [2]. However, data from several studies suggest that risk of CVD in people with diabetes has been declining since the 1990s (Table 1). Despite these improvements, people with diabetes continue to have a two- to fourfold higher risk of hospitalisation for major CVD events and CVD-associated clinical procedures compared with those without diabetes [2].

CVD mortality Among the general population, mortality rates owing to CVD have declined in most high-income countries [12]. However, worldwide, CVD remains a leading cause of death in both people with and without diabetes [2, 13], and individuals with diabetes still have a two- to fourfold increased rate of CVD mortality compared with those without [14]. Data from several studies suggest a decline in CVD-associated mortality among people with diabetes.

In the USA, a 53% relative decline in CVD mortality was observed between 1988 and 1994, and 2010 and 2015, as well as a reduction in the excess risk between populations with and without diabetes [15]. In Australia, a 50% decline in CVD-mortality rates was observed between 2000 and 2011 [16] and, in Iceland, a 46% decline was observed between 1993 and 2004 [17]. In Canada, in-hospital mortality for acute myocardial infarction (AMI) and stroke fell by 44.1% and 17.1%, respectively, between 1992 and 1999, but individuals with diabetes were still 1.6 times more likely to die from these events than those without diabetes [3]. Similar declines for CVD mortality in individuals with type 1 diabetes have also been shown in Australia [16] and Switzerland [18].

Microvascular complications

LEAs LEAs are a major complication for adults with diabetes because of their physical, economical and psychosocial burden. Since several aetiological pathways are associated with conditions leading to LEAs, LEAs are also an important indicator of the success of preventive care, such as that targeting glycaemic control, CVD risk factor management, and screening and treatment of people at high risk of foot complications. Population-based studies indicate that, in general, there have been reductions in the rates of LEAs between 1982 and 2011 (by ~3% to 85%) across diverse populations [9, 19–23] (Fig. 1 and Table 2). Only two studies have specifically examined trends among people with type 1 diabetes; significant declines were observed in Spain [24] and non-significant declines were seen in Australia [21].

Among the 13 countries and major regions of countries with available data, the decline in total LEA incidence appears to be driven by declines in major LEAs (Fig. 2a, Table 2). Smaller relative declines have been reported for minor LEAs, with some countries even reporting increases (Fig. 2b, Table 2). This suggests that there may be a relative increase in the number of minor LEAs being performed in the clinical setting to prevent major LEAs. There also remain important disparities in rates of LEA between subgroups within populations. For example, in the USA, decreases in LEA rates are mainly attributable to greater reductions in LEAs in the elderly, with reductions in rates in young and middle-age people being modest [22]. In addition, the number of LEAs remain higher in non-whites and the male population in the USA [25], and large geographical differences exist [26].

Table 1 Trends in CVD incidence among people with diabetes

Country	Study years	Outcome assessed	Baseline rate[a]	End rate[a]	Relative change (%)[b]	CVD definition
Canada [3]	1992–1999	AMI (length of hospital stay of ≥3 days)	659	554	−16	ICD-9 410.x
		Stroke	420	319	−24	ICD-9 431, 434, 436
USA[c] [4]	1998–2014	ACS	1920	940	−51	ICD-9 410–411
		Cardiac dysrhythmia	740	670	−9	ICD-9 427
		Heart failure	2590	1450	−44	ICD-9 428
		Haemorrhagic stroke	140	110	−21	ICD-9 430–432
		Ischaemic stroke	1060	660	−38	ICD-9 433.x1, 434, 436
Korea [5]	2006–2013	AMI	871	546	−37	ICD-10 I21–I23
		Ischaemic stroke	1889	1191	−37	ICD-10 I63, I64, I693, I694, G45
		Haemorrhagic stroke	664	464	−30	ICD-10 I60, I61, I62, I690, I691, I692
		PCI	695	669	−4	Procedure codes M6551–2, M6561–4, M6571–2
		CABG	82	56	−32	Procedure codes O1641-2, O6147, OA641-2, OA647
Spain[d] [6]	2004–2010	AMI	71	61.9	−13	ICD9 410.0–419.0
Spain[d,e] [7]	2003–2012	AAA	50	78	+56	ICD-9-CM 441.3, 441.4, 441.5
Spain[d] [8]	2003–2012	Ischaemic stroke (primary diagnosis)	492	589	−20	ICD-9-CM 434.01, 434.11, 434.91
Sweden [9]	1996–2003	AMI (women)	1350	850	−37	ICD9 410; ICD-10 I21, I22
		Stroke (women)	2050	900	−56	ICD9 431, 434, 436; ICD-10 I61, I63, I74
		AMI (men)	1650	1130	−32	ICD9 410; ICD-10 I21, I22
		Stroke (men)	1970	860	−56	ICD9 431, 434, 436; ICD-10 I61, I63, I74
UK [10]	2004–2009	Angina (principal or primary diagnosis)	930	701	−25	ICD-10 I20
		AMI (principal or primary diagnosis)	755	574	−24	ICD10 I21, I22
		Stroke (principal or primary diagnosis)	599	579	−3	ICD10 I60–I64
		PCI	436	505	+16	Procedure codes OPCS4 K49, K50, K75
		CABG	266	212	−20	Procedure codes OPCS4 K40–K46
USA[f] [11]	1992–2012	CHF and/or AMI	11,600	8900	−23	ICD-9 428.xx, 398.91, 402.01, 402.11, 402.91, 404.11, 404.91, 410xx, 410.xx
		Stroke	2900	1400	−52	ICD-9 431.xx, 434.01, 436.xx, 997.02, 434.01, 434.11, 434.91

Data are from population-based studies. All data are age-adjusted

CVD events were defined using ICD-9 (www.icd9data.com/2007/Volume1), ICD-9-CM (www.cdc.gov/nchs/icd/icd9cm.htm) and ICD-10 (http://apps.who.int/classifications/icd10/browse/2016/en) codes or procedure codes

[a] Rates are expressed per 100,000 people with diabetes

[b] Relative change (%) = [(baseline rate − end rate)/baseline rate] × 100

[c] Included individuals ≥35 years old

[d] Included individuals with type 2 diabetes only

[e] Included individuals ≥50 years old

[f] Included individuals ≥65 years old

AAA, abdominal aortic aneurysm; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHF, congestive heart failure; OPCS, operating procedure code supplement; PCI, percutaneous coronary intervention

ESRD Worldwide, it is estimated that 80% of ESRD cases are caused by diabetes or hypertension [28]. Between 2002 and 2015, steep increases (approximately 40–700%) in the incidence of diabetes-associated ESRD were reported for Russia, the Philippines, Malaysia, the Republic of Korea, the Jalisco region of Mexico and Singapore, as well as Australia, Taiwan, Bosnia and Herzegovina and Scotland. In the USA, the increase was 11% for the same period [28] (Fig. 3). By contrast, diabetes-associated ESRD incidence declined over the same period in Austria (by 26%), Belgium (16%), Finland (11%),

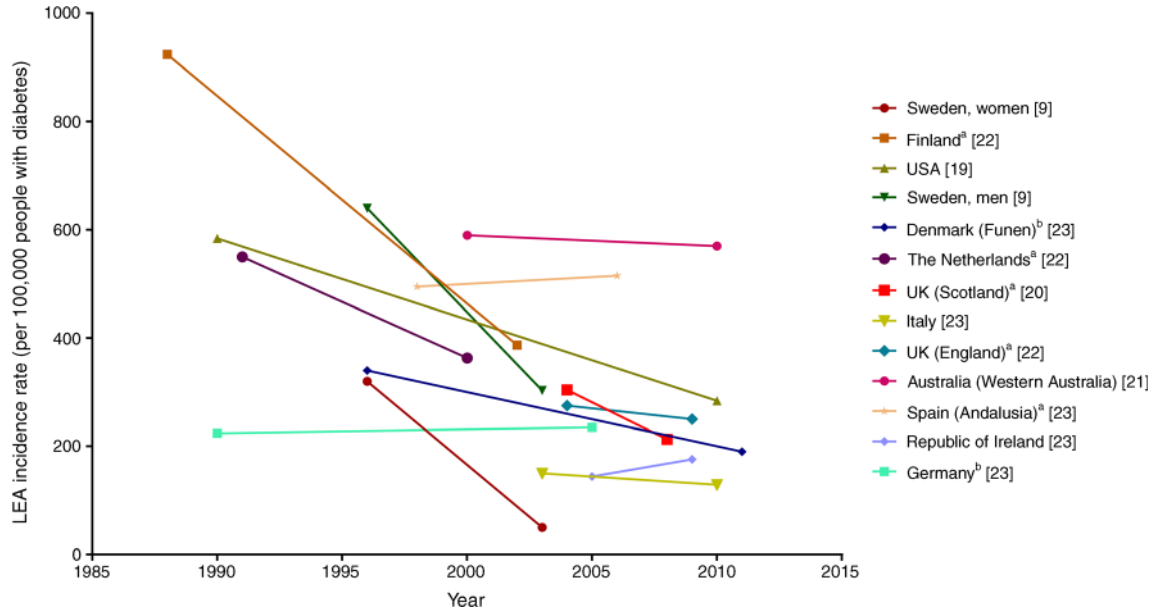

Fig. 1 Trends in LEAs among people with diabetes, by country, between 1988 and 2011. Data in the figure were derived from population-based studies of countries or major regions of countries in which rates of LEAs were examined using the same methods within populations over time. Differences in absolute rates between countries may be affected by variation in age and differences in criteria for diagnosis of both LEA and diabetes. Data are intended to be interpreted as trends over time and should not be used for comparison of absolute rates between countries at any one time point. [a]Unadjusted rate; [b]rate per 100,000 person-years. This figure is available as part of a downloadable slideset

Denmark (2%), and Sweden (1%). All of these rates are reported for overall country-specific populations, not for diabetes populations, and increases likely reflect the increasing prevalence of both type 1 and type 2 diabetes in these populations [28].

Among adults with type 2 diabetes, the incidence of ESRD declined by approximately 6% per year between 2000 and 2012 in a nationwide study of Chinese participants [29]. In the USA, incidence of ESRD in those with diabetes declined by 28% between 1990 and 2010, with a statistically significant decrease across all age groups after the year 2000 [19]. This decline was smaller than for other reported complications of diabetes, such as AMI, stroke, LEAs and death from hypoglycaemia, possibly owing to more inclusive criteria for initiating renal replacement therapy in the earlier years and large reductions in cardiovascular complications, both improving morbidity and mortality rates among people with diabetes.

Trends in the incidence of treated ESRD (i.e. dialysis initiation) among people with diabetes are also known to differ by race/ethnicity. In the USA, the incidence rate of treated ESRD declined between 2000 and 2013, by 28%, 22%, 14%, and 13% in American Indian/Alaska Native, Hispanic, non-Hispanic white and non-Hispanic black people with diabetes, respectively. Within the same timeframe, ESRD incidence remained relatively stable in Asian individuals with diabetes [30].

According to the United States Renal Data System (USRDS) reports, of all new cases of diabetes-associated ESRD, an estimated 91% were attributable to type 2 diabetes. Epidemiological data on trends in the incidence of treated ESRD in type 1 diabetes are less clear, partly because type 1 diabetes is less frequent than type 2 diabetes and also because of uncertainties related to the diagnosis of type 1 diabetes; young people with diabetes or those treated with insulin are often misclassified as having type 1 diabetes. Nonetheless, a review of ESRD in eight countries or regions of Europe, and in non-indigenous Canadians and Australians, found that incidence of type 1 diabetes-related ESRD declined between 1998 and 2002 [31]. Unlike type 2 diabetes, there are no studies among national cohorts with type 1 diabetes populations as the denominator; however, several cohort studies indicate that for a given duration of type 1 diabetes, people diagnosed in more recent decades have a lower incidence of ESRD than those diagnosed in the 1960s and 1970s [32]. Declines in type 1 diabetes-related ESRD may be attributed to the widespread use of renin–angiotensin system inhibitors and statin therapy at younger ages in this population, and recent improvements in insulin delivery technologies. On the other hand, in Taiwan, the incidence of type 1 diabetes-related ESRD increased substantially between 1999 and 2010 (from 0.13 to 3.52 per 1000 people; $p < 0.001$) [33].

Retinopathy Retinopathy affects approximately one third of adults with diabetes and represents the leading cause of blindness in these individuals [34]. Despite how common diabetic retinopathy is, there are few population-based data on

Table 2 Trends in LEA incidence among people with diabetes

Country	Study years	Counting of LEA[a]	Baseline rate[b]	End rate[b]	Relative change (%)[c]	*p* value
All LEAs						
Sweden [9]						
Women	1996–2003	1/person (first)	320	50	−84	ND
Men	1996–2003	1/person (first)	640	330	−48	ND
Finland[d] [22]	1988–2002	1/person (first)	924	387	−58	ND
USA [19]	1990–2010	Any LEAs; hospital discharge rate	584	284	−51	$p < 0.001$
Denmark (Funen)[e] [23]	1996–2011	1/person (highest)	340	190	−44	ND
Netherlands [22]	1991–2000	1/person (first)	550	363	−34	$p < 0.05$
UK (Scotland)[d] [20]	2004–2008	1/person (highest)	304	213	−30	$p < 0.001$
Italy [23]	2003–2010	1/person (highest)	150	129	−14	ND
UK (England)[d] [22]	2004–2009	1/person (first)	275	250	−9	ND
Australia (Western Australia) [21]	2000–2010	Any LEAs; hospital discharge rate	590	570	−3	$p < 0.05$
Spain (Andalusia)[d] [23]	1998–2006	Hospital discharge rate (highest)	495	515	+4	ND
Germany[e] [23]	1990–2005	1/person (first)	224	235	+5	$p = 0.016$
Republic of Ireland [23]	2005–2009	Any LEAs; hospital discharge rate	144	176	+22	$p = 0.11$
Major LEAs[f]						
Sweden[d] [22]	1982–2001	One per person (first)	16	6.8	−58	ND
Finland [23]	1997–2007	One per person (first)	94	48	−49	$p < 0.05$
Australia (Western Australia) [21]	2000–2010	One per person (first)	111.1	60.5	−46	$p < 0.05$
UK (Scotland)[d] [20]	2004–2008	One per person (highest)	187	111	−41	$p < 0.001$
Italy [23]	2003–2010	One per person (highest)	48	36	−25	$p < 0.001$
UK (England)[d] [22]	2004–2009	One per person (first)	118	102	−14	$p = 0.29$
Republic of Ireland [23]	2005–2009	Any LEAs; hospital discharge rate	47.9	48	+0.2	$p > 0.05$
Spain [27]	2001–2008	Hospital discharge rate	7.12	7.47	+5	$p < 0.05$
Minor LEA[g]						
UK (Scotland)[d] [20]	2004–2008	One per person (highest)	117	103	−12	$p > 0.05$
Italy [23]	2003–2010	One per person (highest)	96	89	−7	$p > 0.05$
Australia (Western Australia) [21]	2000–2010	One per person (first)	262	245	−6	$p > 0.05$
UK (England)[d] [22]	2004–2009	One per person (first)	157	149	−5	$p = 0.66$
Spain [27]	2001–2008	Hospital discharge rate	9.23	10.97	+19	ND
Republic of Ireland [23]	2005–2009	Any LEAs; hospital discharge rate	96	128	+33	$p = 0.23$
Sweden[d] [22]	1982–2001	One per person (first)	4.7	6.5	+38	ND

Data are from population-based studies. All data are age-adjusted, unless specified

[a] LEA counting: 1/person (first): only the first amputation per person is counted; 1/person (highest): the highest level of amputation per person is counted (e.g. if both toe and foot were amputated, only the foot amputation was counted); any LEA: includes all amputations (if an individual or a hospitalisation had multiple amputations, all are counted); hospital discharge rate: number of hospitalisations for amputations, rather than number of individuals with an amputation, are counted; hospital discharge rate (highest): the highest level of amputation for one hospitalisation is counted (e.g. if both toe and foot were amputated in the one hospitalisation, only the foot amputation was counted)

[b] Incidence per 100,000 people with diabetes

[c] Relative change (%) = [(baseline rate − end rate)/baseline rate] × 100

[d] Not age-adjusted

[e] Incidence per 100,000 person-years

[f] Major LEA is defined as loss of lower limb through or above the ankle

[g] Minor LEA is defined as loss of lower limb below the level of the ankle

ND, no data

incidence trends. Of the few studies that do report objectively measured annual incidence of retinopathy over time, findings are mixed (Table 3).

Generally, population-based studies conducted from the 1990s onwards report a 50–67% lower incidence of diabetic retinopathy compared with earlier studies [34]. A

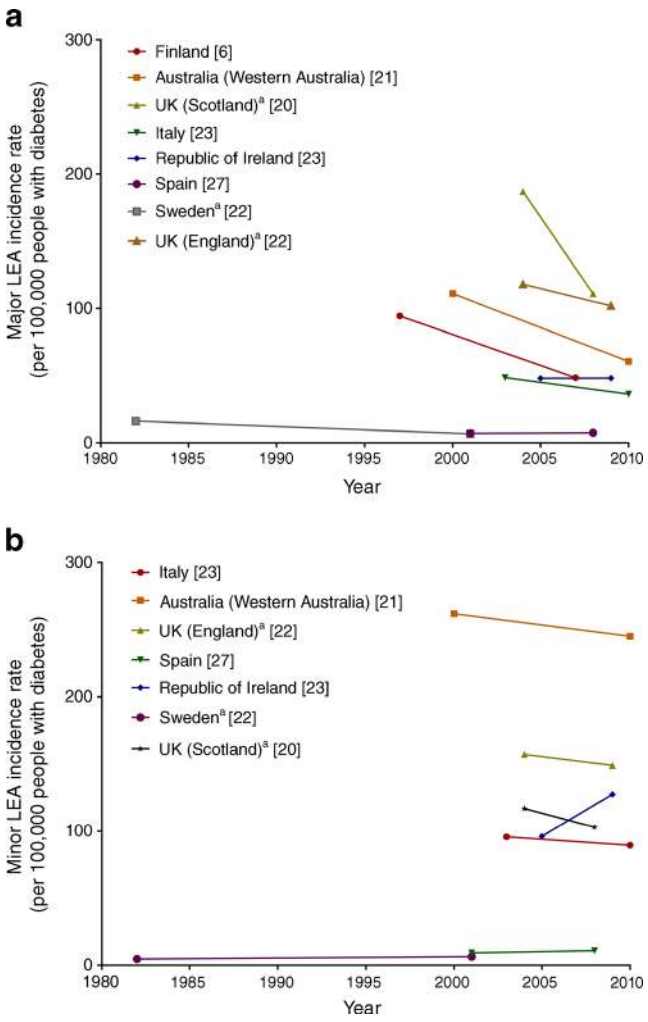

Fig. 2 Trends in (**a**) major and (**b**) minor LEAs among people with diabetes, by country, between 1982 and 2010. Data in the figure were derived from population-based studies of countries or major regions of countries in which rates of LEAs were examined using the same methods within populations over time. Differences in absolute rates between countries may be affected by variation in age and differences in criteria for diagnosis of both LEA and diabetes. Data are intended to be interpreted as trends over time and should not be used for comparison of absolute rates between countries at any one time point. [a]Unadjusted rate. This figure is available as part of a downloadable slideset

meta-analysis of 28 studies and 27,120 participants with type 1 and type 2 diabetes showed that the pooled incidence of proliferative diabetic retinopathy was lower in 1986–2008 (2.6%) compared with 1975–1985 (19.5%) [35]. Likewise, in the Pittsburgh Epidemiology of Diabetes Complications Study, incidence of proliferative diabetic retinopathy reduced from 38% in 1965–1969 to 26.5% in 1975–1980 [36]. These trends are likely to be owing to earlier identification and treatment of both diabetes and diabetic retinopathy and reductions in smoking rates. Moreover, lessons learned from the UK Prospective Diabetes Study (UKPDS) and DCCT trial, leading to better glycaemic and blood pressure control in diabetes, may have also contributed to the reduced incidence of diabetic retinopathy over recent years.

Neuropathy Information on trends in the prevalence or incidence of neuropathy are virtually non-existent due to the lack of data from repeated population surveys. Surveillance data from the US Diabetes Surveillance System (USDSS) show that the rate of hospitalisations for neuropathy (both first admission and any readmissions) increased by 42.1% (from 29.7 to 42.2 per 1000 people with diabetes) between 2000 and 2014; although these data are likely influenced by changes in coding of neuropathy and increased awareness of neuropathy among individuals with diabetes [37]. Historical data from the Pittsburgh Epidemiology of Diabetes Complications Study indicate a decline in the incidence of distal symmetrical polyneuropathy in participants with a 25-year duration of type 1 diabetes who were diagnosed between 1970 and 1974 compared with those diagnosed between 1965 and 1969 [36].

Acute complications

Acute complications of diabetes, such as diabetic ketoacidosis (DKA), the hyperglycaemic hyperosmolar state (HHS), lactic acidosis and hypoglycaemia are largely preventable, yet they still account for high morbidity and mortality among people with diabetes and contribute significantly to the high costs of diabetes care [43]. In the USA, the SEARCH for Diabetes in Youth study reported that 29% of individuals aged <20 years with type 1 diabetes, and 10% with type 2 diabetes presented with DKA at diagnosis [44]. The incidence of DKA in children and adolescents with type 1 diabetes also remains high, with approximately 1–12 episodes per 100 patient-years [43]. Comparable population-based data for adults are not currently available.

Overall, data suggest that DKA-related mortality and hospitalisation rates for acute complications are decreasing among people with diabetes (Table 4). However, in the USA, since 2010, significant increases in hospitalisations for hyperglycaemia and death from hyperglycaemic crisis have been reported by the USDSS, although continued declines in hospitalisations for hypoglycaemia were observed [37].

Decreasing temporal trends in hospitalisations and deaths from acute diabetes complications suggest improvements in in-hospital management of DKA and HHS and outpatient

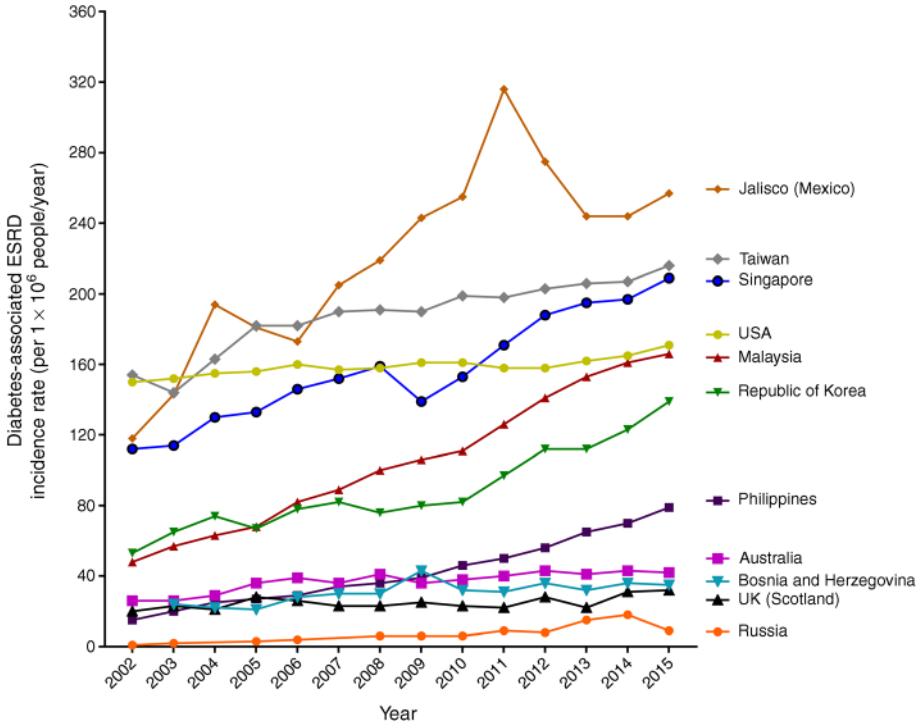

Fig. 3 Trends in the incidence rate (per million people in the general population/year) of diabetes-related ESRD, by country, between 2002 and 2015. The graph was generated based on data from the *United States Renal Data System* (USRDS) annual data report 2017 [28]. This figure is available as part of a downloadable slideset

care, and better patient education in disease management. Reasons for increases in acute complications, as observed in the USA, are, at this stage, unclear.

Mortality

Non-cardiovascular mortality Diabetes is associated with a diverse set of specific, non-cardiovascular causes of death. An international meta-analysis of 97 prospective studies representing 820,900 individuals with diabetes and 123,205 deaths throughout North America and Europe found that diabetes was associated with an increased risk for mortality from several cancers (17–116% increased risk, depending on the cancer site), renal disease, infections, liver disease, digestive system disorders, falls, pneumonia, mental health issues, intentional self-harm, external causes, nervous system disorders, chronic obstructive pulmonary disease (COPD) and related conditions, and other non-cancer, non-vascular causes [48].

Observations of trends in non-cardiovascular mortality are restricted to a few studies. In the USA, the rate of cancer-related deaths declined by 16% every 10 years between 1988–1994 and 2010–2015, while the rate of non-vascular, non-cancer-related deaths declined by a smaller magnitude (8% every 10 years) [15]. In Australia, age-standardised mortality rates (ASMRs) for all-cause, CVD and diabetes decreased significantly between 2000 and 2011, while cancer-related ASMRs remained unchanged in people with type 1 and type 2 diabetes [16]. Data from the same national registry in Australia demonstrated that cancer is now the second leading cause of death among people with diabetes, increasing from 25% of all deaths to 35% between 1997 and 2010 [49]. Similar findings have been reported in the USA [50] and Taiwan [51]. This is important in light of the increasing prevalence of diabetes that is coinciding with an ageing population, the latter being an inherent risk factor for both diabetes and cancer.

All-cause mortality Mortality rates due to diabetes are often estimated from vital statistics systems (based on death certificate data), the efficacy of which may be affected by diabetes prevalence, coding practices and country-level awareness of diabetes. Therefore, to adequately monitor mortality rates among populations with diabetes, rates should ideally be estimated among defined cohorts with diagnosed diabetes. However, data on all-cause and cause-specific mortality among people with diabetes are difficult to compare and come from a relatively small number of high-income countries within North America, Europe, Australia and Asia. Population-based data on all-cause mortality from several of these countries are shown

Table 3 Trends in the incidence of diabetic retinopathy

Country	Study years	Data source	Outcome assessed	Baseline rate[a]	End rate[a]	Relative change (%)[b]	*p* value
Type 1 diabetes							
UK[c] [38]	2004–2014	CPRD	DR	5150	5140	0	$p = 0.004$
			Severe DR	480	250	−48	$p = 0.459$
USA [39]	1980–2007	WESDR	Visual impairment due to DR	1200	300	−75	ND
			Severe visual impairment due to DR	400	20	−95	ND
Type 2 diabetes							
Korea[c] [40]	2006–2013	Korean NHIS insurance claims database	DR	6700	5600	−16	ND
Ireland [41]	2004–2013	NCBI	Visual impairment due to DR	6.4	11.7	+83	$p = 0.79$
			Blindness due to DR	3190	1490	−53	$p < 0.01$
UK[c] [38]	2004–2014	CPRD	DR	1130	3000	+165	$p = 0.001$
			Severe DR	52	100	+92	$p = 0.046$
UK (Scotland) [42]	2000–2009	Fife Society for the Blind in Kirkcaldy	Blindness due to DR	60	24	−60	$p = 0.062$

Data are from population-based studies in individuals with type 1 and type 2 diabetes. All data are age-adjusted

[a] Rates are expressed per 1000 people with diabetes

[b] Relative change (%) = [(baseline rate − end rate)/baseline rate] × 100. Due to rounding, relative change estimated directly from data in the table may be different from that reported

[c] Incidence per 1000 person-years

CPRD, Clinical Practice Research Datalink; DR, diabetic retinopathy; NCBI, National Council for the Blind of Ireland; ND, no data; NHIS, National Health Insurance Service; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy

in Fig. 4 and Table 5. These data are intended to be interpreted as trends over time, rather than as a comparison of absolute rates between countries, as methodologies differ between the studies. Nonetheless, a

Table 4 Trends in hospitalisation admission and mortality rates for acute complications of diabetes

Country	Study years	Outcome assessed	Baseline rate[a]	End rate[a]	Relative change (%)[b]
Canada [45]	1994–1999	Hospitalisations for hyperglycaemia	700	470	−33
		Hospitalisations for hypoglycaemia	100	25	−75
		ED visits for diabetes	5400	4200	−22
USA [37]	2010–2014	ED visits for hypoglycaemia	1510	1310	−13
		ED visits for hyperglycaemia	1850	2530	+37
USA [37]	2010–2015	Death from hyperglycaemic crisis (DKA/HHS)	1700	2420	+42
Italy [46]	2001–2010	Acute diabetes complications (DKA/hyperosmolarity or hypoglycaemic coma)	1440	710	−51
		Acute hyperglycaemic complications	1360	670	−51
		Hypoglycaemic coma	310	170	−45
Taiwan [47]	1997–2005	DKA	600	500	−17

Data are from population-based studies in individuals with diabetes

[a] Rates are expressed per 100,000 people

[b] Relative change (%) = [(baseline rate − end rate)/baseline rate] × 100

ED, emergency department

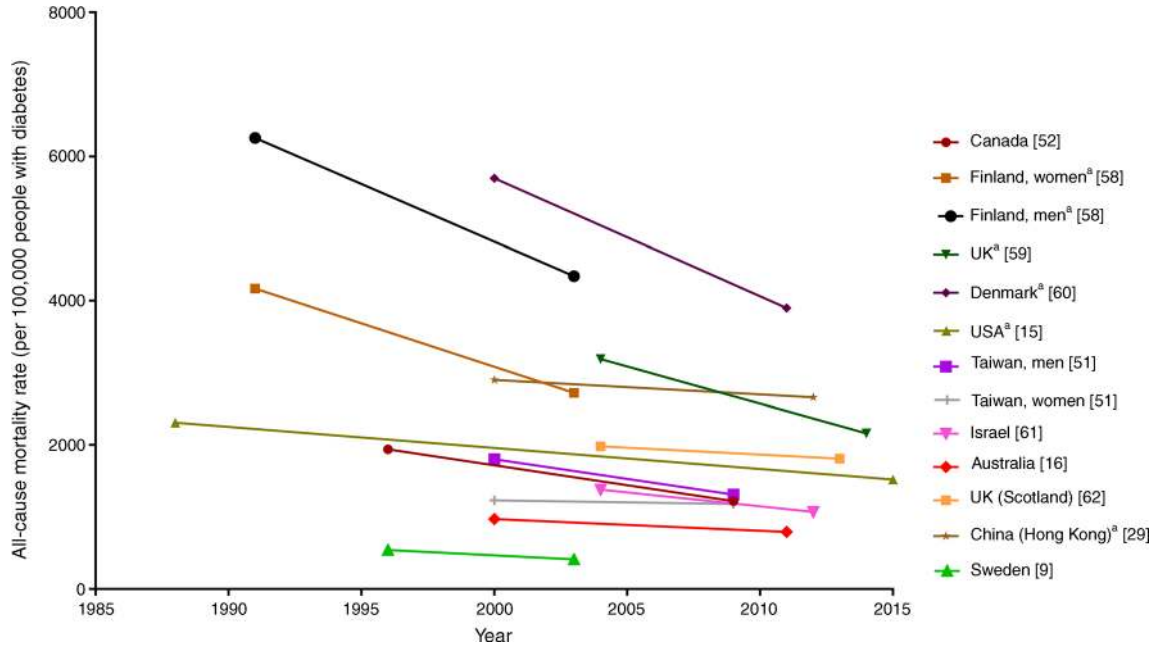

Fig. 4 Trends in all-cause mortality among people with diabetes, by country, between 1988 and 2015. Data in the figure were derived from population-based studies of countries or major regions of countries in which all-cause mortality rates were examined using the same methods within populations over time. Differences in absolute rates between countries may be affected by variation in age, differences in diabetes diagnosis, country-level awareness of diabetes and collection of vital statistics. Data are intended to be interpreted as trends over time and should not be used for comparison of absolute rates between countries at any one time point. [a]Rate per 100,000 person-years. This figure is available as part of a downloadable slideset

Table 5 Trends in all-cause mortality among people with diabetes

Country	Study years	Baseline rate[a]	End rate[a]	Relative reduction (%)[b]	*p* value
Canada [52]	1996–2009	1940	1220	−37	ND
Finland[c] [58]					
Women	1991–2003	4170	2720	−35	$p < 0.001$
Men	1991–2003	6260	4340	−31	$p < 0.001$
USA[c] [15]	1988–2015	2310	1520	−34	$p < 0.001$
UK[c] [59]	2004–2014	3190	2160	−32	ND
Denmark[c] [60]	2000–2011	5700	3900	−32	ND
Taiwan [51]					
Women[c]	2000–2009	1230	1180	−4	$p = 0.06$
Men[c]	2000–2009	1800	1310	−27	$p = 0.06$
Sweden [9]	1996–2003	540	410	−24	ND
Israel [61]	2004–2012	1380	1070	−22	$p < 0.001$
Australia [16]	2000–2011	970	790	−19	$p < 0.001$
UK (Scotland) [62]	2004–2013	1980	1810	−9	ND
China (Hong Kong)[c] [29]	2000–2012	2900	2660	−8	ND

Data are from population-based studies including type 2 diabetes only or all (type 1 and type 2) diabetes. All data are age-adjusted

[a] Rates are expressed per 100,000 people with diabetes

[b] Relative reduction (%) = [(baseline rate − end rate)/baseline rate] x 100

[c] Rates per 100,000 person-years

ND, no data

consistent reduction in mortality among people with diabetes (either type 2 diabetes or all [type 1 and type 2] diabetes) has been observed since the late 1980s, ranging from a 4% relative decline in mortality among Taiwanese women with diabetes (27% in Taiwanese men) between 2000 and 2009 [51], to a 37% decline in Canadians between 1996 and 2009 [52].

Studies that compare populations with and without diabetes show that the relative difference between the two populations is decreasing over time, but excess risk remains among people with diabetes, even at more recent time points [53]. For example, in Ontario, Canada, the mortality rate ratio decreased from 1.90 (95% CI 1.86, 1.94) in 1996 to 1.51 (95% CI 1.48, 1.54) in 2009 [52], and similar declines have been noted in the UK [52], USA [15] and Australia [49].

For type 1 diabetes, there is a 3–18-fold excess risk for death compared with individuals without diabetes [54]. However, continued improvements in mortality rates have been noted by a few studies. For example, in the USA, between 1950 and 2009, marked declines in the number of deaths attributed to type 1 diabetes were observed across all age groups (by 45–90%) [54]. An analysis by the Centers for Disease Control and Prevention also showed a 61% decrease in diabetes-related mortality prior to age 20 years between 1968–1969 and 2008–2009 [55]. Outside of the USA, Japan and Finland reported declines in mortality rates of 69% and 8%, respectively, when comparing mortality among those diagnosed with childhood-onset type 1 diabetes in 1965–1969 with those diagnosed in 1975–1979 [56]. The smaller declines in Finland are most likely explained by the lower absolute mortality in this country as compared with Japan [56]. In Norway, mortality rates among individuals diagnosed with type 1 diabetes between 1973 and 1982, before 15 years of age, was reduced by 81% (from 286 to 53 per 100,000 person-years) compared with those diagnosed in 1999–2012 [57]. In Australia, mortality rates among individuals with type 1 diabetes who were diagnosed before 45 years of age declined by 33% between 2000 and 2011 [16].

Emerging complications of diabetes

The increase in diabetes incidence since the 1980s, combined with declining mortality among people with diabetes, has increased the total years of life spent with diabetes. Longer life expectancy among those with diabetes has also driven the emergence of newly recognised complications, including cancer, infections and physical and cognitive disability. Observations of trends in ‘emerging’ diabetes complications are restricted to a few select studies.

Individuals with diabetes have an increased risk for tuberculosis, severe gram-positive infections, hospital-acquired postoperative infections, urinary tract infections (UTIs) and tropical diseases compared with people without diabetes [63]. Whether the rate of infections among populations with diabetes has changed over time is not clear. In the USA, data from the National Vital Statistics System show that the per cent of deaths with infections listed anywhere on the death certificate decreased from 3.1% in 1999 to 2.7% in 2010 in people with diabetes and from 4.5% to 4.1% in people without, with respiratory tract infections accounting for the highest percentage of deaths in both groups [63]. An analysis of data from the National Nursing Home Surveys between 1999 and 2004 showed that the age-standardised proportion of nursing home residents with infections among people with diabetes increased from 6.1% to 10.3% between 1999 and 2004, while in people without diabetes this increased from 6.0% to 8.5% [63]. In Spain, a 61.3% increase in hospitalisation rates for sepsis was observed between 2008 and 2012 [64], though changes in ICD-9-clinical modification (ICD-9-CM; www.cdc.gov/nchs/icd/icd9cm.htm) codes make it difficult to assess the change in sepsis over time.

A growing body of research suggests that people with diabetes are at increased risk for major depressive disorder [65], anxiety [66], eating disorders (particularly in female adolescents with type 1 diabetes) [67], serious mental illness (e.g. schizophrenia) [68], dementia [69], and several domains of disability, including mobility loss, reduced instrumental activities of daily living (IADL) or basic activities of daily living, and work disability [70]. Again, whether risk has changed over time remains unknown as for many of these complications, prospective data with adequate follow-up is not available. For depression, two studies have explored trends over time. In Spain, the prevalence of depression among hospitalised individuals with type 2 diabetes increased significantly from 3.5% to 5.8% between 2001 and 2011, with increases being much higher in women [71]. In Finland, the use of antidepressants was more common in people with diabetes compared with those without and use of these drugs increased more rapidly between 1997 and 2007 in people with diabetes, particularly younger individuals with type 2 diabetes [72]. For physical disability, data from the USA show that the prevalence of both impaired mobility and IADLs have not changed in recent decades, while work disability declined from 23.8% in 1997 to 17.9% in 2006; however, this then increased to 19.7% in 2011 [70]. In relative terms, similar trends in rates of disability were reported among the non-diabetic population, but, in absolute terms, rates over time were smaller (from 9.8% in 1997 to 5.8% in 2010).

Summary

Diabetes-related complications

Chronic or acute diseases caused by persistent metabolic and haemodynamic disturbances in diabetes.

Generally described as microvascular (kidney disease, retinopathy and neuropathy) and macrovascular (cardiovascular) complications, but may also include consequences of diabetes-specific treatments, such as hyper- or hypoglycaemia.

Despite widespread international assessment of the growth of diabetes prevalence, quantification of the international burden of and variation in diabetes-related complications is lacking.

What are recent and long-term trends in diabetes-related complications globally?

Rates of LEAs, acute complications, CVD, all-cause mortality and CVD mortality among people with diabetes are generally declining.

Data on trends in ESRD, diabetic retinopathy and neuropathy, non-CVD mortality and 'emerging' complications are fewer and, hence, conclusions are limited.

In spite of notable declines in several diabetes complications, people with diabetes remain at significantly higher risk for these complications compared with those without diabetes.

Comparable data on trends in rates of diabetes complications, specifically from low- and middle-income countries, is lacking. Conclusions drawn are mainly limited to high-income countries in North America, Europe and the Asia-Pacific region and the global state of diabetes complications remains unknown.

Clinical outcomes and future perspectives

Declines in all-cause and CVD-related mortality may lead to proportional increases in other forms of morbidity (e.g. renal disease, infections, cancers, and physical and cognitive disability), with important implications for the clinical and public health burden of diabetes.

Future monitoring of global trends in diabetes complications could be enhanced by implementation of standardised reporting methods and the establishment of practical registries that suit the dual needs of population monitoring and providing feedback and decision support for clinical systems.

Discussion

This review of international trends in diabetes-related complications reveals several key conclusions (see Text box); first, rates of LEAs, acute complications, CVD and all-cause and CVD-related mortality among populations of people with diabetes are declining. Data on trends in ESRD, diabetic retinopathy and neuropathy, non-CVD-related causes of death and 'emerging' complications in these populations are scarce, however, and, as such, conclusions are limited. Second, in spite of notable declines in several diabetes complications, people with diabetes remain at significantly higher risk for these complications compared with people without diabetes. Third, declines in all-cause and CVD-related mortality are leading to proportional increases in other forms of morbidity, including renal disease, infections, cancers, and physical and cognitive disability, with important implications for the clinical and public health burden of diabetes. Last, there is a genuine lack of comparable data on trends in rates of diabetes complications, specifically from low- and middle-income countries. Therefore, conclusions drawn from this work are limited to about a dozen high-income countries in North America, Europe and East Asia and, as such, this leaves the status of global trends in diabetes complications unclear.

The explanation for the decline in rates of diabetes complications among selected countries around the world is likely multifactorial, involving trends in the underlying risk factors of the population and changes in preventive care and medical treatment. Reductions in macrovascular complications in high-income countries are likely influenced by improved pharmacotherapy, CVD treatment procedures and better prevention strategies [73]. For example, large reductions in smoking rates occurred in the 1970s and 1980s, followed by gradual reductions thereafter [74, 75]. Blood pressure control also improved in the 1980s and 1990s, driven by new evidence for treatment efficacy from clinical trials and better awareness of blood pressure as a key risk factor for CVD [74, 75]. In addition, lipid levels have declined over time, likely due to increased use of lipid-lowering medications as well as reductions in trans-fat intake [73, 76]. These improvements in risk factor management in high-income countries have likely had additional benefits in terms of microvascular

complications, which have been further buoyed by improvements in glycaemic control since 2000 [73, 76, 77]. In the USA, the improvements in risk factors are also likely driven by improvements in the organisation of care and initiatives to improve quality of diabetes care. Whether improvements in risk factors, treatment options and medical care also occurs in the majority of other countries in the world is unclear due to the lack of continuous monitoring systems.

Trends in rates of diabetes complications are also influenced by background trends in mortality. For example, the large reductions in CVD-related mortality in populations with diabetes that have been observed in the USA, Australia and several other countries in Northern Europe have increased survival rates, resulting in proportional increases in other causes of death, including those due to cancer, renal disease and infections.

The interpretation of trends in rates of diabetes complications also depends on which denominator population (diabetes or whole population) is used. This review has focused primarily on the average risk for the average person with diagnosed diabetes, independent of changes in prevalence of diabetes in the underlying population. When rates are calculated as the frequency of diabetes-related complications in the general population, many countries reveal flat or even increasing trends because the increases in diabetes prevalence offset reductions in risk of complications within the diabetic population [19]. For example, while the average adult with diabetes in the USA has a lower risk of CVD than in previous decades, the average adult in the general population has an increased risk of diabetes-related CVD than in previous decades because of the large increase in diabetes prevalence. The fact that trends differ depending on the choice of general population denominator is a reminder that the burden of the wide spectrum of complications in those with diabetes will ultimately be influenced by efforts to prevent diabetes.

Conclusion

In this review, we have highlighted the scarcity of data outside North America, Europe and high-income Asia-Pacific countries, leaving the global status of diabetes complications rates unclear, especially in low and middle-income countries. This gap in data stems largely from the lack of population-based systems quantifying healthcare utilisation because surveys and cohort studies are generally inadequate for the assessment of diabetic complications. The comparison of trends in complications has also been hampered by varied reporting methods, definitions of complications and methods to identify people with diabetes. Future monitoring of global trends in diabetes complications could be enhanced by implementing standardised reporting methods and establishing practical registries that suit the dual needs of population monitoring and providing feedback and decision support for clinical systems.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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