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The rapidly increasing incidence of type 2 diabetes and macrovascular and microvascular complications disproportionately affects younger age groups: A decade of evidence from an international federated database

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ABSTRACT

Aims: To characterise recent trends in incidence and prevalence of type 2 diabetes (T2D) associated complications, and their relative impact across the lifespan.
Methods: We conducted a retrospective cohort study using the TriNetX global federated database. Incidence and prevalence of T2D and associated complications: ischaemic heart disease (IHD), heart failure, cerebral infarction, neuropathy, nephropathy, and retinopathy were assessed between 2012 and 2023. Incidence odds ratios (IOR) were calculated by age group.
Results: 7,918,666 individuals had T2D. The IOR (95 % CI), comparing individuals aged ≥ 85 years to < 35 years decreased for all complications from 2012 to 2023: **IHD** [IOR 6.82, (6.40, 7.26) to IOR 2.27 (2.17, 2.38)], **heart failure** [IOR 5.38, (5.03, 5.75) to IOR 1.80 (1.72, 1.89)], **cerebral infarction** [IOR 3.06, (2.76, 3.40) to IOR 1.45 (1.34, 1.57)], **neuropathy** [IOR 0.84, (0.74, 0.95) to IOR 0.47 (0.44, 0.49)], **nephropathy** [IOR 1.14, (1.03, 1.27) to IOR 0.90 (0.87, 0.94)] and **retinopathy** [IOR 0.56, (0.50, 0.63) to IOR 0.27 (0.25, 0.29)].
Conclusions: Rising rates of T2D associated complications in younger adults signal an emerging epidemic of early-onset comorbidity with substantial lifetime burden. These findings emphasise the urgent need for earlier detection, aggressive risk factor management, and targeted prevention strategies in younger populations.

1. Introduction

Diabetes is a chronic metabolic disease associated with significant morbidity, mortality, and global health expenditure; attributable for 966 billion USD per year [1]. In 2021, it was estimated that 529 million people worldwide lived with diabetes, a 6.1 % global prevalence [2], expected to increase to 12.2 % by 2045. Whilst the incidence of both type 1 (T1D) and type 2 diabetes (T2D) have increased, T2D accounts for up to 96 % of all cases [2].

There is a major burden of macrovascular and micro-vascular complications in diabetes: ischaemic heart disease, cerebral infarction, heart failure and peripheral vascular disease (macrovascular) and diabetic

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retinopathy, nephropathy and neuropathy (microvascular disease) [3]. T2D is a leading cause of chronic kidney disease (CKD) [4] and non-traumatic lower limb amputation [5]; and diabetic retinopathy is one of the leading causes of blindness in working age adults [6,7]. Individuals living with diabetes are twice as likely to die from cardiovascular (CV) disease compared to the general population [8] and younger onset T2D is associated with a disproportionately higher CV risk incidence and prevalence compared to adults diagnosed later [9]. Therefore, to facilitate future resource allocation and health care planning, and target disease prevention, a better understanding of the temporal trends in diabetes associated complications is required.

The epidemiology of macro- and microvascular disease in T2D is currently poorly characterised. Despite significantly increasing incident diabetes, particularly T2D, there has been a reduction in hospitalisation and death from CV disease [10], primarily driven by intensive pharmacological management of hyperglycaemia and associated CV risk factors (hypertension, hyperlipidaemia, and albuminuria) [11]. Most population-based cohort studies report only core, well established macrovascular endpoints of hospitalisation and all-cause mortality due to CV disease. Whilst clinically important and significant outcomes, such studies fail to capture the holistic burden of all complications, many of which do not reach such a threshold of severity. Therefore, we chose to investigate the incidence and prevalence of micro- and microvascular disease in individuals with T2D over the last decade, with a particular focus on younger onset.

2. Methods

2.1. Database characteristics

We performed retrospective analysis of prospectively collected data in a dynamic cohort design using the TriNetX (TriNetX LLC, Cambridge, MA, USA) platform [12]. The TriNetX research platform is a federated database providing access to real-time anonymised electronic medical records. TriNetX has data usage and publication agreements in place with all health care organisations (HCOs). TriNetX provides comprehensive datasets that encompass a wide range of variables, including patient demographics, diagnoses, procedures, medications, and laboratory results collected mostly from HCOs' electronic medical records (EMRs). This extensive data collection provides a holistic view of patient health and related outcomes, contributing to the completeness of our analyses [13]. TriNetX employs data validation processes to ensure the accuracy and reliability of its data. These processes include regular data quality checks to identify and correct discrepancies, validation against external benchmarks to ensure consistency and accuracy, and collaboration with data contributors to resolve any identified issues and improve data quality continuously. We utilised the TriNetX Global Collaborative network, comprising $>$ 125 million individuals across over 100 health care organisations (HCOs), primarily secondary and tertiary units in North America.

2.2. Cohort creation

We utilised the entire network to report the incidence and prevalence of T2D. The dynamic cohort design represents a study method where the study population is but continuously changing, rather than fixed. In this design, new participants enter the cohort each year, while others leave due to death, migration, or loss to follow-up. Loss to follow-up was handled by not including participants in calculations in subsequent years following their last data entry, for example, if a participant was lost in 2017, for example, they will not be taken into account in the calculations for 2018–19, 2020–21 and 2022–23. T2D was defined according to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) coding: E11. Individuals with a coding of others type of diabetes were excluded (ICD-10 E08, E09, E10, E13). We used data recorded from January 1st, 2012, until December 31st, 2023, divided into 2-yearly time windows. For both cohorts, we calculated the incidence rate and prevalence of macrovascular complications: ischaemic heart disease (ICD-10 I20-25), heart failure (ICD-10 I50) and cerebral infarction (ICD-10 I63), and microvascular complications: diabetic neuropathy (ICD-10 E11.4), nephropathy (ICD-10 E11.2) and diabetic retinopathy/ maculopathy (ICD-10 E11.31–11.35, ICD-10 E11.37, E11.39). **Subgroup analysis** by age and sex was additionally performed.

2.3. Data handling

Data collection, processing, and transmission are performed in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons regarding the processing of personal data, and the Health Insurance Portability and Accountability Act, the US federal law which protects the privacy and security of healthcare data. The TriNetX Global Collaborative Network is a distributed network (with most HCOs located in the USA), and analytics are performed at the HCO with only aggregate results being surfaced and returned to the platform. Data usage and publication agreements are in place with all HCOs. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law which protects the privacy and security of healthcare data, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section 164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section 164.514(b)(1) of the HIPAA Privacy Rule. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval.

2.4. Statistical analysis

Statistical analysis is conducted within the TriNetX platform using the R survival package. Historical data from HCOs includes the dates of the observation, rather than the date in which data became available in TriNetX.

We report incidence rate and prevalence which are both rates and defined by a denominator and a numerator. The **incidence rate** denominator is the product of the number of days covered by the time interval and number of patients who are: in the cohort under analysis, whose fact record overlaps the time window by at least one day, whose fact record does not contain the event of interest during the lookback period and whose demographic categories match the strata under consideration. The incidence rate numerator is defined as all, and only individuals who are in the denominator and whose records includes the event of interest on a data within the time window. Participants with the event of interest in the look-back period were excluded from both numerator and denominator, hence, event of interest (disease) is *new* or *first-time* cases only. Incident rate was defined as cases per 1,000 person years. The Incidence Odds Ratio (IOR) was calculated to compare the odds of disease occurrence between two groups: $<$35 years and $>$ 85 years at the start and end point of the study. **Prevalence** is rate of *all* cases recorded within or before some period of time. For a given time window, the prevalence denominator includes all and only individuals who are in the cohort under analysis, whose fact record overlaps the time window by at least one day and whose demographic categories

match the strata under consideration. The prevalence numerator includes all and only individuals who are in the denominator and whose record includes the event of interest between the start of the lookback period and the end of the time window. The lookback period begins with individuals' earliest observation and ends on the day prior to the start of the time window. In each time interval, only patients with a fact record (starting on the date of the earliest observation and ending on the date of the latest observation in TriNetX) overlapping the time interval was included in the numerator and denominator.

2.5. Sensitivity analysis

The official implementation date of ICD-10 coding practices was 1st October 2015 within the United States. To account for potential differences in diagnostic coding practices before and after the transition from ICD to 9 to ICD-10, we conducted a sensitivity analysis on microvascular outcomes restricted to encounters occurring on or after 1st January 2016.

3. Results

From 128,378,759 individuals across 127 HCOs within the network, we identified 7,918,666 individuals with a diagnosis of T2D within the timeframe. The geographic distribution of individuals with T2D was predominantly within the United States (Table 1), with similar mean ages and sex distribution at the start and end of the study period (Table 1).

3.1. Incidence and prevalence of T2D diagnosis

Incidence of T2D increased from 12.6/1,000 person-years in 2012–13 to 21.1/1,000 person-years in 2022–23 (Fig. 1). Stratified by age, the change of incidence ranged from a 46 % to 71 % increase (Fig. 1) Prevalence of T2D increased from 4.9 % in 2012–13 to 8.9 % in 2022–23.

3.2. Incidence and prevalence of T2D complications

Incidence of macrovascular and microvascular complications increased *substantially* from 2012/13 to 2022/23 (Figs. 2-3). Increase in incidence was seen across both sexes and all age groups (Figs. 4-9), but males, and younger people were more disproportionately affected, with the greatest change in incidence reported in individuals under the age of 35 (Table 2). Prevalence of complications increased over the past decade; diabetic neuropathy and nephropathy had the greatest increase in prevalence (Table 3).

Table 1
Baseline characteristics.

Geography				
Location		**T2D [%]**		
United States	Northeast	25		
	Midwest	13		
	South	33		
	West	10		
Other countries		12		
Unknown		7		
Demographics				
Year		**Number (n)**	**Female/Male/ Unknown [%]**	**Age (years ± standard deviation)**
2012–13		2,194,844	50.0/49.6/0.4	59.5 ± 15.5
2022–23		7,918,666	47.8/49.2/3.0	60.5 ± 15.8

3.3. Macrovascular complications

Incidence of IHD was greater for individuals aged ≥ 85 compared to < 35 years incidence odds ratio (IOR) [IOR 6.82, 95 % CI 6.40–7.26] in 2012–13 which decreased over the study period [IOR 2.27, 95 % CI 2.17–2.38] in 2022–23. Incidence of heart failure was greater for individuals aged ≥ 85 compared to < 35 years [IOR 5.38, 95 % CI 5.03–5.75] in 2012–13 which decreased over the study period [IOR 1.80, 95 % CI 1.72–1.89] in 2022–23. Incidence of cerebral infarction was greater for individuals aged ≥ 85 compared to < 35 years [IOR 3.06, 95 % CI 2.76–3.40] in 2012–13 which decreased over the study period [IOR 1.45, 95 % CI 1.34–1.57] in 2022–23. Compared to females, males had an IOR of 1.33 (95 % CI 1.32–1.34) in 2012–13 which increased across the study period to IOR 1.38 (95 % CI 1.37–1.38) in 2022–23.

3.4. Microvascular complications

Incidence of neuropathy was lower for individuals aged ≥ 85 compared to < 35 years [IOR 0.84, 95 % CI 0.74–0.95] in 2012–13 which decreased over the study period [IOR 0.47, 95 % CI 0.44–0.49] in 2022–23. Incidence of nephropathy was greater for individuals aged ≥ 85 compared to < 35 years [IOR 1.14, 95 % CI 1.03–1.27] in 2012–13 which decreased over the study period [IOR 0.90, 95 % CI 0.87–0.94] in 2022–23. Incidence of retinopathy was lower for individuals aged ≥ 85 compared to < 35 years [IOR 0.56, 95 % CI 0.50–0.63] in 2012–13 which decreased over the study period [IOR 0.27, 95 % CI 0.25–0.29] in 2022–23. Compared to females, males had an IOR of 1.19 (95 % CI 1.17–1.20) in 2012–13 which increased across the study period to IOR 1.29 (95 % CI 1.28–1.29) in 2022–23.

3.5. Sensitivity analysis

Transition from ICD to 9 to ICD-10 appears to have impacted rates of microvascular disease reporting. For nephropathy and neuropathy, the magnitude of difference in IOR between individuals aged ≥ 85 and < 35 was greater when limited to the post ICD-9 era (2016–17), IOR 1.58 (95 % CI 1.46–1.72) and IOR 1.01 (95 % CI 0.96–1.07) respectively. For retinopathy, the IOR were comparable, IOR 0.52 (95 % CI 0.47–0.56).

4. Discussion

We demonstrate that the incidence of T2D has almost doubled, from 12.6 to 21.1/1,000 person years between 2012–2013 and 2022–23 in a dataset encompassing over 125 million individuals, with the greatest % increases in individuals aged < 54 years compared to older adults (≥65 years). Similarly, over the same period in ~ 8 million people with T2D, incidence and prevalence of all micro- and macrovascular disease increased; the burden of all reported complications affecting individuals aged less than 35 increased disproportionally compared to older age groups. Whilst the absolute rates of macrovascular disease were still higher in older age groups, the incidence odds ratios of macro- and microvascular disease for people aged ≥ 85 years, compared to those < 35 years, decreased reflecting a reduction in the relative disparity of disease incidence between older and younger people. Incidence of diabetes associated complications were greater in males than females, with the gender gap widening over time. We observed a transient reduction in incidence of T2D and its complications during 2020–21, which we hypothesise was secondary to underutilisation of healthcare and incomplete data collection during the COVID-19 pandemic. Incidence rates in the 2022–23 year need to be interpreted with caution, as this may reflect a rebound effect following the pandemic. Additionally, switch over from ICD to 9 to ICD-10 coding may have impacted the rates reported for neuropathy and nephropathy in 2012–2015.

Global trends in complications of T2D remain inadequately defined and exhibit considerable variation depending on the methodology used, the region studied, and the specific outcomes assessed. Several

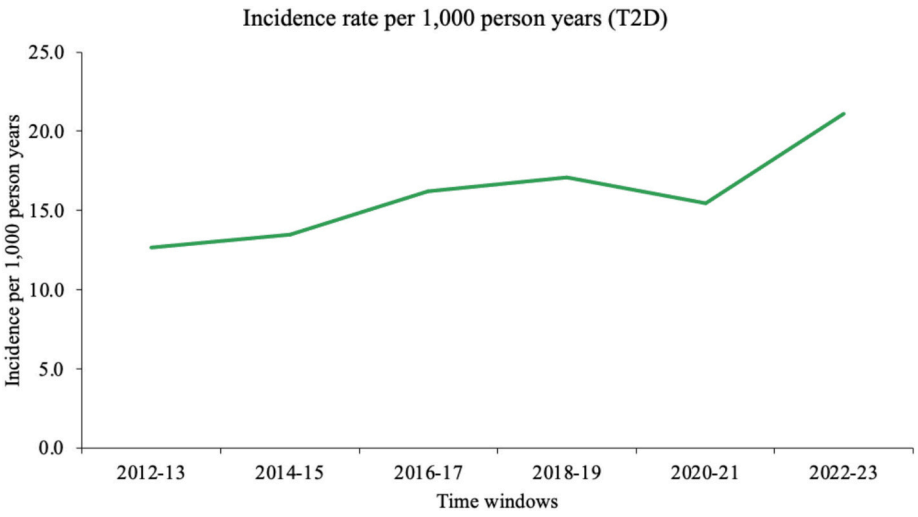
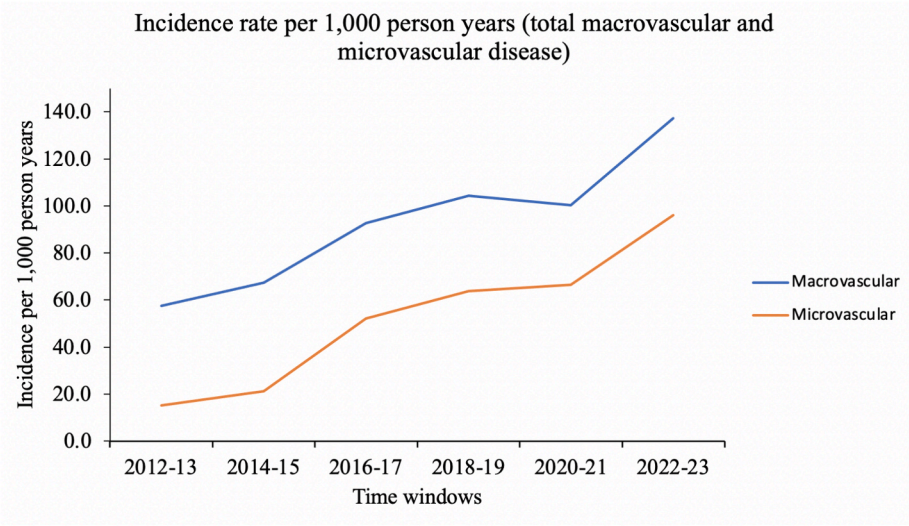


Fig. 1. 1a (Top): Overall **incident rate** of T2D per 1,000 person-years. **1b (Bottom):** Summary of change in **incident rate** of T2D stratified by **age.**



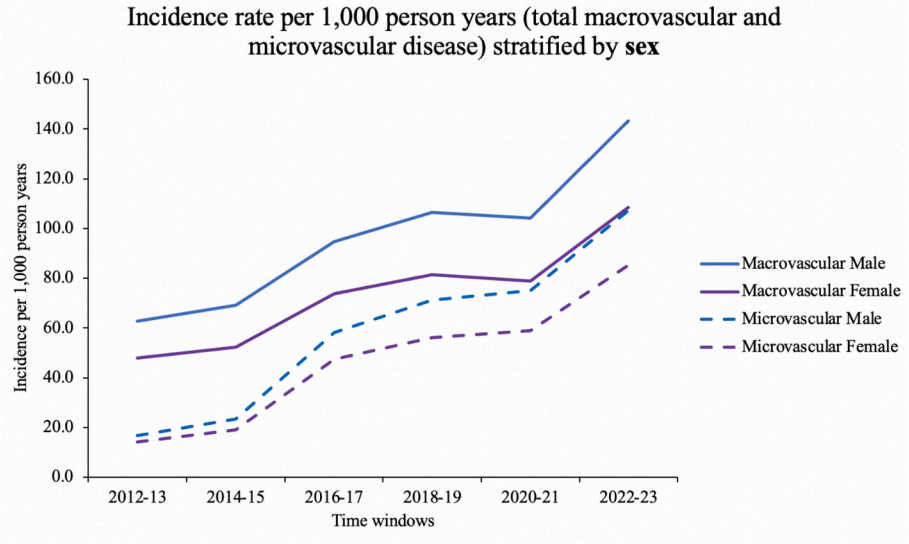
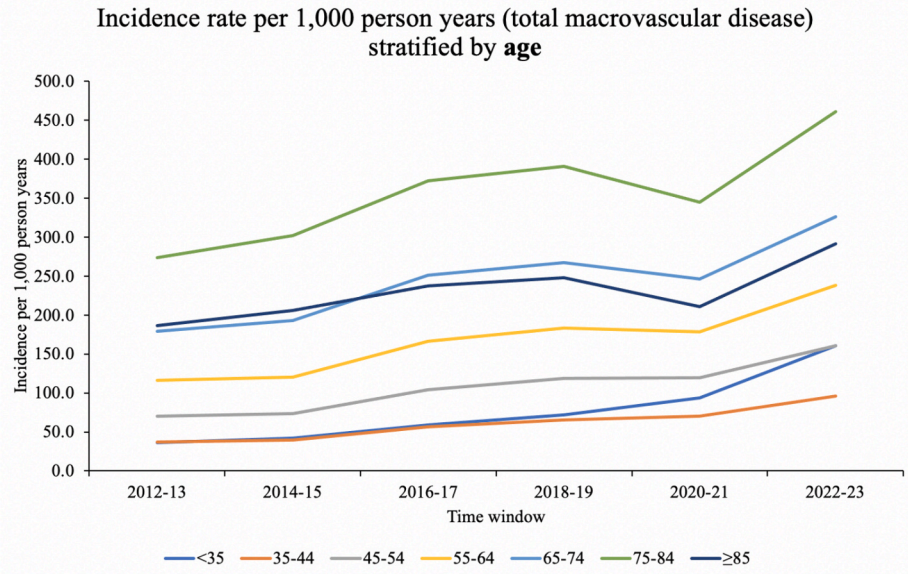


Fig. 2. 2a (Top): Overall change in incidence of total macro- and microvascular disease. **2b (Bottom):** Overall change in incidence of total macro- and microvascular disease stratified by sex.



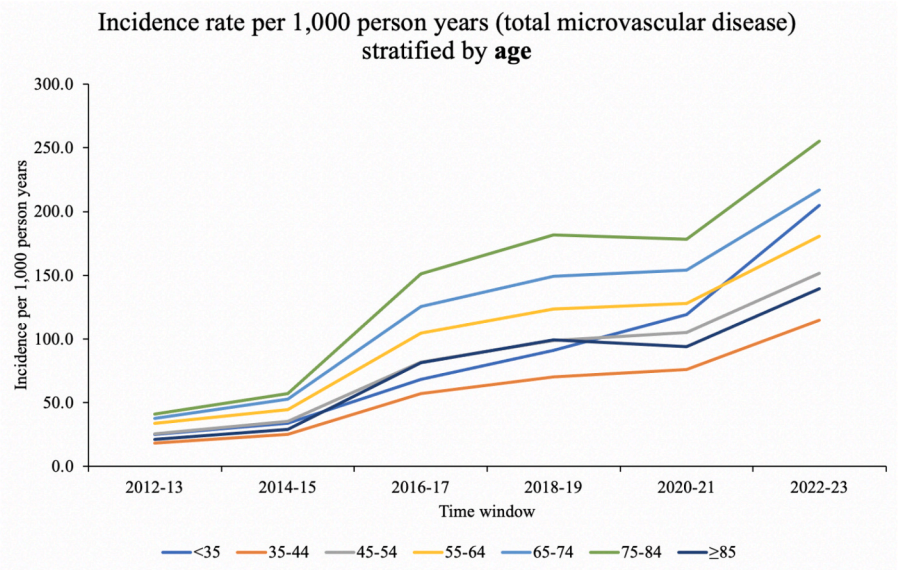


Fig. 3. 3a (Top): Incidence rate of all macrovascular disease (cases per 1,000 person-years) stratified by age. **3b (Bottom):** Incidence rate of all microvascular disease (cases per 1,000 person-years) stratified by age.

population-based data registries describe reducing incidence of cardiovascular disease in T2D [14,15], in contrast to our findings. Commonly reported outcomes from existing epidemiological studies include hospitalisation or death from any cardiovascular cause, both at the extreme end of the disease severity spectrum. Whilst this reduction in event rates is reassuring, a much larger cohort of individuals, with less severe, but perhaps more stable yet clinically meaningful disease burden maybe neglected, and not counted. Therefore, we opted to capture all ICD-10 coding for both macro- and microvascular disease, regardless of severity, and thus comprehensively report temporal changes in ICD-10 coding of the incidence and prevalence of all the most common diabetes associated complications from a large, federated database.

Children and adolescents diagnosed with T2D exhibit complications at an earlier point than age-matched individuals with T1D [16], and adults with early onset T2D have an increased risk of cardiovascular complications [17]. Our reported increase in incidence of all complications is concerning, but important context must be provided. Whether or not the observed increase in rates is truly a *de novo* increase, or we report an unmasking of disease that was already there secondary to increased awareness, screening and diagnosis of complications is challenging to ascertain. Nevertheless, we consistently report a disproportionate increase in incidence of T2D and both macro- and microvascular complications in younger individuals, with significant future health resource planning implications.

4.1. *Macrovascular disease*

There are very few longitudinal studies that are not restricted to the sole reporting of major adverse cardiovascular events (MACE) in T2D. A retrospective cohort study from the US of over 135,000 individuals with T2D by An et al [18]. reported a lower incidence of micro- and macrovascular complications in 2013–14 compared to 2003–4. However, this

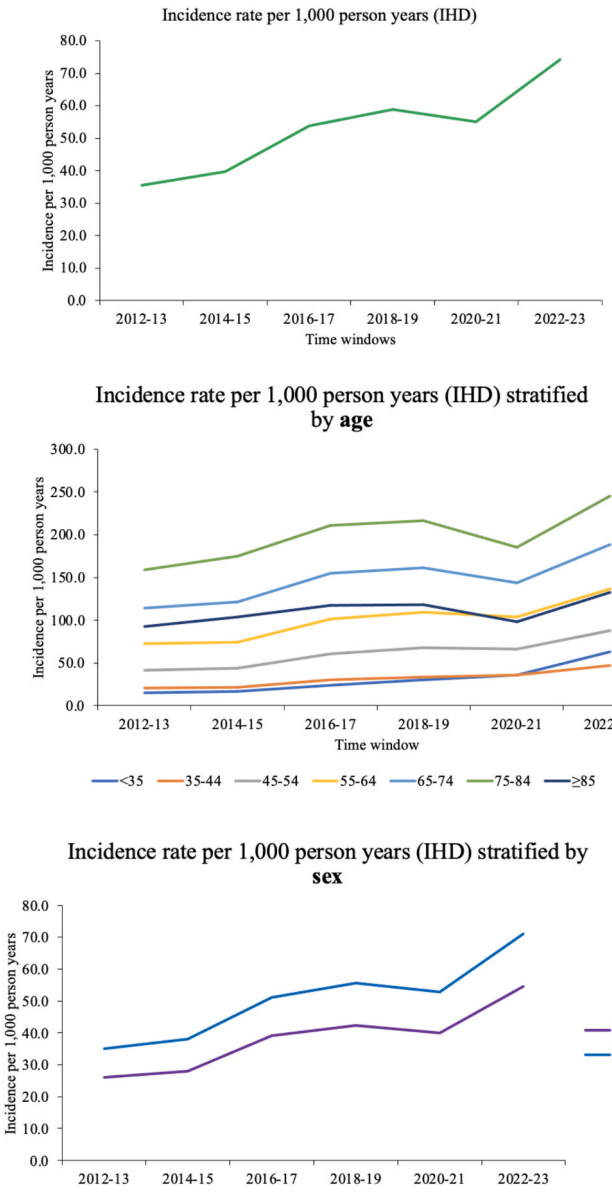


Fig. 4. 4a (Top): Overall incident rate of IHD per 1,000 person-years. **4b (Middle):** Incidence rate of IHD (cases per 1,000 person-years) stratified by age. **4c (Bottom):** Incidence rate of IHD (cases per 1,000 person-years) stratified by sex.

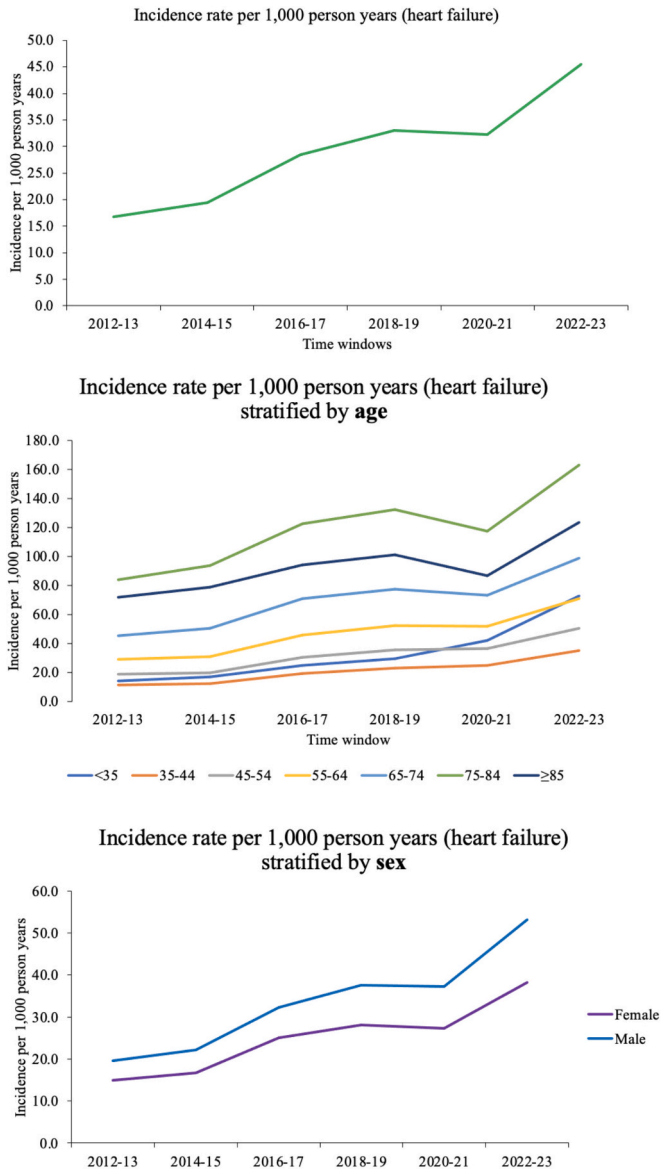


Fig. 5. 5a (Top): Overall incident rate of heart failure per 1,000 person-years. **5b (Middle):** Incidence rate of heart failure (cases per 1,000 person-years) stratified by age. **5c (Bottom):** Incidence rate of heart failure (cases per 1,000 person-years) stratified by sex.

analysis was stratified by year of diabetes diagnosis and cases were only deemed prevalent if they occurred within 2.5 years of diagnosis, thus not capturing the full burden of disease. Most report that hospitalisation for myocardial infarction has consistently fallen in individuals with diabetes [15,19,20]. However, a Spanish study reported a cumulative increase in discharges following myocardial infarction in individuals with T2D from 2001 to 2010 [21] whilst estimates from a Swedish registry reported stable prevalence rates of CV disease in T2D between 1996 and 2003 [22]. Studies that have captured outcomes based on ICD-10 coding and not just hospitalisation and mortality are limited to our data, and evidence from the South Korean national health insurance service, which reported a decrease in incidence of IHD and stroke from 2006 to 2013 [15].

Similarly, hospitalisation and mortality from heart failure has decreased over the past decade [23,24], we however have reported an increase in diagnosis of heart failure by ICD-10 code, and there currently exists no other published dataset to which we can compare our findings. Whilst reduction in hospitalisation is reassuring, and possibly explained by the increase in multi-modal pharmacotherapy, ambulatory services, the widespread increase in new biomarkers of heart failure such as NT-proBNP that may have led to an increase in diagnosis of heart failure, including milder cases [25].

Global age-standardised incidence rate of ischaemic stroke is projected to increase from 2020 to 2030 [26] but this was not stratified by diabetes. However, evidence from populations with diabetes is more mixed. One study between 2004 and 2009 reported stable incidence of stroke in individuals with diabetes [27], and another study of 670,602 individuals with diabetes in Canada reported a significant reduction in hospitalisation for stroke from 1992 to 2000 [19]. Similarly, reduction in incidence reduced from 2005 to 2009, however, authors noted a significant increase in stroke in the latter part of the study (2009–2014) [28] which better reflects the time period that we investigated and the significant increase in ischaemic stroke we observed from 2008. A smaller Swedish study of 9702 reported a reducing incidence of ischaemic stroke in individuals with T2D between 1996 and 2003 [22], yet a study of over 2.5 million individuals within the Korean National

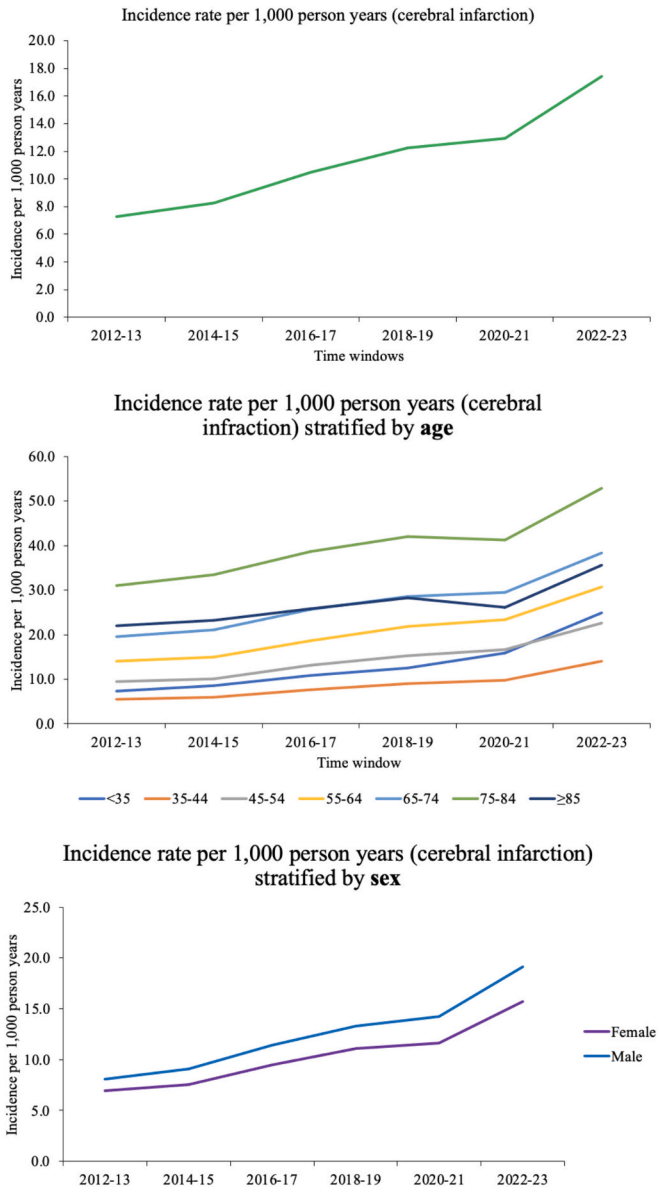


Fig. 6. 6a (Top): Overall incident rate of cerebral infarction per 1,000 person-years. **6b (Middle):** Incidence rate of cerebral infarction (cases per 1,000 person-years) stratified by age. **6c (Bottom):** Incidence rate of cerebral infarction (cases per 1,000 person-years) stratified by sex.

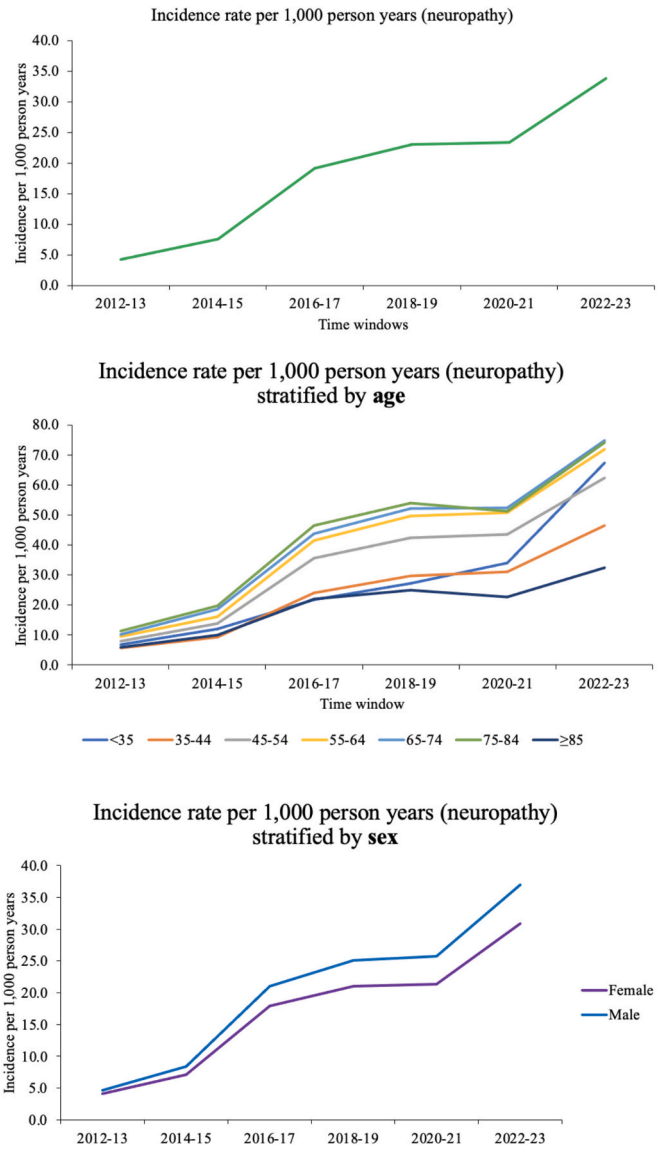


Fig. 7. 7a (Top): Overall incident rate of diabetic neuropathy per 1,000 person-years. **7b (Middle):** Incidence rate of diabetic neuropathy (cases per 1,000 person-years) stratified by age. **7c (Bottom):** Incidence rate of diabetic neuropathy (cases per 1,000 person-years) stratified by sex.

Health Insurance Services demonstrated significant reduction in hospitalisation for ischaemic stroke (−28.92 %) from 2006 to 2013 [15]. In summary, the current epidemiological research is highly heterogenous, and many published reports rely on historic data beyond recent time points, and report only significant disease requiring hospitalisation.

4.2. *Microvascular disease*

There are even fewer epidemiological studies capturing changes in rates of microvascular disease in diabetes. Evidence from the UK Clinical Practice Research Datalink of 7.7 million patients from 2004 to 2014 reported incidence of diabetic retinopathy increased from 2004 to 2011 in both T1D and T2D, and screening for retinopathy increased over time [29]. Data from the National Council for the Blind of Ireland (2004–2013) reported an increase in visual impairment due to diabetic retinopathy but a decrease in blindness from retinopathy [30]. Pooled data from 8 population-based eye surveys within the US predicts the prevalence and burden of diabetic retinopathy to increase substantially over the coming years, driven by an increase in prevalence of T2D and increasing survival of individuals with T2D, which is reflected by our findings [31]. Wider availability of digital fundal imaging, and advances in teleophthalmology and artificial intelligence have increased the rate of early, timely diagnosis of retinopathy. We captured rates of all diabetic retinopathy, regardless of grade and this is mostly reflected by other large population-based analysis where rates of all diabetic retinopathy have increased, despite a reduction in severe disease and blindness.

Diabetic nephropathy remains a leading cause of CKD and end-stage renal disease (ESRD) globally, particularly among individuals with T2D. The annual incidence of albuminuria is ~ 8 % in T2D, with the incidence of low eGFR is approximately 2 % to 4 % per year irrespective of the aetiology of diabetes [4]. When T2D develops between the ages of 15–24 years, the lifetime risk of moderate albuminuria is almost 100 %, underscoring the disproportionate impact of complications on younger individuals [32]. Prevalence of diabetic renal disease varies significantly by comparable regions, ranging from 15 % in the Netherlands to 42 % in

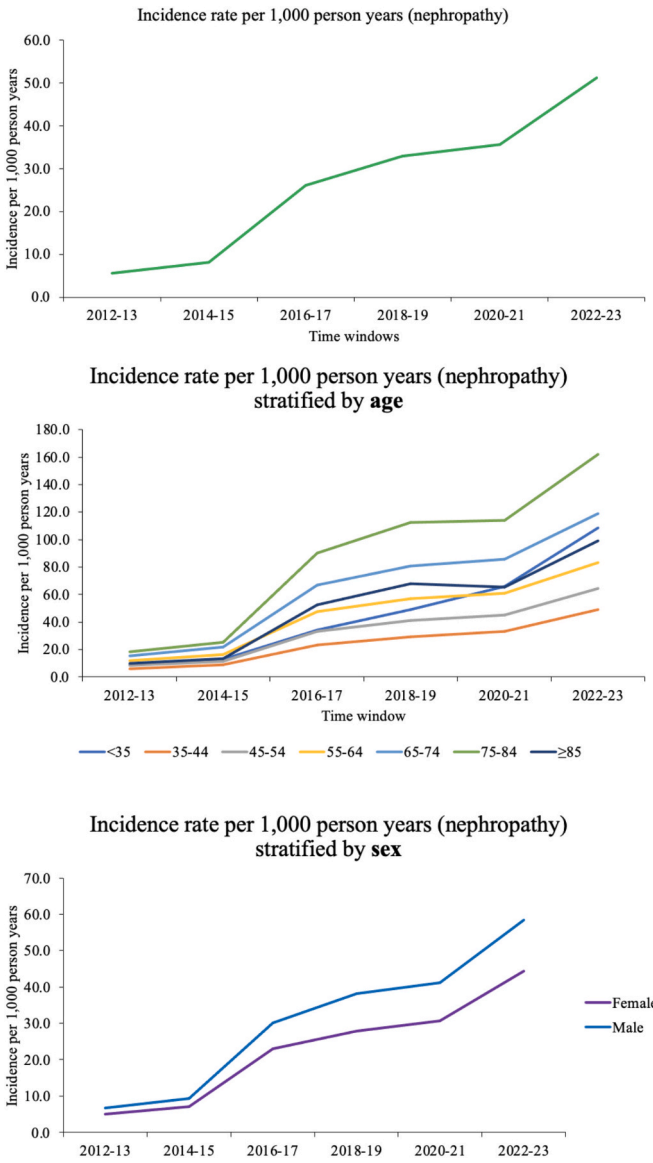


Fig. 8. 8a (Top): Overall incident rate of diabetic nephropathy per 1,000 person-years. **8b (Middle):** Incidence rate of diabetic nephropathy (cases per 1,000 person-years) stratified by age. **8c (Bottom):** Incidence rate of diabetic nephropathy (cases per 1,000 person-years) stratified by sex.

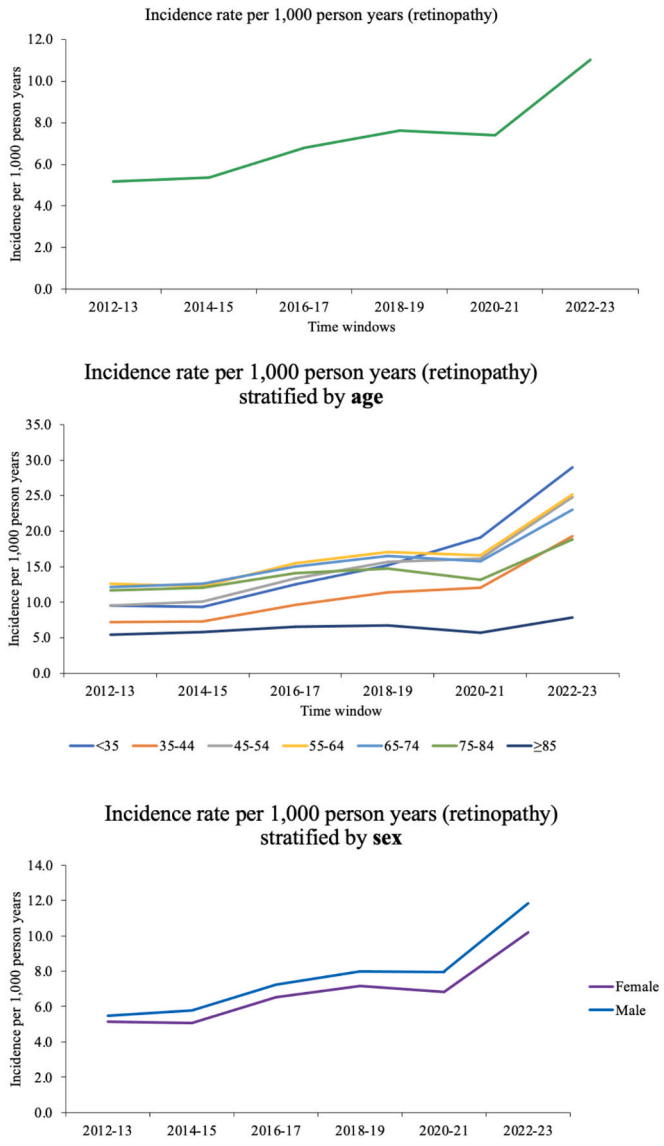


Fig. 9. 9a (Top): Overall incident rate of diabetic retinopathy per 1,000 person-years. **9b (Middle):** Incidence rate of diabetic retinopathy (cases per 1,000 person-years) stratified by age. **9c (Bottom):** Incidence rate of diabetic retinopathy (cases per 1,000 person-years) stratified by sex.

Germany, despite similar population demographics and access to healthcare. The UKPDS reported 38 % of individuals with newly diagnosed T2D developed albuminuria after 15-years [33]. An analysis of NHANES data revealed an increase in prevalence of low eGFR from 1988 to 2014 but no significant change in prevalence of diabetes associated CKD [34]. A Hungarian nationwide analysis revealed declining CKD prevalence in T2D, from 9.8 % in 2016 to 6.5 % in 2020, though this may suggest under-recognition or under-reporting rather than actual decreases [35]. Additionally, the rates of ESRD vary greatly by region studied. From 2002 to 2015, incidences of ESRD secondary to T2D rose in Mexico, Korea, Scotland and the USA, whilst decreasing in much of Scandinavia and Austria [10]. Between 2001 and 2015, significant increase in incidence of ESRD in T2D were observed in Thailand (+1448 %) and Russia (+981 %) [4]. Ultimately, the heterogeneity of coding of diabetic nephropathy compounds efforts to accurately assess any dynamic changes in incidence and prevalence.

Diabetic neuropathy is a complex, multi-faceted condition including distal symmetrical sensory neuropathy, autonomic neuropathy, and Charcot neuroarthropathy. Precise estimates in part may be hampered due to the lack of standardised diagnostic criteria and heterogenous nature of the disease. Evidence from the US Diabetes Surveillance System reports an increase in the rate of hospitalisation for neuropathy [36]. It is well known that rates of neuropathy increase with length of duration of diabetes, a Danish longitudinal study reported a cumulative incidence of 10 % over a 13 year follow up period from initial diagnosis of T2D [37]. Similarly, from over 30 years of data from the Pittsburgh Epidemiology of Diabetes Complications Study of individuals with T1D demonstrated decline in autonomic and distal symmetrical polyneuropathy at 20 and 25 years in individuals diagnosed with T1D later (1975–1980 compared to 1965–1980) [38]. Limitations of this dataset includes relatively small numbers of individuals recruited, 906, the historic nature of the reporting of incidence which cannot be extrapolated to our study period in question and the poor sensitivity of methods used to diagnose neuropathy.

4.3. *Strengths and limitations*

It is the largest study to date to report on the temporal change in

Table 2
Summary of increase in **incident rates** of diabetes associated complications between 2012 and 2023.

Macrovascular Complications		Microvascular Complications	
Age (years)	Percentage change in incidence per 1,000 person years [2012/13 to 2022/23] (%)	Age (years)	Percentage change in incidence per 1,000 person years [2012/13 to 2022/23] (%)
Ischaemic heart disease		Neuropathy	
<35	+326	<35	+885
35–44	+132	35–44	+737
45–54	+112	45–54	+680
55–64	+88	55–64	+664
65–74	+65	65–74	+634
75–84	+55	75–84	+556
≥85	+43	≥85	+464
Heart failure		**Nephropathy**	
<35	+412	<35	+1134
35–44	+205	35–44	+735
45–54	+167	45–54	+685
55–64	+144	55–64	+593
65–74	+118	65–74	+673
75–84	+94	75–84	+785
≥85	+72	≥85	+887
Cerebral Infarction		**Retinopathy**	
<35	+241	<35	+204
35–44	+158	35–44	+170
45–54	+139	45–54	+159
55–64	+118	55–64	+100
65–74	+97	65–74	+91
75–84	+70	75–84	+62
≥85	+62	≥85	+46

Table 3
Summary of increase in **prevalence** and change in prevalence of diabetes associated complications between 2012 and 2023.

	Prevalence (%)		Percentage change in prevalence [2012/13 to 2022/23] (%)
	2012–13	2022–23	
Ischaemic heart disease	12.99	26.86	+107
Heart failure	5.55	14.91	+169
Cerebral infarction	2.41	6.64	+176
Neuropathy	1.49	11.62	+680
Nephropathy	1.97	15.67	+695
Retinopathy	2.12	4.74	+124

incidence and prevalence of macro- and microvascular disease in T2D, using real world data, composes of just under 8 million individuals spanning over a decade with consistent age and sex proportions. Our dynamic cohort design is more representative of actual populations, which are not static but constantly changing. This makes the results more generalisable to real-world settings. However, there are limitations typical of large, federated databases including reliance on accurate coding of diagnosis using ICD-10 (subject to intra-physician variation and threshold for diagnosis). Due to the nature of the data source, this dataset may face some typical data quality challenges of EMRs such as incomplete or inaccurate data entries, limited granularity and exclusion of data not integrated into the HCO's EMR. We may have underestimated the incidence of microvascular complications, as not all patients undergo routine standardised assessments, and exclusive reliance on diagnostic codes without supporting clinical or laboratory data may lead to under- or overestimation of disease rates. The lower-than-expected prevalence of neuropathy and nephropathy, particularly in the earlier years, may be due to the switch over from ICD to 9 to ICD-10 coding, and rates in the first years should be interpreted with caution. Most of our HCOs were US based, and the transition from ICD to 9 to ICD-10 coding occurred between 2014 and 2016, and whilst we mapped diseases across, we cannot guarantee that every code was mapped across accurately. Within the last reporting years (2022–23), we noted a substantial spike in incidence rate across all macro- and microvascular complications, particularly compared to the former years. This we hypothesise may be a 'rebound' effect following the early phases of the COVID 19 pandemic, and the subsequent IOR calculated may have been inflated due to this phenomenon, but nevertheless, the trend towards younger age of diagnosis remains. Because our data overwhelmingly utilised EMRs of individuals within the United States, such demography is subject to a variety of socio-economic biases and insurance coverage, which is not applicable or generalisable to many other regions and territories. The reduction in MACE in diabetes is not universal; lower income countries and underrepresented ethnic and indigenous groups are disproportionately at higher risk of complications and there are some reports of increasing incidence these groups [39,40]. The commonality of increasing incidence and prevalence of macro- and microvascular complications are likely to be multifactorial. The increased survival of individuals with diabetes, an increase in awareness that complications manifest earlier and sub-clinically in the disease course of diabetes, the younger onset of T2D which is typically associated with a more aggressive metabolic phenotype [41], and the utility of diagnostic investigations with great sensitivity and specificity may partially explain the increase in prevalence and incidence respectively that we observed, however the observational nature of our study precludes causal interpretation and should be viewed as hypothesis generating. Importantly however, our findings of increased incidence of disease in younger individuals was consistent throughout all studied complications and highlights the need for continued early screening of younger populations [42].

5. Conclusion

From a cohort of approximately 8 million individuals with T2D, we observed a rising disease burden over the past decade, marked by a substantial increase in both the incidence and prevalence of macrovascular and microvascular complications. Notably, these trends disproportionately affected younger individuals, with a clear shift toward earlier age of onset. These findings stand in contrast to widely reported declines in hospitalisation rates and cardiovascular mortality. Our data highlight an emerging epidemic of early-onset T2D and its associated complications, underscoring the cumulative burden of disease that is accumulating at increasingly younger ages.

6. Contributors

MA conceived the idea of this work. MA conducted the analysis and led the write up the original draft manuscript. AEH and HE assisted with write up of the paper. GHI facilitated access to the TriNetX platform and assisted in generating the results and analysis. IM, SF, AG, GYHP, DW, BAP, KN and DJC provided senior author input, review and editing of the manuscript. UA oversaw all aspects of study development, design and provided senior review of the work.

7. Data sharing statement

The data that support the findings of this study are available from TriNetX, LLC but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. However, for accredited researchers, the TriNetX data is available for licensing at TriNetX, LLC. To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained. No data from Liverpool University Hospitals NHS Foundation Trust was utilized in this analysis.

CRediT authorship contribution statement

Matthew Anson: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Alex E. Henney:** Writing – review & editing, Writing – original draft. **Harry Edwards:** Writing – original draft. **Gema H. Ibarburu:** Methodology. **Ify Mordi:** Writing – review & editing. **Shabbar Jaffar:** Writing – review & editing. **Anupam Garrib:** Writing – review & editing. **Gregory Y.H. Lip:** Writing – review & editing. **Duolao Wang:** Writing – review & editing. **Katarzyna Nabrdalik:** Writing – review & editing. **Bruce A. Perkins:** Writing – review & editing. **Daniel J. Cuthbertson:** Writing – review & editing. **Uazman Alam:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MA receives a fellowship from the Novo Nordisk UK research foundation and JDRF. DJC has received investigator-initiated grants from Astra Zeneca and Novo Nordisk, support for education from Perspectum with any financial remuneration from pharmaceutical company consultation made to the University of Liverpool. GHI is an employee of TriNetX LLC. UA has received honoraria from Eli Lilly, Procter & Gamble, Viatris, Grunenthal and Sanofi for educational meetings and funding for attendance to an educational meeting from Diiachi Sankyo. UA has also received investigator-led funding by Procter & Gamble and is a council member of the Royal Society of Medicine's Vascular, Lipid & Metabolic Medicine Section. B.A.P. has received honoraria for educational events from Medtronic, Novo Nordisk, Sanofi, Insulet, and Abbott. His research institute has received funding from BMO Bank of Montreal and Novo Nordisk for research support. He has served as an advisor to Boehringer Ingelheim, Sanofi, Insulet, Abbott, Nephris, and Vertex Pharmaceuticals. KN received remunerations/fees for activities on behalf of Sanofi-Aventis, Eli Lilly, Novo Nordisk, Servier, Astra Zeneca, Boehringer-Ingelheim, Bioton, Polfa Tarchomin, Roche, and Abbott.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112431.

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