Trends of clinical parameters and incidences of diabetes mellitus complications among patients with type 2 diabetes mellitus in Hong Kong, 2010–2019: a retrospective cohort study

Yuan Wang,[a] Wanchun Xu,[a] Ivy Lynn Mak,[a] Weng Yee Chin,[a] Esther Yee Tak Yu,[a] Cindy Lo Kuen Lam,[a,b,**] and Eric Yuk Fai Wan[a,c,d,*]

[a]Department of Family Medicine and Primary Care, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[b]Department of Family Medicine, The University of Hong Kong - Shenzhen Hospital, Guangdong, China
[c]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[d]Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong SAR, China

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Summary

Background Diabetes mellitus-related characteristics, including available medications, onset ages, and newly-introduced management program, have been changing recently in Hong Kong, especially after the introduction of the Risk Assessment and Management Program–Diabetes Mellitus in all outpatient clinics in 2009. To understand the plural change and improve the management of patients with Type 2 Diabetes Mellitus (T2DM) based on the latest data, we examined the trends of clinical parameters, T2DM complications and mortality in patients with T2DM in Hong Kong from 2010 to 2019.

Methods In this retrospective cohort study, we acquired data from the Clinical Management System of the Hospital Authority in Hong Kong. Among adults with T2DM diagnosed on or before Sept 30, 2010, and with at least one attendance in general outpatient clinics between Aug 1, 2009, to Sept 30, 2010, we investigated the age-standardised trends of clinical parameters including haemoglobin A1c, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), body mass index and estimated glomerular filtration rate (eGFR), complications including cardiovascular disease (CVD), peripheral vascular disease (PVD), sight-threatening diabetic retinopathy (STDR), neuropathy, eGFR<45 mL/min/1.73 m^2 and end-stage renal disease (ESRD), and all-cause mortality from 2010 to 2019 and tested the statistical significance of the trends using generalised estimating equation by sex, level of clinical parameters and age groups.

Findings In total, 82,650 males and 97,734 females with T2DM were identified. LDL-C decreased from 3 to 2 mmol/L in both males and females, while other clinical parameters changed within 5% over the full decade from 2010 to 2019. CVD, PVD, STDR, and neuropathy had declining incidences, while ESRD and all-cause mortality had increasing incidences from 2010 to 2019. The incidence of eGFR<45 mL/min/1.73 m^2 increased in males but decreased in females. The odds ratio (OR) of ESRD (1.13, 95% CI [1.12, 1.15]) was highest in both males and females while the ORs of STDR (0.94, 95% CI [0.92, 0.96]) and neuropathy (0.90, 95% CI [0.88, 0.92]) were lowest in males and females, respectively. Complications and all-cause mortality trends varied among baseline HbA1c, eGFR, and age subgroups. In contrast to the findings in other age groups, the incidence of any outcomes did not decrease in younger patients (<45 years) from 2010 to 2019.

Interpretation Improvements were observed in LDL-C and incidences of most complications from 2010 to 2019. Worse performance in the younger age group and increasing incidence of renal complications and mortality need more attention in managing patients with T2DM.

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*Corresponding author. Department of Family Medicine and Primary Care, The University of Hong Kong, 3/F Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong, China.
**Corresponding author. Department of Family Medicine and Primary Care, The University of Hong Kong, 3/F Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong, China.
E-mail addresses: yfwan@hku.hk (E.Y.F. Wan), clklam@hku.hk (C.L.K. Lam).

Translation For the Chinese translation of the abstract see Supplementary Materials section.

Keywords: Type 2 diabetes mellitus; Complications; Clinical parameters; Trends

Research in context

Evidence before this study

We searched PubMed and Embase on Oct 1, 2022, for articles published in English using the search terms "trend", "diabetes", "parameter" or "risk factor", and "complications", with no date restrictions. Analyses on the trends of diabetes mellitus (DM)-related complications have been conducted in the UK, the US, Japan, Taiwan and Hong Kong, reporting declining incidences of mortality, nephropathy, retinopathy, neuropathy, chronic kidney disease, stroke, coronary heart disease, heart failure and hyperglycaemic crisis. Analysis on the trend of DM-related clinical parameters has been conducted in Singapore, reporting improved control for glycated haemoglobin and low-density lipoprotein cholesterol (LDL-C) but worsened control for blood pressure. However, only limited complications or clinical parameters have been investigated in each study. Comprehensive analysis on the trends of complications and clinical parameters in the same cohort is still lacking. Moreover, the introduction of the Risk Assessment and Management Program–Diabetes Mellitus (RAMP-DM) in August 2009 called for re-examination on the temporal trends of DM-related clinical parameters, complications, and mortality in Hong Kong.

Added value of this study

This is the first population-based study in Hong Kong to comprehensively analyse the trends of clinical parameters, complications and mortality. Our territory-wide study identified 82,650 males and 97,734 females with follow-up period of 10 years. Generalised estimating equations were applied to test the statistical significance of temporal trends by sex, level of clinical parameters and age groups. Findings from this study show declining trend for LDL-C, declining incidences for cardiovascular disease, peripheral vascular disease, sight-threatening diabetes retinopathy, neuropathy, and estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 (females only) and increasing incidences for eGFR < 45 mL/min/1.73 m^2 (males only), end-stage renal disease and all-cause mortality. Heterogeneity of trends was detected in haemoglobin A1c, eGFR and age subgroups. By contrast to the findings in other age groups, the incidence of any outcomes did not decrease in younger patients (<45 years) from 2010 to 2019. In sum, improvements were observed in LDL-C and incidences of most complications from 2010 to 2019. However, worse performance in the younger age group and increasing incidence of renal complications and mortality need more attention in managing patients with T2DM.

Implications of all the available evidence

Consistent with some studies conducted in other countries or regions, the findings of our study in Hong Kong confirmed the improvement in LDL-C and incidences of cardiovascular disease, peripheral vascular disease, sight-threatening diabetic retinopathy, and neuropathy. However, the increasing incidences of renal disease and all-cause mortality seen in our study, which have rarely been mentioned in previous work, suggest that more attention needs to be placed on the management of patients with T2DM. Additionally, the younger age group had poorer trends in all outcomes, indicating the necessity of tighter control and higher quality of care in young patients with T2DM. Further studies are warranted to confirm the reason and mechanisms of the observed trends.

Introduction

Type 2 Diabetes Mellitus (T2DM) has been an increasing epidemic in Asia over the recent decades.[1,2] China has been identified as the country with the second largest population of diabetes by the World Health Organization (WHO), with a predicted diabetic population of 42.3 million in 2030.[3] T2DM increases the risk of cardiovascular disease (CVD), peripheral vascular disease (PVD), sight-threatening diabetic retinopathy (STDR), diabetic neuropathy, and renal complications.[4–8] Furthermore, T2DM and its complications are associated with excess mortality.[9,10] Many studies have addressed the important roles of clinical parameters, including haemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), and estimated glomerular filtration rate (eGFR) in the management of patients with T2DM regarding their risk of complications and mortality.[11–15]

It is worth noting that diabetes mellitus-related characteristics have been changing recently, including younger onset age,[1] changing lifestyle,[16,17] broader choices of available medications such as statins, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLP-2) inhibitors, and glucagon-like peptide 1 (GLP-1) analogue.[18–21] To timely understand the latest trends of T2DM complications and clinical parameters under these changes, several studies have been conducted in the UK, the US, Japan, Taiwan, Hong Kong, and Singapore in past decades.[22–27] However, only a limited number of T2DM complications, including coronary heart disease (CHD), stroke,

heart failure, and hyperglycaemic crisis, without any clinical parameters have been analysed in Hong Kong.[26] Moreover, the Hospital Authority (HA), a statutory body that governs all public hospitals and government outpatient clinics in Hong Kong, introduced the Risk Assessment and Management Program–Diabetes Mellitus (RAMP-DM) in August 2009 to improve the quality of diabetes care in general outpatient clinics (GOPC). Information on the trends of T2DM complications and clinical parameters after the introduction of RAMP-DM is still lacking. To understand the latest trends and improve the management of patients with T2DM, we examined the temporal trends of clinical parameters, T2DM complications and mortality from 2010 to 2019 in this study.

Methods

Ethics

The study was approved by the Institutional Review Board of the University of Hong Kong—the Hospital Authority Hong Kong West Cluster (reference number: UW 19–329). As anonymous data were extracted from an electronic health database, under Hong Kong regulations and approval from the Hospital Authority, consent from participants was not required.

Data source and study design

Data used in this study were acquired from the Clinical Management System of the Hong Kong HA. The HA is the statutory administrative body that serves as the main publicly funded healthcare provider and sole publicly funded acute care provider in Hong Kong Special Administrative Region (HKSAR). It manages 43 public hospitals, 49 specialist outpatient clinics, and 73 primary care clinics and recorded more than 70% of hospitalization in Hong Kong. Over 20 million attendances at public healthcare facilities were recorded by the HA in 2018–2019.[28] In the Clinical Management System, records from all public hospitals, ambulatory clinics, specialist clinics, general out-patient clinics, and emergency rooms managed by HA were linked using patients' Hong Kong identity card numbers to provide real-time updated clinical data including patients' demographic information, diagnoses, medication, and laboratory tests.

This study included adults with T2DM diagnosed on or before September 30, 2010, and at least one GOPC attendance from August 1, 2009, to September 30, 2010. The first GOPC attendance from August 1, 2009, to September 30, 2010, was defined as the baseline. Patients with Type 1 Diabetes Mellitus throughout the whole study period (from January 1, 2006, to December 31, 2019) or with any complications, including CHD, stroke, heart failure, PVD, STDR, diabetic neuropathy, end-stage renal disease (ESRD), and eGFR<45 mL/min/1.73 m^2 on or before baseline were excluded.

Outcomes

Outcomes included the first incidence of CVD, CHD, stroke, heart failure, PVD, STDR, diabetic neuropathy, eGFR <45 mL/min/1.73 m^2, ESRD, and all-cause mortality. The first incidence of CVD was defined as the earliest incidence of CHD, stroke or heart failure. Only the first incidence was counted in the calculation of annual incidence, and patients were censored at any incidence of an outcome event. eGFR was calculated using the formula developed and validated by the Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI).[29] The mortality data were captured by the mortality reports retrieved from the internal population data of Hong Kong Government Death Registry. Detailed operational definitions and diagnostic codes for these outcomes are listed in Supplementary Table S1.

Statistical analysis

Patient characteristics including age, smoking status, comorbidities (hypertension, atrial fibrillation, amputation, dementia, chronic lung disease, connective tissue disease, peptic ulcer disease, liver disease, chronic kidney disease, and cancer), and use of medications (anti-diabetic drugs, anti-hypertensive drugs, and lipid-lowering agents) in each year from 2010 to 2019 of the included patients were reported for males and females separately.

Age-standardised means for the clinical parameters and incidences of outcomes were calculated using the standard age distribution defined in 2015 and visualised by line charts in males and females separately. Generalised estimating equations (GEE) were applied to test the longitudinal trends of clinical parameters and outcome incidences to adjust for the unstructured correlation among the measurements or responses in different calendar years.[30] This method can handle repeated measurements in the same person without specification of correlation structure. The GEE models in this study included the calendar year as the independent variable and were adjusted for the confounding effect of age. Identity and logit links were applied in the GEE models for clinical parameters and outcome incidences, respectively.

Comparisons between different clinical parameter subgroups (HbA1c < 7, HbA1c ≥ 7%; SBP<130 and DBP<80, SBP≥130 or DBP≥80 mmHg; LDL-C<2.6, LDL-C≥2.6 mmol/L; BMI<23, BMI≥23 kg/m^2; eGFR<90, eGFR≥90 mL/min/1.73 m^2) and age subgroups (<45; 45–74; ≥75 years) at baseline were also conducted in the trend analyses of clinical parameters and outcome incidences. Moreover, two more subgroup analyses were conducted to investigate the change of LDL-C and SBP in new users of lipid-lowering agents and anti-hypertensive drugs, respectively. All statistical analyses were conducted in males and females individually. In addition, three sensitivity analyses were performed to ensure the robustness of the findings: 1) the

standard age distribution was defined in 2010; 2) the standard age distribution was defined in 2019; 3) the mean of clinical parameters and incidence of complications were standardised by both age and duration of T2DM. No post-hoc analysis was performed.

Two-tailed tests with p-value significance level of 0.05 were used in this study. Moreover, we also provided corrected significance levels for multiple comparison using Bonferroni correction. The statistical analyses were executed in Stata version 15.1 (College Station, Texas).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

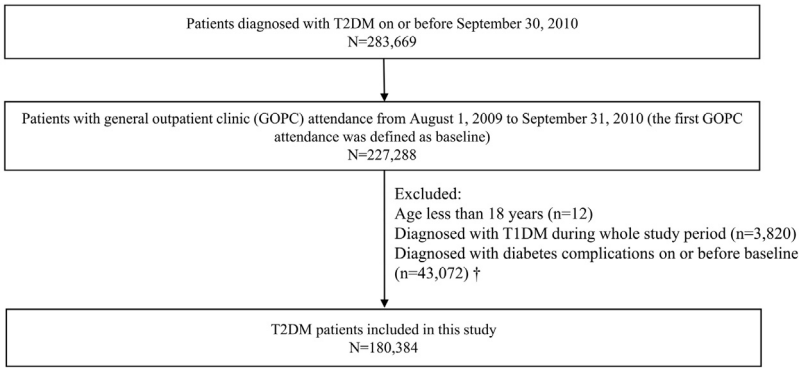
Results

Between Aug 1, 2009, and Sept 30, 2010, 82,650 (45.8%) males and 97,734 (54.2%) female patients with T2DM were included in this study (Fig. 1). The number of surviving patients and their characteristics in each year from 2010 to 2019 were reported in Table 1. Data completion rates of the clinical parameters for each year are summarised in Supplementary Table S2.

Results of the GEE models (Table 2) suggested that all the clinical parameters had statistically significant increasing (HbA1c and BMI) or decreasing (SBP, DBP, LDL-C and eGFR) trends from 2010 to 2019. These trends are also illustrated in Fig. 2. For males, HbA1c remained stable from 2010 to 2014 and increased from 7.1% to 7.4% from 2014 to 2019. SBP decreased from 135.4 mmHg in 2010 to 130.0 mmHg in 2015 and returns to 131.8 mmHg in 2019. DBP decreased from 75.1 mmHg to 73.1 mmHg from 2010 to 2014 and stayed unchanged afterwards. LDL-C showed a rapid decrease from 2.9 mmol/L to 2.0 mmol/L from 2010 to 2019. BMI increased from 25.0 kg/m^2 to 25.4 kg/m^2 from 2010 to 2019. eGFR decreased from 75.1 to 71.8 mL/min/1.73 m^2 from 2010 to 2019. Similar trends of clinical parameters were observed for females.

GEE results for outcome incidences were reported in Table 3 and the longitudinal trends were illustrated in Fig. 3. The incidence for all outcomes, except for PVD and neuropathy, had statistically significantly changed from 2010 to 2019 in both males and females. The incidence of ESRD and all-cause mortality increased, while the incidence of CVD, CHD, stroke, heart failure, and STDR decreased from 2010 to 2019 for both males and females. The incidence of PVD and neuropathy decreased in females only, while the incidence of eGFR<45 mL/min/1.73 m^2 increased in males but decreased in females. Among all complications, the incidence of ESRD had the most rapid increase in both males and females (OR 1.13, 95% CI [1.12, 1.15]), while the incidence of STDR (OR 0.94, 95% CI [0.92, 0.96]) and neuropathy (OR 0.90, 95% CI [0.88, 0.92]) had the most rapid decrease in males and females, respectively.

Trends of clinical parameters and the corresponding GEE results in subgroup analyses are reported in Supplementary Figs. S1–S6 and Supplementary Table S3, respectively. Overall, the investigated clinical parameters demonstrated similar trends between subgroups, except less or no improvements in SBP or LDL-C were found in patients with lower baseline values of SBP and LDL-C, respectively. Trends of outcome incidences in different subgroups based on their clinical parameter values at baseline were illustrated in Supplementary Figs. S7–S11, where eGFR subgroups had different trends for most outcomes and HbA1c subgroups had different trends for PVD, STDR, and neuropathy. Other clinical parameters, including BP, LDL-C, and BMI, showed similar overall trends between subgroups. Supplementary Fig. S12 illustrates the trends of outcome incidence by age groups at baseline



† Diabetes complications include coronary heart disease, stroke, heart failure, peripheral vascular disease, sight-threatening diabetic retinopathy, diabetic neuropathy, estimated glomerular filtration rate <45 mL/min/1.73m² and end-stage renal disease.

Fig. 1: **Flowchart of inclusion and exclusion criteria.**

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Male										
Number[a]	82,464	81,410	80,130	78,777	77,288	75,717	74,074	72,228	70,346	68,368
Age, years (mean(SD))	62.9 (11.3)	63.8 (11.3)	64.6 (11.2)	65.4 (11.2)	66.2 (11.1)	67.0 (11.0)	67.8 (10.9)	68.5 (10.8)	69.3 (10.7)	70.0 (10.6)
Smoker (%)	10,494 (12.7%)	10,398 (12.8%)	10,263 (12.8%)	10,134 (12.9%)	9968 (12.9%)	9803 (12.9%)	9611 (13.0%)	9395 (13.0%)	9152 (13.0%)	8908 (13.0%)
Charlson comorbidity index (mean(SD))	3.7 (1.1)	3.8 (1.0)	3.8 (1.0)	3.9 (1.0)	4.0 (1.0)	4.0 (0.9)	4.1 (0.9)	4.1 (0.9)	4.2 (0.9)	4.3 (0.8)
Hypertension (%)	54,956 (66.6%)	54,475 (66.9%)	54,244 (67.7%)	54,015 (68.6%)	52,934 (68.5%)	51,459 (68.0%)	49,688 (67.1%)	47,736 (66.1%)	45,755 (65.0%)	44,384 (64.9%)
Atrial fibrillation (%)	924 (1.1%)	1000 (1.2%)	1099 (1.4%)	1197 (1.5%)	1283 (1.7%)	1404 (1.9%)	1462 (2.0%)	1548 (2.1%)	1623 (2.3%)	1672 (2.4%)
Amputation (%)	21 (0.0%)	25 (0.0%)	24 (0.0%)	17 (0.0%)	21 (0.0%)	28 (0.0%)	20 (0.0%)	26 (0.0%)	26 (0.0%)	32 (0.0%)
Dementia (%)	272 (0.3%)	334 (0.4%)	390 (0.5%)	403 (0.5%)	408 (0.5%)	426 (0.6%)	424 (0.6%)	408 (0.6%)	393 (0.6%)	381 (0.6%)
Chronic lung disease (%)	1819 (2.2%)	1769 (2.2%)	1877 (2.3%)	1760 (2.2%)	1717 (2.2%)	1767 (2.3%)	1758 (2.4%)	1638 (2.3%)	1574 (2.2%)	2089 (3.1%)
Connective tissue disease (%)	5 (0.0%)	8 (0.0%)	8 (0.0%)	5 (0.0%)	12 (0.0%)	5 (0.0%)	8 (0.0%)	7 (0.0%)	4 (0.0%)	11 (0.0%)
Peptic ulcer disease (%)	648 (0.8%)	629 (0.8%)	635 (0.8%)	575 (0.7%)	624 (0.8%)	612 (0.8%)	565 (0.8%)	551 (0.8%)	581 (0.8%)	772 (1.1%)
Liver disease (%)	1403 (1.7%)	1251 (1.5%)	1322 (1.6%)	1308 (1.7%)	1335 (1.7%)	1314 (1.7%)	1326 (1.8%)	1310 (1.8%)	1321 (1.9%)	1666 (2.4%)
Chronic kidney disease (%)	8237 (10.0%)	10,826 (13.3%)	12,807 (16.0%)	14,634 (18.6%)	15,950 (20.6%)	17,237 (22.8%)	18,435 (24.9%)	19,794 (27.4%)	20,247 (28.8%)	21,146 (30.9%)
Cancer (%)	1883 (2.3%)	1921 (2.4%)	1917 (2.4%)	1902 (2.4%)	1897 (2.5%)	1993 (2.6%)	1959 (2.6%)	1999 (2.8%)	1988 (2.8%)	2166 (3.2%)
Use of anti-diabetic drugs (%)	70,745 (85.8%)	69,806 (85.7%)	69,048 (86.2%)	68,123 (86.5%)	67,102 (86.8%)	65,860 (87.0%)	64,501 (87.1%)	63,008 (87.2%)	61,529 (87.5%)	60,051 (87.8%)
Use of anti-hypertensive drugs (%)	59,956 (72.7%)	61,286 (75.3%)	62,104 (77.5%)	62,501 (79.3%)	62,278 (80.6%)	61,408 (81.1%)	60,372 (81.5%)	58,983 (81.7%)	57,811 (82.2%)	56,361 (82.4%)
Use of lipid-lowering agents (%)	20,424 (24.8%)	29,479 (36.2%)	36,764 (45.9%)	41,952 (53.3%)	45,645 (59.1%)	47,894 (63.3%)	49,165 (66.4%)	49,406 (68.4%)	49,282 (70.1%)	48,948 (71.6%)
Female										
Number[a]	97,564	96,685	95,651	94,445	93,168	91,673	90,076	88,288	86,399	84,426
Age, years (mean(SD))	65.2 (11.7)	66.1 (11.7)	67.0 (11.6)	67.9 (11.6)	68.7 (11.5)	69.5 (11.4)	70.3 (11.3)	71.0 (11.2)	71.8 (11.1)	72.5 (11.0)
Smoker (%)	1193 (1.2%)	1188 (1.2%)	1181 (1.2%)	1167 (1.2%)	1148 (1.2%)	1129 (1.2%)	1106 (1.2%)	1083 (1.2%)	1061 (1.2%)	1036 (1.2%)
Charlson comorbidity index (mean(SD))	3.9 (1.0)	3.9 (1.0)	4.0 (1.0)	4.1 (1.0)	4.1 (0.9)	4.2 (0.9)	4.2 (0.9)	4.3 (0.8)	4.3 (0.8)	4.4 (0.8)
Hypertension (%)	71,006 (72.8%)	69,945 (72.3%)	69,488 (72.6%)	69,013 (73.1%)	67,569 (72.5%)	65,770 (71.7%)	63,729 (70.8%)	61,692 (69.9%)	59,261 (68.6%)	57,735 (68.4%)
Atrial fibrillation (%)	939 (1.0%)	1083 (1.1%)	1183 (1.2%)	1334 (1.4%)	1447 (1.6%)	1555 (1.7%)	1648 (1.8%)	1762 (2.0%)	1796 (2.1%)	1883 (2.2%)
Amputation (%)	42 (0.0%)	29 (0.0%)	27 (0.0%)	28 (0.0%)	33 (0.0%)	23 (0.0%)	12 (0.0%)	28 (0.0%)	27 (0.0%)	27 (0.0%)
Dementia (%)	668 (0.7%)	757 (0.8%)	888 (0.9%)	927 (1.0%)	900 (1.0%)	983 (1.1%)	1001 (1.1%)	1047 (1.2%)	1028 (1.2%)	904 (1.1%)
Chronic lung disease (%)	791 (0.8%)	722 (0.7%)	790 (0.8%)	759 (0.8%)	728 (0.8%)	776 (0.8%)	823 (0.9%)	788 (0.9%)	668 (0.8%)	1818 (2.2%)
Connective tissue disease (%)	25 (0.0%)	18 (0.0%)	21 (0.0%)	23 (0.0%)	25 (0.0%)	29 (0.0%)	34 (0.0%)	18 (0.0%)	23 (0.0%)	27 (0.0%)
Peptic ulcer disease (%)	522 (0.5%)	543 (0.6%)	539 (0.6%)	546 (0.6%)	547 (0.6%)	551 (0.6%)	498 (0.6%)	467 (0.5%)	600 (0.7%)	702 (0.8%)
Liver disease (%)	1376 (1.4%)	1424 (1.5%)	1457 (1.5%)	1517 (1.6%)	1580 (1.7%)	1604 (1.7%)	1699 (1.9%)	1717 (1.9%)	1662 (1.9%)	2276 (2.7%)
Chronic kidney disease (%)	10,457 (10.7%)	13,692 (14.2%)	15,803 (16.5%)	17,810 (18.9%)	19,573 (21.0%)	20,906 (22.8%)	22,531 (25.0%)	24,213 (27.4%)	24,985 (28.9%)	25,982 (30.8%)
Cancer (%)	1912 (2.0%)	1854 (1.9%)	1838 (1.9%)	1951 (2.1%)	1903 (2.0%)	1961 (2.1%)	1932 (2.1%)	1964 (2.2%)	1864 (2.2%)	2240 (2.7%)
Use of anti-diabetic drugs (%)	81,735 (83.8%)	81,685 (84.5%)	81,622 (85.3%)	81,150 (85.9%)	80,314 (86.2%)	79,169 (86.4%)	77,966 (86.6%)	76,397 (86.5%)	75,026 (86.8%)	73,677 (87.3%)
Use of anti-hypertensive drugs (%)	75,023 (76.9%)	75,975 (78.6%)	76,709 (80.2%)	77,065 (81.6%)	76,844 (82.5%)	75,911 (82.8%)	74,753 (83.0%)	73,459 (83.2%)	72,092 (83.4%)	70,684 (83.7%)
Use of lipid-lowering agents (%)	27,561 (28.2%)	39,063 (40.4%)	48,140 (50.3%)	54,415 (57.6%)	58,579 (62.9%)	61,366 (66.9%)	62,904 (69.8%)	63,336 (71.7%)	63,123 (73.1%)	62,731 (74.3%)

SD = Standard deviation. [a]Dead patients were excluded from the calculation from the year of death.

Table 1: **Characteristics of patients with type 2 diabetes mellitus.**

	Male		Female	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Haemoglobin A1c	0.03 (0.03, 0.03)	<0.01[a]	0.02 (0.02, 0.03)	<0.01[a]
Systolic blood pressure	−0.39 (−0.40, −0.37)	<0.01[a]	−0.37 (−0.38, −0.36)	<0.01[a]
Diastolic blood pressure	−0.17 (−0.18, −0.16)	<0.01[a]	−0.21 (−0.22, −0.20)	<0.01[a]
Low-density lipoprotein cholesterol	−0.09 (−0.10, −0.09)	<0.01[a]	−0.10 (−0.10, −0.10)	<0.01[a]
Body mass index	0.04 (0.03, 0.04)	<0.01[a]	0.01 (0.01, 0.01)	<0.01[a]
Estimated glomerular filtration rate	−0.53 (−0.54, −0.51)	<0.01[a]	−0.55 (−0.56, −0.54)	<0.01[a]

CI = confidence interval. [a]Indicates statistical significance with p-value <0.05.

Table 2: **Longitudinal trends of cardiometabolic and renal risk factors from generalized estimating equation models.**

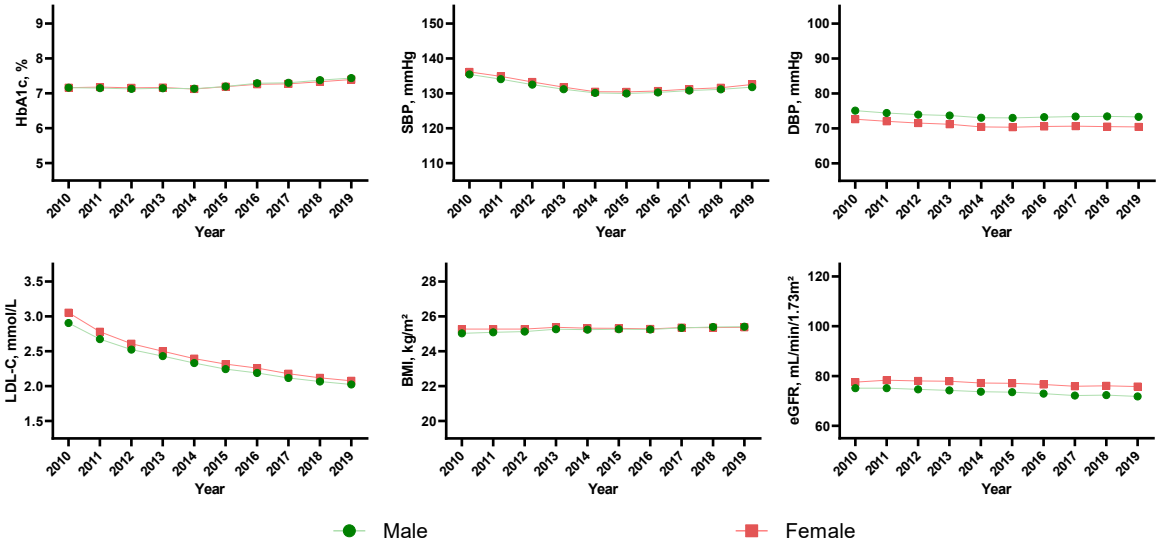


Fig. 2: **Trend of cardiometabolic and renal risk factors from 2010 to 2019 in T2DM population**. T2DM = type 2 diabetes mellitus; HbA1c = haemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C =low-density lipoprotein cholesterol; BMI = body mass index; eGFR = estimated glomerular filtration rate.

	Male		Female	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Cardiovascular disease	0.97 (0.96, 0.97)	<0.01[a]	0.97 (0.96, 0.97)	<0.01[a]
Coronary heart disease	0.98 (0.97, 0.98)	<0.01[a]	0.98 (0.97, 0.99)	<0.01[a]
Stroke	0.97 (0.96, 0.97)	<0.01[a]	0.96 (0.95, 0.97)	<0.01[a]
Heart failure	0.98 (0.97, 0.99)	<0.01[a]	0.98 (0.97, 0.99)	<0.01[a]
Peripheral vascular disease	1.00 (0.98, 1.02)	0.99	0.94 (0.92, 0.96)	<0.01[a]
Sight-threatening diabetic retinopathy	0.94 (0.92, 0.96)	<0.01[a]	0.93 (0.91, 0.95)	<0.01[a]
Neuropathy	0.99 (0.97, 1.01)	0.37	0.90 (0.88, 0.92)	<0.01[a]
eGFR < 45 mL/min/1.73m^2	1.02 (1.01, 1.02)	<0.01[a]	0.99 (0.99, 1.00)	<0.01[a]
End-stage renal disease	1.13 (1.12, 1.15)	<0.01[a]	1.13 (1.12, 1.15)	<0.01[a]
All-cause mortality	1.03 (1.02, 1.03)	<0.01[a]	1.04 (1.03, 1.04)	<0.01[a]

OR = odds ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate. [a]Indicates statistical significance with p-value <0.05.

Table 3: **Odds ratio of diabetes complications and all-cause mortality from generalized estimating equation models.**

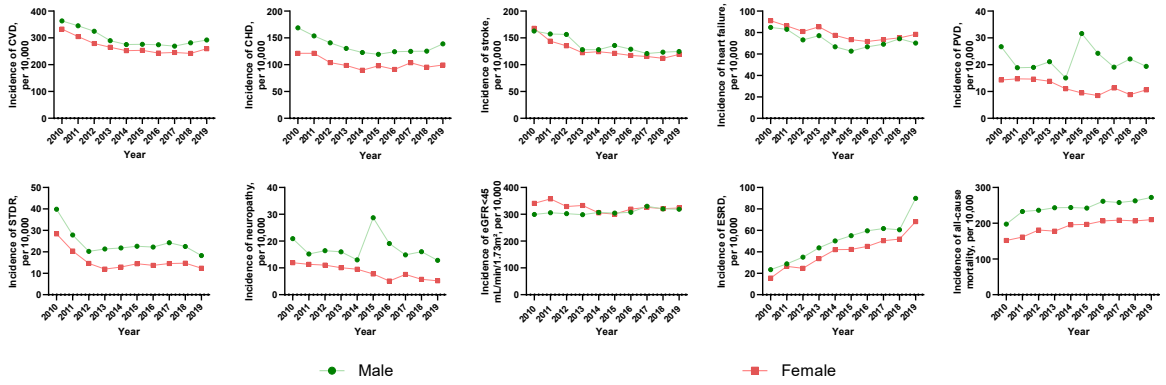


***Fig. 3*: Trend of diabetes complications and mortality from 2010 to 2019 in T2DM population**. T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; CHD = coronary heart disease; PVD = peripheral vascular disease; STDR = sight-threatening diabetic retinopathy; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease

(<45; 45–74; ≥75 years). The incidence of most outcomes changed differently among age subgroups. Among patients aged <45 years, no statistically significant decrease was observed in the incidences of CVD, CHD, stroke, heart failure, PVD, STDR, and neuropathy and there were significant increases in the incidences of stroke (OR 1.11, 95% CI [1.02, 1.20]) in males and heart failure (OR 1.22, 95% CI [1.01, 1.48]) and STDR (OR 1.17, 95% CI [1.08, 1.27]) in females based on the GEE results (Supplementary Table S4). As shown in Supplementary Fig. S13, new users of lipid-lowering medication had relatively higher LDL-C in 2010 and a more rapid decline of LDL-C from 2010 to 2019, compared to patients without lipid-lowering agents. The coefficient of the interaction term of calendar year and new users of lipid-lowering agents (–0.08; 95% CI: [–0.08, –0.08]) in the GEE model was reported in Supplementary Table S5, indicating that the annual decline of LDL-C in new users of lipid-lowering agents was 0.08 mmol/L per year more than that in patients without lipid-lowering agents. Supplementary Fig. S14 showed higher SBP in new users of anti-hypertensive drugs than patients without anti-hypertensive drugs. The SBP in new users of anti-hypertensive drugs declined while the SBP in patients never use anti-hypertensive drugs were relatively stable, which indicated a beneficial effect of anti-hypertensive drugs in lower SBP. Supplementary Table S6 reported the coefficient of the interaction term (–0.57, 95% CI: [–0.61, –0.53] for males; –0.54, 95% CI: [–0.58, –0.50] for females), indicating that the annual decline of SBP in new users of anti-hypertensive drugs was 0.54–0.57 mmHg per year more than that in patients without anti-hypertensive drugs.

The sensitivity analyses demonstrated similar findings to the main analysis (Supplementary Figs. S15–S20). Moreover, we reported results of GEE with significance levels and confidence intervals corrected for multiple comparison using Bonferroni correction in Supplementary Tables S7 and S8

Discussion

This retrospective cohort study investigated the trends of clinical parameters and the incidence of T2DM complications and mortality in patients with T2DM in Hong Kong from 2010 to 2019. LDL-C were well controlled with a rapid decrease while other clinical parameters were relatively stable in both males and females with T2DM. The incidences for most complications changed significantly from 2010 to 2019 in patients with T2DM in Hong Kong. From 2010 to 2019, the incidence of eGFR<45 mL/min/1.73 m^2 (males only), ESRD, and mortality increased while that of CVD, CHD, stroke, heart failure, PVD (females only), STDR, neuropathy (females only), and eGFR<45 mL/min/1.73 m^2 (females only) decreased. The trends of outcome incidence varied among different baseline HbA1c and eGFR values, as well as age subgroups. In contrast to the findings in older patients (≥75 years), the incidence of any outcomes did not decrease in younger patients (<45 years) from 2010 to 2019. The findings of this study indicate an overall improvement in the management of patients with T2DM in Hong Kong and also highlight the potentially insufficient care in young patients and suboptimal control in the risk of renal complications and mortality.

Our study observed a rapid decline in LDL-C levels but relatively stable trends in other clinical parameters from 2010 to 2019. A recent Singapore study on patients with diabetes mellitus, more than 95% of whom had T2DM, reported decreasing HbA1c (from 7.4 to 7.2%) and LDL-C (from 2.4 to 2.2 mmol/L) and increasing SBP (from 132 to 135 mmHg) and DBP (from 70 to 71 mmHg) from 2013 to 2019.[27] Moreover, insignificant trends in BMI and DBP but significant decreases in SBP

(from 135 to 130 mmHg) and LDL-C (from 3.6 to 2.8 mmol/L) from 1999 to 2011 were reported in patients with T2DM in the Tehran Lipid and Glucose Study.[31] The rapid decline in LDL-C and relatively small changes (within 5%) in other clinical parameters in Singapore and Tehran were similar to our findings in Hong Kong. Starting with a mean value of 2.9 (3.1 for females) mmol/L in 2010 for males, patients in this study quickly achieved the treatment target of <2.6 mmol/L, consistent with the recommendations by the Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings[32] in 2012, and kept declining to 2.0 (2.1 for females) mmol/L in 2019 for males. Another study in Hong Kong confirmed the finding of a sharp declining LDL-C trend in the early period (from 2010 to 2012) in our study, where mean LDL-C in patients with T2DM declined from 3.0 mmol/L in 2010 to 2.6 mmol/L in 2012.[33] The better control of LDL-C could have resulted from the increasing use of lipid-lowering drugs in Hong Kong, evident from an increase of 163.5%–188.7% in the proportion of patients using lipid-lowering agents (from 24.8% to 71.6% for males; from 28.2% to 74.3% for females) in 2019 among patients with T2DM (Table 1). A previous study also reported that the prescription prevalence of statins had over 4-fold increase from 1.82% in 2004 to 8.68% in 2015, and the statins initiation rate increased from 0.44% in 2004 to 1.23% in 2013 in Hong Kong, and attributed such changes to the Hong Kong primary care reference frameworks for lipid management in patients with diabetes, which recommend initiating statin therapy with low- or moderate-intensity statins based on the patient's cardiovascular risk.[18,32] Consistent with this finding, a study of US diabetic patients found a continuous decrease in the mean LDL-C level from 3.0 mmol/L to 2.7 mmol/L accompanied an increase in the use of statins from 26.2% to 49.5%, from 1999 to 2002 to 2011–2014.[34] Subgroup analyses in this current study showed no excess incidence for most outcomes in patients with suboptimal baseline LDL-C, which might also be attributed to the remarkable improvement of LDL-C, particularly in the early period from 2010 to 2012.

In addition to LDL-C, the change of other clinical parameters, although relatively smaller, were also statistically significant. The decline of blood pressure implies satisfactory control with more use of antihypertensive drugs. However, the increasing HbA1c and BMI might call for the need of tighter blood glucose control and lifestyle improvement. The declining eGFR, as well as the increasing incidence of ESRD, would draw more attention on the monitoring and treatment of declining renal function in patients with T2DM.

Studies conducted in several high-income countries or regions have reported a decline in T2DM complications and mortality since 2000. The declining incidences of CHD, stroke, and heart failure in an earlier period from 2001 to 2016 in Hong Kong have been revealed based on the Hong Kong Diabetes Surveillance Database.[26] From 2010 to 2019, a declining incidence of heart failure in both males and females with T2DM was reported in Australia.[35] The incidence of STDR in females with T2DM in Taiwan decreased (from 10.8 to 6.0 cases per 1000 person-years) from 2005 to 2011.[36] A study reported a 32% decline in the prevalence of neuropathy from 2004 to 2014 in Japanese patients with T2DM.[24] The incidence rate of kidney failure decreased by 46.8% from 2002 to 2007 and then flattened from 2007 to 2015 in diabetes patients in Hong Kong.[37] The incidences of all-cause mortality decreased by 32% in males and 31% in females with diabetes from 2001 to 2018 in the UK,[22] by 29% from 2000 to 2015 in diabetes patients in the US,[23] by 12% in males and 14% in females with diabetes from 2005 to 2014 in Taiwan,[25] and by 29% in males and 17% in females with T2DM from 2002 to 2014 in Australia.[38] In our study, a similar declining trend in the incidence of most T2DM complications, including CVD, CHD, stroke, heart failure, PVD, STDR, and neuropathy, were observed in patients with T2DM. The declines in Hong Kong might be due to improved lifestyles, the healthcare system and medications. An upward vegetable intake trend was observed among adults in Hong Kong from 2004 to 2016,[16] which might, as a healthier dietary habit, benefit patients with T2DM.[39,40] Additionally, government statistics reported higher physical activity levels from 2006 to 2016 and less consumption of meat from 2007 to 2016, which further indicated improving lifestyles and might contribute to the declining rates of T2DM complications.[17,40] However, it is noteworthy that the proportion of smokers was found to be overall static (slowly increase in males), indicating more education might be needed to prevent smoking in patients with T2DM. Decrease in the incidence of T2DM complications might also benefit from the wider prescription of related drugs including statins and DPP-4 inhibitors, which have been proven to be effective for preventing T2DM complications and mortality, under the advances in local practice guidelines.[18,19,41,42] Last but not least, the initiation of the Risk Assessment and Management Program–Diabetes Mellitus (RAMP-DM) in August 2009, which conducted care planning, multidisciplinary care, and scheduled monitoring of complications in the general out-patient clinics in Hong Kong based on risk level stratification, also enhanced T2DM management in primary care and contributed to reducing the incidences of cardiovascular and microvascular complications in diabetes patients.[43–45]

The incidences of renal disease (eGFR<45 mL/min/1.73 m^2 in males and ESRD in both males and females) and all-cause mortality were increased in our study from 2010 to 2019 (Table 3 and Fig. 3). Interestingly, the GEE model in our study identified opposite trends for the incidence of eGFR<45 mL/min/1.73 m^2 in males and females. In Fig. 3, it could be observed that males had gradually increasing incidence of eGFR<45 mL/min/

1.73 m^2 (from 300 to 320 cases per 10,000 patients from 2010 to 2019) while that of females rapidly decreased from 380 to 300 cases per 10,000 patients from 2011 to 2015 followed by similar increasing trend as males. Consistent with our findings, a cross-sectional survey reported higher prevalence of CKD in females (12.9%, 95% CI: [12.0, 13.7]) compared to males (8.7%, 95% CI [8.0–9.5]) in the period from September 2009 to September 2010.[46] Such a discrepancy could be correlated with not only sex-specific CKD etiologic trends but also different access to care for CKD caused by social disparities between males and females.[47] However, few studies have investigated the sex difference in the incidence of eGFR<45 mL/min/1.73 m^2. The declined incidence of eGFR<45 mL/min/1.73 m^2 in females and the reduced sex disparity might attribute to highlighted importance and conceivable improvement in the management of females with T2DM after 2010 in Hong Kong. Although the observed sex difference in the incidence of eGFR<45 mL/min/1.73 m^2 is less than 60 per 10,000 patients with T2DM, which could not be considered high compared with the total incidence (300–360 per 10,000 patients with T2DM), further studies were still needed to confirm the exact reason for the sex disparities. The deteriorated renal function, evident from both the increasing incidence of renal disease and the decreasing eGFR, was possibly associated with increased HbA1c and BMI (Table 2 and Fig. 2). A previous study reported higher risks of ESRD and mortality in patients with T2DM with increasing HbA1c trend than those with lower stable HbA1c trend.[48] In addition, higher BMI is an independent predictor of major renal events in patients with T2DM.[49] The J-shaped association between BMI and all-cause mortality in patients with T2DM also suggested BMI may be a possible reason for the increasing incidence of all-cause mortality.[50] However, some existing studies reported declining incidences of renal disease and mortality.[22,23,25,37,38] Although such discrepancies could be partially explained by the reduced average duration of T2DM (due to the inclusion of patients with newly diagnosed T2DM in previous studies, compared with the fixed cohort in our study), it is still worthwhile to pay more attention to the management of patients with T2DM in Hong Kong regarding their renal function and survival risk.[22,23,25,37,38]

The findings from the age subgroup analyses suggested that the decreasing incidence of complications was primarily observed in older patients, particularly those aged ≥75 years. In comparison, patients aged <45 years had no improvements regarding the incidences of CVD, CHD, stroke, heart failure, PVD, STDR, and neuropathy. Similar differences among age subgroups were also reported in the previous study in Hong Kong, where improvements in outcomes were observed for older age subgroups (45–64; 65–74; ≥75 years) but not in young patients with T2DM (20–44 years).[26] In recent studies conducted in Asia, progressively younger ages of T2DM onset were reported. Patients with young-onset (<40 years) T2DM had poorer glycaemic control and higher rates of retinopathy and ESRD compared with patients with late-onset (≥40 years) T2DM, possibly associated with poorer lifestyles and medication adherence.[1,51] In western countries, including the UK and Australia, young-onset (UK: <40; Australia: 15–30, years) T2DM was also associated with inadequate treatment to prevent cardiovascular disease, and higher risks of morbidity and mortality.[52,53] Compatible with the higher risk of complications in young-onset T2DM reported by previous studies, our study further suggested inadequate risk factors control in younger patients with T2DM (<45 years at enrolment). No improvement or even faster progression in the incidence of T2DM complications were found in younger patients with T2DM. In addition to possible lifestyle and medication adherence reasons discussed earlier,[19,51] more rapid β-cell decline in younger patients with T2DM (20–35% per year) compared with that in patients with late-onset T2DM (around 7% per year) might also contribute to the different observations in the trends for morbidities, based on the evidence from several large-scale studies including A Diabetes Outcome Progression Trial (ADOPT), the UK Prospective Diabetes Study (UKPDS) and the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial.[54–58] Moreover, the Restoring Insulin Secretion (RISE) study reported distinctly different changes in β-cell function in patients with different age, where β-cell function improved during treatment in adults but deteriorated in youths during treatment and after treatment withdraw.[59] Undiscovered reasons for age differences in the incidence of T2DM complications need to be clarified by further explorations.

Our study has several strengths. First, the territory-wide coverage of the data source ensured high representativeness and minimal selection bias of the studied cohort. Second, we have a follow-up duration of 10 years, which provides sufficient length for performing trend analyses. Thirdly, the large sample size ensured sufficient statistical power. Third, use of a fixed cohort reduced the possible effect of changing cohort on the trends of T2DM complications and clinical parameters. Fourth, our study included complications and clinical parameters that have not been investigated before (incidence of PVD, STDR, neuropathy, and eGFR <45 mL/min/1.73 m^2; BMI and eGFR). Fifth, our study focused on the temporal trends after the introduction of RAMP-DM, which provides the latest review on the management of patients with T2DM under RAMP-DM over a full decade. Some of our findings (e.g. the increasing incidences of renal diseases; the different trends of incidence of eGFR <45 mL/min/1.73 m^2 between males and females), which have not been reported by previous studies, could be important in

improving the management of patients with T2DM in Hong Kong and serve as reference for further studies. Finally, we comprehensively investigated ten outcomes together with clinical parameters and were able to notice any potential associations between the trends of outcomes and either clinical parameters or other outcomes.

Our study also has several limitations. First, only patients attending public hospitals or clinics under the HA were included in this study. Hence, patients attending only private health services facilities might be missed. Nevertheless, the number would be small because most patients in Hong Kong would opt for public sector services provided by HA for chronic disease management as the cost of healthcare is subsidised by the government.[60] Second, diagnostic codes were used to identify outcome events, which might be prone to misclassification. However, the accuracy of coding in the Clinical Management System under HA has been verified in previous studies in Hong Kong.[61,62] Third, detailed information on the trends of the prescription of antidiabetic agents and detailed lifestyle information were not available in our data, which might preclude causative analyses. Fourth, the completion rate of BMI and body weight was relatively low in our study. Fifth, causes of death were not considered in the current study, while cause-specific death would have provided more depth to the analysis. Sixth, the use of a fixed cohort in the current study could not capture variables related to the changing cohort, including disease onset and diagnosis and social-economic factors. Seventh, the generalisability of our study could be restricted since our study period was immediately after the introduction of RAMP-DM, which is a territory-wide program that only affect T2DM patients in Hong Kong. However, with similar ethnicities and lifestyles between Hong Kong and other regions in Asia, our findings could also prompt further studies on the trends of T2DM management not only in Hong Kong but also in China mainland or other Asian countries. Finally, we did not thoroughly investigate the reasons for the observed trends; for example, via statistical models on the association between time-variant clinical parameters and the risk of outcomes. Further studies are warranted to explore the reasons and mechanisms of the findings in this study.

During the 10-year follow-up of patients with T2DM, we observed improvements in LDL-C and incidences for most T2DM complications from 2010 to 2019. However, the incidences of renal complications and mortality increased, suggesting more attention for the management of patients with T2DM may be needed. Additionally, the younger age group had poorer trends in all outcomes, indicating the necessity of tighter control and higher quality of care in young patients with T2DM. More studies are warranted to confirm the reason and mechanisms of the observed trends.

Contributors

YW, CLKL, and EYFW conceived, designed the study and act as guarantors of the study. YW and EYFW have directly accessed and verified the data. YW contributed to the literature review, statistical analysis, result interpretation and draft of the manuscript. All authors reviewed and edited the manuscript. EYFW is the principal investigator and provided oversight for all aspects of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data will not be made available to others because the data custodians have not given permission.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101999.

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