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Does 10-Year Atherosclerotic Cardiovascular Disease Risk Predict Incident Diabetic Nephropathy and Retinopathy in Patients with Type 2 Diabetes Mellitus? Results from Two Prospective Cohort Studies in Southern China

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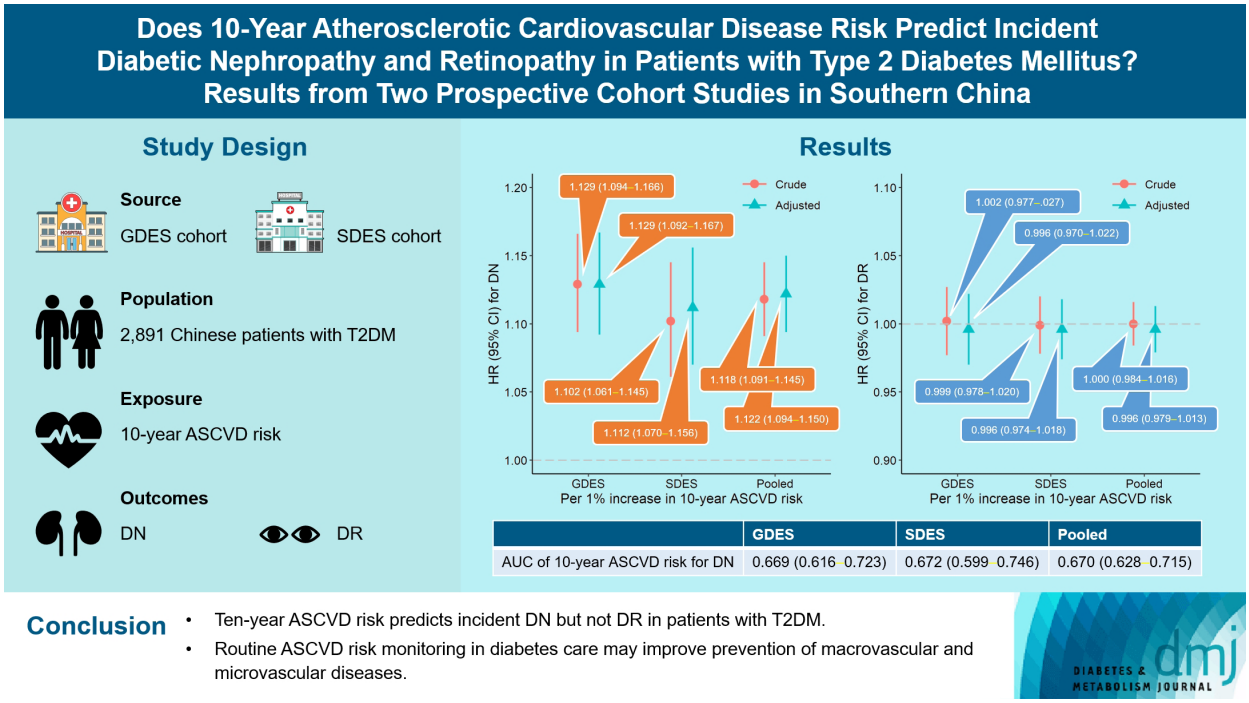

Highlights

- **Ten-year ASCVD risk predicts incident DN but not DR in patients with T2DM.**
- **The association of 10-year ASCVD risk with DN and DR is stronger in women.**
- **Monitoring of ASCVD risk in T2DM management may support early interventions.**

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Does 10-Year Atherosclerotic Cardiovascular Disease Risk Predict Incident Diabetic Nephropathy and Retinopathy in Patients with Type 2 Diabetes Mellitus? Results from Two Prospective Cohort Studies in Southern China

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Background: Diabetic macrovascular and microvascular complications often coexist and may share similar risk factors and pathological pathways. We aimed to investigate whether 10-year atherosclerotic cardiovascular disease (ASCVD) risk, which is commonly assessed in diabetes management, can predict incident diabetic nephropathy (DN) and retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).
Methods: This prospective cohort study enrolled 2,891 patients with clinically diagnosed T2DM who were free of ASCVD, nephropathy, or retinopathy at baseline in the Guangzhou (2017–2022) and Shaoguan (2019–2021) Diabetic Eye Study in southern China. The 10-year ASCVD risk was calculated by the Prediction for ASCVD Risk in China (China-PAR) equations. Multivariable-adjusted Cox proportional hazard models were developed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The area under the receiver operating characteristic curve (AUC) was used to evaluate predictive capability.
Results: During follow-up, a total of 171 cases of DN and 532 cases of DR were documented. Each 1% increment in 10-year ASCVD risk was associated with increased risk of DN (pooled HR, 1.122; 95% CI, 1.094 to 1.150) but not DR (pooled HR, 0.996; 95% CI, 0.979 to 1.013). The model demonstrated acceptable performance in predicting new-onset DN (pooled AUC, 0.670; 95% CI, 0.628 to 0.715). These results were consistent across cohorts and subgroups, with the association appearing to be more pronounced in women.

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Conclusion: Ten-year ASCVD risk predicts incident DN but not DR in our study population with T2DM. Regular monitoring of ASCVD risk in routine diabetes practice may add to the ability to enhance population-based prevention for both macrovascular and microvascular diseases, particularly among women.

Keywords: Cardiovascular diseases; Diabetes mellitus, type 2; Diabetic nephropathies; Diabetic retinopathy; Prospective studies

INTRODUCTION

Diabetes represents a significant global public health challenge. The estimated prevalence of diabetes worldwide was 10.5% (affecting approximately 536.6 million adults) in 2021 and is projected to reach 12.2% (783.2 million adults) by 2045 [1]. Type 2 diabetes mellitus (T2DM) constitutes the vast majority of diabetes cases and is linked to an increased risk of mortality, disability, and costly chronic vascular complications that pose an escalating threat to healthcare systems [2-4]. The growing pandemic of diabetic macrovascular and microvascular complications is a major contributor to disease burden and reduced quality of life [5,6]. Atherosclerotic cardiovascular disease (ASCVD) is a major macrovascular complication which affects approximately one-third of T2DM patients [7-9]. Diabetic nephropathy (DN) and retinopathy (DR), the two most common and severe microvascular complications, are leading causes of end-stage renal disease (ESRD) and visual impairment, including preventable blindness, respectively [10-13]. Therefore, accurate assessment of individual risk profiles is critically important for population-based prevention of diabetic vascular complications [14,15].

The estimation of 10-year absolute ASCVD risk considers multiple risk factors, with clues for preclinical evaluation [16]. Early identification of individuals at high ASCVD risk can facilitate risk-stratified management and targeted interventions in clinical practice, ultimately improving patient outcomes. Prediction equations, e.g., the Pooled Cohort Equations (PCE) developed by the American College of Cardiology/the American Heart Association (ACC/AHA), have been widely used [16]. Recently, the Prediction for ASCVD Risk in China (China-PAR) project has developed and validated the Chinese ASCVD risk equations across multiple contemporary Chinese cohorts [17]. Compared to the PCE derived from Western populations, the China-PAR equations demonstrate better calibration and discrimination for the Chinese population [17]. These equations have been validated in T2DM patients [18,19], and are widely recommended as useful risk assessment tools for this population who have two to four times higher cardiovascular morbidity and mortality [9,20,21]. However, there remains a knowledge gap regarding the potential critical role of ASCVD risk prediction in diabetes care beyond identifying patients at risk for macrovascular complications.

Diabetic macrovascular and microvascular complications often coexist and may share common epidemiological risk factors and pathological pathways [22,23]. Observational studies have suggested that the presence of microvascular complications is associated with increased risk of macrovascular disease in T2DM, independent of established cardiovascular risk factors [24-28]. The impact of macrovascular disease on the risk of microvascular outcomes, however, remains largely unclear [29], and whether early assessment of 10-year ASCVD risk may benefit the prediction of microvascular complications such as DN and DR has yet to be determined. To address these knowledge gaps, we aimed to investigate whether 10-year ASCVD risk predicts incident DN and DR in two prospective cohorts of adult patients with T2DM in southern China.

METHODS

Study design and participants

The Guangzhou Diabetic Eye Study (GDES) and the Shaoguan Diabetic Eye Study (SDES) are both prospective studies conducted in Guangzhou and Shaoguan, respectively, in southern China. The design of these two cohorts was reported in detail elsewhere [30,31]. In brief, both cohorts enrolled patients aged 30 to 80 years with physician-diagnosed T2DM who received free-of-charge, comprehensive ophthalmic examination by trained ophthalmic specialists. In the GDES cohort, patients who had a primary care encounter at community health centers were referred through a community generalist-hospital specialist alliance to attend an ophthalmic examination at the Zhongshan Ophthalmic Center, a national-leading tertiary hospital specialising in ophthalmology. In the SDES cohort, patients enrolled in the primary care-based diabetes management care plans within the nationwide, basic public health ser-

vice were invited for diabetic retinal examination conducted at township health centers as part of a community screening programme initiated by the Zhongshan Ophthalmic Center. Standardised examinations were performed at baseline and during annual follow-up for both cohorts.

The presence of T2DM was ascertained by the attending primary care physician when fasting plasma glucose (PG) ≥7.0 mmol/L, 2-hour PG ≥11.1 mmol/L during a 75-g oral glucose tolerance test, or glycosylated hemoglobin (HbA1c) ≥6.5% [32, 33]. Patients with type 1 diabetes mellitus, gestational diabetes, or serious systemic diseases (e.g., severe cardiovascular or cerebrovascular disease, nephritis, or cancer) were excluded during the eligibility screening. Detailed inclusion and exclusion criteria for study participation were outlined in Supplementary Methods.

A total of 2,975 T2DM patients were enrolled in the GDES cohort between November 2017 and July 2019 and had four follow-up visits until January 2022, while a total of 4,860 T2DM patients were enrolled in the SDES cohort with annual visits between September 2019 and December 2021. Patients were excluded if they had a known or unknown status of DN and DR at baseline or if they had missing information regarding DN or DR at follow-ups. This yielded a final sample of 2,891 patients, consisting of 1,436 GDES participants and 1,455 SDES participants, who met the eligibility criteria and were included in the present analysis (Supplementary Fig. 1).

Data collection

Information on sociodemographic characteristics, lifestyle, medical history, and medication use was collected through a face-to-face questionnaire administered by trained clinical staff. Standing height and weight were measured while barefoot and wearing light clothing, by calibrated digital scale to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference (WC) was measured at the midpoint between the lower edge of the last palpable rib and the top of the iliac crest, using a non-stretchable tape to the nearest 0.1 cm. Blood pressure (BP) was recorded in a seated position after a 10-minute rest, using a routinely validated automatic sphygmomanometer. Fasting venous blood samples were collected in both cohorts. Serum creatinine (SCr), lipid profile, and HbA1c were analyzed centrally at a tertiary-level hospital laboratory unit, following standardised clinical procedures. Clean-catch midstream urine samples were collected in the morning for measurement of urinary microalbumin (mALB). The categorisation and definition of variables were described in detail in Supplementary Methods.

Assessment of diabetic nephropathy and retinopathy

SCr and mALB were measured using an automatic biochemistry analyzer (Cobas 8000, Roche Diagnostics, Basel, Switzerland). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for Asians [34]. Incident DN at follow-up was identified based on decreased renal function (i.e., eGFR <60 mL/min/1.73 m^2 in both the GDES and SDES cohorts) [12] or increased albuminuria (i.e., mALB >20 mg/dL in the GDES cohort) [35] measured according to laboratory quality standards.

A comprehensive ophthalmic assessment was performed by qualified ophthalmic specialists using slit-lamp biomicroscopy with dilated pupils and colour stereoscopic fundus photography adhering to uniform clinical procedure. Seven-standard fields were captured using a digital retinal camera (Canon CR-2, Canon, Ota, Japan). Two trained ophthalmic specialists independently graded the fundus photographs. The grading of DR was determined according to the modified Airlie House Classification scheme as adapted for the Early Treatment Diabetic Retinopathy Study (ETDRS) [36]. Disagreements (<8%) were resolved by a senior ophthalmologist. Incident DR at follow-up was defined as mild non-proliferative diabetic retinopathy (NPDR; level 35 as per the ETDRS scale), moderate NPDR (levels 43–47), severe NPDR (level 53), or proliferative diabetic retinopathy (levels 61–85), based on the worse eye [36].

Estimation of 10-year ASCVD risk

The risk of experiencing a first ASCVD event (i.e., non-fatal acute myocardial infarction, coronary heart disease death, or fatal or non-fatal stroke) within 10 years among individuals free of ASCVD was estimated using the China-PAR equations [17]. Variables in the sex-specific equations included age, geographic region, urban or rural residence, current smoking, diabetes, WC, treated or untreated systolic BP, total cholesterol, high-density lipoprotein cholesterol, and family history of ASCVD [17]. Participants were divided into three groups based on estimated 10-year ASCVD risk, i.e., low risk (<5.0%), medium risk (≥5.0 to 9.9%), and high risk (≥10.0%) according to the Chinese cardiovascular risk assessment and management

guideline [18]. In the sensitivity analysis, we employed the PCE as an equivalent equation to help generalize findings with comparable parameters [16], and 10-year ASCVD risk was categorised into low or borderline risk (<7.5%), intermediate risk (≥7.5% to <20%), and high risk (≥20.0%) following the 2019 ACC/AHA guideline [37]. The calculation was described in detail in Supplementary Methods.

Statistical analysis

Person-years of follow-up were calculated from the date of enrolment at baseline to the date of DN or DR diagnosis, or until the last follow-up visit, whichever occurred first. The cumulative incidence of DN and DR was determined by the Kaplan-Meier plot, and the two-sided log-rank test was used to compare curves across 10-year ASCVD risk categories. Cox proportional hazard regression models were developed to assess the association of 10-year ASCVD risk with incident DN and DR. Model assumptions were tested using Schoenfeld residuals. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated from the crude model and models adjusting for education level, regular drinking, diabetes duration, insulin use, and HbA1c. BP, lipids, and other components of the China-PAR equations were not included as covariates in the multivariable regression models to avoid overadjustment bias. Calculation of variance inflation factors, all of which were <2, indicated the absence of multicollinearity among variables.

Data were modelled as restricted cubic splines (RCS) with 3 knots, located at the 10th, 50th, and 90th percentiles of 10-year ASCVD risk, to assess the shape of the association of ASCVD risk with incident DN and DR. In the presence of a linear relationship, we estimated the HRs for DN and DR associated with each 1% increase in 10-year ASCVD risk, as well as by risk category. Tests for linear trend were based on variables containing the median value for each group. The area under the receiver operating characteristic curve (AUC) was used to evaluate the predictive ability. Cohort-specific estimates derived from separate analysis of the GDES and SDES cohorts were pooled using inverse variance-weighted, fixed-effect meta-analyses given mild to moderate heterogeneity observed between the two cohorts (I^2<50%).

Stratification analyses were performed by sociodemographic (i.e., age, sex, education level, and urban/rural residence), behavioural (i.e., cigarette smoking and alcohol drinking), metabolic (i.e., BMI, WC, hypertension, and dyslipidaemia), and diabetes-related characteristics (i.e., diabetes duration, insulin use, and HbA1c levels) to identify potential effect modifiers. Heterogeneity among subgroups was assessed by Cochrane's Q test and was considered present if *P* value <0.10.

A series of sensitivity analyses were performed. First, we estimated 10-year ASCVD risk using the PCE risk prediction model as recommended by the American Diabetes Association (ADA) [9]. Second, the HRs were directly estimated using combined participant-level data from the two cohorts, instead of pooling the estimates derived within each cohort using a two-step approach. Third, we excluded incident cases that occurred within the first year of follow-up to minimise 'reverse causality.' Fourth, we used average estimates of 10-year ASCVD risk during follow-up to account for time-varying exposure. Fifth, we fitted multivariable Cox models with further adjustment for BMI and the use of oral hypoglycemic and lipid-lowering medications. Last but not least, we examined the association between 10-year ASCVD risk and incidence of DN or DR as a composite outcome, given the data availability in the present study. Statistical analyses were conducted using Stata version 17.0 (StataCorp., College Station, TX, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value <0.05 was considered statistically significant, unless otherwise specified.

Ethical considerations

Data anonymisation was applied by removing all patient identifiers from the dataset before data analysis. Ethics approval was granted by the Zhongshan Ophthalmic Center Medical Ethics Committee (Ref: 2017KYPJ094) at Sun Yat-Sen University in accordance with the Declaration of Helsinki 2013. All study participants provided written, informed consent.

RESULTS

Characteristics of study participants

Of the 1,436 participants in the GDES cohort (mean±standard deviation age 64.3±7.5 years; 40.9% men), 247 (17.2%) had low 10-year ASCVD risk, 573 (39.9%) had medium risk, and 616 (42.9%) had high risk. In the SDES cohort which comprised 1,455 participants (age 62.1±9.3 years; 44.7% men), 222 (15.2%) had low 10-year ASCVD risk, 468 (32.2%) had medium risk, and 765 (52.6%) had high risk. Patients in the high-risk group tended to have lower education, a longer duration of diabetes, lower rates of insulin use, higher levels of BMI, HbA1c, triglycerides, SCr, and mALB, and lower eGFR than

their counterparts (Table 1).

We documented 110 DN and 277 DR events during a median follow-up of 3.04 and 2.15 years, respectively, in the GDES cohort, while 61 DN and 255 DR events were recorded after a median follow-up of 1.87 years in the SDES cohort. A higher 10-year ASCVD risk was observed in cases of DN, but not DR

Table 1. Baseline characteristics of study participants by 10-year ASCVD risk

Characteristic	GDES cohort (n=1,436)			SDES cohort (n=1,455)		
	Low 10-year ASCVD risk	Medium 10-year ASCVD risk	High 10-year ASCVD risk	Low 10-year ASCVD risk	Medium 10-year ASCVD risk	High 10-year ASCVD risk
No. of participants	247	573	616	222	468	765
Socio-demographics						
Age, yr	54.48±6.13	62.83±4.74	69.42±5.22	50.53±6.28	58.56±6.01	67.35±7.38
Male sex	87 (35.2)	235 (41.0)	265 (43.0)	63 (28.4)	171 (36.5)	417 (54.5)
Education level						
Junior secondary school or below	56 (22.7)	148 (25.8)	249 (40.4)	107 (48.2)	237 (50.7)	463 (60.5)
Senior secondary school	115 (46.5)	271 (47.3)	220 (35.7)	85 (38.3)	155 (33.1)	201 (26.3)
College or above	76 (30.8)	154 (26.9)	147 (23.9)	30 (13.5)	76 (16.2)	101 (13.2)
Urban residence	247 (100)	573 (100)	616 (100)	68 (30.6)	157 (33.5)	283 (37.0)
Lifestyle						
Current smoking	29 (11.7)	85 (14.8)	65 (10.6)	28 (13.1)	68 (15.1)	168 (22.9)
Regular drinking	19 (7.7)	50 (8.7)	56 (9.1)	23 (10.8)	58 (13.1)	92 (12.7)
Medical history						
Diabetes duration, yr	5.0 (2.0–9.0)	6.0 (3.0–11.0)	7.0 (3.0–13.0)	4.4 (2.4–6.6)	4.5 (2.6–7.4)	5.3 (2.5–9.3)
Hypertension	64 (25.9)	280 (48.9)	470 (76.3)	153 (68.9)	342 (73.1)	533 (69.7)
Dyslipidaemia	186 (75.3)	406 (70.9)	463 (75.2)	85 (38.3)	167 (35.7)	260 (34.0)
Family history of ASCVD	76 (30.8)	160 (27.9)	143 (23.2)	34 (15.3)	89 (19.0)	82 (10.7)
Use of insulin	48 (19.4)	92 (16.1)	97 (15.7)	23 (10.4)	42 (9.0)	45 (5.9)
Clinical parameters						
BMI, kg/m^2	23.89±3.53	24.23±3.12	24.97±3.09	23.78±3.39	24.44±3.20	24.95±3.53
WC, cm	82.49±10.00	84.61±8.78	87.69±8.36	81.76±9.35	84.98±9.27	87.40±9.27
SBP, mm Hg	115.70±12.90	129.41±13.91	142.93±17.51	120.54±11.38	131.78±13.24	144.21±16.89
DBP, mm Hg	66.71±9.89	70.72±10.13	71.16±10.38	77.35±9.89	81.70±9.35	85.11±11.01
HbA1c, %	6.81±1.46	6.77±1.17	6.85±1.12	7.32±1.90	7.40±1.77	7.42±1.74
TC, mmol/L	4.90±1.07	4.70±1.01	4.88±1.08	5.36±1.24	5.25±1.14	5.35±1.10
TG, mmol/L	1.63 (1.04–2.33)	1.77 (1.24–2.60)	2.13 (1.54–3.20)	1.73 (1.05–2.89)	1.73 (1.13–2.70)	1.84 (1.23–2.70)
LDL-C, mmol/L	3.12±0.98	2.92±0.91	3.09±0.96	2.73±0.84	2.67±0.82	2.74±0.81
HDL-C, mmol/L	1.45±0.45	1.34±0.41	1.20±0.36	1.35±0.61	1.31±0.51	1.23±0.29
SCr, mg/dL	0.75±0.17	0.77±0.19	0.80±0.20	0.84±0.19	0.87±0.22	0.92±0.25
eGFR, mL/min/1.73 m^2	100.19±14.43	94.35±13.30	87.54±13.96	92.70±17.62	86.58±16.65	80.94±15.35
mALB, mg/dL[a]	0.51 (0.21–1.48)	0.64 (0.25–1.63)	0.89 (0.32–2.55)	-	-	-
Estimated cardiovascular disease risk						
10-Year ASCVD risk, %	3.38±1.12	7.53±1.43	14.01±3.49	3.23±1.13	7.45±1.43	15.72±4.28

Values are presented as mean±standard deviation, number (%), or median (interquartile range). The 10-year ASCVD risk estimated by the Prediction for ASCVD Risk in China (China-PAR) equations was categorised into low risk (<5.0%), medium risk (≥5.0 to 9.9%), and high risk (≥10.0%).

ASCVD, atherosclerotic cardiovascular disease; GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; mALB, urinary microalbumin.

[a]Information on mALB in the SDES cohort was not available.

(Supplementary Tables 1 and 2). Most of the baseline characteristics were comparable between patients included in the final analysis and those excluded during follow-up, albeit slightly lower levels of 10-year ASCVD risk and mALB (among the GDES participants) and eGFR (among the SDES participants) in the final sample (Supplementary Table 3).

10-Year ASCVD risk and diabetic nephropathy and retinopathy

Compared to patients with a low 10-year ASCVD risk, those at high risk had a significantly increased cumulative incidence of DN (*P*-log-rank <0.001), but not DR (*P*-log-rank >0.10) (Supplementary Fig. 2). The dose-response diagrams indicated a positive association between 10-year ASCVD risk and DN (*P*-overall <0.001), whereas such association was not evident for DR (*P*-overall >0.10). RCS analyses revealed minimal evidence of deviation from linearity (all *P*-nonlinearity>0.05) (Fig. 1).

After controlling for covariates, each 1% increment in the 10-year ASCVD risk was associated with increased risk of DN (cohort-specific multivariable-adjusted HR: GDES 1.129 [95% CI, 1.092 to 1.167], SDES 1.112 [95% CI, 1.070 to 1.156]; pooled HR: 1.122 [95% CI, 1.094 to 1.150]), but not DR (cohort-specific multivariable-adjusted HR: GDES 0.996 [95% CI, 0.970 to 1.022], SDES 0.996 [95% CI, 0.974 to 1.018]; pooled HR: 0.996 [95% CI, 0.979 to 1.013]) (Fig. 2). Similar trends were observed across 10-year ASCVD risk categories (*P* trend <0.001 for DN; *P* trend >0.10 for DR) (Table 2). Patients with a high 10-year ASCVD risk had a 3.43-fold greater hazard of developing DN compared to those in the low-risk group (pooled HR, 4.43; 95% CI, 2.30 to 8.54). ROC curves indicated that 10-year ASCVD risk was significantly predictive of new-onset DN (pooled AUC, 0.670; 95% CI, 0.628 to 0.715), but not of DR (Supplementary Fig. 3).

Subgroup analyses

When participants were categorised by baseline characteristics, the association observed in the main analysis remained consistent across all subgroups (Fig. 3). A disparity by sex was noted (*P*-heterogeneity=0.060 for DN; *P*-heterogeneity=0.077 for DR), with women exhibiting a higher risk for both DN (pooled HR, 1.162 vs. 1.104) and DR (pooled HR, 1.019 vs. 0.987) at follow-up for each 1% increase in baseline 10-year ASCVD risk compared to men. There was little evidence of effect modification by other sociodemographic, behavioural, metabolic, or diabetes-related characteristics (all *P*-heterogeneity >0.10).

Sensitivity analyses

Sensitivity analyses by applying the PCE for cardiovascular risk estimation yielded similar results, suggesting the predictive ca-

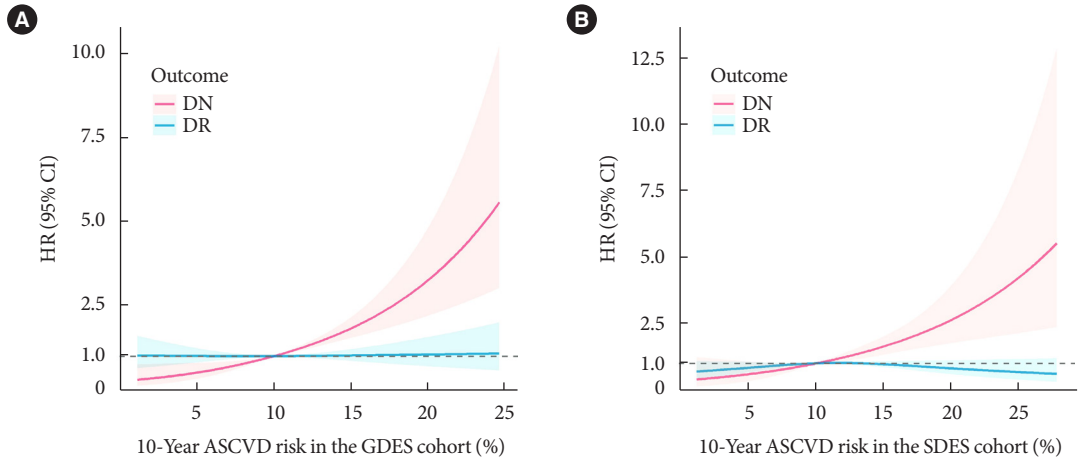

Fig. 1. Dose-response relationship of 10-year atherosclerotic cardiovascular disease (ASCVD) risk with incident diabetic nephropathy (DN) and retinopathy (DR) in the (A) Guangzhou Diabetic Eye Study (GDES) and (B) Shaoguan Diabetic Eye Study (SDES) cohorts. The dose-response relationship was examined using restricted cubic splines with 3 knots, located at the 10th, 50th, and 90th percentiles of the distribution of 10-year ASCVD risk in the GDES and SDES cohorts, respectively. The solid line represents the fitted curve, and the shaded areas represent the 95% confidence interval (CI) bands. GDES cohort: *P*-overall <0.001 and *P*-nonlinearity=0.757 for DN; *P*-overall=0.974 and *P*-nonlinearity=0.865 for DR. SDES cohort: *P*-overall <0.001 and *P*-nonlinearity=0.907 for DN; *P*-overall=0.206 and *P*-nonlinearity=0.075 for DR. HR, hazard ratio.

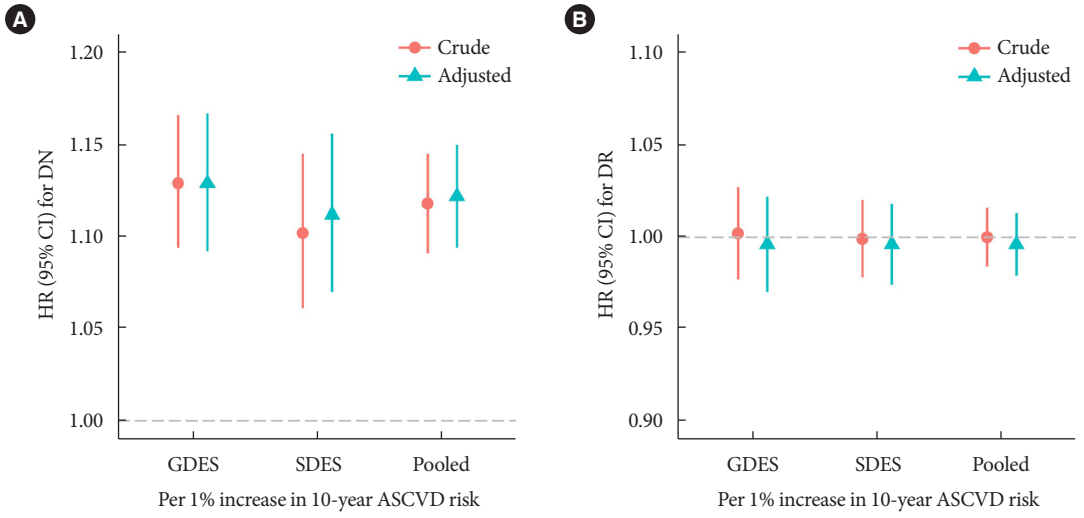

Fig. 2. Hazard ratio (HR) (95% confidence interval [CI]) for (A) diabetic nephropathy (DN) and (B) retinopathy (DR) associated with per 1% increase in 10-year atherosclerotic cardiovascular disease (ASCVD) risk. Crude model refers to Cox proportional hazard model with no adjustment. Adjusted model refers to multivariable-adjusted Cox proportional hazard model in which education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin were included as covariates. Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study.

pacity of 10-year ASCVD risk for new-onset DN (pooled AUC, 0.645; 95% CI, 0.603 to 0.691) (Supplementary Table 4). The findings remained largely unchanged when using a harmonised dataset containing individual-level data from the two cohorts, excluding participants who had new-onset DN or DR within the first year of follow-up, or accounting for time-varying ASCVD risk (Supplementary Table 5). There was a slight, albeit non-significant, attenuation of the association between 10-year ASCVD risk and incidence of DN when further adjusting for BMI or medication use. Similarly, we observed a significant association of each 1% increment in 10-year ASCVD risk with increased risk of composite outcome of incident DN or DR (pooled HR, 1.026; 95% CI, 1.011 to 1.041) (Supplementary Table 6).

DISCUSSION

In two prospective cohorts of adult patients with T2DM in southern China, we investigated whether the commonly assessed macrovascular disease risk in diabetes management can predict new-onset DN and DR, the two most important microvascular complications. We found that elevated 10-year ASCVD risk was associated with increased risk of incident DN, but not DR, in both cohorts. The model demonstrated acceptable performance in predicting DN. The association was consistent across subgroups by baseline sociodemographic, behavioural, metabolic, and diabetes-related characteristics, albeit more pronounced in women.

Experimental studies have suggested similar underlying processes responsible for micro- and macrovascular complications in diabetes, including the formation of advanced glycation end products, insulin resistance, endothelial dysfunction, chronic inflammation, and oxidative stress [22,23,38,39]. Given the similar mechanisms and shared risk factors (e.g., hyperglycaemia, hypertension, dyslipidaemia, and obesity) associated with the progression of both small and large vessel diseases, pathological interactions may exist between diabetic micro- and macrovascular complications [22]. Observational evidence demonstrates that the presence of microvascular complications, particularly DN and DR, significantly increases the risk of cardiovascular disease (CVD) in T2DM [24-28]. An earlier meta-analysis of 54,117 patients reported 2.0-fold and 1.7-fold increased risks in cardiovascular events in patients with DN and DR, respectively [24]. Nevertheless, most studies have mainly focused on the impact of microvascular complications on macrovascular events, rather than the reverse. Cross-sectional studies in Korea and the Netherlands suggested positive association between macrovascular dysfunction and nephrop-

Table 2. HRs (95% CIs) for diabetic nephropathy and retinopathy associated with 10-year ASCVD risk category

Outcome	10-Year ASCVD risk category			*P* trend
	Low risk	Medium risk	High risk	
DN				
GDES cohort				
Cases/Person-years	7/653	33/1,445	70/1,517	-
Crude model	1.00 (reference)	2.15 (0.95–4.88)	4.51 (2.07–9.83)	<0.001
Adjusted model	1.00 (reference)	1.99 (0.87–4.56)	4.15 (1.89–9.11)	<0.001
SDES cohort				
Cases/Person-years	3/341	11/721	47/1,153	-
Crude model	1.00 (reference)	1.61 (0.41–5.86)	4.51 (1.40–14.51)	<0.001
Adjusted model	1.00 (reference)	1.53 (0.41–5.68)	5.15 (1.57–16.88)	<0.001
Pooled				
Cases/Person-years	10/994	44/2,166	117/2,670	-
Crude model	1.00 (reference)	1.99 (0.99–3.99)	4.51 (2.36–8.62)	-
Adjusted model	1.00 (reference)	1.85 (0.92–3.72)	4.43 (2.30–8.54)	-
DR				
GDES cohort				
Cases/Person-years	49/451	107/1,023	121/1,125	-
Crude model	1.00 (reference)	1.00 (0.71–1.42)	1.03 (0.73–1.45)	0.849
Adjusted model	1.00 (reference)	1.03 (0.72–1.47)	1.00 (0.70–1.43)	0.955
SDES cohort				
Cases/Person-years	31/338	87/707	134/1,142	-
Crude model	1.00 (reference)	1.36 (0.90–2.07)	1.31 (0.88–1.95)	0.419
Adjusted model	1.00 (reference)	1.23 (0.81–1.88)	1.18 (0.79–1.77)	0.672
Pooled				
Cases/Person-years	80/789	194/1,730	255/2,267	-
Crude model	1.00 (reference)	1.14 (0.85–1.54)	1.14 (0.88–1.48)	-
Adjusted model	1.00 (reference)	1.11 (0.84–1.46)	1.08 (0.82–1.41)	-

Crude model refers to Cox proportional hazard model with no adjustment. Adjusted model refers to multivariable-adjusted Cox proportional hazard model in which education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin were included as covariates. Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. The 10-year ASCVD risk estimated by the Prediction for ASCVD Risk in China (China-PAR) equations was categorised into low risk (<5.0%), medium risk (≥5.0 to 9.9%), and high risk (≥10.0%).

HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; DN, diabetic nephropathy; GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study; DR, diabetic retinopathy.

athy in T2DM [40,41], while a *post hoc* analysis of multi-national randomised trial revealed that baseline macrovascular disease was associated with increased risk of retinal photocoagulation or blindness, but not ESRD or renal death [29]. The lack of consensus might be due to methodological differences in study design, heterogeneity in macro- and microvascular disease assessment, and ethnic disparities.

The ACC/AHA guideline has emphasised the merits of 10-year ASCVD risk estimation in a large, asymptomatic population aged 40 to 75 years [37]. However, large-scale prospective data available for evaluating the association between risk of CVD and microvascular outcomes in diabetes are relatively scanty. Consistent with our findings are results from a retrospective study among patients attending a tertiary-level hospi-

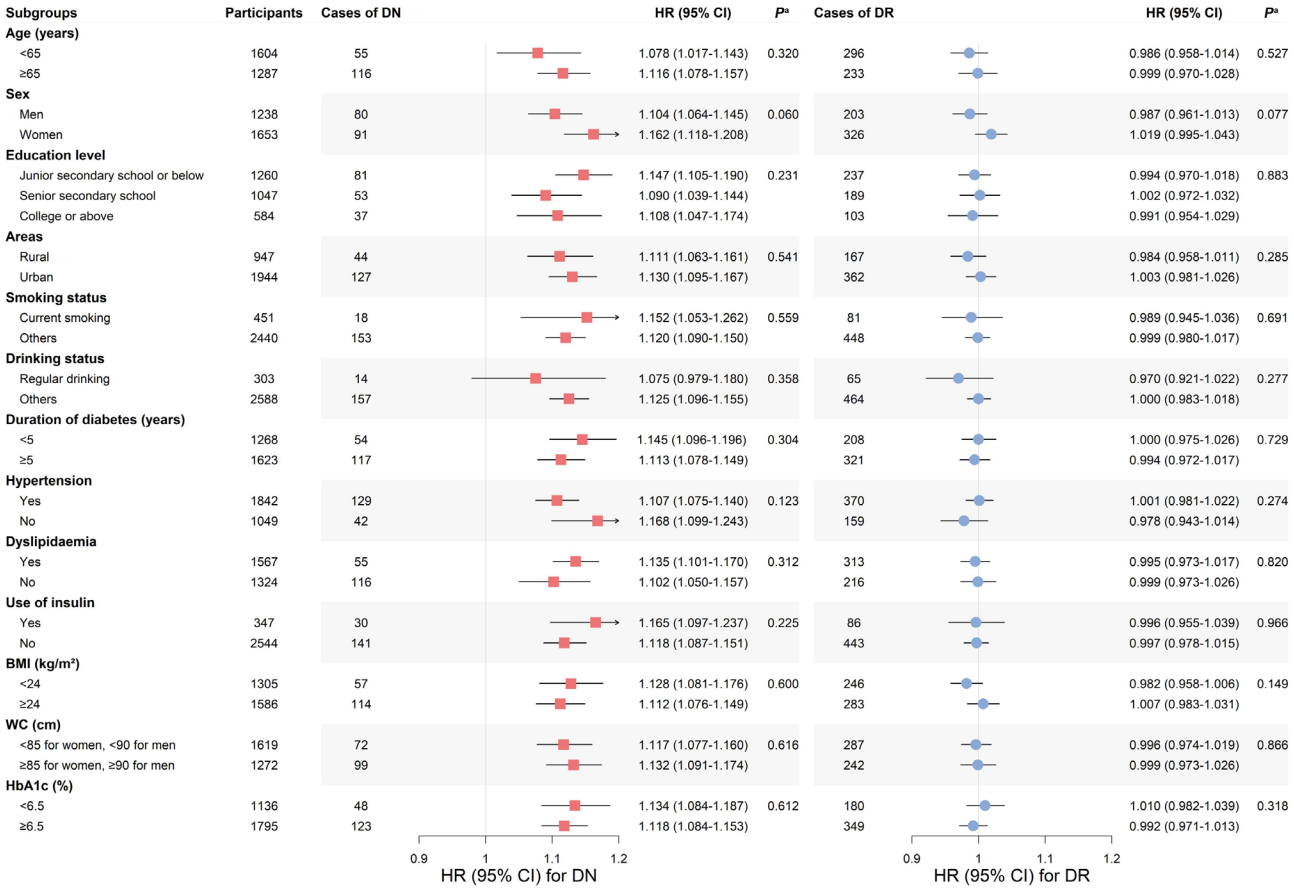

Fig. 3. Pooled hazard ratio (HR) (95% confidence interval [CI]) for diabetic nephropathy (DN) and retinopathy (DR) associated with per 1% increase in 10-year atherosclerotic cardiovascular disease risk across subgroups according to baseline characteristics. Models adjusted for education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin (HbA1c). Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. BMI, body mass index; WC, waist circumference. [a]Heterogeneity between subgroups was assessed by Cochrane's *Q* test.

tal in western China, which reported a correlation between higher levels of PCE-estimated 10-year ASCVD risk and diabetic renal dysfunction [42]. With prolonged poor macrovascular state manifested by CVD risk factors clustering, there may be progressive cardiorenal dysregulation that ultimately leads to cardiorenal syndrome via complex interconnected pathways that exacerbate cardiac or kidney injury [43]. This suggests that microvascular complications in diabetes warrant the same attention as other important macrovascular conditions. In view of the fact that major components of ASCVD risk estimation algorithms—such as age, smoking, obesity, hypertension, and dyslipidaemia—are also designated risk factors for DN [44,45], early identification of individuals at high ASCVD risk may add value in the primary prevention of diabetes-related nephropathy.

In contrast, 10-year ASCVD risk was not predictive of DR in our study, suggesting that other features of the mechanistic pathways for retinal microvascular damage, which might not be reflected by the shared cardiovascular risk factors, could contribute to the risk of retinopathy progression in diabetes. Previous studies have indicated the possibility of biological mechanisms independent of known risk factors that may serve as additional determinants of the risk of DR progression over time, which require further investigation [15,46]. For instance, clinical trial data suggest that HbA1c and diabetes duration may account for only up to 11% of the variation in retinopathy [46]. This may help explain the weak predictive role of 10-year ASCVD risk based on shared known risk factors for incident DR in our study.

Our data revealed more pronounced association between

cardiovascular risk and development of DN and DR in women. Likewise, previous studies showed that microvascular disease contributed to the burden of CVD in the diabetic population, with a greater impact observed in women [22,47,48]. This disparity may be partly attributed to sex differences in physiology (e.g., hormones and genes) [49]. Besides, urban/rural residence and family history of ASCVD were not included in the sex-specific risk equations for women, which may also play a role [17]. Further research is needed to better understand how sex differences in macrovascular risk components manifest in the transition from normal glucose metabolism to hyperglycemia-induced hemodynamics that drive microvascular abnormalities and lesions in the kidney and retina [39].

Early detection, prompt diagnosis, and timely intervention are key to reducing the burden of diabetic complications [50]. Risk assessment plays a crucial role in preventing diabetes-related macro- and microvascular complications [12,13]. Both the PCE and China-PAR equations are guideline-recommended, validated tools for assessing 10-year ASCVD risk [9,20]. We found minimal difference between the two prediction equations in estimating the HRs for DN and DR, providing novel, robust, and interpretable evidence regarding the association of 10-year ASCVD risk with new-onset microvascular complications. Recent reviews suggest that known risk factors appear to be largely ineffective as predictors of microvascular complications [51,52]. Our findings from two prospective cohorts support the utility of CVD risk assessment tools in predicting new-onset DN, indicating the necessity of monitoring 10-year ASCVD risk on top of traditional risk factors in diabetes practice. From a public health perspective, such efforts would allow for proactive approaches to tailored interventions, thereby reducing disease burden due to diabetic macro- and microvascular complications.

To our knowledge, this is among the first studies to investigate whether 10-year ASCVD risk can predict incident DN and DR in Chinese patients with T2DM. Strengths include the prospective study design, population-based patient enrolment, and relatively comprehensive data collection following standardised examination procedures with quality control in both cohorts. We observed consistent results from both pooled and cohort-specific analyses despite variations in patient characteristics, as well as from a fairly extensive range of sensitivity analyses, which may suggest the robustness of our findings.

Our study has several limitations that merit consideration. First, diabetic neuropathy was not assessed, which precluded us from exploring the clinical utility of ASCVD risk estimation for predicting the full spectrum of diabetic microvascular complications. Second, a small proportion of patients (7.2% in the GDES cohort and 7.6% in the SDES cohort) were outside the age range (i.e., 35 to 74 years) of the China-PAR equations [17]. Third, decreased eGFR alone was used to determine incident DN at follow-up in the SDES cohort where albuminuria was not captured, which may result in a more conservative estimate for the microvascular endpoint. However, consistent associations were corroborated by cohort-specific analyses in which both eGFR and mALB were measured in the GDES cohort, thereby suggesting the reliability of our findings. Fourth, selection bias was inevitable, as approximately 30% of patients were either lost to follow-up or with missing information on microvascular outcomes in both cohorts. Despite comparable demographic characteristics, these patients appeared to exhibit higher 10-year ASCVD risk and worse renal status than those who adhered to follow-up. As such, the observed associations were less likely to be unduly over- or underestimated because of the consistent direction of bias. Fifth, the generalisability of our findings from patients in southern China to other geographical or ethnic populations should be interpreted with caution. Last but not least, the association between 10-year ASCVD risk and incident microvascular complications may be underestimated, as DN or DR may not occur during the study period. It is worth noting that our cohort participants were predominantly patients with medium to long-term diabetes duration (mean of 7.9 years in the GDES cohort and 6.1 years in the SDES cohort), which may indicate a more advanced stage of disease with worse outcomes and were therefore likely to provide sufficient events for analysis. Further studies involving multiethnic cohorts of patients and with longer follow-up are warranted.

In conclusion, we provide prospective evidence from two cohorts of Chinese T2DM patients that 10-year ASCVD risk predicts incident DN but not DR, with the association appearing to be more pronounced in women in the study population. Our findings suggest that regular monitoring of ASCVD risk in routine diabetes practice may add to the ability to enhance population-based prevention for both macrovascular and microvascular diseases, particularly among women.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found

online at https://doi.org/10.4093/dmj.2024.0239.

CONFLICTS OF INTEREST

Jose Hernandez previously worked at EDU, a European Institution of Higher Education operated by Digital Education Holdings Ltd. based in Kalkara, Malta. The Institution has ceased operations, and no conflicts of interest exist related to this entity. All authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

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Acquisition, analysis, or interpretation of data: J.C., Y.T.L., W.H., H.H.X.W.
Drafting the work or revising: J.C., Y.T.L., Z.N., Z.H., Y.J.X., J.H., H.H.X.W.
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SUPPLEMENTARY METHODS

Inclusion and exclusion criteria

Eligible participants in the Guangzhou Diabetic Eye Study (GDES) and Shaoguan Diabetic Eye Study (SDES) were as follows: (1) aged 30 to 80 years; (2) clinically diagnosed with type 2 diabetes mellitus; (3) with no previous history of ocular treatment; and (4) able to complete a comprehensive ophthalmoscopic exam. Exclusion criteria included: (1) type 1 diabetes mellitus or gestational diabetes; (2) serious systemic diseases such as resistant hypertension, cardiovascular or cerebrovascular disease, cancer, or nephritis; (3) a history of general surgery, thrombolysis, or renal dialysis; (4) glaucoma, vitreous degeneration, or amblyopia; (5) a history of retinal surgery, laser treatment of the retina, or intraocular injection; (6) cognitive disorders, mental impairment, or inability to communicate independently with clinical staff; and (7) poor-quality fundus images that precluded the assessment of diabetic retinopathy.

Variables

Education levels were categorised as junior secondary school or below, senior secondary school, and college or above. Smoking status was classified as current smoking (i.e., daily cigarette smoking) and others. Drinking status was categorised as regular drinking (i.e., alcohol drinking for ≥4 days per week [1], or an equivalent daily alcohol intake of ≥25 g for men and ≥15 g for women [2]) and others. Body mass index was classified as ≥24 kg/m^2 (overweight or obese) and <24 kg/m^2. Waist circumference (WC) was categorised as ≥90 cm for men or ≥85 cm for women, and <90 cm for men or <85 cm for women. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on repeated clinical measurements, or based on clinical diagnosis and use of antihypertensive medication [3]. Dyslipidaemia was defined as total cholesterol (TC) ≥6.2 mmol/L, low-density lipoprotein cholesterol ≥4.1 mmol/L or triglyceride ≥2.3 mmol/L, or high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L or a combination of these features, or based on clinical diagnosis and use of lipid-lowering medication [4].

Risk estimation

The Prediction for atherosclerotic cardiovascular disease (ASCVD) Risk in China (China-PAR) equations use variables such as age, sex (male/female), geographic region (northern/southern), area of residence (urban/rural), current smoking status (yes/no), diabetes (yes/no), family history of ASCVD (yes/no), WC, TC, HDL-C, treated or untreated SBP, and age-covariate interaction terms where appropriate [5]. The Pooled Cohort Equations (PCE) use variables such as age, age squared, sex (male/female), current smoking status (yes/no), diabetes (yes/no), TC, HDL-C, treated or untreated SBP, and age-covariate interaction terms where appropriate [6,7]. In both China-PAR and PCE equations, continuous variables were transformed to their natural logarithm. Estimated 10-year risk of a first hard ASCVD event is calculated in the equation form as follows:

$$1-S_{10}^{e^{(IndX'B-MeanX'B)}}$$

where S_{10} represents the baseline survival rate of ASCVD at 10 years, IndX'B is the 'individual sum' defined as the sum of the sex-specific 'coefficient×value,' and MeanX'B is the overall mean 'coefficient×value' sum. The sex-specific values of S_{10}, coefficients, and mean sums for China-PAR and PCE equations have been described in detail previously [5,6].

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Supplementary Table 1. Baseline characteristics of the GDES cohort participants by incident diabetic nephropathy and retinopathy

Characteristic	Incident DN			Incident DR		
	Non-cases	Cases	*P* value	Non-cases	Cases	*P* value
No. of participants	1,326	110	-	1,159	277	-
Socio-demographics						
Age, yr	63.97±7.53	67.93±6.39	<0.001	64.47±7.40	63.45±7.97	0.043
Male sex	531 (40.0)	56 (50.9)	0.026	476 (41.1)	111 (40.1)	0.762
Education level						
Junior secondary school or below	410 (30.9)	43 (39.1)	0.150	368 (31.8)	85 (30.7)	0.834
Senior secondary school	569 (42.9)	37 (33.6)		485 (41.8)	121 (43.7)	
College or above	347 (26.2)	30 (27.3)		306 (26.4)	71 (25.6)	
Urban residence	1,326 (100)	110 (100)	-	1,159 (100)	277 (100)	-
Lifestyle						
Current smoking	167 (12.6)	12 (10.9)	0.656	140 (12.1)	39 (14.1)	0.385
Regular drinking	117 (8.8)	8 (7.3)	0.655	87 (7.5)	38 (13.8)	0.001
Medical history						
Duration of diabetes, yr	6.0 (3.0–11.0)	7.0 (4.0–12.0)	0.206	6.0 (3.0–11.0)	7.0 (3.0–12.0)	0.182
Hypertension	735 (55.4)	79 (71.8)	0.001	640 (55.2)	174 (62.8)	0.022
Dyslipidaemia	976 (73.6)	79 (71.8)	0.683	833 (71.9)	222 (80.1)	0.005
Family history of ASCVD	351 (26.5)	28 (25.5)	0.816	326 (28.1)	53 (19.1)	0.002
Use of insulin	216 (16.3)	21 (19.1)	0.451	174 (15.0)	63 (22.7)	0.002
Clinical parameters						
BMI, kg/m^2	24.39±3.20	25.60±3.05	<0.001	24.40±3.19	24.86±3.23	0.030
WC, cm	85.39±9.02	88.59±8.34	<0.001	85.53±9.03	86.09±8.93	0.355
SBP, mm Hg	132.34±18.00	139.08±20.62	<0.001	132.44±18.27	134.62±18.31	0.075
DBP, mm Hg	70.12±10.33	71.30±10.05	0.249	69.90±10.25	71.52±10.49	0.018
HbA1c, %	6.79±1.20	6.94±1.25	0.201	6.72±1.13	7.14±1.40	<0.001
TC, mmol/L	4.83±1.05	4.63±1.09	0.058	4.83±1.07	4.74±0.95	0.195
TG, mmol/L	1.87 (1.30–2.86)	2.10 (1.54–2.86)	0.058	1.86 (1.28–2.82)	2.04 (1.48–3.06)	0.011
LDL-C, mmol/L	3.04±0.94	2.86±0.96	0.049	3.04±0.97	2.99±0.83	0.442
HDL-C, mmol/L	1.31±0.41	1.18±0.36	0.001	1.32±0.42	1.23±0.35	0.001
SCr, mg/dL	0.77±0.18	0.92±0.20	<0.001	0.78±0.19	0.80±0.19	0.127
eGFR, mL/min/1.73 m^2	93.36±14.01	78.91±14.89	<0.001	92.43±14.66	91.51±14.31	0.344
mALB, mg/dL	0.66 (0.26–1.81)	2.26 (0.66–7.28)	<0.001	0.63 (0.24–1.88)	1.00 (0.43–2.28)	<0.001
Estimated cardiovascular disease risk						
10-Year ASCVD risk, %	9.33±4.58	12.79±5.98	<0.001	9.59±4.79	9.61±4.82	0.944
10-Year ASCVD risk category						
Low risk	240 (18.1)	7 (6.4)	<0.001	198 (17.1)	49 (17.7)	0.891
Medium risk	540 (40.7)	33 (30.0)		466 (40.2)	107 (38.6)	
High risk	546 (41.2)	70 (63.6)		495 (42.7)	121 (43.7)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Between-group comparisons of baseline characteristics were examined using two-sample *t*-test, Mann-Whitney *U* test, or chi-square test, as appropriate.
GDES, Guangzhou Diabetic Eye Study; DN, diabetic nephropathy; DR, diabetic retinopathy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; mALB, urinary microalbumin.

Supplementary Table 2. Baseline characteristics of the SDES cohort participants by incident diabetic nephropathy and retinopathy

Characteristic	Incident DN			Incident DR		
	Non-cases	Cases	*P* value	Non-cases	Cases	*P* value
No. of participants	1,394	61	-	1,203	252	-
Socio-demographics						
Age, yr	61.81±9.20	67.51±9.22	<0.001	61.85±9.40	63.00±8.59	0.074
Male sex	627 (45.0)	24 (39.3)	0.386	559 (46.5)	92 (36.5)	0.004
Education level						
Junior secondary school or below	769 (55.2)	38 (62.3)	0.545	655 (54.5)	152 (60.3)	0.239
Senior secondary school	425 (30.5)	16 (26.2)		373 (31.0)	68 (27.0)	
College or above	200 (14.3)	7 (11.5)		175 (14.5)	32 (12.7)	
Urban residence	491 (35.2)	17 (27.9)	0.237	423 (35.2)	85 (33.7)	0.658
Lifestyle						
Current smoking	266 (19.1)	6 (9.8)	0.069	230 (19.1)	42 (16.7)	0.355
Regular drinking	172 (12.5)	6 (10.0)	0.565	151 (12.6)	27 (10.7)	0.473
Medical history						
Duration of diabetes, yr	4.5 (2.4–8.3)	5.5 (3.3–10.4)	0.028	4.5 (2.4–7.7)	5.3 (3.2–10.3)	0.007
Hypertension	978 (70.2)	50 (82.0)	0.047	832 (69.2)	196 (77.8)	0.006
Dyslipidaemia	492 (35.3)	20 (32.8)	0.688	421 (35.0)	91 (36.1)	0.736
Family history of ASCVD	194 (13.9)	11 (18.0)	0.366	162 (13.5)	43 (17.1)	0.136
Use of insulin	101 (7.3)	9 (14.8)	0.030	87 (7.2)	23 (9.1)	0.306
Clinical parameters						
BMI, kg/m^2	24.52±3.41	25.63±3.84	0.013	24.62±3.40	24.27±3.57	0.141
WC, cm	85.52±9.44	89.14±9.24	0.003	85.88±9.53	84.67±9.06	0.064
SBP, mm Hg	136.16±17.41	142.82±18.26	0.004	136.08±17.11	138.15±19.15	0.086
DBP, mm Hg	82.60±10.64	85.39±10.26	0.045	82.69±10.44	82.86±11.53	0.820
HbA1c, %	7.40±1.83	7.28±1.49	0.601	7.33±1.78	7.69±1.98	0.005
TC, mmol/L	5.33±1.13	5.07±1.23	0.080	5.32±1.15	5.32±1.06	0.968
TG, mmol/L	1.77 (1.18–2.70)	2.03 (1.37–2.97)	0.290	1.82 (1.21–2.76)	1.56 (1.14–2.59)	0.169
LDL-C, mmol/L	2.72±0.81	2.45±0.96	0.014	2.70±0.83	2.74±0.79	0.450
HDL-C, mmol/L	1.28±0.46	1.23±0.60	0.336	1.27±0.45	1.33±0.51	0.089
SCr, mg/dL	0.87±0.19	1.25±0.62	<0.001	0.89±0.24	0.88±0.25	0.659
eGFR, mL/min/1.73 m^2	85.81±16.09	61.57±18.83	<0.001	90.41±19.56	90.56±19.36	0.911
Estimated cardiovascular disease risk						
10-Year ASCVD risk, %	10.97±5.86	15.02±6.80	<0.001	11.16±6.02	11.03±5.60	0.771
10-Year ASCVD risk category						
Low risk	219 (15.7)	3 (4.9)	0.001	191 (15.9)	31 (12.3)	0.336
Medium risk	457 (32.8)	11 (18.0)		381 (31.7)	87 (34.5)	
High risk	718 (51.5)	47 (77.1)		631 (52.4)	134 (53.2)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Between-group comparisons of baseline characteristics were examined using two-sample *t*-test, Mann-Whitney *U* test, or chi-square test, as appropriate.
SDES, Shaoguan Diabetic Eye Study; DN, diabetic nephropathy; DR, diabetic retinopathy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; mALB, urinary microalbumin.

Supplementary Table 3. Baseline characteristics of patients included in the final analysis and those excluded during follow-up

Characteristic	GDES cohort			SDES cohort		
	Included in the final analysis	Excluded during follow-up	*P* value	Included in the final analysis	Excluded during follow-up	*P* value
No. of participants	1,436	675	-	1,455	605	-
Socio-demographics						
Age, yr	64.27±7.52	65.16±8.17	0.014	62.05±9.27	62.10±10.91	0.915
Male sex	587 (40.9)	253 (37.5)	0.137	651 (44.7)	264 (43.6)	0.645
Education level						
Junior secondary school or below	453 (31.5)	250 (37.0)	0.001	807 (55.5)	341 (57.3)	0.319
Senior secondary school	606 (42.2)	317 (47.0)		441 (30.3)	161 (27.1)	
College or above	377 (26.3)	108 (16.0)		207 (14.2)	93 (15.6)	
Urban residence	1,436 (100)	675 (100)	-	508 (34.9)	220 (36.4)	0.540
Lifestyle						
Current smoking	179 (12.5)	89 (13.2)	0.697	272 (18.7)	182 (30.1)	<0.001
Regular drinking	125 (8.7)	59 (8.8)	0.981	178 (12.4)	140 (23.1)	<0.001
Medical history						
Duration of diabetes, yr	6.0 (3.0–11.0)	6.0 (2.5–10.1)	0.098	4.7 (2.5–8.3)	3.4 (1.4–6.5)	0.002
Hypertension	814 (56.7)	399 (59.1)	0.293	1,028 (70.7)	329 (54.4)	<0.001
Dyslipidaemia	1,055 (73.5)	410 (60.7)	<0.001	512 (35.2)	163 (26.9)	<0.001
Family history of ASCVD	379 (26.4)	61 (9.0)	<0.001	205 (14.1)	45 (7.4)	<0.001
Use of insulin	237 (16.5)	84 (12.5)	0.024	110 (7.6)	54 (8.9)	0.350
Clinical parameters						
BMI, kg/m^2	24.49±3.21	24.67±3.76	0.260	24.56±3.44	24.47±3.40	0.593
WC, cm	85.64±9.01	87.68±9.50	<0.001	85.67±9.46	86.66±9.61	0.096
SBP, mm Hg	132.86±18.29	133.46±18.45	0.489	136.44±17.49	136.41±19.07	0.976
DBP, mm Hg	70.21±10.31	69.88±10.30	0.498	82.72±10.64	82.61±11.22	0.843
HbA1c, %	6.80±1.20	7.02±1.44	<0.001	7.40±1.82	7.58±2.28	0.060
TC, mmol/L	4.82±1.05	4.92±1.10	0.033	5.32±1.14	5.33±1.20	0.835
TG, mmol/L	1.88 (1.31–2.86)	2.06 (1.39–2.94)	0.025	1.78 (1.19–2.72)	1.83 (1.21–2.85)	0.102
LDL-C, mmol/L	3.03±0.95	3.07±0.99	0.390	2.70±0.82	2.62±0.86	0.046
HDL-C, mmol/L	1.30±0.41	1.29±0.40	0.542	1.28±0.46	1.32±0.56	0.160
SCr, mg/dL	0.78±0.19	0.76±0.18	0.008	0.89±0.24	0.84±0.19	<0.001
eGFR, mL/min/1.73 m^2	92.25±14.59	93.09±14.60	0.223	84.79±16.92	88.58±17.76	<0.001
mALB, mg/dL[a]	0.70 (0.27–2.00)	0.90 (0.34–2.35)	0.003	-	-	-
Estimated cardiovascular disease risk						
10-Year ASCVD risk, %	9.60±4.79	10.53±5.40	0.001	11.13±5.95	11.32±6.35	0.682

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Between-group comparisons of baseline characteristics were examined using two-sample *t*-test, Mann-Whitney *U* test, or chi-square test, as appropriate.
GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; mALB, urinary microalbumin.
[a]Information on mALB in the SDES cohort was not available.

Supplementary Table 4. Predictive capacity of the PCE-estimated 10-year ASCVD risk for incident diabetic nephropathy and retinopathy

Outcome	10-Year ASCVD risk category by PCE			10-Year ASCVD risk score by PCE, per 1% increment
	<7.5%	≥7.5% to <20%	≥20.0%	
DN				
GDES cohort				
Cases/Person-years	8/764	29/1,173	73/1,688	110/3,615
HR (95% CI)	1.00 (reference)	2.09 (0.95–4.62)	3.99 (1.90–8.36)	1.030 (1.021–1.040)
AUC (95% CI)	-	-	-	0.656 (0.602–0.710)
SDES cohort				
Cases/Person-years	5/434	13/567	43/1,214	61/2,225
HR (95% CI)	1.00 (reference)	1.86 (0.64–5.38)	3.38 (1.31–8.70)	1.020 (1.009–1.031)
AUC (95% CI)	-	-	-	0.622 (0.547–0.698)
Pooled				
Cases/Person-years	13/1,198	42/1,740	116/2,902	171/5,840
HR (95% CI)	1.00 (reference)	2.00 (1.06–3.78)	3.75 (2.09–6.71)	1.026 (1.019–1.033)
AUC (95% CI)	-	-	-	0.645 (0.603–0.691)
DR				
GDES cohort				
Cases/Person-years	58/543	89/830	130/1,216	277/2,599
HR (95% CI)	1.00 (reference)	1.01 (0.72–1.42)	0.92 (0.66–1.29)	0.997 (0.990–1.004)
AUC (95% CI)	-	-	-	0.504 (0.466–0.543)
SDES cohort				
Cases/Person-years	42/428	77/393	133/1,362	252/2,183
HR (95% CI)	1.00 (reference)	1.55 (1.05–2.28)	1.17 (0.82–1.69)	0.996 (0.990–1.002)
AUC (95% CI)	-	-	-	0.519 (0.482–0.556)
Pooled				
Cases/Person-years	100/980	166/1,223	263/2,578	529/4,782
HR (95% CI)	1.00 (reference)	1.22 (0.94–1.57)	1.03 (0.80–1.31)	0.996 (0.992–1.001)
AUC (95% CI)	-	-	-	0.512 (0.486–0.539)

Model adjusted for education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin. Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. The 10-year ASCVD risk estimated by the PCE equations was categorised into low or borderline risk (<7.5%), intermediate risk (≥7.5% to <20%), and high risk (≥20.0%).

PCE, Pooled Cohort Equations; ASCVD, atherosclerotic cardiovascular disease; DN, diabetic nephropathy; GDES, Guangzhou Diabetic Eye Study; HR, hazard ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve; SDES, Shaoguan Diabetic Eye Study; DR, diabetic retinopathy.

Supplementary Table 5. HRs (95% CIs) for incident diabetic nephropathy and retinopathy associated with 10-year ASCVD risk in sensitivity analyses

Outcome by analysis	10-Year ASCVD risk category			10-Year ASCVD risk score, per 1% increment
	Low risk	Medium risk	High risk	
Using combined participant-level data from the GDES and SDES cohorts				
DN	1.00 (reference)	1.80 (0.89–3.61)	4.31 (2.24–8.29)	1.123 (1.095–1.151)
DR	1.00 (reference)	1.10 (0.84–1.45)	1.09 (0.83–1.41)	0.998 (0.981–1.015)
Excluding incident cases that occurred within the first year of follow-up				
DN				
GDES cohort	1.00 (reference)	1.94 (0.84–4.44)	3.95 (1.79–8.69)	1.131 (1.093–1.170)
SDES cohort	1.00 (reference)	1.38 (0.36–5.25)	4.37 (1.32–14.53)	1.107 (1.062–1.155)
Pooled	1.00 (reference)	1.76 (0.87–3.58)	4.07 (2.11–7.88)	1.121 (1.092–1.151)
DR				
GDES cohort	1.00 (reference)	1.02 (0.71–1.48)	0.92 (0.64–1.33)	0.991 (0.964–1.019)
SDES cohort	1.00 (reference)	1.51 (0.91–2.49)	1.36 (0.83–2.23)	0.995 (0.970–1.021)
Pooled	1.00 (reference)	1.17 (0.87–1.57)	1.06 (0.79–1.42)	0.993 (0.975–1.012)
Using average estimates of 10-year ASCVD risk during follow-up				
DN				
GDES cohort	1.00 (reference)	1.59 (0.65–3.90)	4.05 (1.75–9.38)	1.135 (1.097–1.176)
SDES cohort	1.00 (reference)	2.09 (0.45–9.75)	6.24 (1.49–26.06)	1.103 (1.057–1.151)
Pooled	1.00 (reference)	1.70 (0.79–3.70)	4.52 (2.19–9.33)	1.122 (1.092–1.153)
DR				
GDES cohort	1.00 (reference)	0.94 (0.64–1.38)	0.98 (0.67–1.43)	1.001 (0.975–1.028)
SDES cohort	1.00 (reference)	1.25 (0.80–1.95)	1.12 (0.73–1.71)	0.993 (0.970–1.016)
Pooled	1.00 (reference)	1.06 (0.79–1.42)	1.04 (0.78–1.38)	0.996 (0.979–1.014)
Models with additional adjustment for body mass index				
DN				
GDES cohort	1.00 (reference)	1.96 (0.85–4.48)	3.87 (1.76–8.50)	1.123 (1.086–1.162)
SDES cohort	1.00 (reference)	1.41 (0.38–5.23)	4.44 (1.35–14.62)	1.108 (1.065–1.153)
Pooled	1.00 (reference)	1.78 (0.88–3.60)	4.04 (2.09–7.78)	1.117 (1.088–1.146)
DR				
GDES cohort	1.00 (reference)	1.02 (0.71–1.46)	0.98 (0.69–1.41)	0.994 (0.968–1.021)
SDES cohort	1.00 (reference)	1.26 (0.83–1.93)	1.22 (0.81–1.83)	0.997 (0.975–1.019)
Pooled	1.00 (reference)	1.12 (0.85–1.47)	1.08 (0.82–1.41)	0.996 (0.979–1.013)
Models with additional adjustment for the use of oral hypoglycemic and lipid-lowering medications				
DN				
GDES cohort	1.00 (reference)	1.99 (0.87–4.56)	4.14 (1.89–9.09)	1.129 (1.092–1.167)
SDES cohort	1.00 (reference)	1.54 (0.41–5.71)	5.19 (1.58–17.02)	1.112 (1.070–1.156)
Pooled	1.00 (reference)	1.80 (0.89–3.62)	4.07 (2.11–7.85)	1.115 (1.087–1.145)
DR				
GDES cohort	1.00 (reference)	1.03 (0.72–1.47)	1.00 (0.70–1.43)	0.996 (0.970–1.022)
SDES cohort	1.00 (reference)	1.24 (0.81–1.88)	1.18 (0.79–1.77)	0.996 (0.975–1.018)
Pooled	1.00 (reference)	1.11 (0.84–1.46)	1.09 (0.83–1.42)	0.997 (0.980–1.014)

Model adjusted for education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin, unless otherwise specified. Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. The 10-year ASCVD risk estimated by the Prediction for ASCVD Risk in China (China-PAR) equations was categorised into low risk (<5.0%), medium risk (≥5.0 to 9.9%), and high risk (≥10.0%).

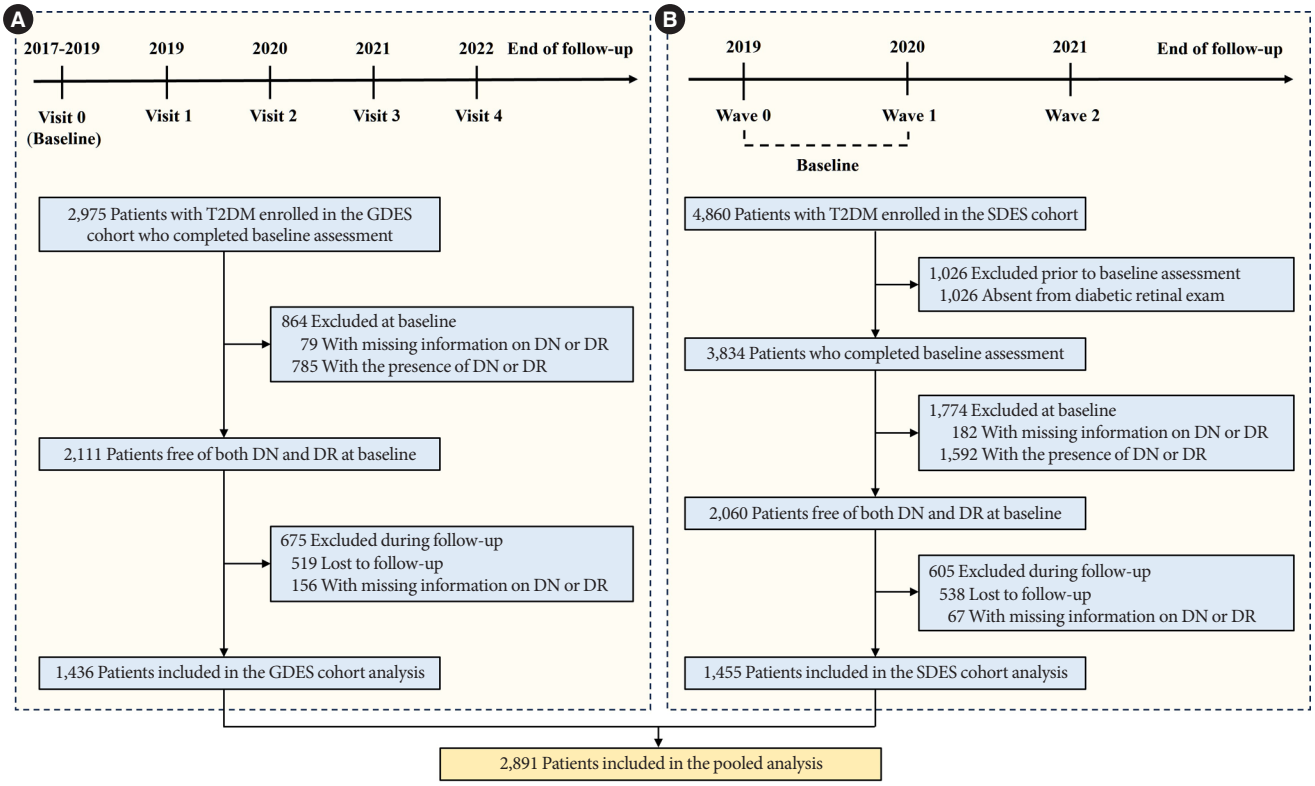
HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study; DN, diabetic nephropathy; DR, diabetic retinopathy.

Supplementary Table 6. HRs (95% CIs) for the composite outcome of incident diabetic nephropathy or retinopathy associated with 10-year ASCVD risk

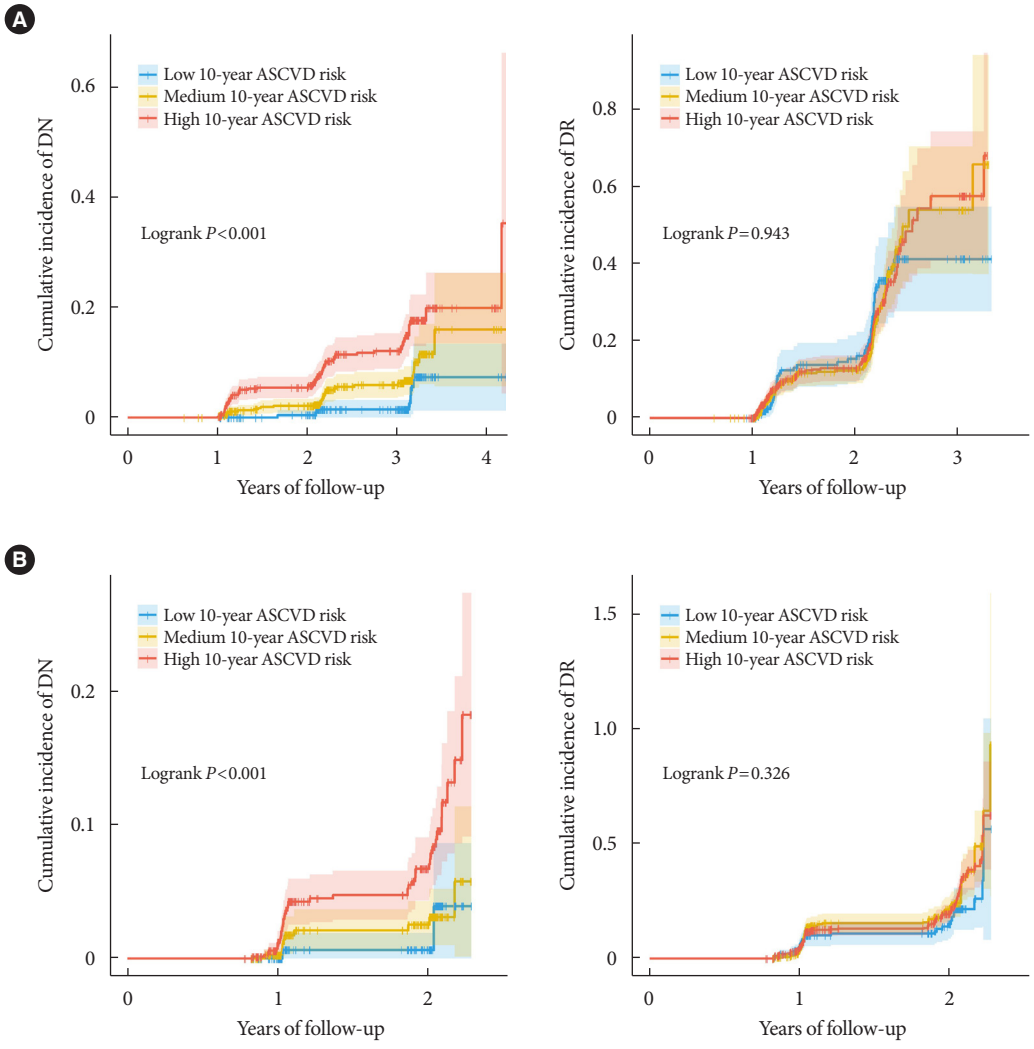
Variable	10-Year ASCVD risk category				10-Year ASCVD risk score, per 1% increment
	Low risk	Medium risk	High risk	*P* trend	
GDES cohort					
Cases/Person-years	53/595	130/1,346	178/1,412	-	361/3,353
Crude model	1.00 (reference)	1.07 (0.77–1.48)	1.43 (1.05–1.96)	0.005	1.045 (1.023–1.067)
Adjusted model	1.00 (reference)	1.09 (0.78–1.52)	1.41 (1.02–1.95)	0.011	1.040 (1.018–1.063)
SDES cohort					
Cases/Person-years	33/337	96/765	170/1,132	-	299/2,234
Crude model	1.00 (reference)	1.39 (0.93–2.08)	1.55 (1.06–2.27)	0.026	1.015 (0.996–1.034)
Adjusted model	1.00 (reference)	1.26 (0.84–1.90)	1.45 (0.99–2.14)	0.049	1.014 (0.995–1.035)
Pooled					
Cases/Person-years				-	
Crude model	1.00 (reference)	1.19 (0.92–1.53)	1.48 (1.16–1.88)	-	1.028 (1.014–1.043)
Adjusted model	1.00 (reference)	1.16 (0.89–1.50)	1.43 (1.11–1.83)	-	1.026 (1.011–1.041)

Crude model refers to Cox proportional hazard model with no adjustment. Adjusted model refers to multivariable-adjusted Cox proportional hazard model in which education level, regular drinking, duration of diabetes, use of insulin, and glycosylated hemoglobin were included as covariates. Cohort-specific results were pooled using inverse variance-weighted, fixed-effect meta-analyses. The 10-year ASCVD risk estimated by the Prediction for ASCVD Risk in China (China-PAR) equations was categorised into low risk (<5.0%), medium risk (≥5.0 to 9.9%), and high risk (≥10.0%).

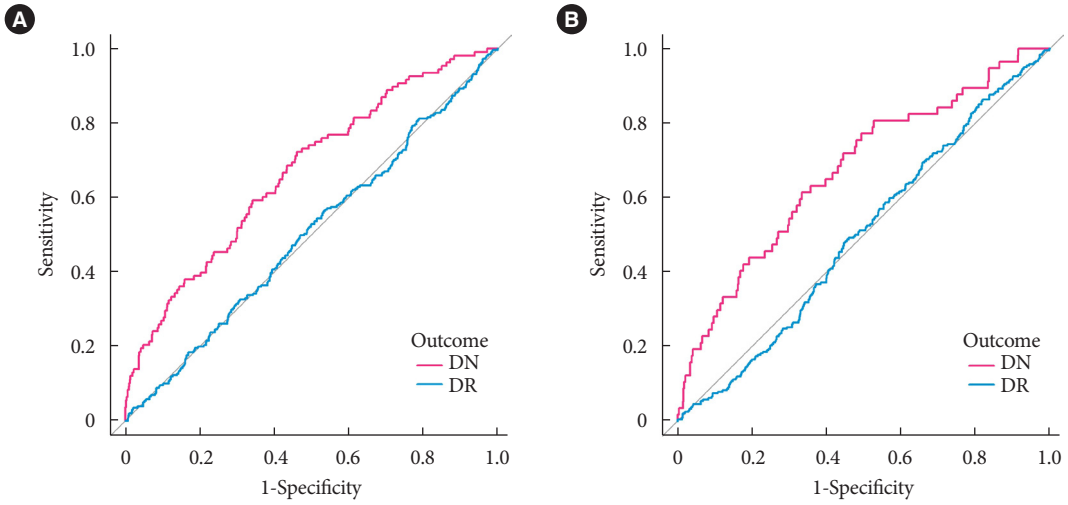
HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; GDES, Guangzhou Diabetic Eye Study; SDES, Shaoguan Diabetic Eye Study.



Supplementary Fig. 1. Participant flow diagram for the (A) Guangzhou Diabetic Eye Study (GDES) and (B) Shaoguan Diabetic Eye Study (SDES) cohorts. T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy; DR, diabetic retinopathy.



Supplementary Fig. 2. Kaplan-Meier curves for incident diabetic nephropathy (DN) and retinopathy (DR) by 10-year atherosclerotic cardiovascular disease (ASCVD) risk categories in the (A) Guangzhou Diabetic Eye Study (GDES) and (B) Shaoguan Diabetic Eye Study (SDES) cohorts. The solid lines represent the fitted Kaplan-Meier curves, and the shaded areas represent the 95% confidence interval bands.



Supplementary Fig. 3. Receiver operating characteristic curves of 10-year atherosclerotic cardiovascular disease (ASCVD) risk for predicting incident diabetic nephropathy (DN) and retinopathy (DR) in the (A) Guangzhou Diabetic Eye Study (GDES) and (B) Shaoguan Diabetic Eye Study (SDES) cohorts. The area under the receiver operating characteristic curve (AUC) values of 10-year ASCVD risk were 0.669 (95% confidence interval [CI], 0.616 to 0.723) for DN and 0.501 (95% CI, 0.462 to 0.540) for DR in the GDES cohort, 0.672 (95% CI, 0.599 to 0.746) for DN and 0.501 (95% CI, 0.463 to 0.539) for DR in the SDES cohort, and 0.670 (95% CI, 0.628 to 0.715) for DN and 0.501 (95% CI, 0.474 to 0.529) for DR in the pooled analysis which combined cohort-specific estimates using inverse variance-weighted, fixed-effect meta-analyses.