

ORIGINAL RESEARCH

Diabetes-Related Macrovascular Complications Are Associated With an Increased Risk of Diabetic Microvascular Complications: A Prospective Study of 1518 Patients With Type 1 Diabetes and 20 802 Patients With Type 2 Diabetes in the UK Biobank

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BACKGROUND: Diabetic vascular complications share common pathophysiological mechanisms, but the relationship between diabetes-related macrovascular complications (MacroVCs) and incident diabetic microvascular complications remains unclear. We aimed to investigate the impact of MacroVCs on the risk of microvascular complications.

METHODS AND RESULTS: There were 1518 participants with type 1 diabetes (T1D) and 20 802 participants with type 2 diabetes from the UK Biobank included in this longitudinal cohort study. MacroVCs were defined by the presence of macrovascular diseases diagnosed after diabetes at recruitment, including coronary heart disease, peripheral artery disease, stroke, and ≥ 2 MacroVCs. The primary outcome was incident microvascular complications, a composite of diabetic retinopathy, diabetic kidney disease, and diabetic neuropathy. During a median (interquartile range) follow-up of 11.61 (5.84–13.12) years and 12.2 (9.50–13.18) years, 596 (39.3%) and 4113 (19.8%) participants developed a primary outcome in T1D and type 2 diabetes, respectively. After full adjustment for conventional risk factors, Cox regression models showed significant associations between individual as well as cumulative MacroVCs and the primary outcome, except for coronary heart disease in T1D (T1D: diabetes coronary heart disease: 1.25 [0.98–1.60]; diabetes peripheral artery disease: 3.00 [1.86–4.84]; diabetes stroke: 1.71 [1.08–2.72]; ≥ 2 : 2.57 [1.66–3.99]; type 2 diabetes: diabetes coronary heart disease: 1.59 [1.38–1.82]; diabetes peripheral artery disease: 1.60 [1.01–2.54]; diabetes stroke: 1.50 [1.13–1.99]; ≥ 2 : 2.66 [1.92–3.68]). Subgroup analysis showed that strict glycemic (glycated hemoglobin $< 6.5\%$) and blood pressure ($< 140/90$ mmHg) control attenuated the association.

CONCLUSIONS: Individual and cumulative MacroVCs confer significant risk of incident microvascular complications in patients with T1D and type 2 diabetes. Our results may facilitate cost-effective high-risk population identification and development of precise prevention strategies.

Key Words: macrovascular disease ■ microvascular disease ■ type 1 diabetes ■ type 2 diabetes

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CLINICAL PERSPECTIVE

What Is New?

- Patients with diabetes-related macrovascular complication are at higher risk to develop diabetic microvascular complication, and ≥ 2 macrovascular morbidities confer even more risk.
- Glycemic and blood pressure control may attenuate the excess risk.

What Are the Clinical Implications?

- Patients with diabetes-related macrovascular complications should be given a special screening strategy and treatment to prevent diabetic microvascular complications.

Nonstandard Abbreviations and Acronyms

ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation
DKD	diabetic kidney disease
DN	diabetic neuropathy
DR	diabetic retinopathy
HELIUS	Healthy Life in an Urban Setting
MacroVCs	macrovascular complications
MacroVDs	macrovascular diseases
MicroVCs	microvascular complications
OPCS-4	<i>Office of Population Censuses and Surveys Classification of Interventions and Procedures, Fourth Revision</i>
T1D	type 1 diabetes
T2D	type 2 diabetes

By 2045, the global prevalence of diabetes is predicted to increase to >700 million, thereby representing approximately 10% of the world population.¹ Half of patients with diabetes will develop diabetic microvascular complications (MicroVCs), which include diabetic retinopathy (DR), diabetic kidney disease (DKD), and diabetic neuropathy (DN).² DR was shown to be the major cause of incident blindness in developed countries,³ DKD could proceed to end-stage renal disease and necessitate dialysis or kidney transplantation,⁴ and DN was shown to significantly impair quality of life and potentially lead to amputation or death.⁵ However, the frequency and costs of diabetes-related MicroVCs have barely improved over the past few decades, despite substantially enhanced risk management,⁶ and individual risk prediction of

diabetic MicroVCs has remained challenging, especially in clinical settings.^{7,8} Hence, to promote routine screening, early detection, and prompt intervention of MicroVCs, easily accessible risk factors to intervene in and identify high-risk populations should be explored in addition to conventional risk assessment algorithms.

Due to their shared pathophysiology,⁹ diabetes-related macrovascular complications (MacroVCs) may herald the onset of MicroVCs. The independent impact of MicroVCs on the excess risk of MacroVCs has been extensively studied.^{10,11} However, the association between MacroVCs and the risk of incident MicroVCs remains poorly understood,¹² with only a few contradictory results reported.^{13–18} In a type 2 diabetes (T2D) population, Mohammadi et al demonstrated a positive association between composite MacroVCs or individual peripheral artery disease (PAD) and incident DR but not DKD,^{15,16} whereas Zhang et al showed that PAD but not coronary heart disease (CHD) or stroke was associated with a slightly higher absolute lifetime risk of chronic kidney disease (CKD).¹⁸ The discrepancy may be due to shorter follow-up or cross-sectional designs^{13,14}; inclusion of only end-stage MicroVCs^{15,16}; insufficient or no adjustment for conventional risk factors¹⁸; lack of discrimination of individual, composite, or cumulative macrovascular burden; and different diabetes types. Therefore, a robust prospective population-level study is still lacking to understand the comprehensive relationships between cumulative and individual macrovascular burden and incident individual and composite diabetic microvascular diseases, especially because no prospective study has been performed in patients with type 1 diabetes (T1D) or DN.

Using a prospective cohort of 1518 patients with T1D and 20 802 patients with T2D in the UK Biobank over a median (interquartile range [IQR]) follow-up of 12.3 (10.6–13.3) years, we aimed to understand the association among individual as well as cumulative MacroVCs and the risk of incident composite and individual MicroVCs. This study was further supported by extensive medical history and covariate data recorded at baseline and electronic health record linkage that allowed clinical MicroVCs to be identified using the corresponding *International Classification of Diseases, Tenth Revision (ICD-10)* codes. Stratification of risk factor control status was implemented to investigate the role that glycemic and blood pressure control may play in this high-risk population. Furthermore, we evaluated the additive value of MacroVCs in MicroVC risk prediction and discrimination over conventional diabetes MicroVC risk factors in patients with both T1D and T2D.

METHODS

Study Design and Study Population

The UK Biobank study was a prospective cohort of >500 000 people aged 40 to 69 years recruited during 2006 to 2010 in 22 assessment centers across the United Kingdom and followed from then on.¹⁹ Extensive information on environmental exposure, lifestyle, and health records was collected through touchscreen questionnaires and verbal interviews. Anthropometric and other physical measurements were performed, and biological samples were collected for comprehensive biochemical, metabolomic, and genetic analysis. Medical information on disease diagnosis and operation was collected at baseline from questionnaires. Health-related outcomes were followed up through linkages to national data sets, primary care, and hospital admissions using the *International Classification of Diseases, Ninth Revision (ICD-9)* and *ICD-10* and the *Office of Population Censuses and Surveys Classification of*

Interventions and Procedures (OPCS-4) as recording codes. Details are described elsewhere.²⁰ The last follow-up date of this study was January 31, 2022, and the end of follow-up was defined as the earliest date among the following dates: the date of incident microvascular event, the date of lost follow-up, the date of death, and the last follow-up date.

This study was conducted in patients with T1D or T2D (Figure 1). Baseline diabetes was defined as (1) an inpatient hospital record of 250 (*ICD-9*) or E10-14 (*ICD-10*); (2) self-reported diabetes in touchscreen questionnaires or verbal interviews; (3) self-reported diabetes-related treatment, including insulin and medication use, in touchscreen questionnaires or verbal interviews; or (4) plasma glycated hemoglobin (HbA1c) ≥ 48 mmol/mol.²¹ T1D was defined as follows: (1) a hospital inpatient record of E10 (*ICD-10*) or (2) self-reported T1D. T2D was defined as diabetes, excluding T1D, malnutrition-related diabetes (E12), and other specified types (E13). Medications were identified through questionnaires or codes.²² Participants with any prior

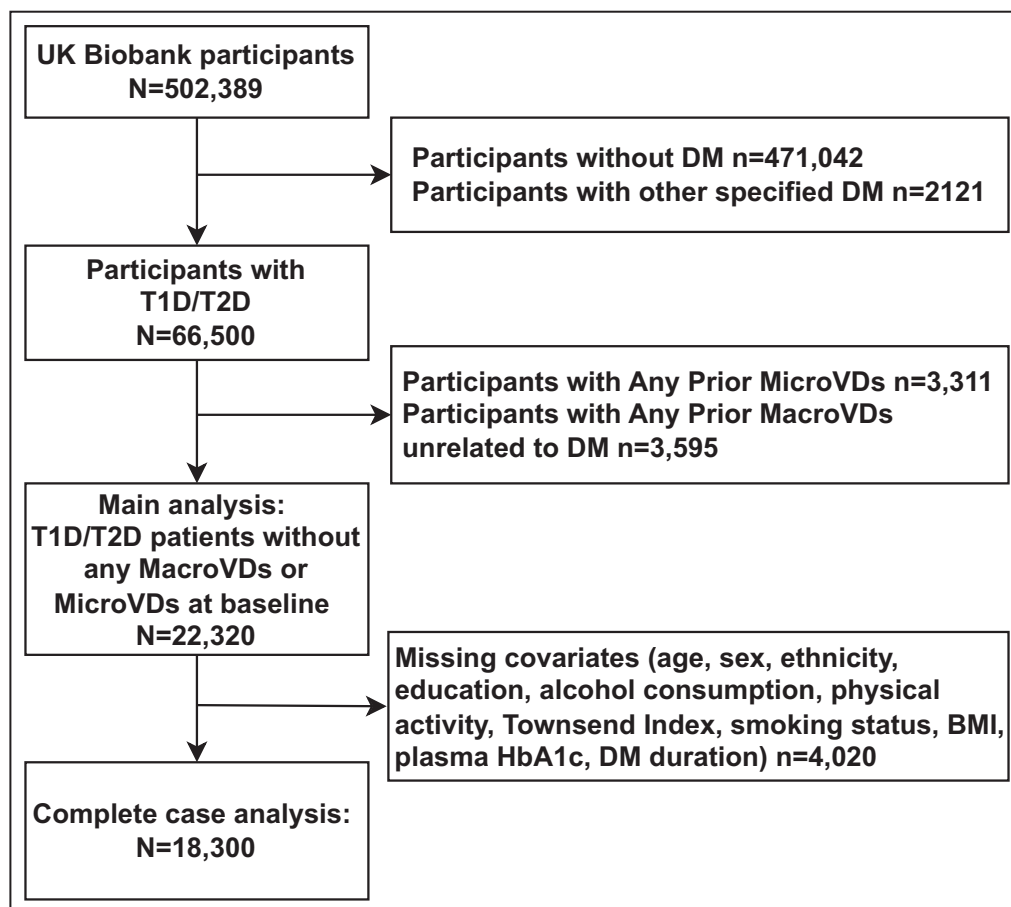


Figure 1. Creation of the study cohort.

Inclusion and exclusion criteria of this study. A total of 1518 patients with T1D and 20802 patients with T2D were included in the main analysis. BMI indicates body mass index; DM, diabetes mellitus; HbA1c, glycated hemoglobin; MacroVCs, macrovascular complications; MicroVCs, microvascular complications; MacroVDs, macrovascular diseases; T1D, type 1 diabetes; and T2D, type 2 diabetes.

MicroVCs before baseline or any macrovascular diseases (MacroVDs) before diabetes diagnosis were excluded from the main analysis. Therefore, 22320 people were included in the main analysis.

All participants provided electronic written informed consent. The UK Biobank study received ethical approval from the North West Multicentre Research Ethics Committee as a Research Tissue Bank and possessed a Human Tissue Authority license. We gained access to the UK Biobank data through an application (ID: 88982). All data and materials are available in UK Biobank (www.ukbiobank.ac.uk) and can be accessed after approval of application.

Identification of Diabetes-Related Macro- and MicroVCs

The exposure of this study was diabetes-related macrovascular disease at baseline. Participants were divided into 5 categories: without any macroVCs, individual diabetes-related CHD (diabetes CHD), individual diabetes-related PAD (diabetes PAD), individual diabetes-related stroke (diabetes stroke), and ≥ 2 comorbidities. Diabetes-related MacroVCs were defined as MacroVCs that occurred after the year or the day (if the date of diagnosis was available) of diabetes diagnosis. The primary outcome of this study was the time to first MicroVC, which is a composite of diabetic MicroVCs, including DR, DKD, and DN. The 3 secondary outcomes were the individual components of incident MicroVCs: DR, DKD, and DN. All diabetes-related vascular diseases were identified according to hospital inpatient records and self-reported medical history using the World Health Organization's *ICD-9* and *ICD-10* codes, and *OPCS-4* and illness and operation codes in the UK Biobank. Detailed fields and codes to identify end points are presented in Data S1. Notably, in this study, DKD included diabetic nephropathy, CKD, and end-stage renal disease due to a lack of precision in diabetic nephropathy definition in clinical practice.²³ Baseline CKD was further defined if the estimated glomerular filtration rate (eGFR) was <60 mL/min per 1.73m^2 . The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation according to specified sex, ethnicity, and serum creatinine.²⁴ Although there was no internationally recognized standardized classification of diabetic complications,²⁵ the definition of diabetes-related vascular diseases in this study was generally in line with high-quality published studies.^{26–29}

Covariates

Age, sex (women or men), ethnicity (*White* or other), education level (college/university or other), Townsend index, smoker status (former smoker, current smoker,

or never), alcohol drinking status (moderate or not), physical activity (regular or nor), body mass index, HbA1c, diabetes duration category, eGFR category (≤ 90 mL/min per 1.73m^2 , >90 mL/min per 1.73m^2), history of hypertension (no, yes), history of hyperlipidemia (no, yes), antihypertensive medication (no, yes), lipid-lowering medication (no, yes), and diabetes medication type (no, insulin, oral medication) were used as covariates.^{30–34}

Ethnicity was categorized as White or other, and other ethnicity included mixed, Asian or Asian British, Black or Black British, Chinese, or other ethnic group. The Townsend Index is an area-based index composite of the percentage of owner-occupied homes, unemployment, car ownership, and crowdedness; a positive value denotes greater material deprivation. Moderate alcohol drinking was defined as 0 to 1 unit per day for women and 0 to 2 units per day for men.³⁵ Regular physical activity was defined as physical activity >150 minutes of moderate activity or 75 minutes of vigorous activity per week.³⁶ A history of hypertension was defined as yes if one was on antihypertensive medication, reported prior doctor-diagnosed hypertension, or had a blood pressure $\geq 140/90$ mmHg at baseline.³⁷ The duration of diabetes was defined according to hospital-recorded date or self-reported age of diabetes diagnosis, and those with neither diabetes diagnosis nor glucose-lowering medication but with an HbA1c $>6.5\%$ were defined as having a diabetes duration of 0 years. For continuous variables that have nonlinear associations with outcome including HbA1c, body mass index, and diabetes duration, restricted cubic splines with 4 knots set at 5th, 35th, 65th, and 95th were used. History of hyperlipidemia was defined as yes if one was on lipid-lowering medication, reported prior doctor-diagnosed hyperlipidemia, had a plasma lipids of cholesterol >240 mg/dL, or triglycerides >200 mg/dL, or high-density lipoprotein cholesterol <1.0 mmol/L (men) and <1.3 mmol/L (women), or low-density lipoprotein cholesterol >4.1 mmol/L.³⁸ Medications were identified through questionnaires and UK Read codes.²²

Statistical Analysis

Categorical variables are described as numbers (percentages) and were compared among groups using the χ^2 test. Continuous variables were described as the mean $\pm$ SD if normally distributed or median (IQR) if skewed and compared among groups using the *F* test in ANOVA or Kruskal-Wallis rank sum test. A Cox proportional hazards model was used to estimate the hazard ratios of baseline diabetes-related macrovascular events on incident microvascular events in T1D and T2D. Healthy participants without macrovascular events at baseline were defined as the reference category. Model 1 was the minimally adjusted model,

adjusting for age, sex, and any incident macrovascular event as a time-varying covariate. Model 2 was the full adjustment model, further adjusted for ethnic, education level, Townsend Index, smoker status, alcohol drinking status, physical activity, restricted cubic splines of body mass index, restricted cubic splines of HbA1c, and restricted cubic splines of diabetes duration, eGFR category, history of hypertension, history of hyperlipidemia, antihypertensive medication, antilipid medication, diabetes medication type, and incorporated any incident diabetes MacroVCs during follow-up as a time-varying covariate. Missing values were imputed using the Multivariate imputation with Chained Equations (MICE) algorithm. Linear regression was performed for continuous variables, logistic regression was performed for binary variables, and multinomial logistic regression was performed for categorical variables. A total of 60% of all included participants had complete records of all covariates. All analyses were performed in the data set after multiple imputation, except for the complete case analysis. A 2-sided P value <0.05 was considered to indicate significance. Schoenfeld residuals were used to ensure no violation of the proportional hazard assumption (global P value for models ranged from 0.078 to 0.960).³⁹ Robust standard errors were used to accommodate potential violations of Cox regression model assumptions.

Subgroup analysis was stratified by risk-control goal achievement according to the National Institute for Health and Care Excellence and American Diabetes Association guidelines.^{40–42} Due to the small sample size and for the sake of validity, the subgroup analysis was only performed for the primary outcome (ie, a composite of MicroVCs). Sensitivity analysis included the following: (1) exclusion of incident cases within 2 years of baseline to avoid reverse causality, (2) complete case analysis for the association between baseline diabetes-related MacroVCs and incident MicroVCs, (3) treatment of nonrenal death as a competing risk using the Fine-Gray method instead of Cox regression, and (4) Cox regression for the association between all prior MacroVCs (both related and not related to diabetes) and incident MicroVCs in T1D and T2D.

The conventional risk factor model for incident diabetic MicroVCs included age, sex, ethnicity, education level, Townsend index, smoker status, alcohol drinking status, physical activity, body mass index category, HbA1c, diabetes duration category, eGFR category, history of hypertension, history of hyperlipidemia, antihypertensive medication, lipid-lowering medication, and diabetes medication type.^{5,23,43} The added value of diabetes-related MacroVCs to predict those who will and will not develop MicroVCs was estimated using differences in C statistics (standard error).⁴⁴

All statistical analyses were performed using Stata/MP version 17 (StataCorp, College Station, TX) and R

version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULT

Study Cohort

A total of 22 320 patients with diabetes without prevalent MacroVCs that were unrelated to diabetes and without prevalent MicroVCs at baseline were included in this study (Figure 1). Among them, 1155 (5.17%) had diabetes-related CHD alone, 119 (0.533%) had diabetes-related PAD alone, 246 (1.10%) had diabetes-related stroke alone, and 159 (0.712%) had ≥ 2 diabetes-related macrovascular comorbidities. The overall mean $\pm$ SD age was 58.79 $\pm$ 7.46 years, and 12 731 (57.0%) were women. Compared with participants without any MacroVCs, those with diabetes-related MacroVCs were older; more likely to be men, current smokers, and more materially deprived; less likely to have a college/university degree; and more likely to have a regular physical exercise habit, worse control of blood glucose, worse eGFR, a longer duration of diabetes, a history of hypertension and hyperlipidemia and relative medication, and more likely to be using insulin (Table 1). Among all participants, 2213 (9.91%) developed DR alone, 2073 (9.29%) developed DKD alone, 541 (2.42%) developed DN alone, and 1173 (5.26%) developed >1 diabetic MicroVC during a median (IQR) follow-up of 12.3 (10.9–13.3) years. Compared with those who did not develop any MicroVCs, those who developed MicroVCs had similar baseline characteristics as those with baseline MacroVCs (Table S1). Baseline characteristics stratified by diabetes type are demonstrated in Table S2.

Incident Diabetic MicroVC Outcomes

In T1D, over a median (IQR) follow-up period of 11.57 (5.84–13.12) years, the incidence rate per 1000 person-years of any MicroVC was 34.0 (30.9–37.4) in the control group, 65.3 (53.8–79.3) in the diabetes CHD group, 115 (72.4–182) in the diabetes PAD group, 74.1 (47.3–116) in the diabetes stroke group, and 131 (90.5–190) in the ≥ 2 comorbidities group. In T2D, over a median (IQR) follow-up period of 12.16 (9.52–13.21) years, the incidence rate of any MicroVC was 16.3 (15.8–16.8) in the control group, 37.0 (33.2–41.3) in the diabetes CHD group, 40.7 (27.7–59.7) in the diabetes PAD group, 30.7 (23.9–39.5) in the diabetes stroke group, and 57.8 (43.0–77.7) in the ≥ 2 comorbidities group (Table 2, Table S3).

Compared with the control group, a substantial risk was evident for the first occurrence of any diabetic microvascular events in groups with diabetes-related MacroVCs at baseline (Figure 2). In the fully

Table 1. Baseline Characteristics of the Study Sample Stratified by Prevalent Diabetes-Related MacroVDs

Baseline characteristics	Overall	None	Diabetes CHD	Diabetes PAD	Diabetes stroke	≥2 MacroVDs	P value
N	22 320	20 811	10 552	98	224	135	
Baseline age, y, mean±SD	58.79±7.46	58.57±7.51	61.90±5.89	61.88±6.26	61.86±5.86	61.10±6.26	<0.001
Men, n (%)	12 731 (57.0)	11 660 (56.0)	755 (71.8)	77 (78.6)	143 (63.8)	96 (71.1)	<0.001
Other ethnicity, n (%)	3130 (14.0)	2935 (14.1)	151 (14.4)	7 (7.1)	25 (11.2)	12 (8.9)	0.074
Below college/university, n (%)	16 804 (75.3)	15 554 (74.7)	878 (83.5)	81 (82.7)	177 (79.0)	114 (84.4)	<0.001
Townsend Index, mean±SD	−0.50±3.41	−0.53±3.39	−0.10±3.56	0.67±3.85	−0.25±3.29	0.45±3.57	<0.001
Smoking status, n (%)							<0.001
Never	10 746 (48.7)	10 179 (49.5)	414 (39.8)	19 (19.8)	89 (40.3)	45 (33.8)	
Former	8870 (40.2)	8141 (39.6)	509 (48.9)	60 (62.5)	99 (44.8)	61 (45.9)	
Current	2455 (11.1)	2260 (11.0)	118 (11.3)	17 (17.7)	33 (14.9)	27 (20.3)	
Excessive drinker, n (%)	14 816 (66.4)	13 766 (66.1)	742 (70.5)	58 (59.2)	152 (67.9)	98 (72.6)	0.009
Regular physical activity, n (%)	8973 (62.3)	8343 (51.9)	442 (57.8)	36 (60.0)	89 (55.6)	63 (67.7)	<0.001
BMI status, n (%)							0.287
<25 kg/m ²	2666 (11.9)	2511 (12.1)	107 (10.2)	10 (10.2)	19 (8.5)	19 (14.1)	
25–30 kg/m ²	7697 (34.5)	7184 (34.5)	363 (34.5)	31 (31.6)	81 (36.2)	38 (28.1)	
>30 kg/m ²	11 957 (53.6)	11 116 (53.4)	582 (55.3)	57 (58.2)	124 (55.4)	78 (57.8)	
HbA1c, mmol/mol, mean±SD	52.14±14.51	51.89±14.44	55.14±13.82	57.39±16.20	53.50±15.68	60.13±19.56	<0.001
HbA1c, mmol/mol, median [IQR]	49.70 [42.80–57.70]	49.60 [42.60–57.30]	52.70 [45.20–63.10]	54.00 [45.80–65.32]	51.50 [43.13–59.60]	56.20 [46.00–67.18]	<0.001
eGFR ≤90 mL/min per 1.73 m ² , n (%)	7911 (38.1)	7219 (37.2)	488 (50.6)	39 (41.9)	105 (49.5)	60 (49.2)	<0.001
Duration of diabetes, n (%)							<0.001
<3 y	8248 (41.3)	8151 (44.1)	71 (6.75)	7 (7.14)	14 (6.25)	5 (3.70)	
3–10 y	7536 (37.7)	6877 (37.2)	454 (43.2)	36 (36.7)	123 (54.9)	46 (34.1)	
≥10 y	4199 (21.0)	3446 (18.7)	527 (50.1)	55 (56.1)	87 (38.8)	84 (62.2)	
History of hypertension, n (%)	17 561 (78.7)	16 210 (77.9)	934 (88.8)	89 (90.8)	200 (89.3)	128 (94.8)	<0.001
History of hyperlipidemia, n (%)	19 279 (86.4)	17 811 (85.6)	1035 (98.4)	89 (90.8)	216 (96.4)	128 (94.8)	<0.001
Antihypertension medication, n (%)	11 901 (53.3)	10 717 (51.5)	827 (78.6)	73 (74.5)	168 (75.0)	116 (85.9)	<0.001
Antilipid medication, n (%)	14 593 (65.4)	13 175 (63.3)	1004 (95.4)	83 (84.7)	207 (92.4)	124 (91.9)	<0.001
Antihyperglycemia treatment, n (%)							<0.001
No	9816 (44.0)	9534 (45.8)	193 (18.3)	15 (15.3)	53 (23.7)	21 (15.6)	
Insulin	1503 (6.7)	1285 (6.2)	147 (14.0)	22 (22.4)	26 (11.6)	23 (17.0)	
Oral medication	11 001 (49.3)	9992 (48.0)	712 (67.7)	61 (62.2)	145 (64.7)	91 (67.4)	

BMI indicates body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IQR, interquartile range; MacroVDs, macrovascular diseases; and PAD, peripheral artery disease. Other includes mixed, Asian or Black British, Black or Black British, Chinese, or other ethnic group.

Table 2. Cumulative Incidence and Incidence Rates for MicroVCs

Prior MacroVCs	Diabetic MicroVCs			
	No. at risk	No. of events/ person-year	IR per 1000 person-year	No. needed to screen
T1D				
No MacroVCs	1228	429/12 615	34.0 (30.9–37.4)	2.9
Diabetes CHD	186	102/1562	65.3 (53.8–79.3)	1.8
Diabetes PAD	26	18/157	115 (72.4–182)	1.4
Diabetes stroke	31	19/256	74.1 (47.3–116)	1.6
≥2 MacroVCs	47	28/213	131 (90.5–190)	1.7
T2D				
No MacroVCs	19583	3662/224 709	16.3 (15.8–16.8)	5.3
Diabetes CHD	845	320/8650	37.0 (33.2–41.3)	2.6
Diabetes PAD	66	26/639	40.7 (27.7–59.7)	2.5
Diabetes stroke	188	61/1987	30.7 (23.9–39.5)	3.1
≥2 MacroVCs	120	44/761	57.8 (43.0–77.7)	2.7

CHD indicates coronary heart disease; IR, incidence rate; MacroVCs, macrovascular complications; MicroVCs, microvascular complications; PAD, peripheral artery disease; T1D, type 1 diabetes; and T2D, type 2 diabetes.

adjusted Cox regression model, the risk of incident MicroVCs was clinically significantly increased in participants with composite MicroVCs (T1D: hazard ratio [HR], 1.25 [95% CI, 0.98–1.60]; T2D: HR, 1.59 [95% CI, 1.38–1.82]), diabetes PAD (T1D: HR, 3.00 [95% CI, 1.86–4.84]; T2D: HR, 1.60 [95% CI, 1.01–2.54]), diabetes stroke (T1D: HR, 1.71 [95% CI, 1.08–2.72]; T2D: HR, 1.50 [95% CI, 1.13–1.99]), and ≥2 MacroVCs (T1D: HR, 2.57 [95% CI, 1.66–3.99]; T2D: HR, 2.66 [95% CI, 1.92–3.68]) in patients with both T1D and T2D, except for diabetes CHD in patients with T1D (Figure 3, Table S4). The significant associations persisted for all individual diabetes MicroVCs (Table S5), except that there was only a trend toward risk in associations between diabetes CHD as well as diabetes stroke and DR in T1D, diabetes PAD and DR in T2D, and ≥2 MacroVCs and DN in T2D.

Subgroup and Sensitivity Analysis

In the subgroup analysis, participants were stratified into 3 groups according to whether HbA1c and blood pressure were controlled at goal levels. Among them, only 111 (7.33%) patients with T1D and 3915 (18.8%) patients with T2D were in full control. The elevated incidence rate of MicroVCs in MacroVCs persisted when assessed across strata of established risk factors controlling for HbA1c (<6.5% and ≥6.5%) and blood pressure (<140/90 mmHg and ≥140/90 mmHg) in patients with T1D and T2D, except for the diabetes stroke and diabetes CHD groups in patients with T1D (Figure 4A through 4B). Compared with those with full control and with ≥2 MacroVCs, the highest incidence rate was 4.50 times higher in T1D and 2.50 times higher in T2D. Among those without any MacroVCs at

baseline, compared with those with full control, poor control conferred a 3.0 times higher risk of T1D and a 1.5 times higher risk of T2D. A Cox regression model was used to assess the excess risk of MacroVCs in each risk category (Figure 4C through 4D). In the fully controlled group, only diabetes CHD was significantly associated with MicroVCs in the fully adjusted model in patients with T1D and T2D. In contrast, in the poorly controlled group, diabetes PAD, diabetes stroke, and ≥2 diabetes MacroVCs were all significantly associated with incident MicroVCs in T2D in the fully adjusted model, and diabetes CHD and ≥2 diabetes MacroVCs were significantly associated with incident MicroVCs.

Four sensitivity analyses were performed to assess the robustness of our finding, including Fine-Gray competing risk models, excluding incident cases within 2 years, not incorporating incident MacroVCs during follow-up as a time-varying covariate, and complete case analysis without multiple imputation of missing covariates (Tables S6–S9). For incident diabetes MicroVCs, associations in T2D persisted except for diabetes PAD, whereas in T1D, only the associations of diabetes PAD and ≥2 diabetes MacroVCs persisted significantly.

In an analysis adopting all prior MacroVCs (both related and not related to diabetes [ie, MacroVCs]) as exposure (Table S10), all MacroVCs were significantly associated with incident diabetes MicroVCs in T2D, whereas only PAD and ≥2 MacroVCs significantly conferred excess risk to diabetes MicroVCs in T1D.

Additive Value of Diabetes-Related MacroVCs in MicroVC Prediction

A standard Cox model based on established risk factors for MicroVCs was constructed, and survival

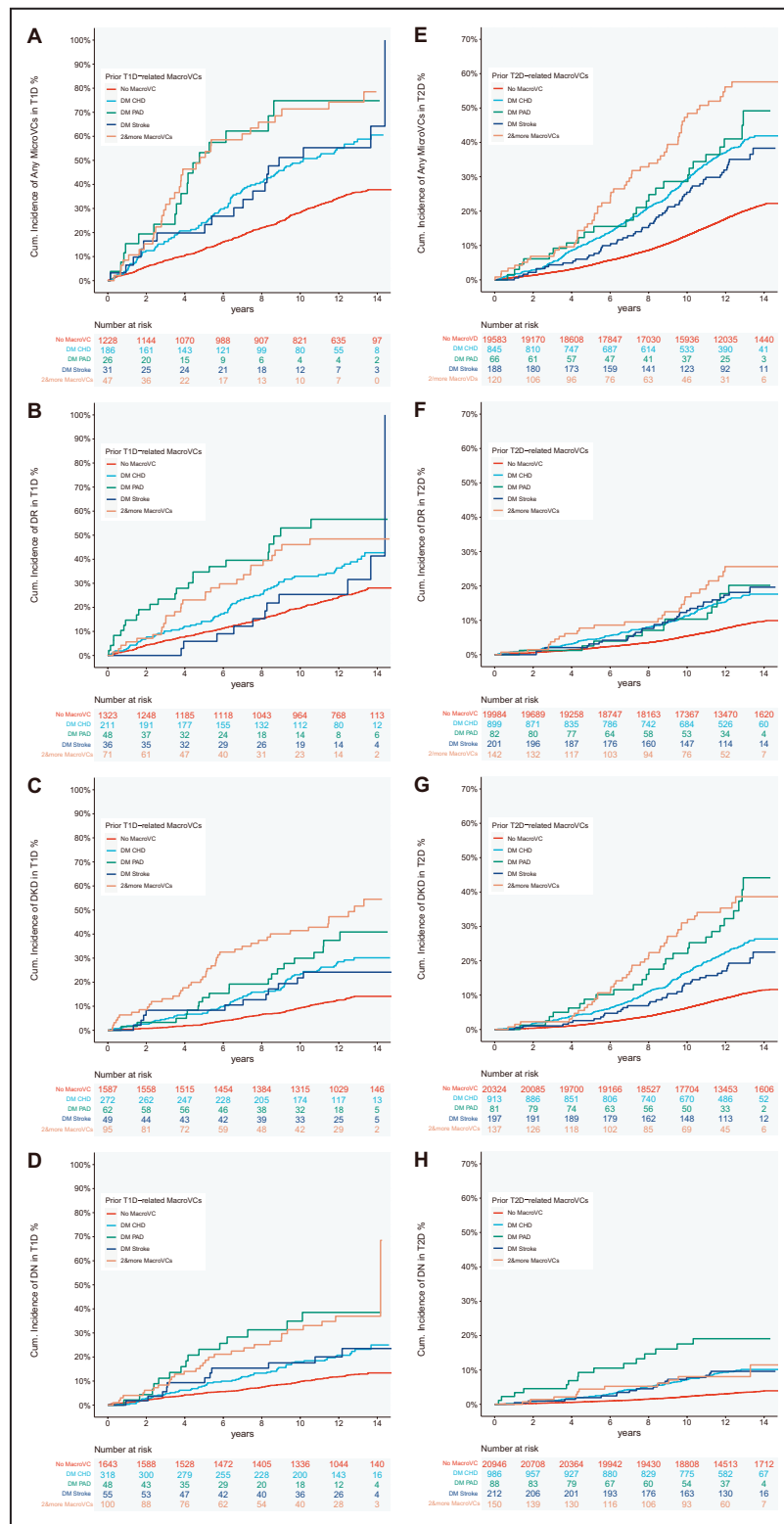


Figure 2. Incident microvascular complications by prevalent diabetic MacroVCs.

A through **D**, Kaplan-Meier survival curve for incident composite and individual MicroVCs in T1D. **E** through **H**, Kaplan-Meier survival curve for incident composite and individual MicroVCs in T2D. CHD indicates coronary heart disease; DKD, diabetic kidney disease; DM, diabetes mellitus; DN, diabetic neuropathy; DR, diabetic retinopathy; MacroVCs, macrovascular complications; MicroVCs, microvascular complications; PAD, peripheral artery disease; T1D, type 1 diabetes; and T2D, type 2 diabetes.

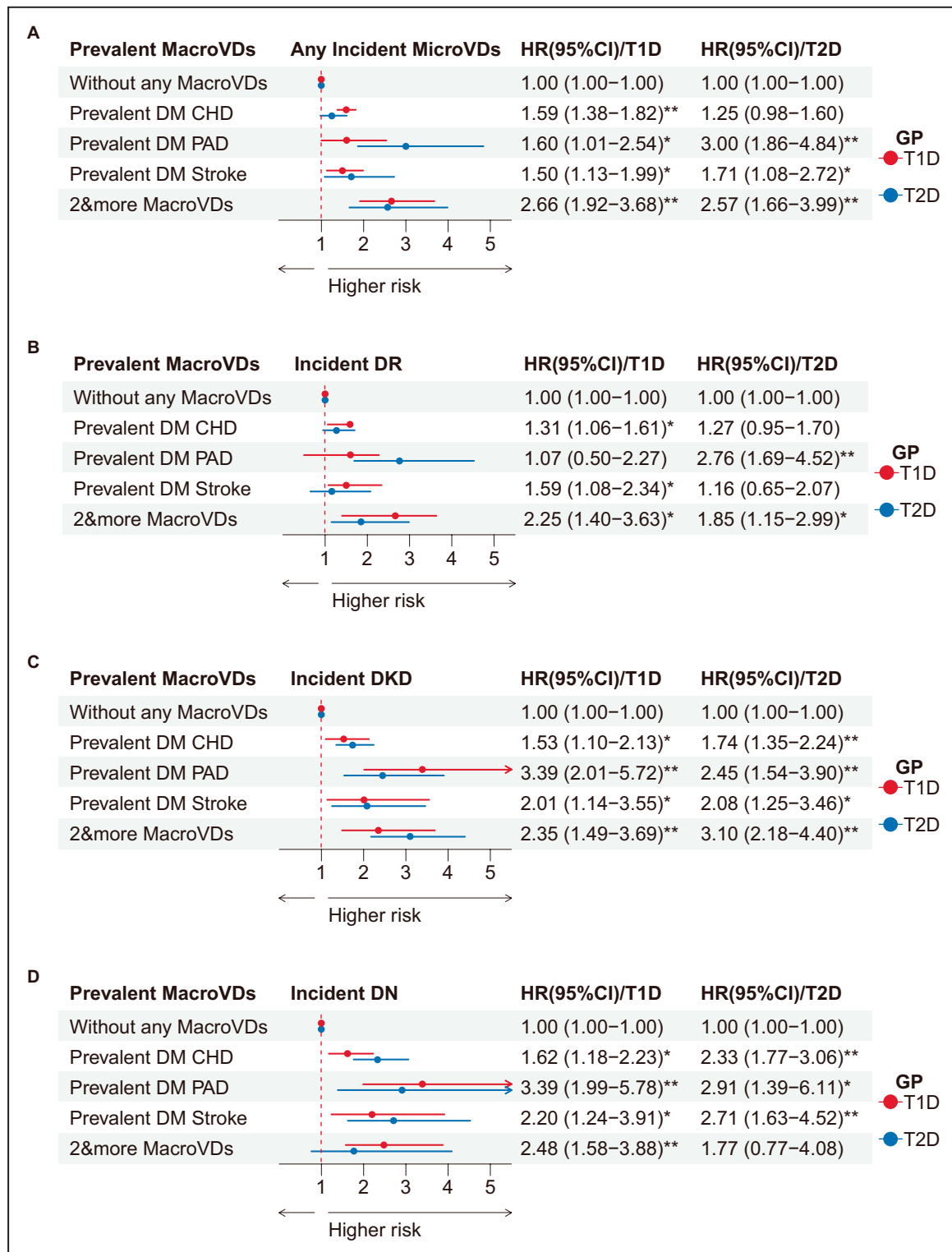


Figure 3. Forest plot of adjusted hazard ratios for incident MicroVCs.

A through D. Multivariate Cox regression models for incident composite and individual MicroVCs in T1D and T2D. The full model adjusted for age, sex, ethnicity, education level, Townsend index, smoker status, alcohol drinking status, physical activity, BMI, HbA1c, DM duration, eGFR category, history of hypertension, history of hyperlipidemia, antihypertensive medication, lipid-lowering medication, diabetes medication type, and incorporation of any incident macrovascular event during follow-up as a time-varying covariate. * $P < 0.05$, ** $P < 0.001$. CHD, coronary heart disease. DKD indicates diabetic kidney disease; DM, diabetes mellitus; DN, diabetic neuropathy; DR, diabetic retinopathy; GP, group; HR, hazard ratio; MacroVCs, macrovascular complications; MicroVCs, microvascular complications; PAD, peripheral artery disease; T1D, type 1 diabetes; and T2D, type 2 diabetes.

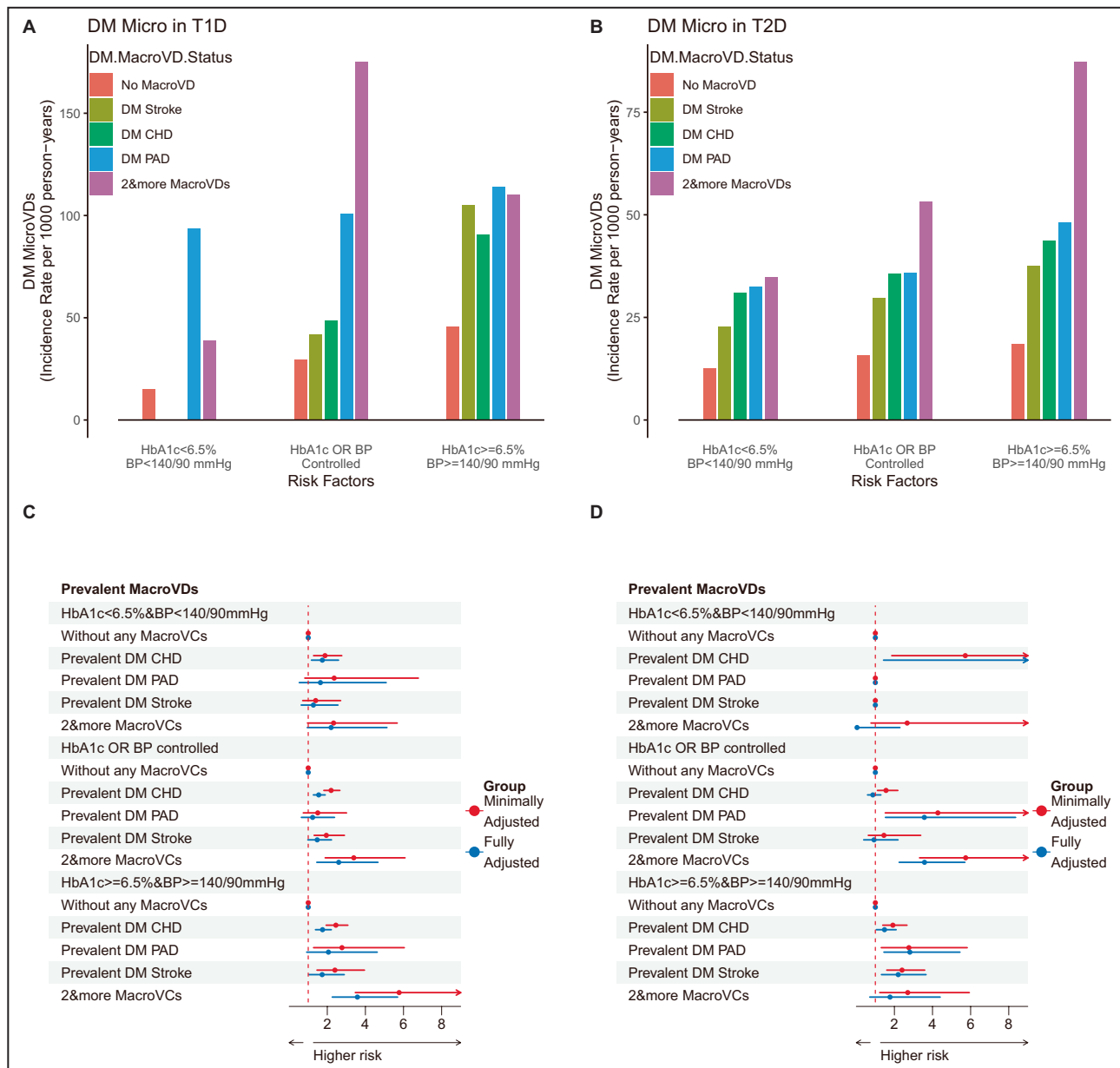


Figure 4. Incidence rates and adjusted hazards ratio of baseline diabetic MacroVDs for the primary outcome stratified by established risk factor goals.

A and B, Incident rate of MicroVCs in T1D and T2D. **C and D,** Multivariate Cox regression model for incident MicroVCs stratified by risk factor control in T1D and T2D. The primary outcome was the first occurrence of diabetic microvascular disease (a composite of DR, DKD, and DN). Risk factor goals were grouped into 3 categories: (1) well controlled, which was HbA1c <6.5% and BP <140/90 mmHg; (2) partly controlled, which was HbA1c ≥6.5% and BP <140/90 mmHg, or HbA1c <6.5% and BP <140/90 mmHg; and (3) poorly controlled, which was HbA1c ≥6.5% and BP ≥140/90 mmHg. The minimally adjusted model was adjusted for age, sex, and any incident macrovascular event as a time-varying covariate. The fully adjusted model was further adjusted for ethnicity, education level, Townsend index, smoker status, alcohol drinking status, physical activity, BMI, HbA1c, DM duration, eGFR category, history of hyperlipidemia, antilipid medication, and incorporated any incident macrovascular event during follow-up as a time-varying covariate. BP indicates blood pressure; CHD indicates coronary heart disease; DKD, diabetic kidney disease; DM, diabetes mellitus; DN, diabetic neuropathy; DR, diabetic retinopathy; MacroVCs, macrovascular complications; MicroVCs, microvascular complications; MacroVDs, macrovascular diseases; PAD, peripheral artery disease; T1D, type 1 diabetes; and T2D, type 2 diabetes.

C statistics were calculated (Table S11). The addition of diabetes-related MacroVCs yielded significant improvements in C statistics only in T2D (difference, 0.0021 [95% CI, 0.0008–0.0034]).

DISCUSSION

In a longitudinal cohort of 1518 individuals with T1D and 20802 individuals with T2D, this study showed that

MacroVCs are a determinant of future MicroVC risk. After full adjustment, the prevalence of diabetes CHD, diabetes PAD, diabetes stroke, and ≥ 2 MacroVCs conferred independent risk to both composite MicroVCs and individual DR, DKD, and DN, except that there was no significant association between diabetes stroke as well as diabetes CHD and incident DR in T1D, and no significant association between diabetes PAD and incident DR in T2D. Risk control categories did not abolish the increased incidence rates of composite MicroVCs in patients with T1D and T2D with MacroVCs, and the significant associations disappeared in the well-controlled T1D and T2D groups (except for diabetes CHD) after full adjustment. As current guidelines suggested providing individualized care to patients with morbidities such as cardiovascular disease or heart failure, our results further provided the perspective of excessive risk of microvascular complications in patients with high-risk diabetes MacroVCs and potential benefit of glycemic and blood pressure control.

Consistent with our results, previous cross-sectional studies have identified positive associations between MacroVCs and MicroVCs in T2D. Dai et al showed that stroke, cardiovascular diseases, and PAD were positively associated with the prevalence of DKD in 1620 patients with T2D.¹³ Additionally, Hayfron-Benjamin et al demonstrated a positive association between stroke and albuminuria in 986 patients with T2D from the multi-ethnic HELIUS (Healthy Life in an Urban Setting) study.¹⁴ On the other hand, Chen et al demonstrated a positive association between PAD and proliferative DR in T2D.⁴⁵ Furthermore, there were also longitudinal studies that were in line with our findings. Analysis from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation) and ADVANCE-ON (the post-trial follow-up of the ADVANCE-Observational Study) studies showed a positive association between a history of composite MacroVDs and incident major composite microvascular events after full adjustment.^{15,16} Zhang et al also demonstrated that baseline PAD was associated with a higher absolute lifetime risk of CKD in T2D.¹⁸ However, previous reports may misestimate the effect due to a lack of full adjustment and not accounting for individual or multiple MacroVCs, and our study design has avoided this shortcoming. Furthermore, to the best of our knowledge, this study was the first in a longitudinal cohort to reveal the positive association between MacroVCs and DN in patients with T2D and the incremental risk that MacroVCs conferred to composite and individual MicroVCs in patients with T1D.

Our findings of the adverse effect of diabetes MacroVCs on diabetes MicroVCs could be explained by currently known physio-pathological mechanisms and have consistent population-level evidence. First, stiffness in larger arteries, a common reason for MacroVDs,

may play an important role in microcirculation damage through buffering capacity impairment and consequently increased flow pulsatility.^{46,47} Higher carotid plaque score¹³ and aortic stiffness, defined as aortic pulse wave velocity >12 m/s,¹⁴ were found to be independently associated with DKD. The results from the Canadian Study of Longevity in Type 1 Diabetes also showed that atherosclerosis, defined as coronary artery calcification >300 , was related to the presence of DN and DR.⁴⁸ Of note, organs with high flow (eg, endocrine pancreas) and low impedance (eg, kidneys) were more vulnerable to these changes and showed deteriorating disease progression.^{49,50} Second, the different impacts of diabetes-related and nondiabetes-related MacroVCs on MicroVCs may be explained by shared pathogenetic pathways of chronic hyperglycemia-induced angiopathies. For example, oxidative stress, induced by hyperglycemia-related mitochondrial overproduction of reactive oxygen species and decreased antioxidant capacity, accelerates insulin resistance and premature vascular morbidity.^{51,52} Accumulation of advanced glycation end products and increased expression of the advanced glycation endproducts (AGE) receptor and its activating ligand were also induced, leading to a diminished anti-atherogenic role of the vascular endothelium and neo-vascularization and vascular permeability, which are critical biological pathways in both macrovascular and microvascular complication development and progression.^{9,53} The importance of hyperglycemia in this angiopathy network was further supported by a retrospective study, which showed the greater risk of diabetes-related hypertension, representing disturbed macrovascular function, on CKD, vision-threatening DR, and leg amputation, compared with hypertension-related diabetes.⁵⁴ Our study provided real-world evidence for the independent role that macrovascular diseases should play in microvascular pathogenesis. Future laboratory and genetic studies are warranted to reveal the pathogenic mechanism and susceptibility of macro- and microcirculation to metabolic and mechanical changes.

Our findings added evidence to the importance of glycemic and blood pressure control in T1D and T2D, especially in patients with comorbid MacroVCs. Among patients with ≥ 2 MacroVCs at baseline, complete risk control reduced the risk of incident microvascular events by 78% in T1D and 60% in T2D. Among those without any MacroVCs at baseline, overall risk was reduced risk by 67% in T1D and 33% in T2D. Furthermore, in the well-controlled group, MacroVCs did not confer an independently increased risk of incident MicroVCs, which was the opposite in the poorly controlled group. However, because our study was observational in nature, future intervention studies are warranted to prove the benefit of intensive treatments in this population. Although plasma dyslipidemia was also an important modifiable risk factor in MicroVC

development,^{5,23,43,55,56} our study failed to include this factor due to the small sample size in each group after further categorization, which may undermine the validity of the study. Of note, because the increased incidence rate of MicroVCs in patients with MacroVC persisted across risk categories, our results could also partly explain why some people with poor control did not develop MicroVCs, whereas others with good control still developed MicroVCs and progressed.^{8,57}

Our study showed a less robust association between diabetes MacroVCs and diabetes MicroVCs in patients with T1D. Our investigation into secondary outcomes (ie, individual microvascular complications) indicated that the reduced robustness could be largely explained by a nonsignificant association between prevalent diabetic CHD and diabetic stroke with incident DR in T1D. This disparity could be attributed to longer duration of diabetes in the T1D group (median of 19 years) than the T2D group (median of 3 years). The onset of DR was greatly influenced by diabetes duration.⁵⁸ Prevalence of any DR was only 18% in patients with T2D with a diabetes duration <10 years, and about 86% in patients with T1D with a diabetes duration >20 years,⁵⁶ which means many patients with T1D have already developed DR and have been excluded from the current study. Rodent models also showed that diabetic retinal vasculopathy either preceded or occurred simultaneously with the onset of heart microangiopathy or encephalopathy in T1D, which was not exactly the same case in T2D, although diabetic macroangiopathy was not able to be studied in the same model.¹² On the other hand, the weakened robustness of association may also be due to the relatively smaller sample size of patients with T1D (T1D 1518 participants versus T2D 20802 participants), as trend of risk persisted while significance failed to sustain. Future studies of a larger sample size are warranted to further investigate associations between diabetic vascular complications in T1D.

Our study demonstrated a modest yet statistically significant additive value of both individual and cumulative MacroVCs in MicroVC prediction in patients with T2D. Other studies of composite MacroVCs were consistent with our results,¹⁶ and several recent prediction models for MicroVCs in T1D or T2D have included the history of cardiovascular events (yes/no) or cardiac/vascular factors.^{59–62} Considering the poor control of diabetic microvascular incident events and costs,⁶ there should still be clinical importance to pay special attention to this high-risk population and provide management to alleviate the disease. However, future studies are warranted to weigh between the clinical cost of enhanced management of patients with diabetes MacroVCs and the maximum increase in net benefit of $\approx 0.3\%$.

The strengths of this study include a relatively large cohort of 22320 patients with T1D or T2D, a median

follow-up duration of >12 years, continuously monitored MicroVCs, and a comprehensive record of covariates at baseline, including anthropometry, plasma biochemistry, lifestyle information, and medical history. There were also some limitations in this study. First, the population was mainly composed of White participants (86%), who are less materially deprived in the United Kingdom, so our findings should be validated elsewhere. However, although the healthy bias of our cohort existed, it has been widely accepted that the exposure-disease association should be generalizable.⁶³ Second, because we used ICD-9, ICD-10, and OPCS-4 codes in hospital inpatient records because few objective data were available in the study cohort, this study was limited by accurate coding of MicroVCs and MacroVCs, and subclinical-to-mild vascular complications were not included. Third, dyslipidemia control was also important for primary and secondary prevention of vascular complications, but our study did not include it in our subgroup analysis. Future studies are warranted to investigate the role of lipid management in this population. Fourth, because the medication history was collected during recruitment (2006–2010), novel treatments like sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1ra) that have cardio and renal benefits were not available at that time. Therefore, the effects of novel treatment could not be taken into account in this study. Last, due to the observational nature of this study and potential unadjusted variables, residual confounding could not be excluded despite confounding factors that we have adjusted in our analysis.

In conclusion, in this study of 22320 T1D and T2D participants from the UK Biobank with a median follow-up of 12 years, MacroVC prevalence, including diabetes CHD, diabetes PAD, diabetes stroke, and ≥ 2 MacroVCs, was found to confer significant risk to both composite and individual MicroVCs and had significant additive value in the conventional MicroVC 10-year risk prediction algorithm. This increased risk could be attenuated by glycemic and blood pressure control. Our results imply that in both patients with T1D and T2D, MacroVC prevention and control should be given more attention, and more intensive screening and prevention strategies should be studied and made for patients with MacroVCs, because they are at higher risk of MicroVCs.

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Disclosures

None.

Supplemental Material

Data S1

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