

Supplementary Table 1. Definitions and sources of information for MVD in the UK Biobank.

Retinopathy ICD-9	Neuropathy ICD-9	CKD ICD-9
2504: Diabetes with ophthalmic manifestations	2505: Diabetes with neurological manifestations 3572: Polyneuropathy in diabetes	2503: Diabetes with renal manifestations 4039: Hypertensive renal disease, not specified as malignant or benign 4401: Atherosclerosis of renal artery 5829: Chronic glomerulonephritis, unspecified 5845: Acute renal failure with lesion of tubular necrosis 5849: Acute renal failure, unspecified
Retinopathy ICD-10	Neuropathy ICD-10	CKD ICD-10
E10.3: Insulin-dependent diabetes mellitus with ophthalmic complications	E10.4: Insulin-dependent diabetes mellitus with neurological complications	E10.2: With renal complications
E11.3: Non-insulin-dependent diabetes mellitus with ophthalmic complications	E11.4: Non-insulin-dependent diabetes mellitus with neurological complications	E11.2: With renal complications
E12.3: Malnutrition-related diabetes mellitus with ophthalmic complications	E13.4: with neurological complications	E13.2: With renal complications
E13.3: Other specified diabetes mellitus with ophthalmic complications	E14.4: Other specified diabetes mellitus with neurological complications	E14.2: With renal complications
E14.3: Unspecified diabetes mellitus with ophthalmic complications	G59.0: Diabetic mononeuropathy	N18-N19: Chronic renal failure or Unspecified renal failure
H28.0: Diabetic cataract	G62.9: Polyneuropathy, unspecified	N28.0: Other disorders of kidney and ureter, not elsewhere classified
H33: retinal detachments and breaks		I70.1: Atherosclerosis of renal artery (without gangrene)
H35.3: Degeneration of macula and posterior pole	G63.2: Diabetic polyneuropathy	
H36.0: Diabetic retinopathy	G99.0: Autonomic neuropathy in endocrine and metabolic diseases	
H40-H42: Glaucoma		
Self-report*		
Non-cancer illness code: 20002		

MVD, microvascular disease; CKD, chronic kidney disease; ICD, International Classification of Disease.

*20002 is the data code used in UK Biobank: Non-cancer illness code.

Supplementary Table 2. Equations for eGFR, expressed for specified sex and serum creatinine level.

Sex	Serum creatinine, mg/dl	Equation of eGFR
Female	≤ 0.7	$144 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{Age}} [\times 1.159 \text{ if black}]$
Female	> 0.7	$144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{Age}} [\times 1.159 \text{ if black}]$
Male	≤ 0.9	$141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{Age}} [\times 1.159 \text{ if black}]$
Male	> 0.9	$141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{Age}} [\times 1.159 \text{ if black}]$

eGFR, estimated glomerular filtration rate

Supplementary Table 3. Definitions and sources of information for HF in the UK Biobank.

ICD-9

Congestive heart failure: 4280

Left heart failure: 4281

Heart failure, unspecified: 4289

ICD-10

Hypertensive heart disease with (congestive) heart failure: I11.0

Hypertensive heart and renal disease with (congestive) heart failure: I13.0

Hypertensive heart and renal disease with both (congestive) heart failure and renal failure: I13.2

Congestive heart failure: I50.0

Left ventricular failure: I50.1

Heart failure, unspecified: I50.9

Self-report*

Non-cancer illness code: 20002

ICD, International Classification of Disease.

*20002 is the data code used in UK Biobank: Non-cancer illness code.

Supplementary Table 4. The proportion of different antihyperglycemic drug classes and antihypertensive drug classes.

Drug classes	T1DM	T2DM
Antihyperglycemic drug classes		
Insulin alone	1,368 (79.9%)	1,492 (5.2%)
Metformin alone	25 (1.5%)	6,978 (24.4%)
Other antihyperglycemic drug classes alone	32 (1.9%)	5,380 (18.8%)
2 drug classes	242 (14.1%)	6,240 (21.8%)
≥3 drug classes	31 (1.8%)	1,140 (4.0%)
With DM but not treated	15 (0.9%)	7,394 (25.8%)
Antihypertensive drug classes		
No hypertension	455 (26.6%)	4,741 (16.6%)
ACEI alone	245 (14.3%)	2,845 (9.9%)
ARB alone	116 (6.8%)	1,512 (5.3%)
BB alone	65 (3.8%)	2,217 (7.7%)
CCB alone	89 (5.2%)	2,308 (8.1%)
Other antihypertensive drug classes alone	240 (14.0%)	4,412 (15.4%)
2 drug classes	178 (10.4%)	3,756 (13.1%)
≥3 drug classes	34 (2.0%)	689 (2.4%)
With hypertension but not treated	291 (17.0%)	6,144 (21.5%)

Values are presented by numbers and percentages.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, β -blocker; CCB, calcium channel blocker; DM, diabetes mellitus.

Percentages may not total 100 because of rounding.

Supplementary Table 5. Summary of missing variables from main analyses of individuals with type 1 DM or type 2 DM.

	T1DM (<i>n</i> =1,713)		T2DM (<i>n</i> =28,624)	
	N Missing	% Missing	N Missing	% Missing
HbA1c	143	8.34	2,067	7.22
Diabetes duration	89	5.19	2,811	9.82
Townsend deprivation index	2	0.12	44	0.15
BMI	31	1.81	342	1.19
Smoking status	3	0.18	320	1.12
SBP	3	0.18	158	0.55
Heart rate	3	0.18	157	0.55
Sedentary time	76	4.43	1,801	6.29
TC	130	7.58	1,998	6.98
HDL	293	17.09	4,179	14.59
LDL	134	7.82	2,084	7.28
CRP	133	7.76	2,088	7.29

BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

Supplementary Table 6. Baseline characteristics among participants with T1DM by No. of MVD.

	No. of MVD			<i>P</i> value	
	0 (n =806)	1 (n =623)	2 (n =225)	3 (n =59)	
HbA1c, mmol/L	57.0 (50.7-66.1)	60.6 (52.2-68.6)	65.4 (54.0-74.0)	61.1 (50.7-73.0)	<0.001
DM duration, y	26.0 (14.0-33.0)	32.0 (21.0-41.0)	32.0 (19.0-41.0)	33.0 (28.0-41.0)	<0.001
Age, y	51.0 (45.0-59.0)	56.0 (48.0-62.0)	59.0 (52.0-64.0)	54.0 (49.0-60.0)	<0.001
Women, n (%)	380 (47.2)	283 (45.4)	107 (47.6)	23 (39.0)	0.607
White, n (%)	747 (92.7)	576 (92.5)	205 (91.1)	57 (96.6)	0.551
Townsend deprivation index	-1.74 (-3.4-1.4)	-1.2 (-3.2-2.0)	0.01 (-3.0-2.6)	0.03 (-3.3-2.8)	0.002
BMI, kg/m ²	26.2 (23.8-29.7)	27.2 (24.3-30.7)	28.6 (25.6-31.6)	28.1 (24.8-30.6)	<0.001
Current smokers, n (%)	95 (11.8)	81 (13.0)	30 (13.3)	7 (11.9)	0.009
SBP, mmHg	135.0 (125.0-149.0)	141.0 (129.0-153.0)	146.0 (132.0-160.0)	155.0 (137.0-166.0)	<0.001
Heart rate, bpm	72.0 (64.0-81.0)	73.0 (66.0-83.0)	74.0 (67.0-84.0)	81.0 (73.0-92.0)	<0.001
Alcohol consumption, g/d	8.6 (0.0-20.0)	8.6 (0.0-20.0)	2.0 (0.0-14.3)	0.3 (0.0-14.3)	<0.001
Sedentary time, h/d	5.0 (3.0-6.0)	5.0 (3.5-6.0)	5.0 (3.5-6.5)	5.0 (4.0-8.5)	0.087
TC, mg/dL	4.6 (4.1-5.0)	4.5 (4.0-5.0)	4.5 (4.0-5.0)	4.7 (4.1-5.1)	0.381
HDL, mmol/L	1.4 (1.2-1.7)	1.4 (1.2-1.7)	1.2 (1.1-1.6)	1.3 (1.2-1.6)	<0.001
CRP, mg/L	1.6 (0.7-2.8)	1.9 (0.9-3.6)	2.2 (1.2-3.9)	2.3 (1.6-6.0)	<0.001
eGFR, ml/min/1.73 m ²	100.5 (92.3-107.6)	96.9 (83.6-106.2)	88.1 (59.6-99.9)	52.2 (39.0-82.3)	<0.001
History of CHD, n (%)	51 (6.3)	94 (15.1)	61 (27.1)	20 (33.9)	<0.001
History of stroke, n (%)	12 (1.5)	20 (3.2)	16 (7.1)	4 (6.8)	<0.001
Antihyperglycemic drug use, n (%)	796 (98.8)	622 (99.8)	224 (99.6)	56 (94.9)	0.001
Antihypertensive drug use, n (%)	308 (38.2)	371 (59.6)	159 (70.7)	46 (78.0)	<0.001
Statin use, n (%)	467 (57.9)	417 (66.9)	171 (76.0)	40 (67.8)	<0.001

Values (continuous covariates) are reported as median (interquartile range) or number (%).

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HbA1c, glycated haemoglobin; MVD, microvascular disease; SBP, systolic blood pressure; TC, total cholesterol; T1DM, type 1 diabetes.

Supplementary Table 7. Baseline characteristics among participants with T2DM by No. of MVD.

	N. of MVD			P value	
	0 (n =19,116)	1 (n =7,844)	2 (n =1,534)	3 (n =130)	
HbA1c, mmol/L	49.9 (42.9-55.6)	50.7 (45.5-59.4)	52.0 (47.1-65.0)	55.5 (50.0-67.6)	<0.001
DM duration, y	4.0 (1.0-7.0)	5.0 (2.0-10.0)	8.0 (4.0-15.0)	13.0 (6.0-19.0)	<0.001
Age, y	60.0 (54.0-65.0)	62.0 (57.0-66.0)	63.0 (58.0-67.0)	63.0 (57.0-66.0)	<0.001
Women, n (%)	7,849 (41.1)	2,941 (37.5)	524 (34.2)	35 (26.9)	<0.001
White, n (%)	16,674 (87.2)	6,517 (83.1)	1,199 (78.2)	109 (83.9)	<0.001
Townsend deprivation index	-1.4 (-3.3-1.9)	-0.7 (-3.0-2.5)	0.1 (-2.6-3.2)	0.0 (-2.5-3.4)	<0.001
BMI, kg/m ²	30.5 (27.3-34.4)	31.2 (27.9-35.3)	31.4 (28.3-35.5)	33.2 (29.9-37.4)	<0.001
Current smokers, n (%)	2,184 (11.4)	917 (11.7)	169 (11.0)	10 (7.7)	0.115
SBP, mmHg	142.0 (130.0-154.0)	145.0 (133.0-159.0)	148.0 (134.0-161.0)	148.0 (137.0-160.0)	<0.001
Heart rate, bpm	73.0 (65.0-82.0)	75.0 (66.0-84.0)	75.0 (66.0-85.0)	77.0 (67.0-86.0)	<0.001
Alcohol consumption, g/d	5.7 (0.0-18.6)	2.3 (0.0-17.1)	1.3 (0.0-14.3)	1.3 (0.0-17.1)	<0.001
Sedentary time, h/d	5.0 (4.0-7.0)	5.0 (4.0-7.0)	5.0 (4.0-7.0)	5.5 (4.0-8.0)	<0.001
TC, mg/dL	4.7 (4.0-5.3)	4.5 (3.9-5.1)	4.3 (3.7-4.9)	4.0 (3.6-4.7)	<0.001
HDL, mmol/L	1.2 (1.0-1.3)	1.2 (1.0-1.3)	1.2 (1.0-1.3)	1.1 (0.9-1.2)	<0.001
CRP, mg/L	2.1 (1.0-3.8)	2.2 (1.1-4.2)	2.2 (1.1-4.5)	2.5 (1.6-5.0)	<0.001
eGFR, ml/min/1.73 m ²	94.8 (85.3-101.8)	92.0 (75.1-100.3)	84.9 (58.0-98.1)	66.3 (48.6-93.6)	<0.001
History of CHD, n (%)	2,769 (14.5)	1,627 (20.7)	419 (27.3)	57 (43.9)	<0.001
History of stroke, n (%)	518 (2.7)	336 (4.3)	90 (5.9)	11 (8.5)	<0.001
Antihyperglycemic drug use, n (%)	13,478 (70.5)	6,269 (79.9)	1,359 (88.6)	123 (94.6)	<0.001
Antihypertensive drug use, n (%)	10,094 (52.8)	5,307 (67.7)	1,175 (76.6)	109 (83.9)	<0.001
Statin use, n (%)	11,097 (58.1)	5,238 (66.8)	1,102 (71.8)	94 (72.3)	<0.001

Values (continuous covariates) are reported as median (interquartile range) or number (%).

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HbA1c, glycated haemoglobin; MVD, microvascular disease; SBP, systolic blood pressure; TC, total cholesterol; T2DM, type 2 diabetes.

Supplementary Table 8. HR and 95% CI for the associations of different covariates with the risk of HF.

Covariates	T1DM		T2DM	
	HR (95% CI)	P value	HR (95% CI)	P value
Age per year increase	1.09 (1.07, 1.13)	<0.001	1.08 (1.07, 1.08)	<0.001
Men	1.06 (0.71, 1.57)	0.788	1.46 (1.32, 1.61)	<0.001
TDI per SD increase	0.94 (0.79, 1.13)	0.523	1.15 (1.11, 1.20)	<0.001
Nonwhite	0.87 (0.41, 1.88)	0.727	1.09 (0.96, 1.24)	0.180
History of CHD	2.03 (1.37, 3.01)	<0.001	2.42 (2.21, 2.65)	<0.001
History of stroke	1.46 (0.67, 3.09)	0.323	1.42 (1.20, 1.69)	<0.001
BMI per SD increase	1.28 (1.07, 1.52)	0.006	1.32 (1.26, 1.38)	<0.001
Ever smoke	1.40 (0.99, 1.97)	0.054	1.32 (1.21, 1.44)	<0.001
Alcohol consumption per SD increase	0.83 (0.67, 1.04)	0.111	1.00 (0.96, 1.04)	0.946
Sedentary time per SD increase	1.08 (0.91, 1.28)	0.353	1.02 (0.98, 1.06)	0.321
HbA1c per SD increase	1.32 (1.11, 1.57)	0.002	1.11 (1.08, 1.15)	<0.001
DM duration per SD increase	1.09 (0.90, 1.32)	0.383	1.06 (1.02, 1.10)	0.002
SBP per SD increase	1.10 (0.92, 1.30)	0.308	1.03 (0.99, 1.07)	0.204
TC per SD increase	0.92 (0.44, 1.91)	0.817	0.89 (0.74, 1.07)	0.205
LDL-C per SD increase	1.10 (0.55, 2.21)	0.778	1.17 (0.98, 1.40)	0.077
HDL-C per SD decrease	1.00 (0.73, 1.37)	0.984	1.02 (0.96, 1.08)	0.573
CRP per SD increase	1.10 (0.94, 1.28)	0.230	1.09 (1.05, 1.12)	<0.001
Heart rate per SD increase	1.26 (1.06, 1.51)	0.011	1.08 (1.03, 1.12)	0.001
Antihyperglycemic medication use				
Metformin alone	Ref.	-	Ref.	
Insulin alone	0.52 (0.15, 1.77)	0.292	1.54 (1.30, 1.82)	<0.001
Other antihyperglycemic drug classes	0.63 (0.11, 3.48)	0.598	1.11 (0.97, 1.26)	0.127
2 drug classes	0.42 (0.11, 1.52)	0.186	1.18 (1.05, 1.32)	0.005
≥3 drug classes	0.61 (0.12, 2.98)	0.538	1.16 (0.96, 1.39)	0.125
With DM but not treated	0.56 (0.05, 5.89)	0.632	0.88 (0.77, 1.00)	0.057
Antihypertensive medication use				

No hypertension	Ref.	-	Ref.
ACEI alone	1.23 (0.60, 2.52)	0.578	1.53 (1.24, 1.89) <0.001
ARB alone	0.58 (0.20, 1.69)	0.321	1.64 (1.30, 2.08) <0.001
BB alone	2.11 (0.92, 4.81)	0.077	1.73 (1.40, 2.13) <0.001
CCB alone	1.04 (0.43, 2.54)	0.931	1.61 (1.30, 2.00) <0.001
Other antihypertensive drug classes	0.85 (0.41, 1.77)	0.663	1.57 (1.29, 1.91) <0.001
2 drug classes	1.67 (0.84, 3.35)	0.146	2.00 (1.65, 2.43) <0.001
≥3 drug classes	0.65 (0.21, 2.02)	0.458	2.56 (2.01, 3.25) <0.001
With hypertension but not treated	1.06 (0.50, 2.23)	0.888	1.10 (0.90, 1.36) 0.350
Statin use	0.95 (0.63, 1.45)	0.826	0.89 (0.81, 0.98) 0.018

Adjustments were made for No. of MCD, age, sex, ethnicity, BMI, SBP, TC, HDL, LDL-C, smoking status, Townsend deprivation index, alcohol consumption, sedentary time, heart rate, history of CHD, history of stroke, CRP, HbA1c, antihypertensive drugs, antihyperglycemic drugs, statin use, and diabetes duration.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, β -blocker; CCB, calcium channel blocker; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CHD, coronary heart disease; DM, diabetes mellitus; HR, hazard ratio; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HF, heart failure; MVD, microvascular disease; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TDI, Townsend deprivation index

Supplementary Table 9. HR and 95% CI for the associations between different types of MVD and risk of incident HF among participants with T1DM and T2DM, stratified by sex*.

Women		No. of MVD		
T1DM	0	1	2	3
Events/person-y	7/4,406	23/3,138	28/1,031	4/183
HR (95% CI)	Ref.	3.05 (1.25, 7.44)	8.41 (3.30, 21.6)	12.8 (3.26, 50.19)
T2DM	0	1	2	3
Events/person-y	369/89,276	260/31,934	95/5,266	10/324
HR (95% CI)	Ref.	1.37 (1.16, 1.62)	2.12 (1.66, 2.71)	3.75 (1.77, 10.89)
Men		No. of MVD		
T1DM	0	1	2	3
Events/person-y	13/4,808	28/3,619	27/1,130	15/246
HR (95% CI)	Ref.	1.31 (0.64, 2.67)	3.76 (1.80, 7.84)	10.27 (4.29, 24.62)
T2DM	0	1	2	3
Events/person-y	825/124,106	684/50,195	228/9,556	44/729
HR (95% CI)	Ref.	1.52 (1.37, 1.68)	2.20 (1.89, 2.57)	4.35 (3.16, 5.94)

Adjustments were made for age, ethnicity, BMI, SBP, TC, HDL-C, LDL-C, smoking status, Townsend deprivation index, alcohol consumption, sedentary time, heart rate, history of CHD, history of stroke, CRP, HbA1c, antihypertensive drugs, antihyperglycemic drugs, statin use, and diabetes duration.

*For T1DM and T2DM, the *P* for interaction for sex were 0.581 and 0.677, respectively.

CI, confidence interval; HR, hazard ratio; MVD, microvascular disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

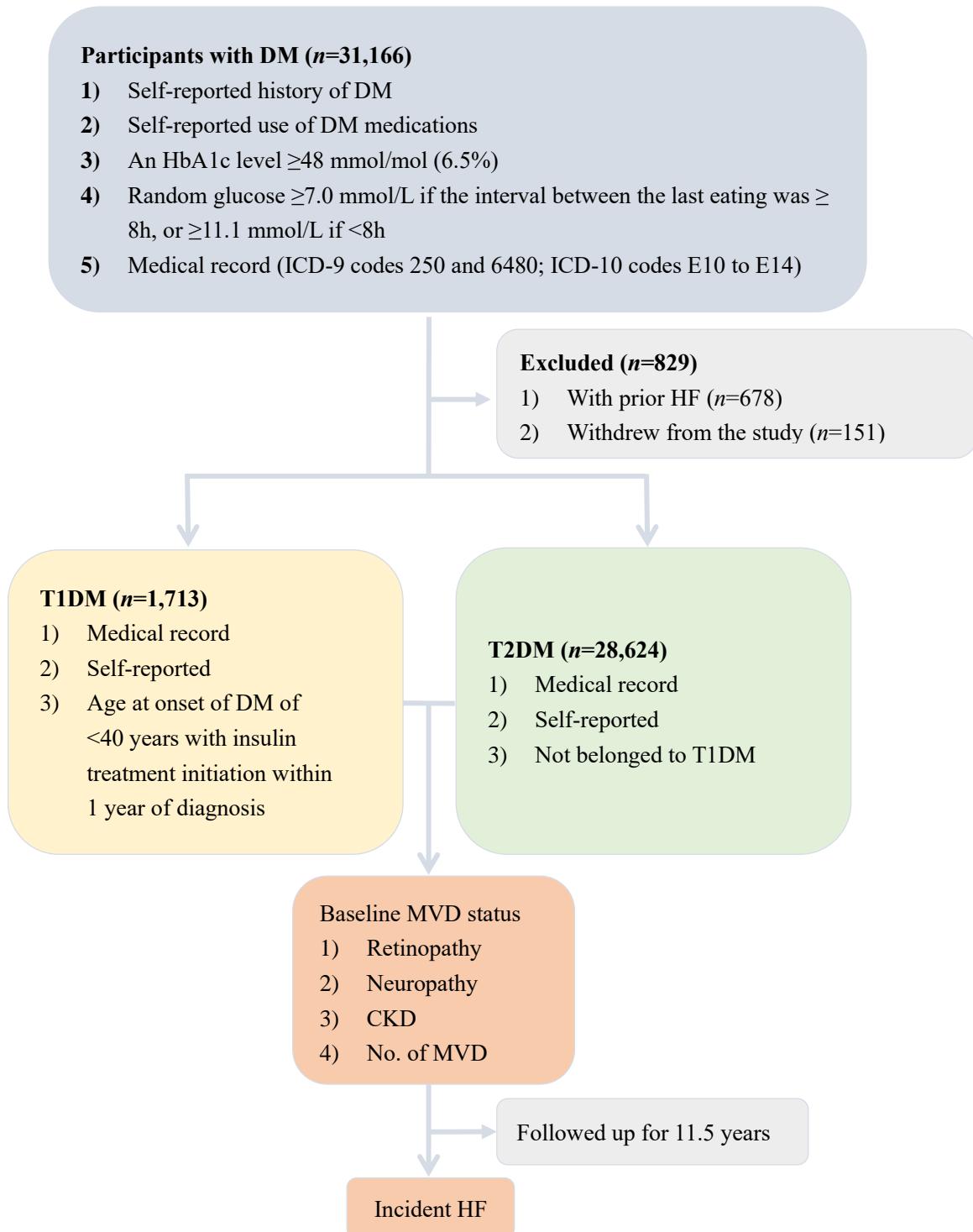
Supplementary Table 10. Sensitivity analysis for the HR and 95% CI for the associations between No. of MVD and risk of incident HF among participants with T1DM or T2DM.

Exclusion of missing data		No. of MVD		
T1DM	0	1	2	3
Events/person-y	13/6,661	37/4,892	31/1,423	12/273
HR (95% CI)	Ref.	2.44 (1.26, 4.74)	4.45 (2.17, 9.12)	10.34 (4.16, 25.80)
T2DM	0	1	2	3
Events/person-y	812/145,950	678/57,942	208/10,109	37/721
HR (95% CI)	Ref.	1.52 (1.37, 1.69)	2.11 (1.80, 2.48)	4.06 (2.89, 5.71)
Redefined type 1 DM		No. of MVD		
T1DM	0	1	2	3
Events/person-y	11/6,665	45/5,263	40/1,692	16/332
HR (95% CI)	Ref.	3.16 (1.59, 6.29)	6.57 (3.22, 13.39)	17.59 (7.35, 42.08)
T2DM	0	1	2	3
Events/person-y	1,206/215,933	950/83,622	338/15,292	54/1,150
HR (95% CI)	Ref.	1.46 (1.34, 1.60)	2.23 (1.96, 2.53)	3.70 (2.80, 4.90)
Using only the ICD codes to define MVD		No. of MVD		
T1DM	0	1	2	3
Events/person-y	73/15,194	44/2,764	22/462	6/143
HR (95% CI)	Ref.	2.00 (1.34, 3.01)	5.90 (3.43, 10.14)	7.53 (2.82, 20.12)
T2DM	0	1	2	3
Events/person-y	2,219/298,088	244/12,287	41/865	11/147
HR (95% CI)	Ref.	1.70 (1.49, 1.95)	3.09 (2.25, 4.24)	3.79 (2.07, 6.93)
Exclusion of non-HF deaths as a potential competing risk		No. of MVD		
T1DM	0	1	2	3
Events/person-y	11/8,760	24/6,094	25/1,714	6/267
HR (95% CI)	Ref.	1.94 (0.91, 4.13)	5.89 (2.70, 12.85)	9.40 (3.09, 28.61)
T2DM	0	1	2	3
Events/person-y	733/197,235	501/71,600	142/11,954	19/733
HR (95% CI)	Ref.	1.40 (1.25, 1.58)	1.87 (1.55, 2.25)	3.25 (2.04, 5.18)

Adjustments were made for age, sex, ethnicity, BMI, SBP, TC, HDL, smoking status, Townsend deprivation index, alcohol consumption, sedentary time, heart rate, history of CHD, history of stroke, CRP, HbA1c, antihypertensive drugs, antihyperglycemic drugs, statin use, and diabetes duration.

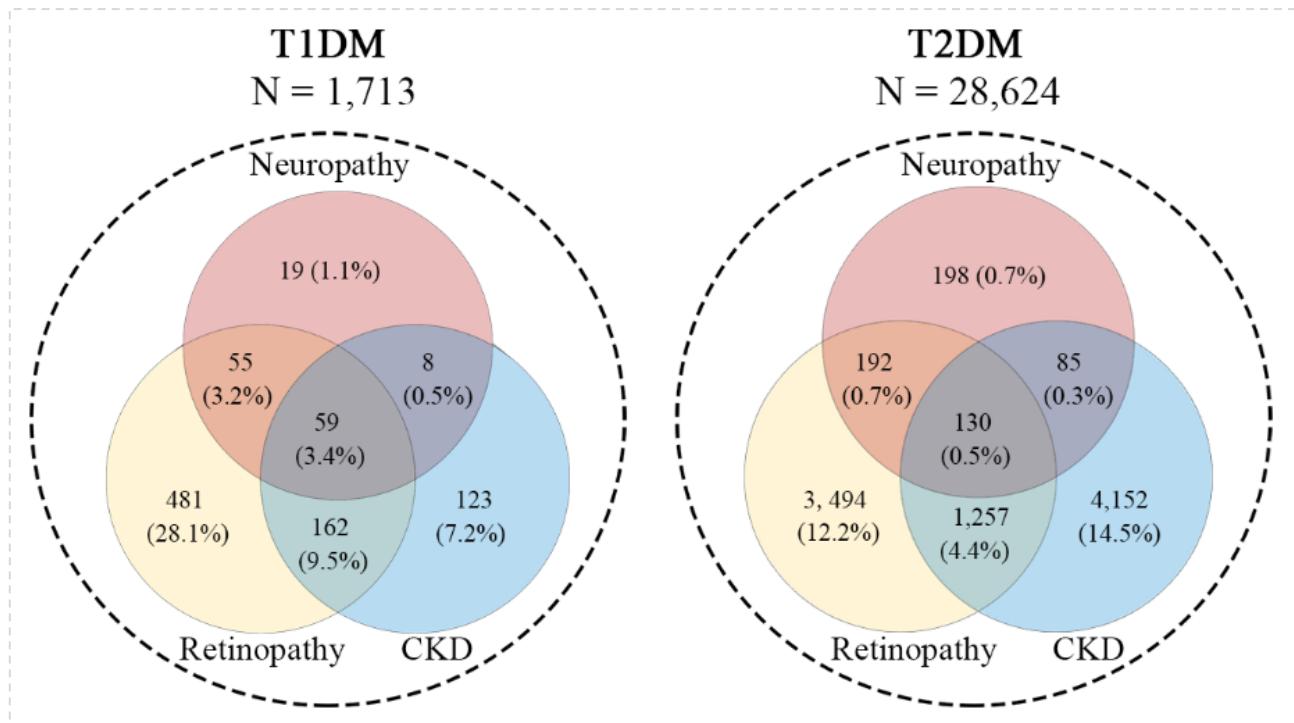
CI, confidence interval; HR, hazard ratio; MVD, microvascular disease; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Supplementary Figure 1. Flowchart of the study protocol.



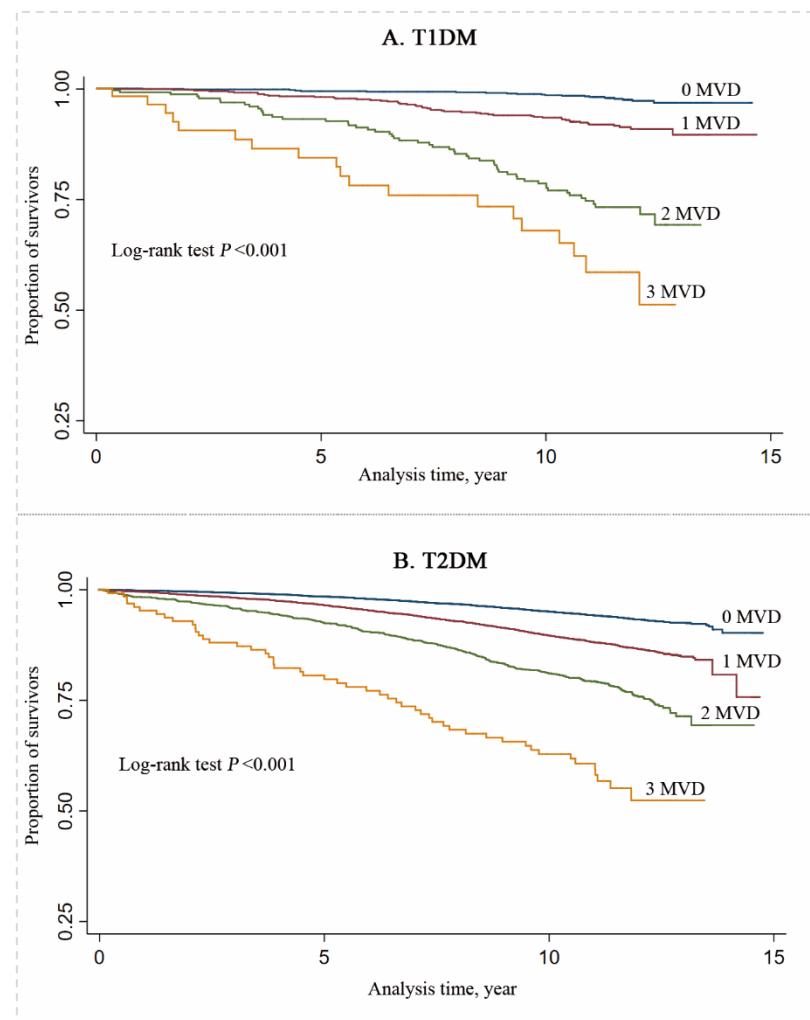
CKD, chronic kidney disease; HF, heart failure; MVD, microvascular disease

Supplementary Figure 2. Venn diagram showing No. of participants with different types of MVD at baseline.



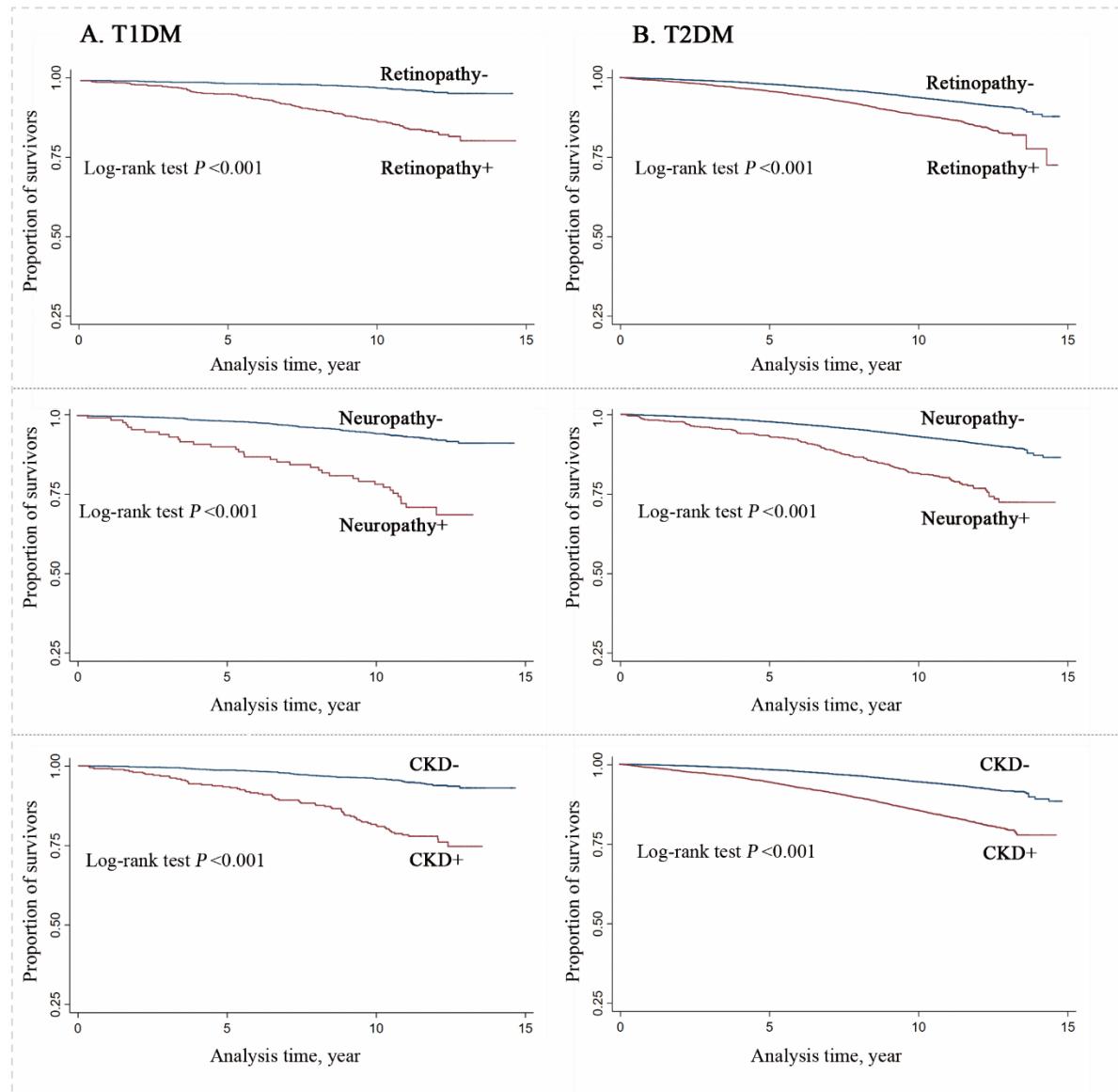
CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Supplementary Figure 3. Kaplan-Meier plot showing risk of HF by No. of MVD among participants with T1DM or T2DM.



MVD, microvascular disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Supplementary Figure 4. Kaplan-Meier plot showing risk of HF by individual MVD among participants with T1DM or T2DM.



CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus