

Supplemental Materials

**Indexing metabolic vulnerability stratifies risks of vascular complications
of type 2 diabetes**

Contents

Supplemental Table S1. Data fields and resources used in the UK Biobank study to identify vascular complications and baseline cardiovascular diseases

Supplemental Table S2. Medical treatment codes used in the UK biobank to identify drug use history

Supplemental Table S3. The CKD-EPI Equation for Estimating GFR, specified by race, sex and serum creatinine level

Supplemental Table S4. Detailed criteria of defining healthy diet

Supplemental Table S5. The calculation of sex-specific MVX, IVX and MMX

Supplemental Table S6. Baseline characteristics of participants included for microvascular complications analysis

Supplemental Table S7. Baseline characteristics of participants included for macrovascular complications analysis

Supplemental Table S8. Sex-specific multiplicative and additive interactions of MVX across different subgroups on microvascular complications

Supplemental Table S9. Association between MVX and microvascular complications

Supplemental Table S10 Sensitivity analysis of the association between vascular complications and MVX using Fine-Gray competing risk model

Supplemental Table S11 Sensitivity analysis of the association between vascular complications and MVX excluding events occurring within the first two years of follow-up

Supplemental Table S12. Hazard ratios(95% CIs) of macrovascular complications with MVX components after fully adjusted

Supplemental Table S13 Hazard ratios(95% CIs) of microvascular complications with MVX components after fully adjusted

Supplemental Table S14. Measures of model improvement for macrovascular complications

Supplemental Table S15. Measures of model improvement for microvascular complications

Supplemental Figure S1. Flowchart of enclusion and exclusion criteria for the population

Supplemental Figure S2. Directed acyclic graph

Supplemental Figure S3. Summary of missing variables from main analyses of participants

Supplemental Figure S4. Kaplan-Meier curves for diabetic nephropathy grouped by sex-specific MVX quartiles

Supplemental Figure S5. Kaplan-Meier curves for diabetic neuropathy grouped by sex-specific MVX quartiles

Supplemental Figure S6. Kaplan-Meier curves for diabetic retinopathy grouped by sex-specific MVX quartiles

Supplemental Figure S7. Kaplan-Meier curves for non-fatal stroke grouped by sex-specific MVX quartiles

Supplemental Figure S8. Kaplan-Meier curves for non-fatal myocardial infarction grouped by sex-specific MVX quartiles

Supplemental Figure S9. Kaplan-Meier curves for cardiovascular mortality grouped by sex-specific MVX quartiles

Supplemental Figure S10. Histogram of baseline MVX score stratified by sex in MACP

Supplemental Figure S11. Histogram of baseline MVX score stratified by sex in MAP

Supplemental Table S1. Data fields and resources used in the UK Biobank study to identify vascular complications and history of vascular diseases at baseline

Complications	ICD-10 from hospital inpatient admission records or national death registries	ICD-9	Self-reported	Other resources
Microvascular complications	E112, E142, N180, N183, N184, N185, N083, E113, E143, H360, H280, E114, E144, G590, G629, G632, G990	2503,2504,2505	20002(1276,1468,1607)	Estimated glomerular filtration rate<60 mL/min/1.73 m ²
Diabetic Retinopathy	E113, E143, H360, H280	2504	20002(1276) 20002(1468)	
Diabetic Neuropathy	E114, E144, G590, G629, G632, G990	2505		
Diabetic Kidney Disease	E112, E142, N180, N183, N184, N185, N083	2503	20002(1607)	Estimated glomerular filtration rate<60 mL/min/1.73 m ²
Macrovascular complications	Hospital inpatient admission records: I21-I23, I60-I69(excluded I60, I62, I67.1, I68.2, I67.5) National death registries: I10-I16, I20-25, I46-52, I60-69, I70-73, R96.0-96.1(excluded I51.4, I60, I62, I67.1, I68.2, I67.5)			
Non-fatal myocardial infarction	I21-I23	410		
Non-fatal stroke	I60-69(excluded I60, I62, I67.1, I68.2, I67.5)	430-438(430, 432.1, 437.3, 437.4, 437.5)		

Fatal cardiovascular disease(cause specific mortality due to specific diseases)	I10-I16, I20-25, I46-52, I60-69, I70-73, R96.0-96.1(excluded I51.4, I60, I62, I67.1, I68.2, I67.5)	401-405, 410-414, 426-429, 430-438, 440-443, 798.1, 798.2(excluded 426.7, 429, 430, 432.1, 437.3, 437.4)
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History of vascular disease at baseline	Coronary heart disease: I20-I25 Stroke: I60-I69 TIA: G45 Peripheral artery disease: I70-I71
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ICD = International Classification of Diseases

Supplemental Table S2. Medical treatment codes used in the UK biobank to identify drug use history

Category	Drug Code	Drug Description
Antihypertensive agent	1140860426	atenolol+nifedipine 50mg/20mg m/r capsule
	1140861088	nifedipine
	1140861190	isradipine
	1140861276	lacidipine
	1140872568	nimodipine
	1140879802	amlodipine
	1140879810	nicardipine
	1140888646	felodipine
	1140923572	adipine mr 10 m/r tablet
	1140928226	nisoldipine
	1141150500	slofedipine 20mg m/r tablet
	1141153026	lercanidipine
	1141165470	felodipine+ramipril
	1140888510	verapamil
	1141153328	trandolapril+verapamil hydrochloride
	1140860696	lisinopril
	1140860728	quinapril
	1140860738	quinapril+hydrochlorothiazide 10mg/12.5mg tablet
	1140860750	captopril
	1140860752	acepril 12.5mg tablet
	1140860764	captopril+hydrochlorothiazide 25mg/12.5mg tablet
	1140860790	enalapril maleate+hydrochlorothiazide 20mg/12.5mg tablet
	1140860806	ramipril
	1140860882	cilazapril
	1140860904	trandolapril
	1140864952	lisinopril+hydrochlorothiazide 10mg/12.5mg tablet
	1141201038	valsartan+hydrochlorothiazide 80mg/12.5mg tablet
	1140916356	losartan
	1141145660	valsartan
	1141151016	losartan potassium+hydrochlorothiazide 50mg/12.5mg tablet
	1141152998	irbesartan
	1141156836	candesartan cilexetil
	1141166006	telmisartan
	1141171336	eprosartan
	1141172682	irbesartan+hydrochlorothiazide 150mg/12.5mg tablet
	1141187788	telmisartan+hydrochlorothiazide 40mg/12.5mg tablet
	1141193282	olmesartan
	1140860192	nadolol
	1140860292	pindolol
	1140860308	metoprolol tartrate+chlorthalidone 100mg/12.5mg tablet
	1140860312	nadolol+bendrofluazide 40mg/5mg tablet
	1140860316	nadolol+bendrofluazide 80mg/5mg tablet
	1140860320	penbutolol sulphate+frusemide 40mg/20mg tablet
	1140860322	pindolol+clopamide 10mg/5mg tablet
	1140860404	metoprolol tartrate+hydrochlorothiazide 100mg/12.5mg tablet
	1140860418	propranolol hydrochloride+bendrofluazide 80mg/2.5mg capsule
	1140860422	acebutolol+hydrochlorothiazide 200mg/12.5mg tablet

1140860426	atenolol+nifedipine 50mg/20mg m/r capsule
1140864950	bisoprolol fumarate+hydrochlorothiazide 10mg/6.25mg tablet
1140866704	angilol 10mg tablet
1140866724	acebutolol
1140866738	atenolol
1140866764	apsolol 10mg tablet
1140866784	berkolol 10mg tablet
1140879758	betaxolol
1140879760	bisoprolol
1140879762	celiprolol
1140879830	oxprenolol
1140879834	penbutolol
1140879842	propranolol
1140879824	labetalol
1140879818	metoprolol
1140909368	carvedilol
1140910614	prindolol
1140916730	sloprolol 80mg m/r capsule
1141146124	atenolol+chlorthalidone
1141146126	atenolol+bendrofluazide
1141146128	atenolol+co-amilozone
1141164276	nebivolol
1141180778	atenolol+chlortalidone
1141194804	nadolol+bendroflumethiazide 40mg/5mg tablet
1141194808	timolol maleate+bendroflumethiazide 10mg/2.5mg tablet
1141194810	atenolol+bendroflumethiazide
1140888552	enalapril
1140888556	fosinopril
1140888560	perindopril
1140923712	moexipril
1141151382	hypapril 12.5mg tablet
1141153328	trandolapril+verapamil hydrochloride
1141164148	imidapril hydrochloride
1141165470	felodipine+ramipril
1141167822	tensopril 12.5mg tablet
1141180592	perindopril+indapamide
1140871986	clonidine hydrochloride 25micrograms tablet
1140883468	clonidine
1140928284	moxonidine
1140888582	bethanidine
Antiglycemic drugs	1140883066 insulin product
	1140874674 tolbutamide
	1140874706 chlorpropamide
	1140874718 glibenclamide
	1140874646 glipizide
	1141157284 glipizide product
	1140874744 gliclazide
	1141152590 glimepiride
	1140884600 metformin
	1141171646 pioglitazone

	1141177600	rosiglitazone
	1141189090	rosiglitazone 1mg / metformin 500mg tablet
Lipid-lowering drugs	1140861958	simvastatin
	1140888594	fluvastatin
	1140888648	pravastatin
	1140910632	eptastatin
	1140910654	velastatin
	1141146234	atorvastatin
	1141192410	rosuvastatin
	1141192736	ezetimibe
	1140861924	bezafibrate
	1140861944	clofibrate
	1140861954	fenofibrate
	1140862026	ciprofibrate
	1141157260	bezafibrate product

ICD = International Classification of Diseases.

*the drug code were extracted from UK Biobank Data-coding

Supplemental Table S3 The CKD-EPI Equation for Estimating GFR, specified by race, sex and serum creatinine level

Race and Sex	Serum Creatinine Level, (mg/dL)	Equation of the eGFR
Black		
Female	≤ 0.7	$166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 0.7	$166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 0.9	$163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 0.9	$163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
White or other		
Female	≤ 0.7	$144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 0.7	$144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 0.9	$141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 0.9	$141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$

eGFR, estimated glomerular filtration rate

Supplemental Table S4. Detailed criteria of defining healthy diet

Diet Component	Intake Goal	Field IDs	Amount per Serving
Fruit	3 servings/day	1309 (pieces fresh fruit/day), 1319 (pieces dried fruit/day)	1309 – 1 piece, 1319 – 5 pieces
Vegetable	3 servings/day	1289 (tablespoons cooked vegetables/day), 1299 (salad/raw vegetables/day)	3 heaped tablespoons
Whole grains	3 servings/day	1438, 1448 (wholemeal/wholegrain bread slices/week), 1458, 1468 (bran/oat/muesli cereal bowls/week)	1438/1448 – 1 slice/day, 1458/1468 – 1 bowl/day
(Shell)fish	≥2 servings/week	1329 (oily fish/week), 1339 (non-oily fish/week)	Once/week
Dairy	2 servings/day	1408 (cheese/week), 1418 (milk type)	1408 – 1 piece/day, 1418 – 1 glass/day if consumption of any type of milk)
Vegetable oils	2 servings/day	1428 (Flora Pro-Active/Benecol spread), 2654 (Flora Pro-Active/Benecol, soft margarine -, olive oil based -, polyunsaturated/sunflower oil based -, other low/reduced fat spread), 1438 (bread slices/week)	1 serving/day if in combination with eating at least 2 slices of bread (ID 1438)
Refined grains	≤2 servings/day	1438, 1448 (white, brown, other bread slices/week), 1458, 1468 (biscuit, other cereals/week)	1438/1448 – 1 slice/day, 1458/1468 – 1 bowl/day
Processed meats	≤1 serving/week	1349 (processed meat/week or daily), 3680 (age when last ate meat)	1349 – 1 piece/day, 3680 – 0 pieces/day if indicated having never eaten meat
Unprocessed meats	≤2 servings/week	1359 (poultry/week or day), 1369 (beef/week or day), 1379 (lamb or mutton/week or day), 1389 (pork/week or day), 3680 (age when last ate meat)	1359-1389 – once/week, 3680 – 0 pieces/day if indicated having never eaten meat
Sugar-sweetened beverages	Don't drink	6144 (never consumes drinks containing sugar)	Only 0 servings were possible here.

Field IDs and serving sizes for each diet component derived from the UK Biobank general baseline questionnaire. Participants who achieved the intake goal were considered to have an adequate intake of the diet component. Adequate intake of at least half of all diet components was

defined as a healthy diet (healthy diet = yes), whereas adequate intake of less than half of all diet components was defined as a poor diet (healthy diet = no).

Supplemental Table S5. The calculation of sex-specific MVX, IVX and MMX

Female multimarker score equations	
IVX _F	= 9 + (GlycA * -0.000187) + (S-HDLP * -0.3585) + ((GlycA * S-HDLP) * 0.000348)
MMX _F	= ((4 + (Leu * -0.03142) + (Leu ² * 0.0000893)) * 0.353) + ((7 + (Val * -0.03362) + (Val ² * 0.0000689)) * 0.684) + (Ileu * 0.00332) + ((1 + (Citr * -0.0072) + (Citr ² * 0.0000573)) * 0.7135)
MVX _F	= (IVX _F * 2.27278) + (lnMMX _F * 12.13511) + (IVX _F * lnMMX _F) * -1.09312
Male multimarker score equations	
IVX _M	= 9 + (GlycA * -0.00437) + (S-HDLP * -0.52307) + ((GlycA * S-HDLP) * 0.000817)
MMX _M	= ((4 + (Leu * -0.01594) + (Leu ² * 0.0000291)) * 1.076) + ((7 + (Val * -0.0239) + (Val ² * 0.00005)) * 0.414) + (Ileu * 0.01265) + ((1 + (Citr * 0.00906) + (Citr ² * -0.0000126)) * 0.5881)
MVX _M	= (IVX _M * 3.54601) + (lnMMX _M * 14.41428) + (IVX _M * lnMMX _M) * -1.43438

Values for each input variable were winsorized at the 1st and 99th percentile. Quadratic transformations of leucine, valine, and citrate and log transformation of MMX improved model fit. Coefficients are from Cox proportional hazards models for 3-year all-cause mortality in CATHGEN adjusted for age and sex. Multimarker scores (1-100) were calculated by dividing the range into 100 equal parts.

Citr = citrate; Ileu = isoleucine; IVX = inflammation vulnerability index; Leu = leucine; MMX = metabolic malnutrition index; MVX = metabolic vulnerability index; S-HDLP = small HDL particle number; Val = valine.

Supplemental Table S6. Baseline characteristics of participants included for microvascular complications analysis

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i>-value²
Demographics						
Age, years	61.00 (55.00-65.00)	61.00 (56.00-65.00)	61.00 (55.00-65.00)	61.00 (55.00-65.00)	60.00 (54.00-65.00)	<0.001
Male, n (%)	8,659 (62.3%)	2,165 (62.3%)	2,165 (62.3%)	2,165 (62.3%)	2,164 (62.3%)	>0.999
Ethnicity, n (%)						<0.001
White	12,173 (88.3%)	2,950 (85.6%)	3,039 (88.2%)	3,071 (88.9%)	3,113 (90.4%)	
Black	428 (3.1%)	177 (5.1%)	110 (3.2%)	91 (2.6%)	50 (1.5%)	
Others	1,190 (8.6%)	319 (9.3%)	297 (8.6%)	292 (8.5%)	282 (8.2%)	
Lifestyle and risk factors						
Current Smoking status, n (%)	1,645 (11.9%)	315 (9.1%)	395 (11.4%)	450 (13.0%)	485 (14.0%)	<0.001
Healthy diet, n(%)	4,210 (30.3%)	1,139 (32.8%)	1,081 (31.1%)	1,009 (29.0%)	981 (28.2%)	<0.001
History of cardiovascular diseases, n(%)	2,140 (41.2%)	545 (44.4%)	561 (42.7%)	559 (41.5%)	475 (36.3%)	<0.001
Antihypertensive drug use, n (%)	8,805 (63.5%)	2,086 (60.1%)	2,219 (63.9%)	2,309 (66.6%)	2,191 (63.3%)	<0.001
Lipid-lowering drug use, n (%)	9,939 (71.6%)	2,589 (74.6%)	2,553 (73.5%)	2,463 (71.0%)	2,334 (67.4%)	<0.001
Antihyperglycemic drug use, n	7,977 (57.5%)	2,057 (59.3%)	2,041 (58.8%)	2,009 (57.9%)	1,870 (54.0%)	<0.001

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i> -value ²
(%)						
DM duration, years	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-8.00)	0.835
BMI, kg/m ²	31.63 (5.80)	30.16 (5.13)	31.52 (5.86)	32.20 (5.91)	32.64 (5.98)	<0.001
Systolic blood pressure, mmHg	141.77 (17.42)	139.65 (16.95)	140.90 (17.26)	142.51 (17.75)	144.04 (17.42)	<0.001
Laboratory biomarkers						
TC, mmol/L	4.50 (3.87-5.31)	4.18 (3.64-4.92)	4.34 (3.75-5.10)	4.54 (3.94-5.32)	4.97 (4.27-5.88)	<0.001
HDL-C, mmol/L	1.13 (0.97-1.34)	1.17 (0.99-1.42)	1.12 (0.95-1.33)	1.12 (0.97-1.31)	1.13 (0.99-1.31)	<0.001
HbA1c, mmol/mol	49.90 (43.60-57.70)	48.20 (41.30-55.00)	49.55 (43.30-56.80)	50.60 (44.50-58.30)	51.70 (45.80-60.60)	<0.001
eGFR, mL/min/1.73 m ²	93.40 (83.53-100.29)	93.06 (84.51-99.62)	93.05 (83.26-99.69)	93.31 (82.39-100.38)	94.20 (83.85-101.72)	<0.001
GlycA, mmol/L	858.44 (777.79-944.95)	737.19 (691.45-784.89)	824.54 (779.41-870.81)	890.91 (845.23-943.01)	1,004.70 (942.38-1,065.20)	<0.001
Small HDL particles, mmol/L	9.45 (8.59-10.35)	8.86 (8.07-9.78)	9.13 (8.37-9.95)	9.51 (8.79-10.26)	10.28 (9.47-11.15)	<0.001
Leucine, mmol/L	113.83 (96.38-135.04)	112.86 (98.09-130.93)	110.79 (94.56-130.59)	113.74 (94.35-135.80)	119.30 (98.17-144.70)	<0.001
Isoleucine, mmol/L	56.06 (45.51-69.27)	53.87 (44.81-65.16)	54.48 (44.35-67.03)	57.02 (45.23-70.73)	59.98 (47.86-75.59)	<0.001
Valine, mmol/L	232.93 (205.07-265.28)	223.52 (200.66-248.02)	227.35 (200.54-256.59)	235.92 (206.04-267.69)	251.56 (217.84-290.98)	<0.001

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i>-value²
Citrate, mmol/L	67.21 (58.78-76.64)	64.37 (55.91-73.49)	66.54 (58.31-75.49)	68.07 (59.70-77.25)	69.96 (61.48-79.88)	<0.001
MMX score	46.00 (28.00-55.00)	42.00 (22.00-51.00)	46.00 (27.00-54.00)	48.00 (31.00-56.00)	49.00 (34.00-59.00)	<0.001
IVX score	30.00 (18.00-46.00)	14.00 (10.00-28.00)	21.00 (17.00-42.00)	29.00 (25.00-50.00)	49.00 (38.00-67.00)	<0.001
MVX score	35.00 (26.00-47.00)	21.00 (17.00-30.00)	28.00 (25.00-41.00)	36.00 (32.00-50.00)	56.00 (44.00-64.00)	<0.001

¹Median (Q1-Q3); n (%); Mean (SD)

²Kruskal-Wallis rank sum test; Pearson's Chi-squared test; One-way analysis of means (not assuming equal variances)

Supplemental Table S7. Baseline characteristics of participants included for macrovascular complications analysis

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i> -value ²
Demographics						
Age, years	61.00 (55.00-65.00)	61.00 (56.00-65.00)	61.00 (55.00-65.00)	61.00 (55.00-65.00)	60.00 (54.00-65.00)	< 0.001
Male, n (%)	7,765 (60.1%)	1,942 (60.1%)	1,941 (60.1%)	1,941 (60.1%)	1,941 (60.1%)	>0.999
Ethnicity, n (%)						< 0.001
White	11,292 (88.0%)	2,744 (85.6%)	2,805 (87.5%)	2,847 (88.7%)	2,896 (90.2%)	
Black	439 (3.4%)	177 (5.5%)	119 (3.7%)	89 (2.8%)	54 (1.7%)	
Others	1,101 (8.6%)	284 (8.9%)	282 (8.8%)	274 (8.5%)	261 (8.1%)	
Lifestyle and risk factors						
Current Smoking status, n (%)	1,451 (11.3%)	287 (8.9%)	353 (11.0%)	388 (12.0%)	423 (13.2%)	< 0.001
Healthy diet, n(%)	3,904 (30.2%)	1,049 (32.4%)	1,012 (31.3%)	938 (29.0%)	905 (28.0%)	< 0.001
Antihypertensive drug use, n (%)	7,826 (60.7%)	1,817 (56.3%)	1,970 (61.0%)	2,052 (63.7%)	1,987 (61.6%)	< 0.001
Lipid-lowering drug use, n (%)	8,915 (69.1%)	2,326 (72.1%)	2,282 (70.7%)	2,208 (68.5%)	2,099 (65.1%)	< 0.001
Antihyperglycemic drug use, n (%)	7,593 (58.9%)	1,972 (61.1%)	1,939 (60.1%)	1,916 (59.4%)	1,766 (54.8%)	< 0.001
DM duration, years	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-9.00)	5.00 (2.00-9.00)	0.857

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i>-value²
BMI, kg/m2	31.66 (5.86)	30.09 (5.18)	31.51 (5.87)	32.29 (5.91)	32.74 (6.11)	<0.001
Systolic blood pressure, mmHg	142.26 (17.32)	140.24 (16.93)	141.36 (17.08)	143.09 (17.55)	144.37 (17.43)	<0.001
Laboratory biomarkers						
TC, mmol/L	4.53 (3.90-5.35)	4.22 (3.66-4.98)	4.39 (3.79-5.16)	4.56 (3.96-5.36)	4.99 (4.28-5.91)	<0.001
HDL-C, mmol/L	1.15 (0.98-1.35)	1.19 (1.00-1.45)	1.13 (0.97-1.34)	1.13 (0.98-1.32)	1.13 (0.99-1.31)	<0.001
HbA1c, mmol/L	50.20 (43.80-58.20)	48.50 (41.50-55.40)	49.80 (43.50-57.20)	50.70 (44.70-58.70)	52.00 (46.10-61.00)	<0.001
eGFR, mL/min/1.73 m2	93.15 (81.78-100.30)	93.16 (83.94-99.86)	92.83 (81.98-99.83)	92.90 (80.86-100.24)	93.60 (80.96-101.62)	0.027
GlycA, mmol/L	859.72 (779.36-947.17)	738.78 (693.77-785.56)	827.02 (782.52-873.35)	893.35 (846.60-945.92)	1,007.90 (945.09-1,069.50)	<0.001
Small HDL particles, mmol/L	9.48 (8.62-10.38)	8.93 (8.10-9.86)	9.17 (8.43-9.98)	9.54 (8.80-10.29)	10.29 (9.46-11.19)	<0.001
Leucine, mmol/L	113.35 (95.97-134.80)	112.55 (97.67-130.31)	110.49 (94.88-130.11)	113.57 (94.05-136.20)	118.28 (97.26-144.84)	<0.001
Isoleucine, mmol/L	55.93 (45.46-69.24)	53.82 (44.75-64.98)	54.42 (44.51-66.64)	57.17 (45.23-71.01)	59.65 (47.53-75.85)	<0.001
Valine, mmol/L	232.48 (205.00-265.06)	222.98 (200.87-247.89)	227.20 (200.94-256.67)	235.45 (205.80-268.27)	250.88 (216.68-290.43)	<0.001

Characteristic	Overall	MVX Group 1	MVX Group 2	MVX Group 3	MVX Group 4	<i>p</i> -value ²
Citrate, mmol/L	67.54 (59.03-77.30)	64.71 (56.06-73.86)	66.77 (58.38-76.07)	68.63 (60.07-78.09)	70.20 (61.96-80.37)	<0.001
MMX score	48.00 (27.00-58.00)	44.00 (21.00-54.00)	48.00 (25.00-57.00)	50.00 (30.00-60.00)	52.00 (32.00-62.00)	<0.001
IVX score	31.00 (19.00-46.00)	14.00 (9.00-28.00)	21.00 (17.00-42.00)	29.00 (25.00-51.00)	50.00 (38.00-67.00)	<0.001
MVX score	36.00 (26.00-48.00)	21.00 (18.00-31.00)	28.00 (25.00-42.00)	36.00 (32.00-50.00)	56.00 (44.00-64.00)	<0.001

1Median (Q1-Q3); n (%); Mean (SD)

2Kruskal-Wallis rank sum test; Pearson's Chi-squared test; One-way analysis of means (not assuming equal variances)

Supplemental Table S8. Association between MVX and microvascular complications

Subgroup	Multiplicative effect <i>P</i>		RERI		AP(%)		Synergy Index	
	Male	Female	Male	Female	Male	Female	Male	Female
Age	0.715	0.322	0.034(- 0.207,0.275)	0.150(- 0.139,0.439)	0.020(- 0.126,0.167)	0.095(- 0.089,0.280)	1.055(0.711,1. 564)	1.355(0.667,2. 752)
BMI	0.442	0.548	0.028(- 0.401,0.457)	0.017(- 0.495,0.529)	0.018(- 0.252,0.287)	0.012(- 0.343,0.367)	1.052(0.486,2. 277)	1.045(0.307,3. 562)
Duration of diabetes	0.323	0.946	-0.120(- 0.389,0.149)	0.134(- 0.154,0.421)	-0.081(- 0.260,0.099)	0.090(- 0.104,0.284)	0.805(0.516,1. 257)	1.386(0.584,3. 288)

All analyses were adjusted for age, ethnicity(White, Black or other), current smoking status (yes or no), diabetes duration, BMI, TC, HDL-C, HbA1c, eGFR, average SBP, healthy diet(yes or no), fasting time, antihypertensive drug use (yes or no), lipid-lowering drug use (yes or no), antihyperglycemic medication use (yes or no) for MVX per SD increase.

AP attributable proportion due to interaction; BMI Body Mass Index; eGFR estimated Glomerular Filtration Rate; MVX metabolic vulnerability index; RERI relative excess risk due to interaction

Supplemental Table S9. Association between MVX and microvascular complications

Outcome	Model 1		Model 2		Model 3	
	Male	Female	Male	Female	Male	Female
Microvascular complications	1.16 (1.00-1.22)	1.14 (1.07-1.22)	1.16 (1.10-1.21)	1.14 (1.07-1.22)	1.14 (1.08-1.19)	1.11 (1.04-1.19)
Nephropathy	1.27 (1.19-1.36)	1.22 (1.11-1.35)	1.27 (1.18-1.36)	1.23 (1.12-1.35)	1.24 (1.15-1.33)	1.20 (1.09-1.32)
Neuropathy	1.21 (1.11-1.33)	1.15 (1.00-1.33)	1.21 (1.11-1.33)	1.15 (1.00-1.33)	1.19 (1.09-1.31)	1.11 (0.96-1.28)
Retinopathy	1.04 (0.97-1.11)	1.07 (0.97-1.17)	1.04 (0.97-1.11)	1.07 (0.97-1.17)	1.02 (0.95-1.10)	1.03 (0.94-1.13)

Values are HR (95% CI). HRs and 95% CIs are shown per 1 SD.

Model 1: adjustment for age, ethnicity, current smoking status, BMI(continuous), history of CVD diagnosis and laboratory biomarkers (TC, HDL-C, LDL-C, HbA1c, and eGFR and average systolic blood pressure). Model 2: model 1 adjustments plus fasting time(continuous), healthy diet(yes or no). Model 3 (full model): model 2 adjustments plus baseline diabetes duration(continuous), antihyperglycemic drug use, antihypertensive drug use and lipid-lowering drug use.

Supplemental Table S10. Sensitivity analysis of the association between vascular complications and MVX using Fine-Gray competing risk model

	Male		Female	
	SHR(95% CI)	p-value	SHR(95% CI)	p-value
Microvascular complications				
*Composite complications	1.12 (1.07-1.18)	<0.01	1.09 (1.02-1.16)	0.01
Diabetic nephropathy	1.21 (1.13-1.3)	<0.01	1.17 (1.07-1.29)	<0.01
Diabetic neuropathy	1.17 (1.07-1.29)	<0.01	1.08 (0.94-1.25)	0.28
Diabetic retinopathy	1.01 (0.94-1.08)	0.80	1.01 (0.92-1.1)	0.91
Macrovascular complications				
**Composite complications	1.02 (0.97-1.08)	0.36	1.06 (0.98-1.14)	0.14
Stroke	0.95 (0.88-1.03)	0.22	1.02 (0.92-1.12)	0.76
Myocardial infarction	1.13 (1.05-1.22)	<0.01	1.09 (0.95-1.26)	0.23
Cardiovascular Mortality	1.06 (0.97-1.16)	0.18	1.14 (0.99-1.33)	0.07

Models were adjusted for adjusted for age, ethnicity(White, Black or other), current smoking status (yes or no), diabetes duration, BMI, TC, HDL-C, HbA1c, eGFR, average SBP, healthy diet(yes or no), fasting time, antihypertensive drug use (yes or no), lipid-lowering drug use (yes or no), antihyperglycemic medication use (yes or no) for MVX per SD increase.

*Composite outcome = the presence of any of the following diabetic microvascular complications including nephropathy, neuropathy and retinopathy

** Composite outcome = the presence of any of the following diabetic macrovascular complications including non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality

Supplemental Table S11. Sensitivity analysis of the association between vascular complications and MVX excluding events occurring within the first two years of follow-up

	Male		Female	
	HR(95% CI)	p-value	HR(95% CI)	p-value
*Microvascular complications				
Composite complications	1.14 (1.08-1.2)	<0.001	1.12 (1.05-1.20)	<0.001
Diabetic nephropathy	1.24 (1.15-1.33)	<0.001	1.21 (1.10-1.33)	<0.001
Diabetic neuropathy	1.19 (1.08-1.31)	<0.001	1.11 (0.96-1.29)	0.165
Diabetic retinopathy	1.02 (0.95-1.1)	0.552	1.03 (0.94-1.14)	0.497
**Macrovascular complications				
Composite complications	1.01 (0.96-1.07)	0.621	1.07 (0.98-1.16)	0.118
Stroke	0.94 (0.87-1.02)	0.139	1.02 (0.92-1.13)	0.748
Myocardial infarction	1.12 (1.03-1.23)	0.010	1.11 (0.96-1.29)	0.162
Cardiovascular Mortality	1.07 (0.97-1.17)	0.181	1.17 (1.00-1.36)	0.049

*Models were adjusted for age, ethnicity(White, Black or other), current smoking status (yes or no), diabetes duration, BMI, TC, HDL-C, HbA1c, eGFR, average SBP, healthy diet(yes or no), fasting time, antihypertensive drug use (yes or no), lipid-lowering drug use (yes or no), antihyperglycemic medication use (yes or no) for MVX per SD increase.

Composite outcome = the presence of any of the following diabetic microvascular complications including nephropathy, neuropathy and retinopathy.

** Models were adjusted for Score2-Diabetes, healthy diet(yes or no), fasttime.

Composite outcome = the presence of any of the following diabetic macrovascular complications including non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality

Supplemental Table S12. Hazard ratios(95% CIs) of macrovascular complications with MVX components after fully adjusted

Components	Composite outcome		Myocardial infarction		Stroke		Cardiovascular mortality	
	Male	Female	Male	Female	Male	Female	Male	Female
GlycA	1.06 (1.01-1.12)	1.03 (0.95-1.11)	1.23 (1.12-1.34)	1.13 (0.98-1.32)	0.94 (0.87-1.02)	0.98 (0.88-1.08)	1.13 (1.02-1.24)	1.11 (0.95-1.30)
S-HDLP	0.92 (0.87-0.98)	0.92 (0.85-1.00)	0.99 (0.90-1.08)	0.92 (0.79-1.06)	0.91 (0.84-0.98)	0.93 (0.84-1.02)	0.86 (0.78-0.95)	0.90 (0.77-1.04)
IVX	1.02 (0.96-1.07)	1.04 (0.96-1.13)	1.15 (1.06-1.25)	1.13 (0.97-1.31)	0.93 (0.86-1.01)	0.99 (0.90-1.10)	1.04 (0.95-1.14)	1.14 (0.98-1.33)
Leucine	0.97 (0.92-1.03)	0.99 (0.91-1.07)	1.02 (0.93-1.12)	1.13 (0.98-1.30)	0.94 (0.87-1.02)	0.95 (0.86-1.06)	0.98 (0.89-1.09)	0.95 (0.81-1.11)
Isoleucine	0.99 (0.94-1.05)	0.97 (0.89-1.05)	1.03 (0.94-1.13)	1.09 (0.95-1.26)	0.97 (0.90-1.04)	0.91 (0.82-1.01)	1.01 (0.92-1.12)	0.96 (0.82-1.12)
Valine	0.98 (0.93-1.04)	0.98 (0.90-1.06)	1.07 (0.98-1.17)	1.13 (0.98-1.31)	0.94 (0.87-1.01)	0.92 (0.84-1.02)	1.00 (0.91-1.10)	0.99 (0.84-1.15)
Citrate	1.07 (1.01-1.13)	0.99 (0.92-1.07)	1.02 (0.93-1.12)	0.99 (0.86-1.14)	1.09 (1.01-1.18)	0.97 (0.88-1.07)	1.14 (1.04-1.26)	1.00 (0.87-1.16)
MMX	1.03 (0.98-1.09)	1.07 (0.99-1.15)	0.94 (0.86-1.04)	0.97 (0.84-1.13)	1.08 (1.00-1.16)	1.08 (0.98-1.19)	1.10 (1.00-1.20)	1.06 (0.92-1.23)

Values are HR (95% CI). HRs and 95% CIs are shown per 1 SD.

All analyses were adjusted for Score2-Diabetes, healthy diet(yes or no), fasttime.

IVX = inflammation vulnerability index; MMX = metabolic malnutrition index; S-HDLP = small high-density lipoprotein particles.

Composite outcome = the presence of any of the following diabetic macrovascular complications including non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality.

Supplemental Table S13. Hazard ratios(95% CIs) of microvascular complications with MVX components after fully adjusted

Components	Composite outcome		Nephropathy		Neuropathy		Retinopathy	
	Male	Female	Male	Female	Male	Female	Male	Female
GlycA	1.15 (1.09-1.21)	1.09 (1.02-1.17)	1.27 (1.18-1.37)	1.17 (1.06-1.3)	1.27 (1.15-1.4)	1.01 (0.86-1.18)	1.02 (0.95-1.10)	1.03 (0.93-1.14)
S-HDLP	1.01 (0.95-1.07)	0.94 (0.88-1.01)	1.04 (0.95-1.14)	0.96 (0.87-1.07)	1.01 (0.9-1.14)	1.00 (0.86-1.16)	1.00 (0.92-1.08)	0.91 (0.83-1.00)
IVX	1.13 (1.07-1.18)	1.10 (1.03-1.18)	1.22 (1.14-1.31)	1.19 (1.08-1.31)	1.18 (1.07-1.29)	1.04 (0.89-1.21)	1.03 (0.96-1.10)	1.04 (0.94-1.16)
Leucine	0.99 (0.95-1.04)	0.96 (0.90-1.03)	0.92 (0.86-0.98)	0.85 (0.77-0.94)	1.01 (0.93-1.11)	0.95 (0.83-1.1)	1.07 (1.01-1.14)	1.05 (0.97-1.15)
Isoleucine	1.00 (0.96-1.05)	0.96 (0.90-1.03)	0.94 (0.88-1.00)	0.86 (0.78-0.95)	1.03 (0.94-1.13)	1.00(0.87-1.15)	1.07 (1.01-1.14)	1.05 (0.97-1.15)
Valine	1.00 (0.95-1.05)	0.96 (0.90-1.03)	0.93 (0.87-1.00)	0.83 (0.75-0.92)	1.04 (0.95-1.15)	0.96 (0.83-1.11)	1.06 (0.99-1.13)	1.07 (0.98-1.17)
Citrate	1.08 (1.03-1.13)	0.99 (0.93-1.06)	1.1 (1.03-1.17)	1.03 (0.94-1.13)	1.18 (1.08-1.29)	0.90 (0.78-1.03)	1.06 (0.99-1.13)	0.98 (0.90-1.07)
MMX	1.05 (1.01-1.10)	1.05 (0.99-1.12)	1.08 (1.01-1.16)	1.05 (0.97-1.15)	1.10 (1.00-1.20)	1.15 (1.01-1.30)	1.00 (0.93-1.07)	1.00 (0.92-1.09)

Values are HR (95% CI). HRs and 95% CIs are shown per 1 SD.

All analyses were adjusted for age, ethnicity(White, Black or other), current smoking status (yes or no), diabetes duration, BMI, TC, HDL-C, HbA1c, eGFR, average SBP, healthy diet(yes or no), fasting time, antihypertensive drug use (yes or no), lipid-lowering drug use (yes or no), antihyperglycemic medication use (yes or no).

IVX = inflammation vulnerability index; MMX = metabolic malnutrition index; S-HDLP = small high-density lipoprotein particles.

Composite outcome = the presence of any of the following diabetic microvascular complications including nephropathy, neuropathy and retinopathy.

Supplemental Table S14. Measures of Model Improvement for macrovascular complications

		Macrovascular complications	Myocardial infarction	Stroke	Cardiovascular Mortality
	Difference in C-index	<0.001	0.002	0.001	0.001
Male	NRI, %(95%CI)	0%(-0.06% - 0.06%)	0.2%(-0.01% - 0.41%)	0%(-0.02% - 0.02%)	0%(-0.1% - 0.1%)
	IDI, %(95%CI)	1.72%(-2.5% - 5.94%)	7.74%(2.26% - 13.22%)	3.34%(-3.29% - 9.97%)	7.22%(-3.3% - 17.74%)
	Difference in C-index	-0.001	-0.002	-0.001	<0.001
Female	NRI, %(95%CI)	0.1%(-0.05% - 0.25%)	0.1%(-0.05% - 0.25%)	0%(-0.06% - 0.06%)	0%(-0.15% - 0.15%)
	IDI, %(95%CI)	4.56%(-0.77% - 9.89%)	6.76%(-4.52% - 18.04%)	3.52%(-3.51% - 10.55%)	10.66%(-1.22% - 22.54%)

All analyses were adjusted for Score2-Diabetes, healthy diet(yes or no), fasting time for MVX per SD increase.

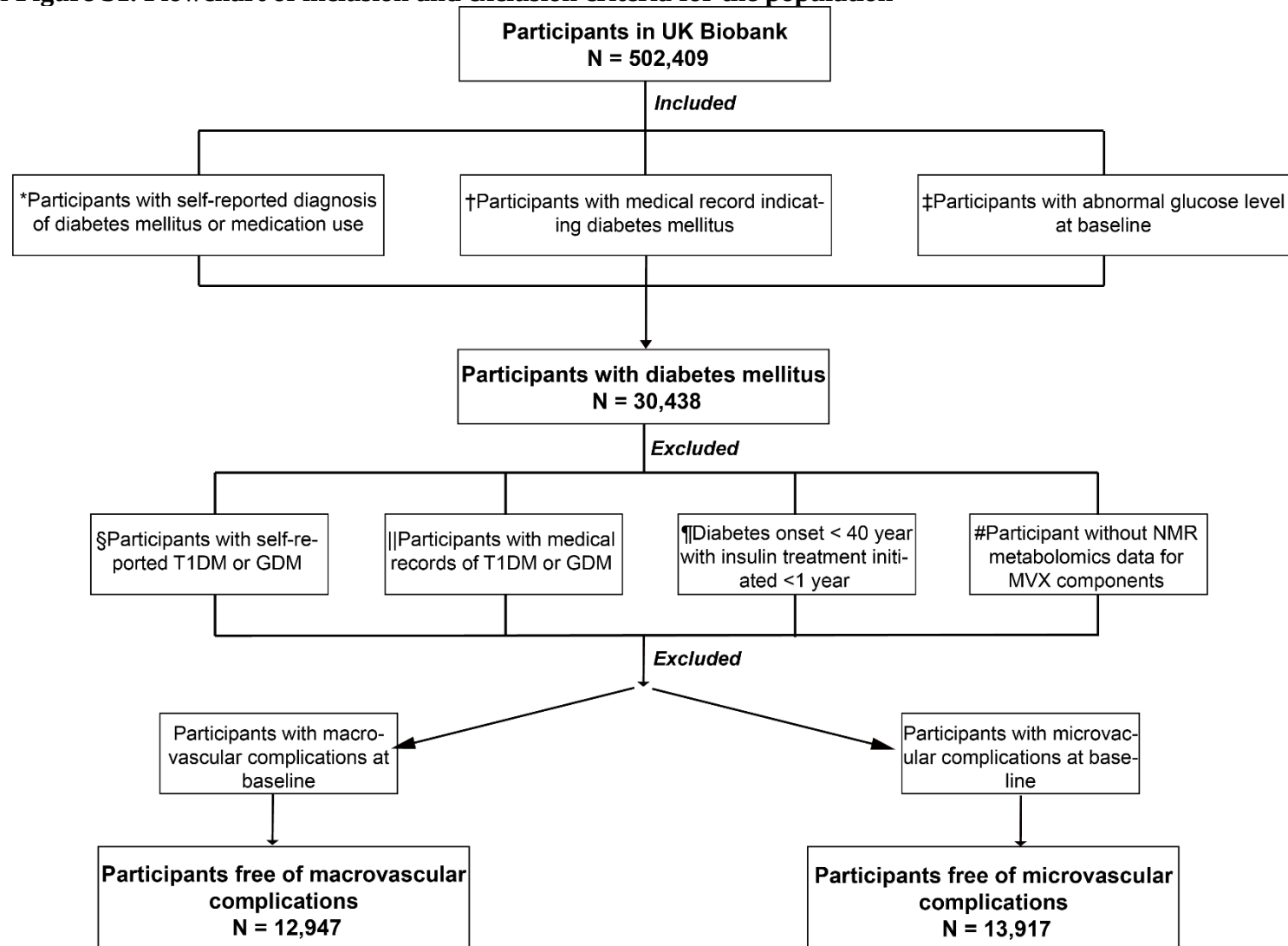
MVX metabolic vulnerability index; IDI integrated discrimination improvement; NRI net reclassification improvement; Bold indicates statistical significance

Supplemental Table S15. Measures of Model Improvement for microvascular complications

		Microvascular complications	Diabetic kidney diseases	Diabetic retinopathy	Diabetic neuropathy
Female	Difference in C-index	0.002	0.004	<0.001	0.003
	IDI, %(95%CI)	0.18%(-0.04% - 0.40%)	0.44%(0.05% - 0.83%)	0%(-0.06% - 0.06%)	0%(-0.15% - 0.15%)
	NRI, %(95%CI)	5.94%(1.52% - 10.36%)	10.08%(3.52% - 16.64%)	1.94%(-3.97% - 7.85%)	5.26%(-3.76% - 14.28%)
Male	Difference in C-index	0.002	0.005	<0.001	0.004
	IDI, %(95%CI)	0.20%(0.05% - 0.35%)	0.34%(-0.03% - 0.71%)	0%(-0.05% - 0.05%)	0.10%(-0.05% - 0.25%)
	NRI, %(95%CI)	4.82%(1.59% - 8.05%)	7.20%(2.00% - 12.4%)	2.16%(-3.43% - 7.75%)	7.66%(1.81% - 13.51%)

All analyses were adjusted for age, ethnicity(White, Black or other), current smoking status (yes or no), diabetes duration, BMI, TC, HDL-C, HbA1c, eGFR, average SBP, healthy diet(yes or no), fasting time, antihypertensive drug use (yes or no), lipid-lowering drug use (yes or no), antihyperglycemic medication use (yes or no) for MVX per SD increase. Bold indicates statistical significance
 MVX metabolic vulnerability index; IDI integrated discrimination improvement; NRI net reclassification improvement

Supplemental Figure S1. Flowchart of inclusion and exclusion criteria for the population

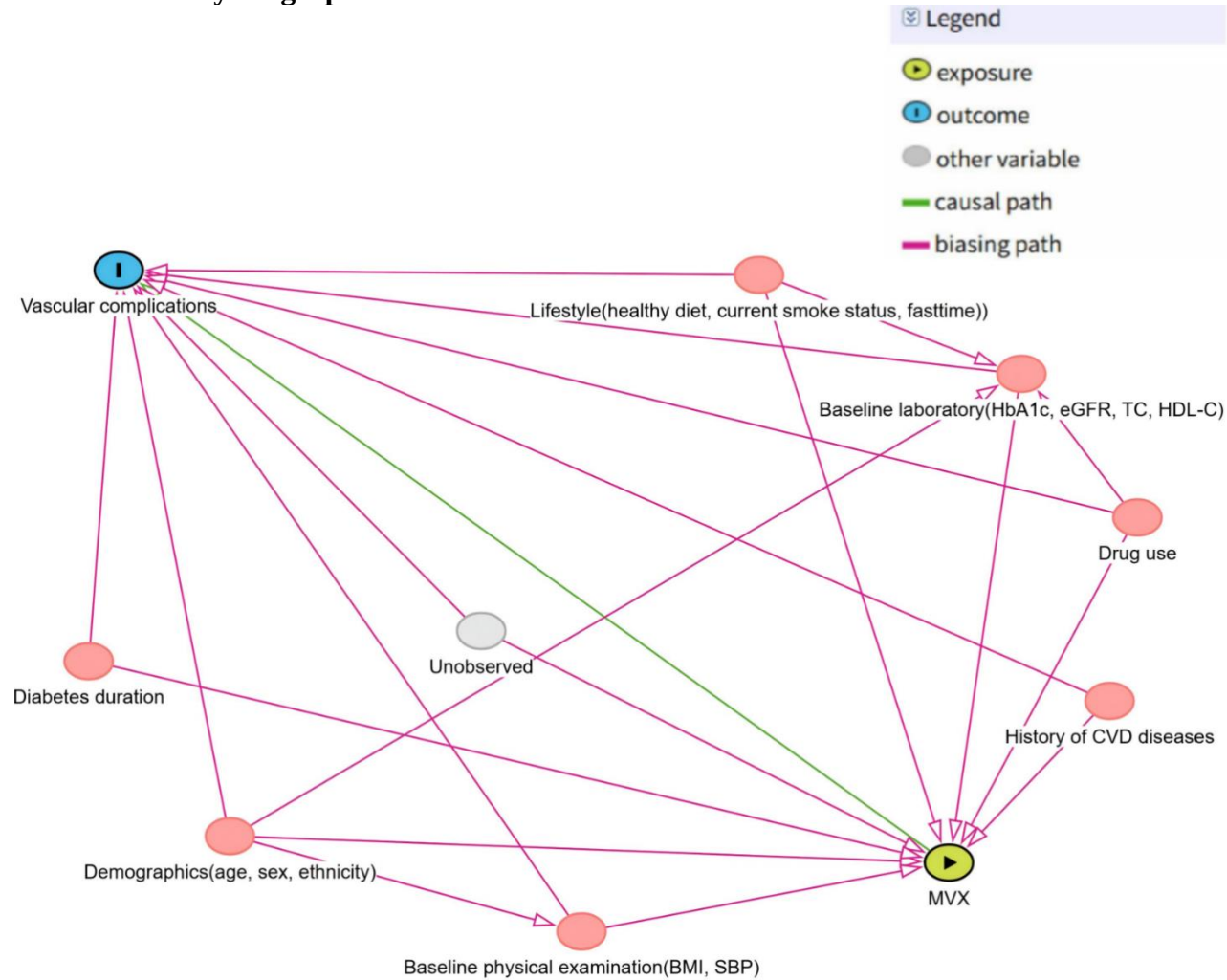


*Self-reported diagnosis based on codes 1220-1223 for diabetes, Gestational Diabetes Mellitus (GDM), Type 1 Diabetes Mellitus (T1DM), and Type 2 Diabetes Mellitus (T2DM). †Medical record refers to ICD-9 codes 250 and 6480; ICD-10 codes E10–E14. ‡Abnormal glucose refers to a

glycated hemoglobin (HbA1c) level $\geq 4(2)8$ mmol/mol (6.5%) or random glucose ≥ 7 mmol/L after at least 8 hours of fasting, or ≥ 11.1 mmol/L if fasting for less than 8 hours based on the 2020 American Diabetes Association guideline. § Self-reported diagnosis based on codes 1221 for GDM and 1222 for T1DM. || Medical records refers to ICD-10 codes including E10, O240, O244. ¶ Participants diagnosed with diabetes mellitus before 40 and started insulin treatment within 1 year of diagnosis were recorded as T1DM, # NMR, Nuclear Magnetic Resonance. MVX components included GlycA, S-HDL, valine, leucine, isoleucine and citrate.

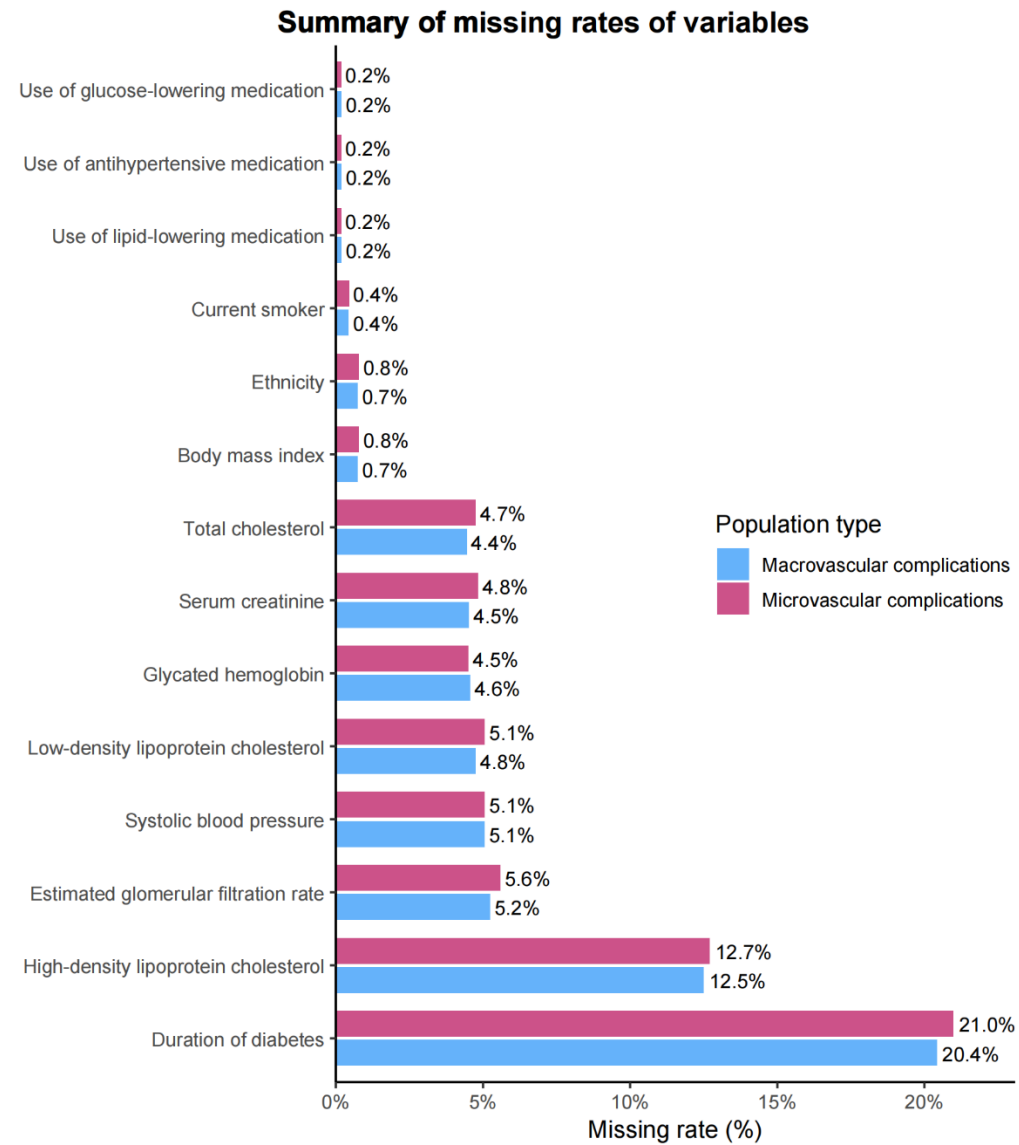
GDM, Gestational Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; ICD, International Classification of Diseases; NMR, Nuclear Magnetic Resonance; eGFR, estimated glomerular filtration rate; uACR, urinary Albumin-to-Creatinine Ratio; MVX, metabolic vulnerability index; GlycA, Glycosylated Acute-Phase Proteins; S-HDL, small high density lipoprotein.

Supplemental Figure S2. Directed acyclic graph

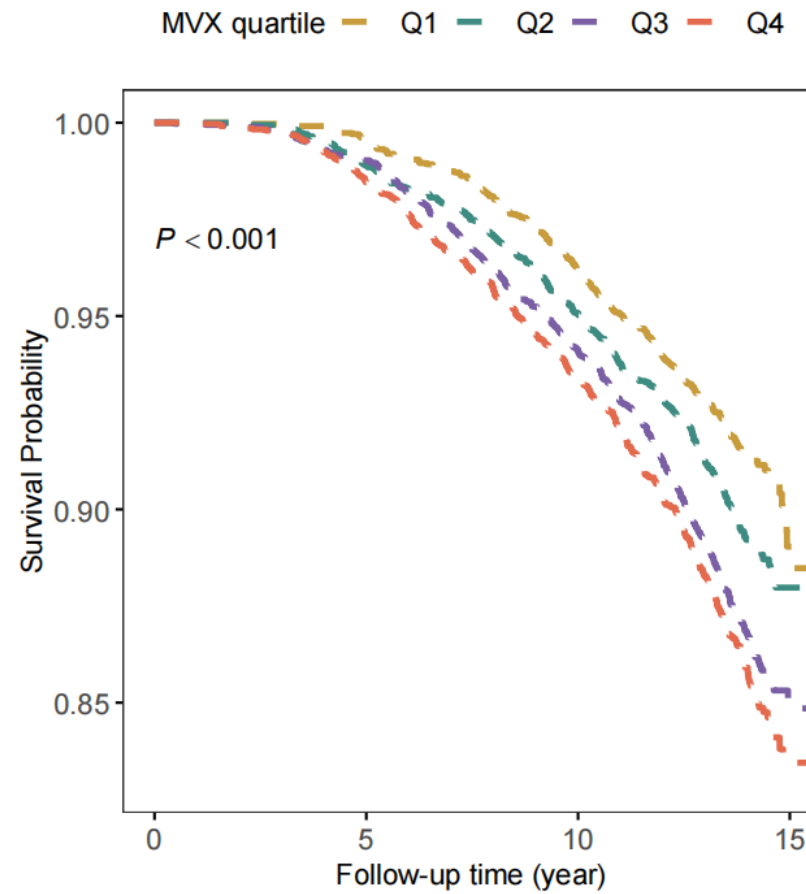


eGFR, estimated glomerular filtration rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular diseases; BMI, body mass index; SBP, systolic blood pressure; MVX, metabolic vulnerability index

Supplemental Figure S3. Summary of missing variables from main analyses of participants

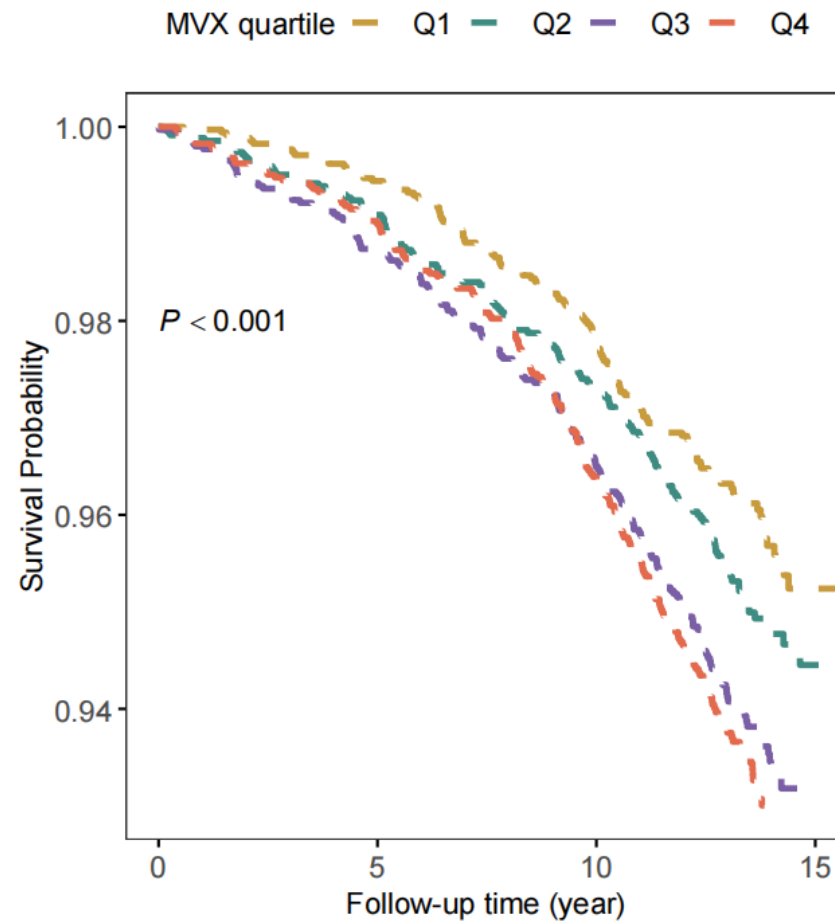


Supplemental Figure S4. Kaplan-Meier curve for diabetic nephropathy grouped by sex-specific MVX quartiles



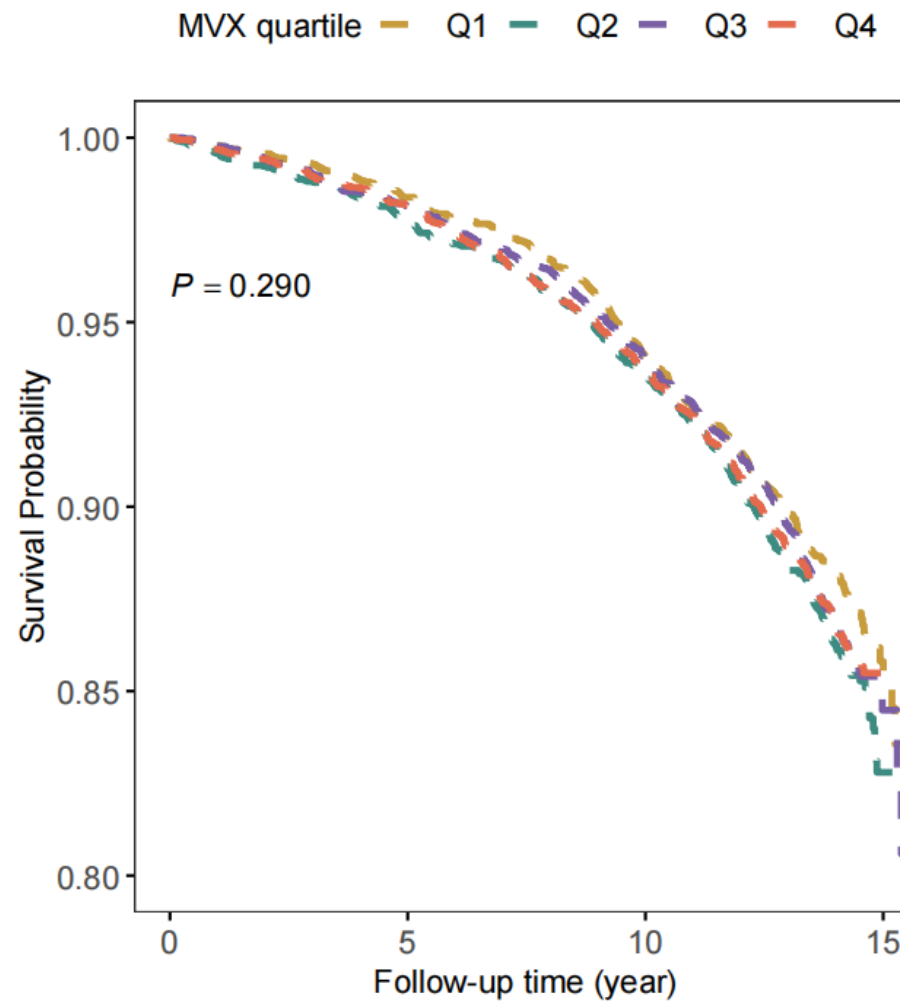
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S5. Kaplan-Meier curve for diabetic neuropathy grouped by sex-specific MVX quartiles



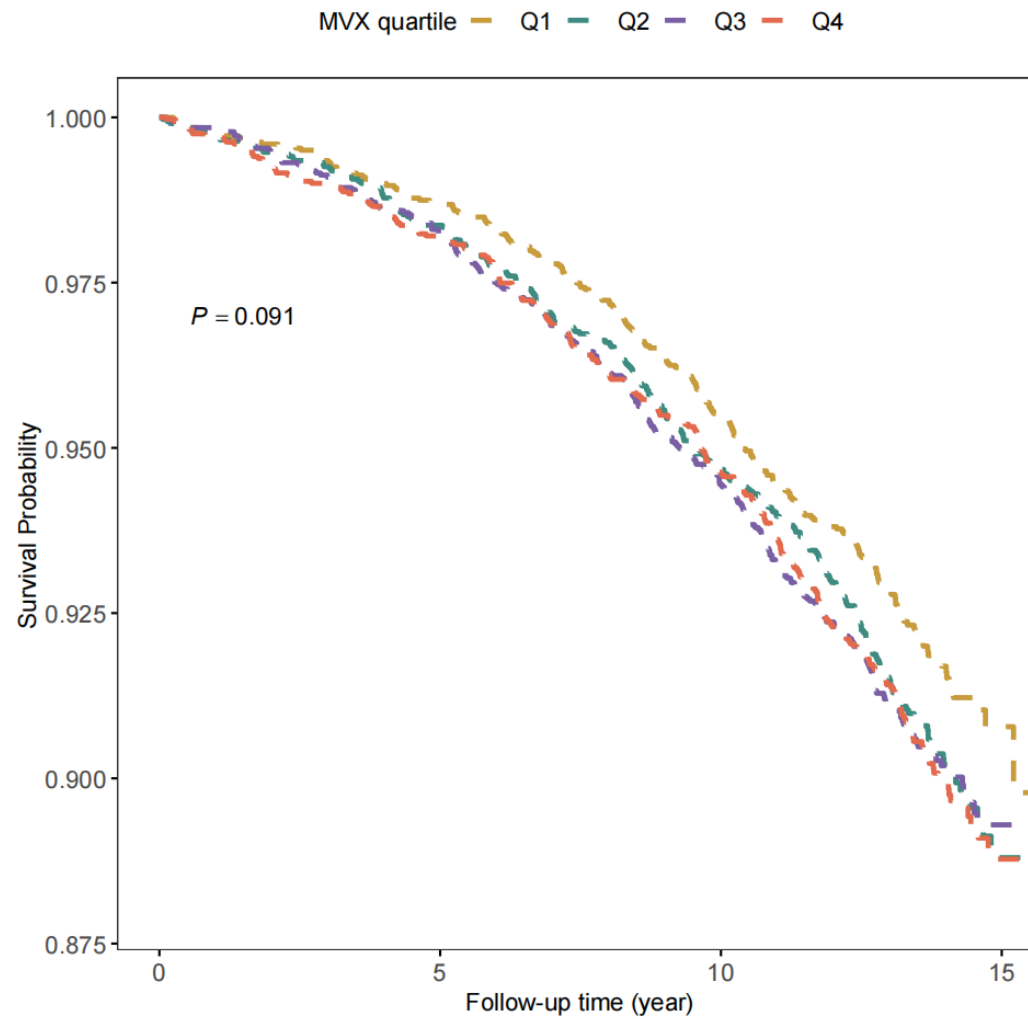
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S6. Kaplan-Meier curve for diabetic retinopathy grouped by sex-specific MVX quartiles



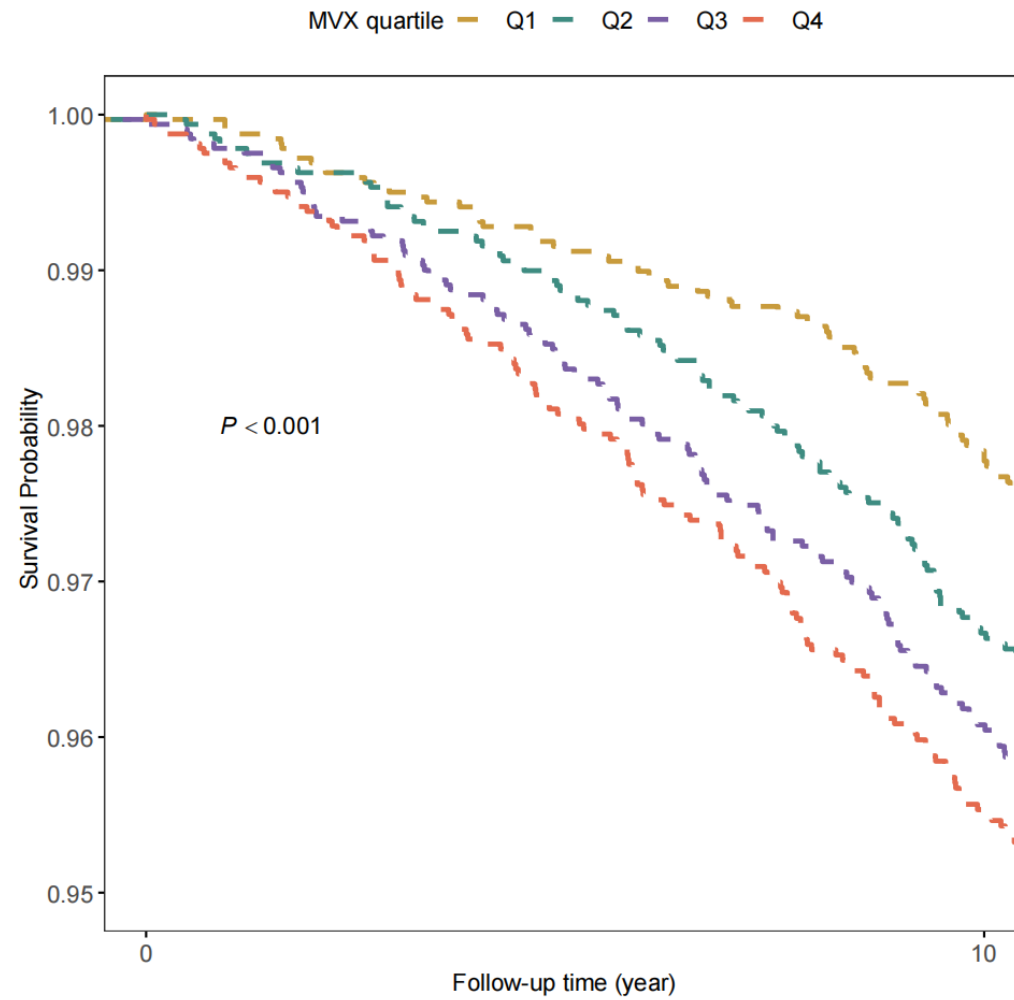
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S7. Kaplan-Meier curve for non-fatal stroke grouped by sex-specific MVX quartiles



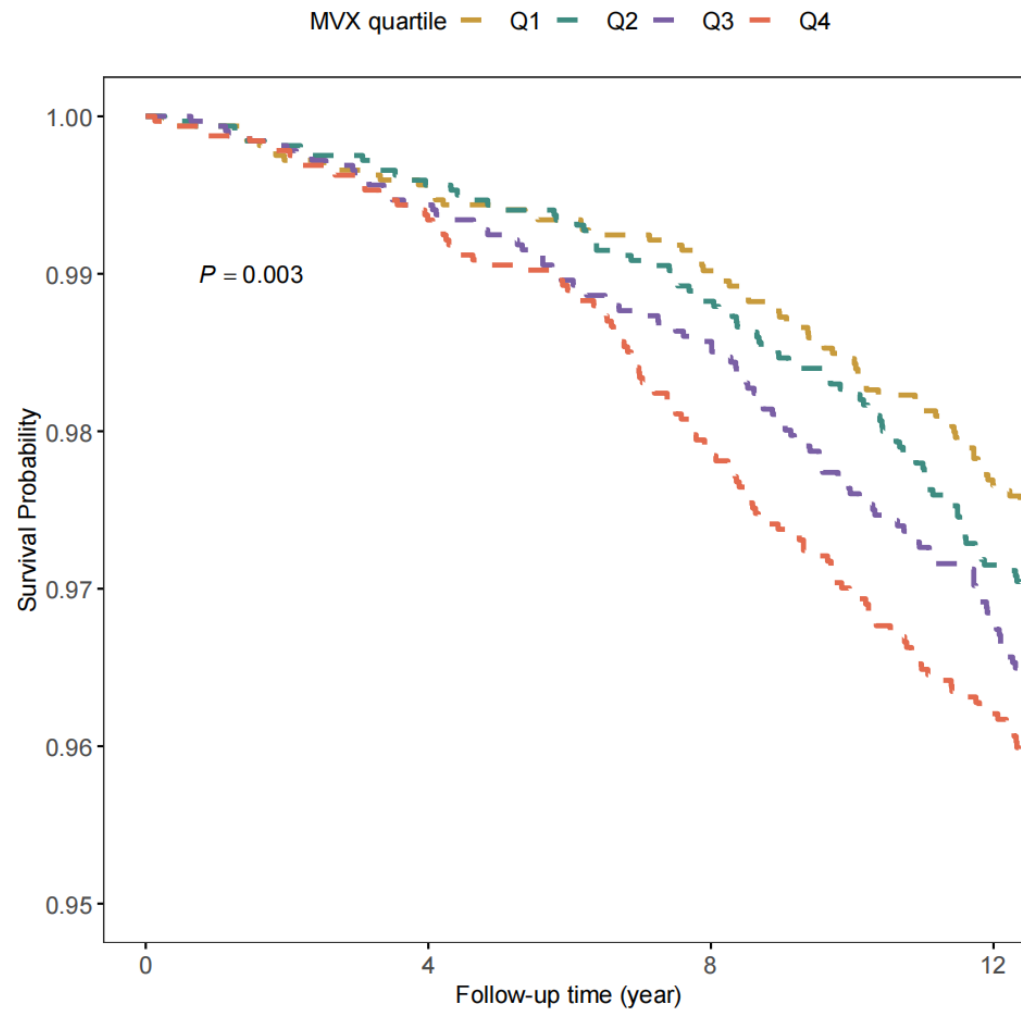
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S8. Kaplan-Meier curve for non-fatal myocardial infarction grouped by sex-specific MVX quartiles



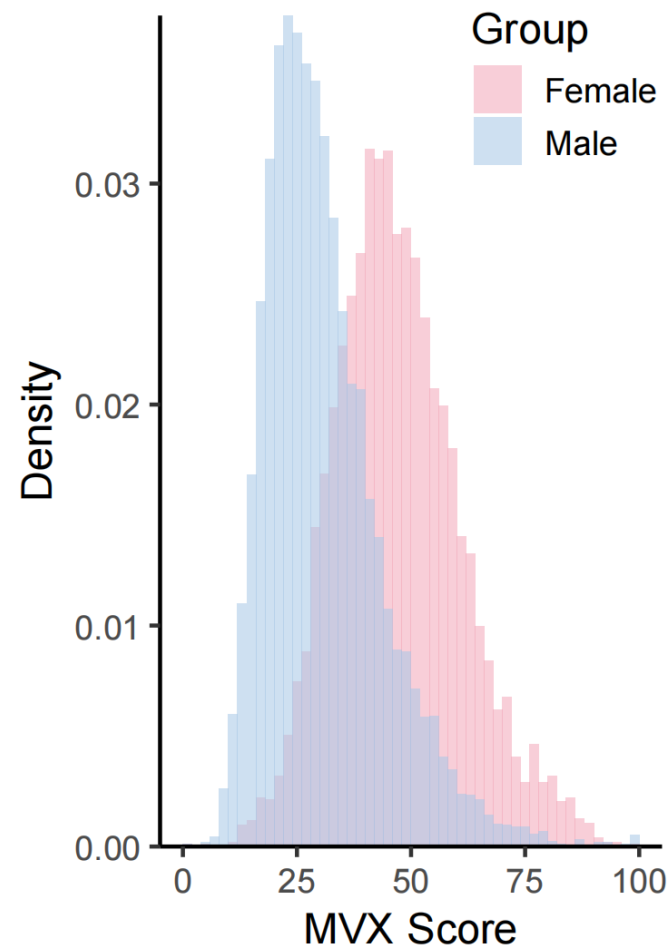
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S9. Kaplan-Meier curve for cardiovascular mortality grouped by sex-specific MVX quartiles



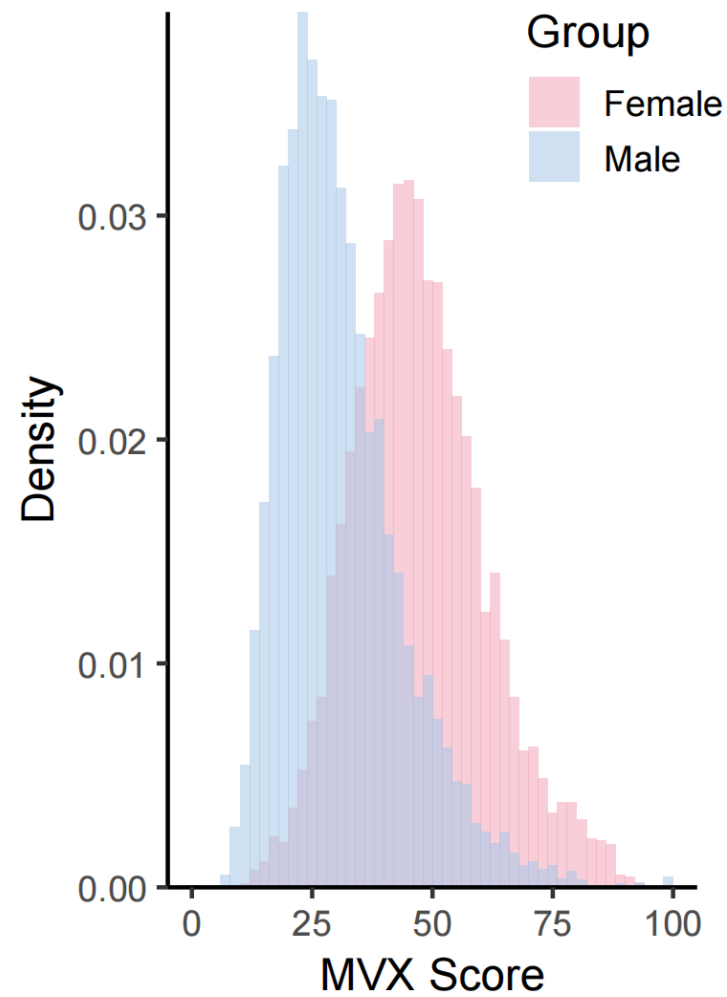
P values were calculated using the log-rank test; MVX, metabolic vulnerability index

Supplemental Figure S10. Histogram of baseline MVX score stratified by sex in MACP



MVX metabolic vulnerability index; MACP the analysis cohort for macrovascular complications

Supplemental Figure S11. Histogram of baseline MVX score stratified by sex in MAP



MVX metabolic vulnerability index; MCP the analysis cohort for microvascular complications