

Online Supplementary material

Supplementary Detailed methods

Supplementary Table S1. Baseline characteristics of patients with estimated insulin resistance assessed by $ISI_{0,120}$.

Supplementary Table S2. Baseline characteristics of patients with estimated insulin resistance assessed by HOMA-IR.

Figure S1. Flow chart.

Detailed methods

Information on MRI scans

Magnetic Resonance Imaging (MRI) scans were obtained on a 3.0T scanner (Ingenia 3.0T, Philips, Best, The Netherlands) at baseline and included three-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient-echo (3D T1w MPRAGE), two-dimensional T2-weighted (2D T2w), two-dimensional fluid-attenuated inversion recovery (2D FLAIR), and susceptibility-weighted imaging (SWI). The parameters of 3D T1w MPRAGE are as follows: TE=3.0ms, TR=6.7ms, TI=880ms, shot interval=2000ms, Flip angle=8°, with voxel of 1.00×1.00×1.00 mm and scan time of 4 min 30 sec. The parameters of T2w imaging are as follows: TE=105ms, TR=2500ms, SPIR fat suppression, with voxel of 0.51×0.51×6.50mm and scan time of 1 min 5 sec. The parameters of FLAIR imaging are as follows: TE=110ms, TR=7000ms, TI=2300ms, SPIR fat suppression, with voxel of 0.53×0.53×6.50mm and scan time of 2 min 27 sec. The parameters of SWI are as follows: first TE=7.2ms, echo spacing = 6.2ms, 5 echoes, Flip angle=17°, TR =37ms, with voxel of 0.63×0.63×0.80mm and scan time of 2 min 20 sec.

Supplementary Table S1. Baseline characteristics of patients with estimated insulin resistance assessed by ISI_{0,120}

Baseline characteristics	ISI _{0,120}				P value
	Q1 (n=687)*	Q2(n=684)	Q3(n=688)	Q4(n=686)	
Age (mean ± SD)	61.9±6.7	61.0±6.7	60.3±6.4	60.5±6.4	<0.001
Male (n, %)	297 (43.2)	297 (43.4)	296 (43.0)	402 (58.6)	<0.001
SBP, mmHg (mean ± SD)	133.9±15.1	129.3±15.5	126.7±16.1	124.2±16.2	<0.001
DBP, mmHg (mean ± SD)	77.3±9.0	75.4±9.1	74.5±9.0	73.0±9.1	<0.001
BMI (kg/m ²), mean ± SD)	25.1±3.1	23.8±2.8	23.5±2.8	22.4±2.8	<0.001
Medical history					
Hypertension	411 (59.8)	286 (41.8)	228(33.1)	188(27.4)	<0.001
Coronary artery disease	5 (0.7)	1 (0.2)	2(0.3)	1(0.2)	0.19
Atrial fibrillation	9 (1.3)	7 (1.0)	5(0.7)	2(0.3)	0.20
Dyslipidemia	194 (28.2)	135 (19.7)	113(16.4)	72(10.5)	<0.001
Stroke	25 (3.6)	20 (2.9)	7(1.0)	14(2.0)	0.01
Current drinker	98 (14.3)	122 (17.8)	127(18.5)	179(26.1)	<0.001
Current smoker	97 (14.1)	112 (16.4)	137(19.9)	225(32.8)	<0.001
Fasting glucose (mmol/L), median (IQR)	5.94 (5.49-6.56)	5.52 (5.25-5.87)	5.38 (5.09-5.73)	5.32 (5.02-5.60)	<0.001
2h-OGTT glucose (mmol/L), median (IQR)	10.38 (9.06-12.49)	7.71 (7.06-8.46)	6.55 (6.02-7.15)	5.43 (4.65-6.04)	<0.001
HbA1c (%), median (IQR)	5.90 (5.60-6.30)	5.70 (5.50-5.90)	5.60 (5.40-5.80)	5.60 (5.40-5.80)	<0.001
Total Cholesterol (mmol/L), mean ± SD	5.40±1.03	5.30±0.99	5.27±0.93	5.18±0.94	<0.001
LDL-C (mmol/L), mean ± SD	2.83±0.82	2.80±0.82	2.80±0.75	2.75±0.76	0.18
HDL-C (mmol/L), mean ± SD	1.28±0.31	1.35±0.31	1.39±0.33	1.48±0.37	<0.001
Estimated GFR _{cr} (ml/min/1.73 m ²)	103.67 (95.87-110.20)	104.52 (96.25-110.25)	105.74 (97.64-110.58)	104.38 (96.82-110.01)	0.22
Medications					
Antihypertensive	267 (38.9)	182 (26.6)	131 (19.0)	99 (14.4)	<0.001

Lipid-lowering	40 (5.8)	24 (3.5)	14 (2.0)	14 (2.0)	<0.001
Antiplatelet	27 (3.9)	16 (2.3)	6 (0.9)	8 (1.2)	<0.001
Anticoagulant	0	2(0.3)	0	0	0.11

ISI indicates insulin sensitivity index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; GFR_{cr}, creatinine-based glomerular filtration rate; SD, standard deviation; IQR, interquartile range.

*Quartiles of ISI_{0,120}: Q1≤54.30; Q2,54.30-72.88; Q3, 72.88-97.08; Q4≥97.08.

Supplementary Table S2. Baseline characteristics of patients with estimated insulin resistance assessed by HOMA-IR

Baseline characteristics	HOMA-IR				P value
	Q1 (n=671)*	Q2(n=696)	Q3(n=683)	Q4(n=702)	
Age (mean ± SD)	61.7±6.7	60.7±6.6	60.6±6.5	60.6±6.5	0.003
Male (n, %)	430 (64.1)	334 (48.0)	273 (40.0)	258 (36.8)	<0.001
SBP, mmHg (mean ± SD)	124.3±16.4	127.6±16.2	129.6±16.2	132.4±14.6	<0.001
DBP, mmHg (mean ± SD)	72.7±9.1	74.9±9.2	75.3±8.9	77.2±8.9	<0.001
BMI (kg/m ²), mean ± SD)	21.6±2.3	23.1±2.5	24.2±2.7	25.8±2.9	<0.001
Medical history					
Hypertension	176 (26.2)	258 (37.1)	285 (41.7)	397 (56.6)	<0.001
Coronary artery disease	4 (0.6)	2 (0.3)	2 (0.3)	2 (0.3)	0.72
Atrial fibrillation	2 (0.3)	6 (0.9)	5 (0.7)	10 (1.4)	0.15
Dyslipidemia	50 (7.5)	121 (17.4)	158 (23.1)	186 (26.5)	<0.001
Stroke	14 (2.1)	18 (2.6)	18 (2.6)	16 (2.3)	0.90
Current drinker	207 (30.9)	128 (18.4)	102 (14.9)	89 (12.7)	<0.001
Current smoker	217 (32.3)	152 (21.8)	105 (15.4)	97 (13.8)	<0.001
Fasting glucose (mmol/L), median (IQR)	5.21 (4.95-5.50)	5.45 (5.17-5.76)	5.55 (5.27-5.94)	5.87 (5.52-6.36)	<0.001
2h-OGTT glucose (mmol/L), median (IQR)	10.38 (9.06-12.49)	7.71 (7.06-8.46)	6.55 (6.02-7.15)	5.43 (4.65-6.04)	<0.001
HbA1c (%), median (IQR)	5.90 (5.60-6.30)	5.70 (5.50-5.90)	5.60 (5.40-5.80)	5.60 (5.40-5.80)	<0.001
Total Cholesterol (mmol/L), mean ± SD	5.08±0.95	5.35±0.96	5.42±0.98	5.31±0.98	<0.001
LDL-C (mmol/L), mean ± SD	2.65±0.74	2.85±0.79	2.88±0.78	2.80±0.81	<0.001
HDL-C (mmol/L), mean ± SD	1.51±0.37	1.43±0.36	1.32±0.29	1.25±0.28	<0.001
Estimated GFR _{cr} (ml/min/1.73 m ²)	104.13 (97.19-110.03)	105.19 (97.08-110.46)	103.89 (96.21-110.14)	104.89 (94.71-110.63)	0.70
Medications					
Antihypertensive	84 (12.5)	148 (21.3)	181 (26.5)	267 (38.0)	<0.001

Lipid-lowering	7 (1.0)	19 (2.7)	28 (4.1)	38 (5.4)	<0.001
Antiplatelet	6 (0.9)	11 (1.6)	14 (2.1)	26 (3.7)	0.002
Anticoagulants	0	1 (0.1)	0	1 (0.1)	0.59

HOMA-IR indicates Homeostatic Model Assessment for Insulin Resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; GFRcr, creatinine-based glomerular filtration rate; SD, standard deviation; IQR, interquartile range.

*Quartiles of HOMA-IR: Q1≤1.07; Q2, 1.07-1.55; Q3, 1.55-2.24; Q4≥2.24.

Supplementary Figure S1. Flow chart.

MRI indicates magnetic resonance imaging; cSVD, cerebral small vessel disease.

