

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=599)*	Q2(n=598)	Q3(n=598)	Q4(n=598)	
Age (mean ± SD)	61.5±6.8	60.8±6.5	60.2±6.4	60.4±6.4	0.005
Male (n, %)	247 (41.2)	269 (45.0)	250 (41.8)	358 (59.9)	<0.001
SBP, mmHg (mean ± SD)	132.7±15.3	128.1±14.6	126.3±16.3	124.0±16.1	<0.001
DBP, mmHg (mean ± SD)	77.2±9.0	74.9±8.7	74.2±9.0	72.9±9.0	<0.001
BMI (kg/m ²), mean ± SD)	24.9±3.0	23.7±2.8	23.3±2.7	22.3±2.8	<0.001
Medical history					
Hypertension	322 (53.8)	230 (38.5)	189 (31.6)	168 (28.1)	<0.001
Coronary artery disease	3 (0.5)	0	2 (0.3)	1 (0.2)	0.34
Atrial fibrillation	7 (1.2)	8 (1.3)	4 (0.7)	1 (0.2)	0.11
Dyslipidemia	148 (24.7)	115 (19.2)	95 (15.9)	62 (10.4)	<0.001
Stroke	24 (4.0)	13 (2.2)	7 (1.2)	12 (2.0)	0.01
Current drinker	89 (14.9)	99 (16.6)	113 (18.9)	157 (26.3)	<0.001
Current Smoker	89 (14.9)	105 (17.6)	115 (19.2)	208 (34.8)	<0.001
Fasting glucose (mmol/L), median (IQR)	5.60 (5.34-5.94)	5.47 (5.21-5.78)	5.34 (5.06-5.71)	5.31 (5.01-5.60)	<0.001
2h-OGTT glucose (mmol/L), median (IQR)	8.88 (8.11-9.78)	7.32 (6.74-7.91)	6.39 (5.85-6.98)	5.32 (4.51-5.92)	<0.001
HbA1c (%), median (IQR)	5.80 (5.60-6.00)	5.60 (5.40-5.80)	5.60 (5.40-5.80)	5.55 (5.40-5.80)	<0.001
Total Cholesterol (mmol/L), mean ± SD	5.37±1.02	5.30±0.93	5.25±0.94	5.17±0.95	0.003
LDL-C (mmol/L), mean ± SD	2.82±0.79	2.83±0.80	2.78±0.73	2.75±0.77	0.18
HDL-C (mmol/L), mean ± SD	1.29±0.29	1.35±0.31	1.41±0.34	1.48±0.37	<0.001
Estimated GFR _{cr} (ml/min/1.73 m ²), median (IQR)	103.14 (94.84-110.24)	104.43 (96.71-110.23)	105.93 (98.23-110.63)	104.47 (96.82-110.03)	0.053
Medications					

Antihypertensive	218 (36.4)	135 (22.6)	113 (18.9)	86 (14.4)	<0.001
Lipid-lowering	30 (5.0)	15 (2.5)	12 (2.0)	12 (2.0)	0.004
Antiplatelet	22 (3.7)	10 (1.7)	5 (0.8)	8 (1.3)	0.002
Anticoagulant	1 (0.2)	1 (0.2)	0	0	0.57

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≤60.59; Q2,60.59-78.06; Q3, 78.06-100.49; Q4≥100.49.

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

Baseline characteristics	HOMA-IR				P value
	Q1 (n=598)*	Q2(n=587)	Q3(n=604)	Q4(n=608)	
Age (mean ± SD)	61.6±6.6	60.5±6.5	60.2±6.3	60.4±6.6	<0.001
Male (n, %)	381 (63.7)	273 (46.5)	248 (41.1)	224 (36.8)	<0.001
SBP, mmHg (mean ± SD)	124.1±16.2	126.8±16.1	128.9±15.9	131.33±14.50	<0.001
DBP, mmHg (mean ± SD)	72.6±9.0	74.5±9.0	75.5±8.9	76.6±8.8	<0.001
BMI (kg/m ²), mean ± SD)	21.6±2.3	23.0±2.5	24.1±2.6	25.6±2.9	<0.001
Medical history					
Hypertension	153 (25.6)	205 (34.9)	249 (41.2)	304 (50.0)	<0.001
Coronary artery disease	3 (0.5)	1 (0.2)	1 (0.2)	2 (0.3)	0.67
Atrial fibrillation	2 (0.3)	6 (1.0)	5 (0.8)	7 (1.2)	0.42
Dyslipidemia	36 (6.0)	105 (17.9)	135 (22.4)	145 (23.9)	<0.001
Stroke	11 (1.8)	14 (2.4)	15 (2.5)	16 (2.6)	0.82
Current drinker	179 (29.9)	111 (18.9)	94 (15.6)	74 (12.2)	<0.001
Current Smoker	196 (32.8)	131 (22.3)	97 (16.1)	93 (15.3)	<0.001
Fasting glucose (mmol/L), median (IQR)	5.18 (4.94-5.45)	5.41 (5.14-5.71)	5.48 (5.20-5.79)	5.70 (5.42-6.01)	<0.001
2h-OGTT glucose (mmol/L), median (IQR)	6.39 (5.41-7.44)	6.68 (5.76-7.74)	6.98 (6.06-8.16)	7.51 (6.33-8.78)	<0.001
HbA1c (%), median (IQR)	5.50 (5.30-5.80)	5.60 (5.40-5.80)	5.60 (5.40-5.90)	5.70 (5.50-6.00)	<0.001
Total Cholesterol (mmol/L), mean ± SD	5.06±0.93	5.35±0.95	5.39±0.96	5.30±0.97	<0.001
LDL-C (mmol/L), mean ± SD	2.65±0.73	2.85±0.76	2.87±0.77	2.81±0.80	<0.001
HDL-C (mmol/L), mean ± SD	1.50±0.35	1.45±0.36	1.34±0.30	1.25±0.27	<0.001
Estimated GFR _{cr} (ml/min/1.73 m ²), median (IQR)	104.10 (97.01-109.92)	105.30 (97.56-110.60)	104.10 (96.73-110.20)	104.24 (93.79-110.55)	0.46
Medications					

Antihypertensive	71 (11.9)	122 (20.8)	159 (26.3)	201 (33.1)	<0.001
Lipid-lowering	6 (1.0)	16 (2.7)	18 (3.0)	29 (4.8)	0.002
Antiplatelet	6 (1.0)	8 (1.4)	10 (1.7)	21 (3.5)	0.009
Anticoagulants	0	1 (0.2)	0	1 (0.2)	0.57

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≤1.05; Q2, 1.05-1.48; Q3, 1.48 -2.12; Q4≥2.12.

Supplementary Figure S1. Flow chart.

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

