

Supplementary material

Supplementary Table 1 – Definitions of CVD at baseline

CVD at baseline	Definition
Coronary artery Disease (CAD)	<ul style="list-style-type: none">- Myocardial infarction- Angina pectoris- Coronary stenosis in ≥ 1 major coronary artery- Self-reported history of MI, cardiac arrest or revascularization
Peripheral artery Disease (PAD)	<ul style="list-style-type: none">- Fontaine stage of at least IIa (i.e. intermittent claudication and resting ankle-brachial index (ABI) <0.9 in at least one leg),- Self-reported history of amputation or vascular surgery of the lower extremities.
Cerebrovascular Disease (CeVD)	<ul style="list-style-type: none">- Transient ischemic attack- Ischemic stroke- Amaurosis fugax- Retinal infarction- Self-reported stroke or carotid artery operation in the past.
Abdominal aortic aneurysm (AAA)	<ul style="list-style-type: none">- Aneurysm of the abdominal aorta (distal aortic diameter ≥ 3 cm) during screening- AAA surgery in the past.

Supplementary Table 2 – Definitions of outcomes

Outcome	Definition
Cardiovascular events	<ul style="list-style-type: none">- Nonfatal myocardial infarction- Nonfatal stroke (ischemic/hemorrhagic)- Retinal infarction/hemorrhage- Vascular death (death from myocardial infarction, stroke, heart failure, or rupture of abdominal aortic aneurysm; vascular death from other causes; or sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence)).
Limb events	<ul style="list-style-type: none">- Major amputation (at level of the foot or more proximal)- Lower limb revascularization (vascular intervention or thrombolysis).
Type 2 diabetes mellitus (T2DM)	<ul style="list-style-type: none">- A self-reported diagnosis and/or the use of glucose-lowering agents. Patients who reported new-onset T2DM were sent an additional questionnaire for confirmation and detailed information of the diagnosis, including the date of diagnosis, initial and current treatment, and family history of diabetes.

Supplementary Table 3 – Additive effect of presence of rs2281279 (G allele) on metabolic parameters with cut-off 0.05 (n=3930)

	Beta (95% CI)
(log)Triglycerides	0.002 (-0.010 - 0.015)
Non-HDL-cholesterol	0.012 (-0.060 - 0.083)
(log)Insulin^a	-0.011 (-0.031 - 0.008)
QUICKI^a	0.002 (-0.001 - 0.004)

HDL; high-density lipoprotein, QUICKI; quantitative insulin sensitivity check index, CI; confidence interval.

^a n=2202.

Model adjusted for age + sex.

Supplementary Table 4 – Additive effect of presence of rs2281279 (G allele) on vascular events and T2DM with cut-off 0.05

	Number of patients	Number of events (%)	HR (95% CI)
Cardiovascular events	3930	933 (24%)	1.07 (0.97 – 1.19)
Limb events	3930	281 (7%)	0.96 (0.79 – 1.16)
T2DM	2945	357 (12%)	1.08 (0.92 – 1.28)

T2DM; type 2 diabetes mellitus HR; hazard ratio, CI; confidence interval.

Model adjusted for age + sex.

Supplementary Table 5 – Additive effect of rs2281279 (G allele) on metabolic parameters, stratified for T2DM status at baseline (n=4386)

	In patients without T2DM (n=3668)	In patients with T2DM (n=718)	P-value for interaction
	Beta (95% CI)	Beta (95% CI)	
(log)Triglycerides	0.010 (-0.002 – 0.023)	-0.020 (-0.051 – 0.011)	0.04
Non-HDL-cholesterol	0.022 (-0.049 – 0.094)	-0.019 (-0.198 – 0.159)	0.52
(log)Insulin^a	-0.007 (-0.027 – 0.013)	-0.011 (-0.056 – 0.033)	0.88
QUICKI^a	0.001 (-0.002 – 0.003)	0.002 (-0.003 – 0.008)	0.74
(log)HOMA-IR^a	0.009 (-0.032 – 0.014)	NA	NA

T2DM; type 2 diabetes mellitus, HDL; high-density lipoprotein, QUICKI; quantitative insulin sensitivity check index, HOMA-IR; Homeostatic Model Assessment for Insulin Resistance, CI; confidence interval.

^a Patients without T2DM (n=2063) and patients with T2DM (n=404)

Model adjusted for age + sex

Supplementary Table 6 – Triglyceride levels according to T2DM status and rs2281279 genotype

No T2DM (n=3668)	Triglycerides (IQR) in mmol/L
Total	1.40 (1.00 – 2.01)
AA (n=2029)	1.35 (1.00 – 2.00)
AG (n=1381)	1.40 (0.98 – 2.06)
GG (n=258)	1.40 (1.00 – 2.30)

T2DM (n=718)	Triglycerides (IQR) in mmol/L
Total	1.70 (1.19 – 2.46)
AA (n=409)	1.70 (1.18 – 2.60)
AG (n=261)	1.69 (1.19 – 2.35)
GG (n=48)	1.74 (1.28 – 2.33)

Supplementary Table 7 – Additive effect of presence of rs2281279 (G allele) on vascular events, stratified for T2DM status at baseline (n=4386)

	In patients without T2DM (n=3668)		In patients with T2DM (n=718)		P-value for interaction
	Number of events (%)	HR (95% CI)	Number of events (%)	HR (95% CI)	
Cardiovascular events	802 (22%)	1.00 (0.90 – 1.12)	224 (31%)	1.16 (0.94 – 1.42)	0.25
Limb events	237 (6%)	0.93 (0.76 – 1.15)	83 (12%)	0.89 (0.62 – 1.27)	0.85

HR; hazard ratio; CI; confidence interval.

Model adjusted for age + sex.

Supplementary Table 8 – Baseline characteristics, stratified for *SULF2* and *APOE* genotype

	SULF2 AA + ε2ε2 (n=29)	SULF2 GG + ε2ε2 (n=4)	SULF2 AA + ε3ε3 (n=1318)	SULF2 GG + ε3ε3 (n=166)
	HSPG – / LDLR – FD model	HSPG + / LDLR – 'Healthy' ε2ε2 model	HSPG – / LDLR + Decreased HSPG	HSPG + / LDLR + Healthy model
Male sex (n, %)	18 (62%)	3 (75%)	907 (69%)	116 (70%)
Age	56.8 ± 14.5	52.7 ± 20.7	58.1 ± 12.3	58.5 ± 11.6
Vascular disease (n,%)	20 (69%)	2 (50%)	989 (75%)	128 (77%)
Diabetes mellitus type 2 (n, %)	4 (14%)	0 (0%)	221 (17%)	34 (20%)
<i>Medication use</i>				
- Lipid lowering treatment	20 (69%)	1 (25%)	744 (56%)	95 (57%)
- Statins	20 (69%)	1 (25%)	732 (56%)	95 (57%)
- High intensity statins	1 (3%)	0 (0%)	69 (5%)	10 (6%)
- Fibrates	0 (0%)	0 (0%)	30 (2%)	4 (2%)
- Ezetimibe	1 (3%)	0 (0%)	37 (3%)	2 (1%)
- Bile acid sequestrant	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Current smoking	11 (38%)	1 (25%)	403 (31%)	51 (31%)
Current alcohol consumption	9 (31%)	1 (25%)	646 (49%)	77 (46%)
Body Mass Index (kg/m ²)	28.3 ± 5.5	32.0 ± 12.9	26.9 ± 4.23	26.9 ± 4.3
Waist circumference (cm)	98 ± 14	95 ± 22	95 ± 12	95 ± 12
Waist-to-hip ratio	0.93 ± 0.11	0.85 ± 0.07	0.91 ± 0.08	0.92 ± 0.09
Metabolic syndrome	17 (59%)	2 (50%)	684 (52%)	93 (56%)
Systolic blood pressure (mmHg)	149 ± 22	135 ± 6	141 ± 21	141 ± 21
Diastolic blood pressure (mmHg)	86 ± 12	76 ± 12	82 ± 12	83 ± 11
<i>Laboratory values</i>				
- Total cholesterol (mmol/L)	6.20 ± 3.52	4.78 ± 1.58	5.15 ± 1.42	5.26 ± 1.37
- HDL-cholesterol (mmol/L)	1.39 ± 0.53	1.16 ± 0.12	1.24 ± 0.39	1.21 ± 0.35
- Non-HDL-cholesterol (mmol/L)	4.81 ± 3.62	3.62 ± 1.69	3.92 ± 1.42	4.05 ± 1.35
- Apolipoprotein B (g/L)	0.52 ± 0.16	0.67 ± 0.11	0.90 ± 0.28	0.94 ± 0.28
- LDL-cholesterol (mmol/L)	3.01 ± 2.00	2.62 ± 1.59	3.15 ± 1.20	3.24 ± 1.23
- Triglycerides (mmol/L)	2.48 (1.75 - 4.11)	2.31 (1.85 - 2.68)	1.35 (1.00 - 2.00)	1.49 (1.04 - 2.31)
- Glucose (mmol/L)	6.8 ± 3.4	6.0 ± 0.57	6.3 ± 2.1	6.6 ± 2.1

HDL; high-density lipoprotein, LDL; low-density lipoprotein.