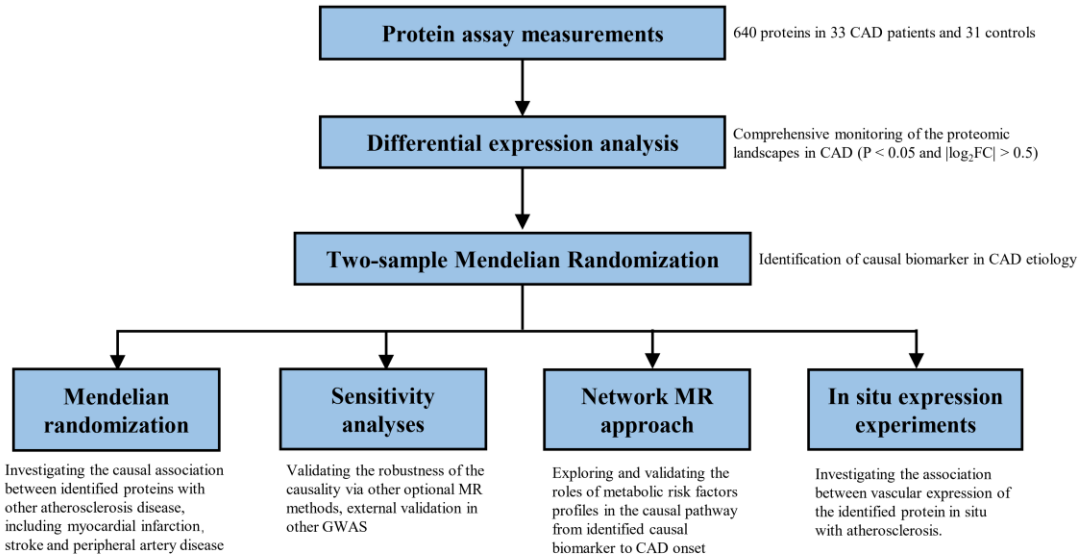
Causal Association of Golgi Protein 73 With Coronary Artery Disease: Evidence from Proteomics and Mendelian Randomization

Brief title: GP73 and CAD

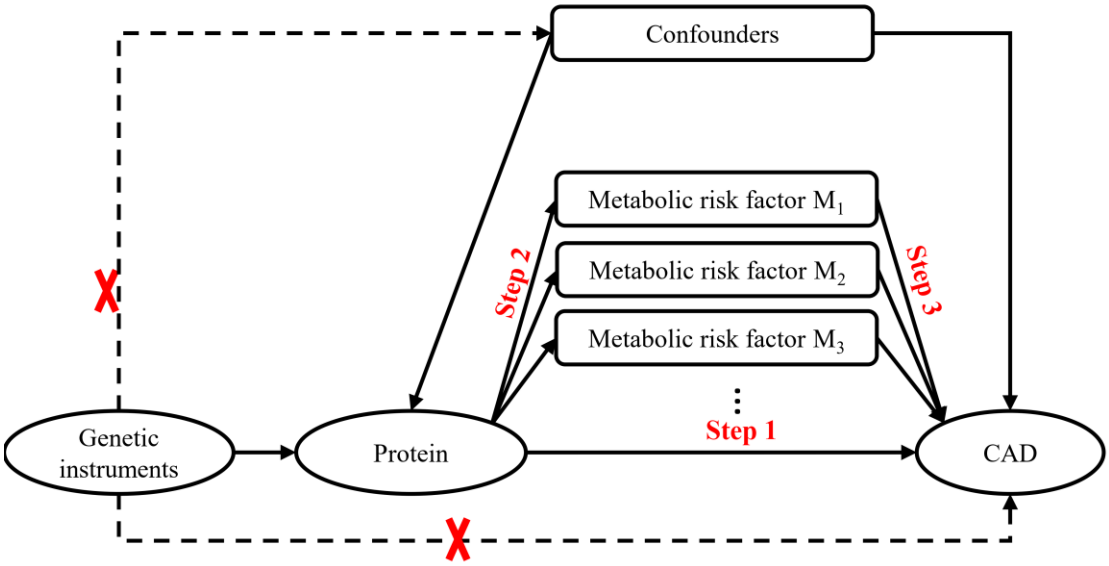
Supplemental Material

Figure S1 Flowchart of study design



(1) Measurement of 640 circulating plasma proteins for via protein arrays in 33 coronary artery disease (CAD) patients and 31 controls; (2) Differential expression analysis was performed to panoramically identify proteins correlated with CAD; (3) Two-sample mendelian randomization was conducted to screen causative agents for CAD; (4) For the identified proteins, causal inferences on other atherosclerosis outcomes sharing similar etiology (myocardial infarction, stroke and PAD) were performed; (5) Further validating the robustness of the causality using other optional MR methods and external replication in other GWAS; (6) Performing network Mendelian randomization to explore the role of metabolic risk factors of CAD in the causal pathway from identified causal agents to CAD; (7) Investigating the association between vascular expression of the identified protein in situ with atherosclerosis using both mouse and human samples.

Figure S2 Framework of network Mendelian randomization[1]



Step 1: Assess the causality between candidate protein with CAD; Step 2: Assess the causality between candidate protein with metabolic risk factors; Step 3: Assess the causality between metabolic risk factors with CAD. Only when causality exists in all three steps, the metabolic risk factor was considered as a mediator.

Figure S3 Funnel plot for MR analysis of causal effect of GP73 on CAD

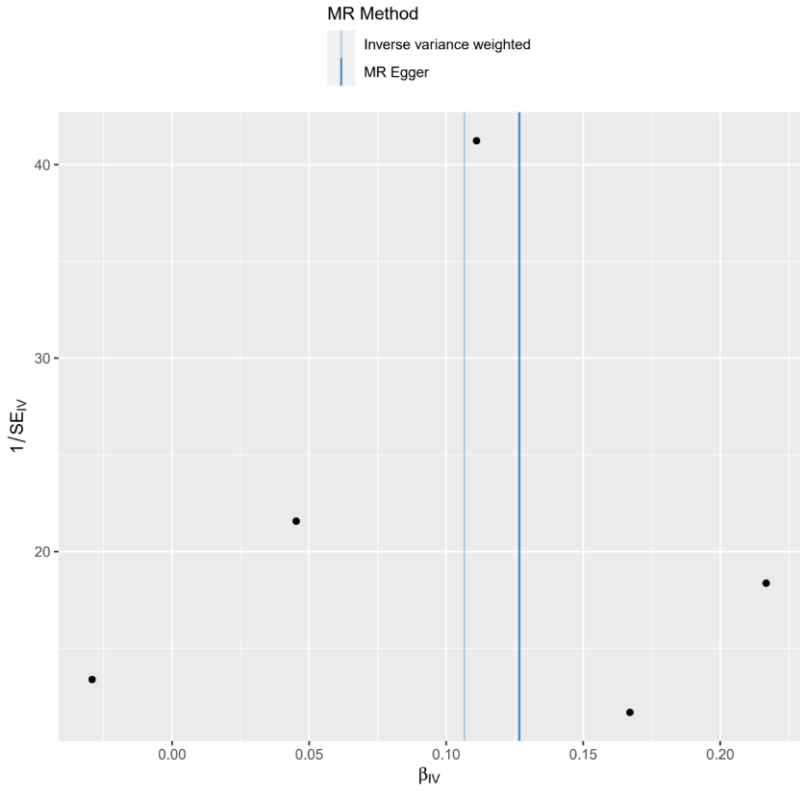


Table S1 The genome-wide association studies (GWAS) in the Mendelian randomization study

Outcome	GWAS	Phenotypes	Ancestry	Adjustments	pQTL	Sample size	URL for data download
CAD (Discovery)	CARDIoGRAMplus C4D 1000 Genomes-based GWAS	MI, ACS, chronic stable angina, or coronary stenosis of >50%	Multi-ancestry (77% European)	Age, gender	9,455,779	60,801 cases /123,504 controls	http://www.cardiogramplusc4d. org/data-downloads/[2]
CAD (Replication)	FinnGen study	Angina pectoris, MI, IHD, cardiac arrest, and other unattended or cause unknown sudden death	European	Age, gender	16,380,466	21,012 cases / 197,780 controls	http://www.finngen.fi/fi
Stroke	MEGASTROKE	AIS and subtypes (LAS, SVS)	Multi-ancestry	Age, gender	~8,000,000	67,162 cases /454,45 controls	http://megastroke.org/download.html[3]
PAD	UK Biobank	PAD	European	Age, gender	9,637,467	1,230 cases /359,964 controls	http://www.nealelab.is/ukbiobank
Lipid profile (Discovery)	GLGC	LDL-c, HDL-c, TC	Multi-ancestry	Age, gender	2,447,422	188,577	http://lipidgenetics.org/[4]
Lipid profile (Replication)	BioBank Japan	LDL-c	East Asian	Age, gender	6,108,953	72,866	http://jenger.riken.jp/en/ [5]
Glycemic profile (Discovery)	MAGIC	HbA1c，HOMA-β HOMA-IR	European	Age, gender	~2,500,000	46,368	https://magicinvestigators.org/[6-7]
Glycemic profile (Replication)	UK Biobank	HbA1c	European	Age, gender	13,586,180	344,182	http://www.nealelab.is/ukbiobank

Abbreviation:

Outcome name: CAD, coronary artery disease; PAD, peripheral artery disease.

GWAS names: CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics; GLGC, Global Lipids Genetics Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium.

Phenotype names: MI, myocardial infarction; ACS, acute coronary syndrome; IHD, ischemic heart disease; AIS, any ischemic stroke; LAS, large artery stroke; SVS, small vessel stroke; PAD, peripheral artery disease; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance.

Table S2 Genetic instruments in AGES study used in Mendelian randomization analysis

Uniprot ID	Protein name	pQTL	CHR: POS	Sample size	EA	EAF	β	SE	P-value	F-statistics
P02741	C-reactive protein	rs876537	1:31613465	5343	T	0.3712	-0.153	0.01999	2.29E-14	58.58
		rs7953249	12:31612724	5342	G	0.3915	-0.126	0.01952	1.17E-10	41.67
		rs2075650	19:45395619	5343	G	0.153	-0.1848	0.02663	4.45E-12	48.16
P05362	Intercellular adhesion molecule 1	rs657152	9:136139265	5340	T	0.279	-0.156	0.02121	2.19E-13	54.10
		rs3745600	19:10224526	5333	T	0.474	-0.1264	0.01897	2.99E-11	44.40
		rs34495400	19:10664661	5341	T	0.008878	0.6987	0.1012	5.75E-12	47.67
		rs55762744	19:10488926	5341	T	0.005504	0.8845	0.1275	4.52E-12	48.13
		rs8109578	19:31613048	5335	A	0.09154	-0.2322	0.03232	7.61E-13	51.62
		rs113197610	19:10363251	5341	C	0.02486	-0.4727	0.06119	1.33E-14	59.68
		rs5030400	19:10395796	5341	T	0.009677	0.9559	0.09907	7.53E-22	93.10
		rs34536443	19:10463118	5341	C	0.04252	0.4857	0.04665	3.79E-25	108.40
		rs2304256	19:10475652	5341	A	0.2579	0.3423	0.02119	2.31E-57	260.95
		rs2230399	19:10444603	5341	G	0.0799	0.6239	0.03426	6.30E-72	331.63
		rs1799969	19:10394792	5341	A	0.1349	-0.7812	0.02589	8.807E-185	910.46
		rs2228615	19:10403368	5340	A	0.3974	-1.014	0.01358	0	5575.40
P09341	Growth-regulated alpha protein	rs2251746	1:159272060	5335	C	0.2805	0.1396	0.02011	4.33E-12	48.19
		rs12075	1:159175354	5334	G	0.4357	-0.1978	0.01791	4.77E-28	121.97
		rs241771	17:26592946	5334	T	0.4498	-0.1831	0.01795	3.18E-24	104.05
P12821	Angiotensin-converting enzyme	rs9898	3:31615480	5335	T	0.3004	0.1868	0.02057	1.52E-19	82.47

		rs4962153	9:136323754	5336	A	0.09641	-0.2202	0.03191	5.75E-12	47.62
		rs4968639	17:61055390	5335	G	0.2149	-0.2279	0.02284	2.95E-23	99.56
		rs3730025	17:61557773	5336	G	0.01696	-1.181	0.07238	1.79E-58	266.23
		rs4343	17:61566031	5336	A	0.4999	-0.5652	0.01733	6.51E-213	1063.67
P14210	Hepatocyte growth factor	rs2511241	11:72945341	5340	C	0.08638	-0.3751	0.03387	3.39E-28	122.65
P15941	Mucin-1	rs241771	17:26592946	5327	T	0.4498	-0.1147	0.01748	5.92E-11	43.06
		rs9910163	17:31615623	5333	A	0.2539	-0.2035	0.02109	7.51E-22	93.11
P22894	Neutrophil collagenase	rs3130481	6:31839756	5339	G	0.4788	-0.12	0.01879	1.84E-10	40.79
		rs2857105	6:32790059	5340	G	0.02779	0.3615	0.0565	1.72E-10	40.94
		rs6924270	6:30681980	5339	G	0.01092	0.5813	0.09072	1.60E-10	41.06
		rs154989	6:32877173	5340	T	0.4611	0.1223	0.01905	1.48E-10	41.22
		rs11963870	6:30735229	5340	A	0.01589	0.4782	0.0743	1.33E-10	41.42
		rs2523674	6:31436789	5339	C	0.4007	0.123	0.01896	9.45E-11	42.09
		rs1705003	6:33385953	5338	G	0.1083	0.199	0.03065	9.27E-11	42.15
		rs2075798	6:31846741	5340	A	0.08034	0.2274	0.03421	3.29E-11	44.18
		rs138097363	6:32942386	5340	A	0.003285	1.084	0.1624	2.72E-11	44.55
		rs141444056	6:33283955	5340	T	0.006392	0.7902	0.1167	1.43E-11	45.85
		rs6457452	6:31795550	5338	T	0.0444	0.311	0.04593	1.42E-11	45.85
		rs61751507	10:101829514	5338	T	0.0453	-0.3181	0.04455	1.05E-12	50.98
		rs2846365	11:102571892	5342	A	0.4653	-0.1505	0.01931	7.65E-15	60.74
		rs2511241	11:72945341	5343	C	0.08638	-0.3502	0.03446	4.91E-24	103.28
		rs35231465	11:102584135	5343	A	0.02193	-0.9681	0.06474	1.48E-49	223.61
P48023	Tumor necrosis factor ligand	rs7617480	3:31611817	5339	A	0.2055	-0.152	0.02363	1.36E-10	41.38

	superfamily member 6	rs6762477	3:50093209	5339	G	0.4336	-0.1251	0.01921	8.13E-11	42.41
		rs6442117	3:48419897	5340	C	0.4678	0.1303	0.01911	1.01E-11	46.49
		rs146179438	3:48229366	5341	A	0.01341	0.5601	0.08117	5.80E-12	47.61
		rs17080138	3:48414274	5341	T	0.0237	0.4416	0.0632	3.15E-12	48.82
		rs388483	3:50615539	5340	G	0.4638	-0.1341	0.01903	2.11E-12	49.66
		rs35761247	3:48623124	5337	A	0.06503	0.314	0.03856	4.74E-16	66.31
		rs739983	3:50178011	5341	G	0.3127	0.1809	0.02056	1.82E-18	77.42
		rs9834639	3:31615434	5341	T	0.06294	0.4298	0.03949	2.63E-27	118.46
		rs2005557	3:49701298	5340	G	0.4782	0.2487	0.01867	7.14E-40	177.44
P49862	Kallikrein-7	rs61729512	12:7637769	5325	A	0.1165	0.1931	0.02908	3.48E-11	44.09
		rs1654528	19:51480840	5324	G	0.04049	-0.3927	0.0467	5.24E-17	70.71
P50895	Basal Cell Adhesion Molecule	rs505922	9:136149229	5332	C	0.2571	0.1353	0.02085	9.47E-11	42.11
		rs7853989	9:31612595	5331	C	0.09005	0.2315	0.03166	2.98E-13	53.47
P55287	Cadherin-11	rs4967857	16:64886822	5335	C	0.4087	-0.1298	0.0189	7.19E-12	47.17
		rs141063325	16:65005934	5337	A	0.009499	-0.7798	0.09652	8.05E-16	65.27
		rs35195	16:65025718	5335	A	0.3409	0.1616	0.01967	2.69E-16	67.50
		rs9910163	17:31615725	5317	A	0.2539	-0.2178	0.01948	1.10E-28	125.01
		rs241771	17:26592946	5316	T	0.4498	0.2216	0.01702	3.75E-38	169.52
P78380	Oxidized low-density lipoprotein receptor 1	rs2511241	11:72945341	5343	C	0.08638	-0.2886	0.03455	8.44E-17	69.77
Q76LX8	A disintegrin and metalloproteinase with thrombospondin motifs 13	rs142572218	9:136319670	5334	T	0.002663	-1.49	0.1814	2.68E-16	67.47
		rs1053878	9:136131651	5333	A	0.06109	0.335	0.03975	4.50E-17	71.03
		rs8176720	9:31613094	5334	C	0.3888	-0.1805	0.01949	2.90E-20	85.77

		rs34024143	9:136287582	5333	T	0.1465	-0.3216	0.0264	1.10E-33	148.40
		rs28515121	9:136291594	5332	A	0.4715	-0.3227	0.01866	3.01E-65	299.07
Q8NBJ4	Golgi membrane protein 1/ Golgi protein 73	rs549446	9:136135238	5336	T	0.2986	-0.1306	0.0203	1.36E-10	41.39
		rs4962153	9:136323754	5336	A	0.09641	0.2784	0.03092	2.97E-19	81.07
		rs1053878	9:136131651	5335	A	0.06109	0.3749	0.03843	2.68E-22	95.17
		rs505922	9:136149229	5335	C	0.2571	0.3908	0.02045	9.05E-79	365.19
		rs2287921	19:49228272	5336	T	0.3936	0.134	0.0188	1.16E-12	50.80
Q92563	Testican-2	rs148641213	10:73827379	5336	A	0.008347	-0.7373	0.1054	3.02E-12	48.93
		rs1245541	10:73849639	5335	T	0.4131	0.1565	0.01935	7.53E-16	65.41
Q9BY76	Angiopoietin-related protein 4	rs9910163	17:31615950	5327	A	0.2539	0.1478	0.02057	7.64E-13	51.63
		rs241771	17:26592946	5326	T	0.4498	-0.1779	0.01797	6.79E-23	98.01
Q9UNG2	Tumor necrosis factor ligand superfamily member 18	rs9910163	17:31616047	5314	A	0.2539	-0.1256	0.01871	2.09E-11	45.06

bbreviation: CHR: chromosome; POS: position; EA: effect allele; EAF: effect allele frequency.

Table S3 The associations between genetic variant with outcome

pQTL	Gene	EA	Association parameters for CAD (CARDIoGRAMplusC4D)		Association parameters for CAD in FINNGEN		Association parameters for MI		Association parameters for any ischemic stroke		Association parameters for large artery stroke	
			effect	se	effect	se	effect	se	effect	se	effect	se
rs1053878	*ABO*	A	0.01696	0.01738	-0.00720	0.02100	0.01108	0.02007	-0.00260	0.01950	0.06810	0.05470
rs2287921	*RASIP1*	T	-0.00392	0.01001	-0.00360	0.01300	-0.00177	0.01101	-0.01950	0.01000	0.47860	-0.04170
rs4962153	*ADAMTS13*	A	0.06034	0.01516	0.04340	0.01810	0.07396	0.01688	0.03760	0.01740	0.14980	0.07810
rs505922	*ABO*	C	0.04341	0.00948	0.03470	0.01300	0.07653	0.01058	-0.04980	0.01160	0.65520	-0.13710
rs549446	*ABO*	T	-0.02182	0.01117	-0.02580	0.01690	-0.02921	0.01249	-0.01330	0.01330	0.29900	-0.04610
pQTL	**Gene**	**EA**	**Association parameters for small vessel stroke**		**Association parameters for peripheral artery disease**		**Association parameters for LDL-c (GLGC)**		**Association parameters for HDL-c**		**Association parameters for TC**	
			effect	**se**	**effect**	**se**	**effect**	**se**	**effect**	**se**	**effect**	**se**
rs1053878	*ABO*	A	-0.01500	0.04740	0.00018	0.00027	0.00350	0.01160	-0.01620	0.01050	-0.01170	0.01070
rs2287921	*RASIP1*	T	-0.03330	0.02290	-0.00014	0.00014						
rs4962153	*ADAMTS13*	A	0.03860	0.03650	0.00024	0.00020	0.04570	0.00730	0.01380	0.00690	0.03430	0.00700
rs505922	*ABO*	C	0.00500	0.02640	0.00033	0.00015						
rs549446	*ABO*	T	0.05270	0.02940	-0.00009	0.00016	-0.01260	0.00600	-0.02070	0.00570	-0.02080	0.00570
pQTL	**Gene**	**EA**	**Association parameters for LDL-c (Biobank Japan)**		**Association parameters for HbA1c (MAGIC)**		**Association parameters for HOMA-β**		**Association parameters for HOMA-IR**		**Association parameters for HbA1c (UK Biobank)**	
			effect	**se**	**effect**	**se**	**effect**	**se**	**effect**	**se**	**effect**	**se**

rs1053878	*ABO*	A	0.04679	0.00626	0.01250	0.00690	-0.00180	0.00630	-0.00130	0.00800	0.08154	0.03006
rs2287921	*RASIP1*	T	-0.01037	0.01177	0.00390	0.00360	0.00360	0.00340	0.00260	0.00410	0.02804	0.01542
rs4962153	*ADAMTS13*	A	-0.02085	0.00847	0.01660	0.00540	-0.00040	0.00560	0.00740	0.00670	0.17399	0.02246
rs505922	*ABO*	C	0.02504	0.00523	0.01020	0.00350	-0.00170	0.00340	0.00330	0.00420	0.16345	0.01652
rs549446	*ABO*	T	-0.01480	0.00591	-0.00640	0.00400	0.00050	0.00400	-0.00480	0.00480	-0.06023	0.01782

Table S4 Description of GSE100927 and GSE28829

Accession number	**GSE100927**[8]	**GSE28829**[9]
Title	Atherosclerotic and control peripheral arteries gene expression	Gene Expression in early and advanced atherosclerotic plaque from human carotid arteries
Organism	Homo sapiens	Homo sapiens
Experiment type	Expression profiling by array	Expression profiling by array
Summary	Transcriptome analysis of human peripheral arteries from carotid, femoral and infra-popliteal territories in atherosclerotic and control tissue	To identify genes and pathways involved in the progression of atherosclerotic plaques from early to advanced stage in humans
Overall design	Atherosclerotic lesions (n=69) and control arteries (n=35) without atherosclerotic lesions (from deceased organ donors) were obtained from carotid, femoral and infra-popliteal arteries	Samples were extracted from atherosclerotic carotid artery segments, from early ((pathological) intimal thickening and intimal xanthoma, n=13) and from advanced (thin or thick fibrous cap atheroma, n=16) lesions

Table S5 Differentially expressed proteins between the CAD group and control group (P-value<0.05 and $log_2FC>0.263$ or $log_2FC< -0.263$)

Protein name	Uniprot ID	Fold change (CAD /Control)	P-value	Direction
IL-17B	Q9UHF5	-0.43502	0.000791	Down-regulated
ACE	P12821	-0.60947	0.002798	Down-regulated
FAS L	P48023	-0.31654	0.003452	Down-regulated
LOX-1	P78380	0.60751	0.004407	Up-regulated
Periostin	Q15063	0.947869	0.005337	Up-regulated
MMP-8	P22894	0.663479	0.007132	Up-regulated
Kallikrein 7	P49862	-0.37082	0.009262	Down-regulated
Thrombospondin-5	P49747	1.175349	0.018151	Up-regulated
Testican 2	Q92563	0.290883	0.015549	Up-regulated
Midkine	P21741	0.448534	0.018224	Up-regulated
ICAM-1	P05362	-0.29314	0.029055	Down-regulated
ANGPTL4	Q9BY76	-0.54942	0.018489	Down-regulated
ADAMTS13	Q76LX8	-0.40764	0.018121	Down-regulated
FSH	P01225	-0.76342	0.019319	Down-regulated
HTRA2	O43464	0.302938	0.019246	Up-regulated
Cadherin-11	P55287	-0.54401	0.018224	Down-regulated
Hepsin	P05981	0.302118	0.019696	Up-regulated
CA15-3	P15941	-0.65434	0.021515	Down-regulated
MCP-4	Q99616	0.354489	0.022022	Up-regulated
HGF	P14210	0.352365	0.02396	Up-regulated
Adipsin	P00746	-0.90153	0.0244	Down-regulated
GP73	Q8NBJ4	0.361246	0.033029	Up-regulated
IL-3	P08700	-0.55323	0.031375	Down-regulated
CRP	P02741	-0.72296	0.027308	Down-regulated
Renin	P00797	0.516599	0.034687	Up-regulated
EMMPRIN	P35613	0.541476	0.039866	Up-regulated
FLRG	O95633	0.578827	0.039792	Up-regulated
BCAM	P50895	-0.50288	0.041368	Down-regulated
Endoglycan	Q9NZ53	-0.32526	0.047729	Down-regulated
GITR L	Q9UNG2	0.48922	0.041055	Up-regulated
GROa	P09341	-0.38825	0.048254	Down-regulated
AFP	P02771	-0.40215	0.047859	Down-regulated

Table S6 The causal association between candidate protein with CAD in Mendelian randomization

UniprotID	Gene symbol	Protein full name	$P_{heterogeneity}$	No. of Instruments	OR	95%CI	P-value	FDR
Q8NBJ4[a]	*GOLM1*	Golgi membrane protein 1, Golgi protein 73	0.05	5	1.11	1.05-1.18	<0.001	0.005
P48023[a]	*FASLG*	Tumor necrosis factor ligand superfamily member 6	0.01	10	0.93	0.88-0.99	0.02	0.15
Q76LX8[b]	*ADAMTS13*	A disintegrin and metalloproteinase with thrombospondin motifs 13	0.11	4	1.04	1.00-1.09	0.05	0.23
P02741[a]	*CRP*	C-reactive protein	<0.001	3	0.82	0.66-1.01	0.07	0.23
P05362[a]	*ICAM1*	Intercellular adhesion molecule 1	<0.001	11	0.98	0.95-1.00	0.07	0.23
Q9BY76[b]	*ANGPTL4*	Angiopoietin-related protein 4	0.26	2	0.93	0.86-1.02	0.11	0.31
P78380[c]	*OLR1*	Oxidized low-density lipoprotein receptor 1	-	1	0.91	0.78-1.07	0.25	0.48
P15941[b]	*MUC1*	Mucin-1	0.12	2	0.95	0.87-1.04	0.25	0.48
P14210[c]	*HGF*	Hepatocyte growth factor	-	1	0.93	0.82-1.05	0.25	0.48
P55287[b]	*CDH11*	Cadherin-11	0.29	4	1.03	0.97-1.08	0.34	0.57
P49862[b]	*KLK7*	Kallikrein-7	0.56	2	0.97	0.88-1.07	0.57	0.88
P50895[a]	*BCAM*	Basal Cell Adhesion Molecule	<0.001	2	1.09	0.75-1.57	0.67	0.94
P09341[b]	*CXCL1*	Growth-regulated alpha protein	0.08	3	0.99	0.93-1.05	0.74	0.94

Q92563[c]	*SPOCK2*	Testican-2	-	1	0.99	0.88-1.12	0.88	0.94
P22894[b]	*MMP8*	Neutrophil collagenase	0.40	7	1.00	0.95-1.04	0.89	0.94
P12821[a]	*ACE*	Angiotensin-converting enzyme	<0.001	5	1.00	0.95-1.06	0.89	0.94
Q9UNG2[c]	*TNFSF18*	Tumor necrosis factor ligand superfamily member 18	-	1	1.00	0.83-1.19	0.97	0.97

Abbreviations: CAD, coronary artery disease; OR, odds ratio; 95% CI, 95% confidential interval; FDR, false discovery rate.

[a] Inverse variance weighted (random-effect) method;

[b] Inverse variance weighted (fixed-effect) method;

[c] Wald ratio method

Table S7 Replication of causal association between GP73 level with coronary artery disease using CAD GWAS in FINNGEN study

Exposure-outcome	Method	Causal estimate			
		pQTL	OR	95% CI	P-value
GP73-CAD	Inverse variance weighted[a]	5	1.08	1.03-1.13	0.003
	Weighted median	5	1.08	1.02-1.14	0.01
	Weighted mode	5	1.09	1.02-1.17	0.06
	MR Egger	5	1.07	0.91-1.28	0.47
	Test for Heterogeneity: P=0.09 (MR-Egger) and P=0.16 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept=0.001, se = 0.025, P=0.98				

[a] Inverse variance weighted (fixed-effect) method

Table S8 Causal associations between GP73 level and atherosclerosis disease

Secondary outcome	Method	Causal estimate			
		pQTL	OR	95% CI	P-value
Myocardial infarction	Inverse variance weighted [a]	5	1.18	1.09-1.28	<0.001
	Weighted median	5	1.19	1.13-1.26	<0.001
	Weighted mode	5	1.23	1.15-1.30	0.003
	MR Egger	5	1.23	1.00-1.52	0.14
	Test for Heterogeneity: P=0.002 (MR-Egger) and P=0.004 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept=-0.014, se = 0.03, P=0.68				
Ischemic stroke	Inverse variance weighted [a]	5	1.08	0.99-1.18	0.07
	Weighted median	5	1.13	1.07-1.19	<0.001
	Weighted mode	5	1.14	1.07-1.21	0.01
	MR Egger	5	1.20	1.00-1.43	0.14
	Test for Heterogeneity: P=0.02 (MR-Egger) and P=0.004 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept=-0.031, se = 0.024, P=0.29				
Large artery atherosclerotic stroke	Inverse variance weighted [a]	5	1.29	1.07-1.55	0.008
	Weighted median	5	1.37	1.21-1.56	<0.001
	Weighted mode	5	1.41	1.22-1.63	0.01
	MR Egger	5	1.67	1.17-2.38	0.07
	Test for Heterogeneity: P=0.09 (MR-Egger) and P=0.02 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept=-0.078, se = 0.048, P=0.20				
Small vessel stroke	Inverse variance weighted [b]	5	0.97	0.87-1.07	0.49
	Weighted median	5	0.98	0.87-1.10	0.76
	Weighted mode	5	0.99	0.87-1.13	0.92
	MR Egger	5	1.17	0.94-1.46	0.26
	Test for Heterogeneity: P=0.46 (MR-Egger) and P=0.19 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept=-0.056, se = 0.030, P=0.16				
Peripheral artery disease	Inverse variance weighted [b]	5	1.001	1.000-1.001	0.02
	Weighted median	5	1.001	1.000-1.001	0.02
	Weighted mode	5	1.001	1.000-1.002	0.07
	MR Egger	5	1.001	1.000-1.003	0.13
	Test for Heterogeneity: P=0.67 (MR-Egger) and P=0.55 (IVW)				
	Test for Horizontal pleiotropy: MR-Egger intercept<0.001, se <0.001, P=0.31				

[a] Inverse variance weighted (random-effect) method;

[b] Inverse variance weighted (fixed-effect) method.

Table S9 Discovery and replication of causal association between GP73 and metabolic risk factors

Metabolic trait	Causal estimates between GP73 with traits (Discovery)				Causal estimates between GP73 with traits (Replication)			
	pQTL	β	SE	P-value	pQTL	β	SE	P-value
TC	3	0.072 [a]	0.056	0.20	-	-	-	-
HDL-c	3	0.032 [a]	0.048	0.51	-	-	-	-
LDL-c	**3**	**0.099** [a]	**0.049**	**0.04**	**5**	**0.071** [a]	**0.029**	**0.02**
HbA1c	**5**	**0.033** [b]	**0.007**	**<0.001**	**5**	**0.405** [a]	**0.063**	**<0.001**
HOMA-β	5	-0.002 [b]	0.007	0.78	-	-	-	-
HOMA-IR	5	0.011 [b]	0.008	0.18	-	-	-	-

Abbreviation: IVW, inverse variance weighted; CAD, coronary artery disease; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance.

[a] Inverse variance weighted (random-effect) method;

[b] Inverse variance weighted (fixed -effect) method.

Table S10 Gene Ontology (GO) - Biological Process for GOLM1 Gene

GO ID	Qualified GO term	Evidence
GO:0006997	nucleus organization	IEA [a]
GO:0019216	regulation of lipid metabolic process	IEA [a]
GO:0043687	post-translational protein modification	TAS [b]
GO:0044267	cellular protein metabolic process	TAS [b]

[a] IEA: Inferred from Electronic Annotation;

[b] TAS, Traceable Author Statement.

Text S1 Introduction on RED-CARPED study and data collection method

REal-world Data of CARdiometabolic ProtEcTion is a single-center, ambispective cohort study aimed at identifying risk factors associated with metabolic cardiovascular diseases and explore their relationship with long-term cardiovascular endpoints (registration number: ChiCTR2000039901). This is achieved through conducting long-term follow-up of patients with metabolic cardiovascular diseases in a real-world setting. Patients admitted to the Cardiology department of the First Affiliated Hospital of Sun Yat-sen University with metabolic cardiovascular diseases between 2003 and 2033 were consecutively enrolled. The registry includes patients with any of the following conditions: coronary heart disease, hypertension, heart failure, stroke, diabetes, obesity, dyslipidemia, or hyperuricemia. From 2017 to 2018, a total of 2,361 patients (67.6% male; mean age 63.5±11.7 years) were diagnosed with coronary heart disease in the RED-CARPET study, among whom 64 patients were randomly selected for high-throughput proteomics.

Information on gender, age, and smoking status were self-reported. After a 15 minutes rest in a sitting position, systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) were measured three times every 5 minutes at right arm using mercury sphygmomanometer, and the mean values were used for analysis. Standing height and weight were measured with the subjects wearing light clothes without shoes in a standardized posture. Body mass index (BMI) was calculated as weight (in kilograms) divided by squared height (in meters). Hypertension (HTN) was ascertained if a participant has systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, prior history of hypertension, or antihypertensive medication[10]. We defined diabetes mellitus (DM) as fasting glucose ≥126 mg/dL, non-fasting glucose ≥ 200 mg/dL, A1C ≥ 6.5%, self-report of a previous diabetes diagnosis, or taking medication for diabetes[11]. Total cholesterol, low-density lipoprotein cholesterol, and triglycerides were detected by the automatic enzyme method. Glycated hemoglobin (HbA1c) was tested via automated immunochemistry method. Creatine kinase-MB (CK-MB), and Cardiac troponin T (cTNT) were measured using immunoassays.

Text S2 Protein arrays protocol

A. Completely Air Dry The Glass Slide

1. Take out the glass slide from the box, and let it equilibrate to room temperature inside the sealed plastic bag for 20-30 minutes. Remove slide from the plastic bag, peel off the cover film, and let it air dry for another 1-2 hours.

Incomplete drying of slides before use may cause the formation of "comet tails," thin directional smearing of antibody spots.

B. Blocking & Incubation

2. Add 100 µl Sample Diluent into each well and incubate at room temperature for 30 minutes to block slides.

3. Decant buffer from each well. Add 100 µl of sample to each well. Incubate arrays at room temperature for 1-2 hour.

Longer incubation time is preferable for higher signals. This step may be done overnight at 4°C.

We recommend using 50 to 100 µl of original or diluted serum, plasma, conditioned media, or other body fluid, or 50-500 µg/ml of protein for cell and tissue lysates. Cover the incubation chamber with adhesive film during incubation, especially if less than 70 ul of sample or reagent is used.

4. Wash:

- Decant the samples from each well, and wash 5 times (5 min each) with 150 µl of 1X Wash Buffer I at room temperature with gentle shaking. Completely remove wash buffer in each wash step. Dilute 20x Wash Buffer I with H2O.
- (Optional for Cell and Tissue Lysates) Put the glass slide with frame into a box with 1X Wash Buffer I (cover the whole glass slide and frame with Wash Buffer I), and wash at room temperature with gentle shaking for 20 min.
- Decant the 1x Wash Buffer I from each well, wash 2 times (5 min each) with 150 µl of 1X Wash Buffer II at room temperature with gentle shaking.

  Completely remove wash buffer in each wash step. Dilute 20X Wash Buffer II with H2O.

"Incomplete removal of the wash buffer in each wash step may cause "dark spots," the background signals higher than the spots.

C. Incubation with Biotinylated Antibody Cocktail & Wash

5. Reconstitute the detection antibody by adding 1.4 ml of Sample Diluent to the tube. Spin briefly.

6. Add 80 µl of the detection antibody cocktail to each well. Incubate at room temperature for 1-2 hour. Longer incubation time is preferable for higher signals

7. Decant the samples from each well, and wash 5 times (5 mins each) with 150 µl of 1X Wash Buffer I and then 2 times with 150 µl of 1x Wash Buffer II at room temperature with gentle shaking. Completely remove wash buffer in each wash step.

D. Incubation with Cy3 Equivalent Dye-Streptavidin & Wash

8. After briefly spinning down, add 1.4 ml of Sample Diluent to Cy3 equivalent dye-conjugated streptavidin tube. Mix gently.

9. Add 80 µl of Cy3 equivalent dye-conjugated streptavidin to each well. Cover the device with aluminum foil to avoid exposure to light or incubate in dark room. Incubate at room temperature for 1 hour.

10. Decant the samples from each well, and wash 5 times (5 mins each) with 150 µl of 1X Wash Buffer I at room temperature with gentle shaking. Completely remove wash buffer in each wash step.

E. Fluorescence Detection

11. Disassemble the device by pushing clips outward from the slide side. Carefully remove the slide from the gasket.

12. Place the slide in the Slide Washer/Dryer (a 4-slide holder/centrifuge tube), add enough 1x Wash Buffer I (about 30 ml) to cover the whole slide, and then gently shake at room temperature for 15 minutes. Decant Wash Buffer I. Wash with 1x Wash Buffer II (about 30 ml) and gently shake at room temperature for 5 minutes.

13. Remove water droplets completely by gently applying suction with a pipette to remove water droplets. Do not touch the array, only the sides.

14. Imaging: The signals can be visualized through use of a laser scanner equipped with a Cy3 wavelength (green channel) such as Axon GenePix or Innopsys Innoscan.

F. Data Analysis

15. Data extraction can be done using the GAL file that is specific for this array along with the microarray analysis software (GenePix, ScanArray Express, ArrayVision, MicroVigene, etc.).

Text S3 STROBE-MR: Guidelines for strengthening the reporting of Mendelian randomization studies[12]

1. TITLE and ABSTRACT

Indicate Mendelian randomization as the study's design in the title and/or the abstract.

Title; Abstract – Methods

INTRODUCTION

2. Background

Explain the scientific background and rationale for the reported study. Is causality between exposure and outcome plausible? Justify why MR is a helpful method to address the study question.

Introduction – Paragraphs 1-2.

3. Objectives

State specific objectives clearly, including pre-specified causal hypotheses (if any).

Introduction – Paragraph 3.

METHODS

4. Study design and data sources

Present key elements of study design early in the paper. Consider including a table listing sources of data for all phases of the study.

Methods – Publicly available GWAS summary data for 2-sample MR analyses - Paragraphs 1; Table S1.

5. Assumptions

Explicitly state assumptions for the main analysis (e.g. relevance, exclusion, independence, homogeneity) as well assumptions for any additional or sensitivity analysis.

Methods –Two-sample Mendelian Randomization – Paragraph 1.

6. Statistical methods: main analysis

Describe statistical methods and statistics used.

a) Describe how quantitative variables were handled in the analyses (i.e., scale, units, model).

N/A. (Two-sample design)

b) Describe the process for identifying genetic variants and weights to be included in the analyses (i.e, independence and model)

Methods – Selection of genetic instruments – Paragraph 1.

c) Describe the MR estimator, e.g. two-stage least squares, Wald ratio, and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples.

Methods –Two-sample Mendelian Randomization – Paragraph 1-2; Table S1.

d) If applicable, say how multiple testing was dealt with.

Methods –Two-sample Mendelian Randomization – Paragraph 1.

7. Assessment of assumptions

Describe any methods used to assess the assumptions or justify their validity.

Methods –Two-sample Mendelian Randomization – Paragraph 2-3.

8. Sensitivity analyses

Describe any sensitivity analyses or additional analyses performed.

Methods –Two-sample Mendelian Randomization – Paragraph 2-3.

9. Software and pre-registration

a) Name statistical software and package(s), including version and settings used.

Methods – Statistical Analysis – Paragraph 1.

b) State whether the study protocol and details were pre-registered (as well as when and where).

N/A.

RESULTS

10. Descriptive data

For two-sample Mendelian randomization:

Provide information on extent of sample overlap between the exposure and outcome data sources.

Methods – Publicly available GWAS summary data for 2-sample MR analyses – Paragraph 1.

11. Main results

a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale (e.g. comparing 25th and 75th percentile of allele count or genetic risk score, if individual-level data available).

   Table S3.

b) Report causal effect estimate between exposure and outcome, and the measures of uncertainty from the MR analysis. Use an intuitive scale, such as odds ratio, or relative risk, per standard deviation difference.

   Results Table 2-3; Table S7-9.

c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time-period.

   N/A.

d) Consider any plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure).

   Result Figure 2; Figure S3.

12. Assessment of assumptions

a) Assess the validity of the assumptions.

Results Table 2; Figure S3.

b) Report any additional statistics (e.g., assessments of heterogeneity, such as I^2, Q statistic).

Results – paragraph 3.

13. Sensitivity and additional analyses

a) Use sensitivity analyses to assess the robustness of the main results to violations of the assumptions.

Results – paragraph 3.

b) Report results from other sensitivity analyses (e.g., replication study with different dataset, analyses of subgroups, validation of instrument(s), simulations, etc.)

Results – Paragraph 4-5 (External replication, secondary outcome with similar etiology).

c) Report any assessment of direction of causality (e.g., bidirectional MR).

N/A.

DISCUSSION

14. Key results

Summarize key results with reference to study objectives.

Discussion – Paragraph 1.

15. Limitations

Discuss limitations of the study, taking into account the validity of the MR assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias, and any efforts to address them.

Discussion – Strengths and Limitations – Paragraph 2.

16. Interpretation

a) Give a cautious overall interpretation of results considering objectives and limitations. Compare with results from other relevant studies.

Discussion – Paragraph 1-2.

b) Discuss underlying biological mechanisms that could be modelled by using the genetic variants to assess the relationship between the exposure and the outcome.

NA.

c) Discuss whether the results have clinical or policy relevance, and whether interventions could have the same size effect.

Discussion – Paragraph 2-4.

17. Generalizability

Discuss the generalizability of the study results (a) to other populations (i.e. external validity), (b) across other exposure periods/timings, and (c) across other levels of exposure.

Discussion – Strengths and limitations.

OTHER INFORMATION

18. Funding

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study or studies on which the present article is based.

Funding

19. Data and data sharing

Present data used to perform all analyses or report where and how the data can be accessed. State whether statistical code is publicly accessible and if so, where.

Acknowledge; Table S1.

20. Conflicts of Interest

All authors should declare all potential conflicts of interest.

Conflicts of Interest

Text S4 Concept of mediation analysis

Mediation analysis determines **if potential mediators mediate the association** between independent variable with dependent variable and **quantifies their contribution**[113]. Several criteria should be satisfied in mediation analysis: 1) Independent variable (X) must be significantly associated with dependent variable (Y) (The effect from X to Y is *c*); 2) X must be significantly associated with mediator (M) (The effect from X to M is *a*); 3) M must be significantly associated with Y (The effect from M to Y is *b*). *c*' is the effect of from X to Y bypassing the investigated mediator, calculated through adjustment for the investigated mediator in model. Based on the design of mediation analysis (as shown in the following Figure), the total effect of X on Y (*c*) was divided into direct effect (*c'*, the effect that was not transmitted by selected mediators) and indirect effect (*a*b*, the effect that was mediated by the investigated mediator) (*c=a*b+c'*). Proportion mediated (PM, %) was defined as indirect effect/total effect (PM= *a*b* /*c*).

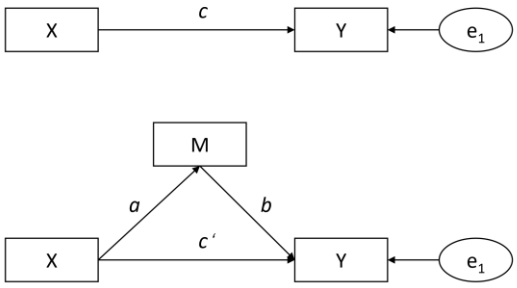


Figure Frame of mediation analysis

In the present study, we used mediation analysis to assess the extent to which the association of GP73 with CAD was mediated by two mediators (LDL-c and HbA1c). The total effect [log(odds ratio, OR)] of GP73 on CAD was 0.107 [log(1.11)]. The effect of GP73 on LDL-c was 0.099, and LDL-c was associated with CAD [log(OR)=log(1.58)=0.456]. Hence, the mediated effect of LDL-c was 0.099×0.456=0.0451. The mediated proportion was 0.0451/0.107 = 42.1%.

Text S5 Information on experimental procedures

All experimental procedures involving animals were performed according to the Guide for the Care and Use of Laboratory Animals (NIH Publication, 8th edition, 2011) and were approved by the ethic committees of Sun Yat-sen University.

ApoE−/− mice (8weeks; male; Vital River, Beijing, China) were housed in specific pathogen-free conditions and randomly allocated into either high-fat diet (15% lard, 20% sugar, and 1.2% Cholesterol; n = 5) or normal diet group (n = 5) for 12 weeks. High-fat diet was used to induce atherosclerosis and normal diet group served as the control group. After the modeling is completed, mice were weighted then anesthetized by intraperitoneal injection of 1% pentobarbital sodium. Regular vital signs (respiratory rate and pulse) but absence of toe-pinch reflex indicated the adequacy of anesthesia. Blood samples was collected for extracting Serum specimens were extracted from whole blood samples and stored at -80℃ until measurement. Aortic tissues were isolated for Western blotting and immunofluorescence staining. The aortic roots were processed into optimum cutting temperature compound (OCT) and sequentially sectioned into 8 μm-thick with a cryostat. Enzymatic kits (Jiancheng Biotechnology, Nanjing, China) were implemented for measurements of plasma total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.

Text S6 MEGASTROKE CONSORTIUM

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