SUPPLEMENTAL MATERIALS

PLASMA PROTEIN PROFILE OF CAROTID ARTERY ATHEROSCLEROSIS AND ATHEROSCLEROTIC OUTCOMES - META-ANALYSES AND MENDELIAN RANDOMIZATION ANALYSES

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Supplemental Table I. SNPs chosen from the SCALLOP study to be used as instrumental variables.
The SNPs are not in LD. * following the rs-number indicates a cis-SNP.

ADM	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	11:10363157:A_G	rs148339496*	A	G	.7287
	6:31239227:C_T	rs9264664	T	C	.6684
	4:187145222:C_G	rs4862669	C	G	.517
	2:163120823:C_T	rs12465701	T	C	.0208
AGRP	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	2:177544551:C_G	rs4894192	C	G	.6667
	12:115554085:A_AT	rs11451130	A	AT	.6108
CA-125	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	19:9136306:C_G	rs11672713*	C	G	.7221
	2:242728098:C_T	rs62193063	T	C	.1745
	16:828080:C_T	rs114590746	T	C	.0116
	2:242758326:A_G	rs2293761	A	G	.3809
MMP-12	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	19:54759361:C_T	rs12975366	T	C	.6016
	11:102721251:C_T	rs72981675*	T	C	.1374
	11:104661163:C_T	rs1201821	T	C	.8572
	13:72450627:C_T	rs117953762	T	C	.9808
GAL	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	17:67081278:A_G	rs77542162	A	G	.9815

	6:1690341:A_G	rs9405503	A	G	.9023
	3:12127827:A_G	rs307575	A	G	.2376
	2:60493485:A_G	rs4672375	A	G	.4165
NT-proBNP	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	1:11919271:A_G	rs198389*	A	G	.5961
CD40	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	19:57835252:C_T	rs4801216	T	C	.6029
	20:44747947:G_T	rs4810485**	T	G	.2631
	20:44243169:C_T	rs45497891*	T	C	.023
MCP-1	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	1:159175354:A_G	rs12075	A	G	.5596
	3:128321226:A_G	rs9811380	A	G	.7063
	3:46370803:C_T	rs2888526	T	C	.094
	17:32533423:A_T	rs12601658*	A	T	.2341
	1:189005771:C_T	rs189403619	T	C	.989
	3:42906116:C_T	rs2228467	T	C	.9289
	3:46215107:A_G	rs34198655	A	G	.0915
ECP	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	14:21385991:C_T	rs147307766*	T	C	.0414
	2:33319380:A_T	rs72793754	A	T	.8545
CASP-8	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	2:202150914:A_G	rs35550815*	A	G	.8723

	19:54321933:A_G	rs10424405	A	G	.7796
PAPPA	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	3:128306757:A_G	rs13089722	A	G	.1214
	11:54899333:A_C	rs2262535	A	C	.0401
	3:47220341:C_T	rs12497115	T	C	.1809
	7:2446680:A_T	rs7808353	A	T	.8314
	11:47534637:A_G	rs139689864	A	G	.9654
	9:119066203:C_T	rs17372936*	T	C	.7763
	11:57157405:A_G	rs490358	A	G	.2758
	12:111932800:C_T	rs7137828	T	C	.5314
	11:49726596:A_C	rs151199595	A	C	.0382
	3:126237413:C_T	rs1687479	T	C	.6638
	4:102896591:G_T	rs13109404	T	G	.9367
CD40-L	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	8:106590706:A_G	rs4602861	A	G	.7511
HSP-27	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	7:75861673:C_T	rs57272821*	T	C	.6242
	7:75930759:C_G	rs2868371**	C	G	.7405
TM	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	1:179526214:C_T	rs61747728	T	C	.0398
	20:22684265:C_T	rs13039845*	T	C	.7317
	19:36329387:A_G	rs71354106	A	G	.0688
	20:23028724:A_G	rs1042579**	A	G	.1994

	9:136143442:A_G	rs612169	A	G	.6245
GDF-15	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	19:18501034:C_T	rs1227734*	T	C	.1362
TIM-1 (KIM-1)	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	16:20392332:A_G	rs77924615	A	G	.198
	17:46683800:C_T	rs12952262	T	C	.1648
	15:58726744:C_G	rs261334	C	G	.7821
	8:126500031:C_G	rs28601761	C	G	.5823
	5:156472149:A_C	rs6555820*	A	C	.469
	17:66882466:G_T	rs4148005	T	G	.6873
	1:43741713:A_G	rs2991996	A	G	.4294
	15:39221710:A_G	rs2411218	A	G	.5815
IL-6	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	1:154426970:A_C	rs2228145	A	C	.6214
U-PAR	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	19:44156472:C_T	rs2302524**	T	C	.8425
	19:44292166:A_G	rs12463370*	A	G	.5487
	17:7173279:C_G	rs12449427	C	G	.2523
	11:126232385:C_T	rs3967200	T	C	.1462
	10:75682176:A_G	rs2688619	A	G	.4588
	4:187161211:C_T	rs66530140	T	C	.4796
	2:160708645:C_G	rs2162500	C	G	.4624

TRAIL-R2	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	8:22885331:A_T	rs2293400**	A	T	.6624
	8:22955307:C_G	rs4871846*	C	G	.6012
LOX-1	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	17:38140927:A_C	rs2305482	A	C	.4569
	12:10333347:A_G	rs10505752*	A	G	.1639
	1:27173449:C_T	rs6686271	T	C	.8383
	11:72945341:C_T	rs2511241	T	C	.9191
	3:141125186:A_G	rs1344674	A	G	.5582
MMP-10	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	11:102590777:A_G	rs2012390*	A	G	.7679
	11:102649482:C_T	rs17860955**	T	C	.9832
	19:49206674:A_G	rs601338	A	G	.4498
LEP	snpid	rsid	effect_allele_exposure	other_allele_exposure	eaf_exposure
	7:127898800:A_G	rs12537573*	A	G	.6117
	16:53803574:A_T	rs1558902	A	T	.4183

Supplemental Table II. Relationships between cardiovascular proteins and intima-media thickness of the common carotid artery (IMT-CCA) in the discovery analysis performed in the MDC study. This table only show the proteins with FDR<5% following adjustment for age and sex. Also data following further adjustment for cardiovascular (CV) risk factors are shown.

	Age and sex-adjusted			Adjusted for CV risk factors		
Protein	Beta	SE	*p*-value	Beta	SE	*p*-value
Hepatocyte growth factor (HGF)	.023	.003	1.00e-17	.013	.003	4.04e-06
Matrix metalloproteinase-12 (MMP-12)	.021	.003	6.84e-15	.013	.003	1.63e-06
T-cell immunoglobulin and mucin domain 1 (TIM-1)	.018	.003	5.40e-11	.008	.003	.004
Matrix metalloproteinase-7 (MMP-7)	.016	.003	3.00e-10	.01	.003	.000177
Urokinase plasminogen activator surface receptor (U-PAR)	.016	.003	4.40e-10	.01	.003	.0001467
Placenta growth factor (PlGF)	.015	.003	1.00e-08	.009	.003	.00043
Interleukin-6 (IL-6)	.015	.003	1.00e-08	.008	.003	.003
Growth/differentiation factor 15 (GDF-15)	.015	.003	2.30e-08	.009	.003	.002
C-X-C motif chemokine 6 (CXCL6)	.014	.003	6.00e-08	.01	.003	.0001228
Cathepsin D (CTSD)	.014	.003	9.60e-08	.003	.003	.292
Fibroblast growth factor 23 (FGF-23)	.014	.003	1.00e-07	.009	.003	.001
Vascular endothelial growth factor A (VEGF-A)	.014	.003	1.00e-07	.007	.003	.007
Cystatin-B (CSTB)	.014	.003	1.00e-07	.006	.003	.02
Tumor necrosis factor ligand superfamily member 14 (TNFSF14)	.014	.003	1.00e-07	.008	.003	.003
N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	.014	.003	1.04e-07	.015	.003	1.11e-08
Osteoprotegerin (OPG)	.014	.003	2.00e-07	.008	.003	.003
Caspase-8 (CASP-8)	.013	.003	2.25e-07	.008	.003	.001

Heparin-binding EGF-like growth factor (HB-EGF)	.013	.003	6.00e-07	.009	.003	.000294
Follistatin (FS)	.013	.003	6.61e-07	.006	.003	.025
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)	.013	.003	1.10e-06	.007	.003	.008
Lectin-like oxidized LDL receptor 1 (LOX-1)	.012	.003	1.30e-06	.007	.003	.01
Zscore: 169_ITGB1BP2	.012	.003	1.56e-06	.008	.002	.001
Interleukin-1 receptor antagonist protein (IL-1RA)	.012	.003	1.60e-06	.002	.003	.581
Platelet-derived growth factor subunit B (PDGF subunit B)	.012	.003	3.20e-06	.007	.003	.004
Interleukin-16 (IL-16)	.012	.003	3.40e-06	.005	.003	.036
Dickkopf-related protein 1 (DKK-1)	.012	.003	3.50e-06	.008	.003	.001
Interleukin-8 (IL-8)	.012	.003	6.50e-06	.007	.003	.005
Tumor necrosis factor receptor superfamily member 6 (FAS)	.012	.003	7.90e-06	.006	.003	.013
Adrenomedullin (AM)	.012	.003	8.60e-06	.006	.003	.038
Zscore: 172_SIRT2	.011	.003	9.10e-06	.007	.002	.003
Macrophage colony-stimulating factor 1 (CSF-1)	.011	.003	9.80e-06	.007	.003	.005
Tumor necrosis factor receptor 1 (TNF-R1)	.011	.003	.00002	.005	.003	.054
Epidermal growth factor (EGF)	.011	.003	.000039	.006	.003	.013
E-selectin (SELE)	.011	.003	.0000435	.002	.003	.374
C-C motif chemokine 20 (CCL20)	.01	.003	.0000462	.005	.003	.08
Proteinase-activated receptor 1 (PAR-1)	.01	.003	.0000536	.007	.002	.004
Platelet endothelial cell adhesion molecule (PECAM-1)	.01	.003	.0000947	.006	.003	.027
Heat shock 27 kDa protein (HSP 27)	.01	.003	.0001171	.006	.003	.011
TNF-related apoptosis-inducing ligand (TRAIL)	.01	.003	.0001769	.004	.003	.169

Fatty acid-binding protein 4 (FABP4)	.01	.003	.00026	-.002	.003	.582
C-X-C motif chemokine 16 (CXCL16)	.009	.003	.000284	.004	.003	.135
C-X-C motif chemokine 1 (CXCL1)	.009	.003	.0004191	.005	.003	.039
C-C motif chemokine 3 (CCL3)	.008	.003	.001	.002	.003	.348
Myeloperoxidase (MPO)	.009	.003	.001	.004	.003	.114
Interleukin-18 (IL-18)	.009	.003	.001	.003	.003	.323
CD40 ligand (CD40L)	.008	.003	.001	.004	.003	.1
Zscore: 192_NEMO	.009	.003	.001	.006	.003	.019
Cathepsin L1 (CTSL1)	.009	.003	.001	.003	.003	.19
Angiopoietin-1 receptor (TIE2)	.009	.003	.001	.004	.003	.106
C-C motif chemokine 4 (CCL4)	.008	.003	.001	.003	.003	.171
CD40L receptor (CD40)	.008	.003	.001	.005	.003	.056
Tumor necrosis factor receptor 2 (TNF-R2)	.008	.003	.003	.003	.003	.256
Spondin-1 (SPON1)	.008	.003	.003	.003	.003	.205
Matrix metalloproteinase-10 (MMP-10)	.008	.003	.003	.006	.003	.02
Kallikrein-11 (hK11)	.007	.003	.004	.007	.003	.007
Galanin peptides (GAL)	-.007	.003	.005	-.004	.003	.158
Leptin (LEP)	.009	.003	.006	-.006	.004	.163
Thrombomodulin (TM)	.007	.003	.007	.002	.003	.384
Stem cell factor (SCF)	-.007	.003	.011	-.002	.003	.523
Interleukin-6 receptor subunit alpha (IL-6RA)	.006	.003	.013	.002	.003	.541
Pappalysin-1 (PAPPA)	.007	.003	.014	.004	.003	.091
Monocyte chemotactic protein 1 (MCP-1)	.006	.003	.016	.003	.003	.302
Ovarian cancer-related tumor marker CA 125 (CA-125)	.006	.003	.016	.003	.003	.206
Matrix metalloproteinase-1 (MMP-1)	.006	.003	.017	.005	.003	.055
Vascular endothelial growth factor D (VEGF-D)	.006	.003	.02	.006	.003	.027

Eosinophil cationic protein (ECP)	.006	.003	.031	.002	.003	.514

Supplemental Table III. Relationships between cardiovascular proteins and intima-media thickness of the common carotid artery (IMT-CCA) in the secondary meta-analysis performed in all samples. This table only show the proteins with the Bonferroni-adjusted p-value<0.00058 following adjustment for age and sex. Also data following further adjustment for cardiovascular (CV) risk factors are shown.

	Age and sex-adjusted			Adjusted for CV risk factors		
Protein	Beta	SE	*p*-value	Beta	SE	*p*-value
C-X-C motif chemokine 6 (CXCL6)	.019136	.000966	<1.00e-20	-.0003077	.0009195	.7379182
Matrix metalloproteinase-12 (MMP-12)	.0086274	.0009674	4.75e-19	.0070895	.0009207	1.36e-14
Galanin peptides (GAL)	-.0066507	.0009664	5.89e-12	-.0043581	.0009218	2.27e-06
Matrix metalloproteinase-3 (MMP-3)	-.0059752	.0009745	8.69e-10	-.0040527	.0009244	.0000116
T-cell immunoglobulin and mucin domain 1 (TIM-1)	.0038917	.0009664	.0000565	.002177	.0009217	.0181727
N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	.0038128	.0009679	.0000817	.0038116	.0009134	.00003
CD40L receptor (CD40)	-.0037488	.000966	.0001041	-.0030464	.0009195	.0009227
Monocyte chemotactic protein 1 (MCP-1)	-.0036474	.0009664	.0001604	-.0022522	.0015258	.1399173
Caspase-8 (CASP-8)	-.0035877	.0009584	.0001814	-.0025357	.0009131	.0054852

Supplemental Table IV. Relationships between cardiovascular proteins and plaque of the common carotid artery (CCA) in the discovery analysis performed in the MDC study. This table only show the proteins with FDR<5% following adjustment for age and sex. Also data following further adjustment for cardiovascular (CV) risk factors are shown.

	Age and sex-adjusted			Adjusted for CV risk factors		
Protein	Beta	SE	*p*-value	Beta	SE	*p*-value
Matrix metalloproteinase-12 (MMP-12)	.243	.033	2.53e-13	.107	.036	.003
Growth/differentiation factor 15 (GDF-15)	.191	.034	2.03e-08	.082	.037	.024
Lectin-like oxidized LDL receptor 1 (LOX-1)	.15	.031	2.00e-06	.051	.033	.125
Urokinase plasminogen activator surface receptor (U-PAR)	.139	.032	.000012	.001	.035	.972
T-cell immunoglobulin and mucin domain 1 (TIM-1)	.142	.033	.0000165	.042	.035	.232
Leptin (LEP)	-.156	.039	.0000494	-.127	.052	.015
Stem cell factor (SCF)	-.122	.031	.0001	-.071	.034	.034
Interleukin-6 (IL-6)	.125	.032	.0001	.054	.035	.116
Hepatocyte growth factor (HGF)	.109	.033	.001	.016	.036	.653
Galanin peptides (GAL)	-.111	.032	.001	-.075	.034	.03
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)	.109	.033	.001	.021	.034	.537
Matrix metalloproteinase-10 (MMP-10)	.096	.031	.002	.009	.033	.786
Platelet endothelial cell adhesion molecule (PECAM-1)	-.085	.031	.007	-.117	.033	.00031

Supplemental Table V. Relationships between cardiovascular proteins and plaque of the common carotid artery in the secondary meta-analysis performed in all samples. This table only show the proteins with the Bonferroni-adjusted p-value<0.00058 following adjustment for age and sex. Also data following further adjustment for cardiovascular (CV) risk factors are shown.

	Age and sex-adjusted			Adjusted for CV risk factors		
Protein	Beta	SE	*p*-value	Beta	SE	*p*-value
Matrix metalloproteinase-12 (MMP-12)	.2476898	.022633	7.12e-28	.1608395	.0244375	4.65e-11
Growth/differentiation factor 15 (GDF-15)	.2017453	.0242145	7.98e-17	.1242752	.0265576	2.88e-06
T-cell immunoglobulin and mucin domain 1 (TIM-1)	.1478769	.0224153	4.19e-11	.0809469	.0240449	.0007613
Urokinase plasminogen activator surface receptor (U-PAR)	.1314875	.0219339	2.04e-09	.0530132	.0235323	.0242729
Lectin-like oxidized LDL receptor 1 (LOX-1)	.1280879	.0218167	4.33e-09	.062087	.0230768	.0071356
Interleukin-6 (IL-6)	.1286548	.0220108	5.06e-09	.0789739	.0238778	.0009416
Renin (REN)	.1200568	.0222867	7.17e-08	.1282493	.023854	7.60e-08
Matrix metalloproteinase-7 (MMP-7)	.1054806	.0210252	5.25e-07	.0479172	.0219947	.0293633
Osteoprotegerin (OPG)	.1147989	.0230127	6.08e-07	.0684991	.0243023	.004823
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)	.113087	.0231741	1.06e-06	.0572704	.0241544	.0177396
Growth hormone (GH)	.1194808	.0245569	1.14e-06	.1216194	.0261506	3.31e-06
Stem cell factor (SCF)	-.1036326	.0214536	1.36e-06	-.0482845	.0233011	.0382469
Leptin (LEP)	-.1213664	.0257292	2.39e-06	-.1434985	.0351148	.0000438
Matrix metalloproteinase-10 (MMP-10)	.0959627	.0212494	6.30e-06	.0469172	.0224864	.0369361
Hepatocyte growth factor (HGF)	.0992593	.0222543	8.19e-06	.03362	.0244219	.1686262
N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	.0907383	.0218535	.0000329	.0848782	.0227822	.0001948
Galanin peptides (GAL)	-.0900753	.0220996	.0000458	-.0471975	.0236347	.04583

Supplemental Table VI. Mendelian randomization analysis for proteins vs intima-media thickness in the common carotid artery (IMT-CCA). The Wald ratio is given for the cis-SNP.

ADM	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.021	-.043	.0009	.05986072
	IVW	.0016	-.0056	.009	.65874466
	Weighted median	.0003	-.0082	.009	.95112012
	Heterogeneity	Q-test = .11023551			.95
	Pleiotropy	.0029	.0003	.006	.03183598
	Wald ratio	-.0025	-.0126951	.0075371	.62
AGRP	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	-0.0001	-0.016	0.015	0.98
CA-125	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.0011	-.0074	.0051	.7181645
	IVW	.002	-.0022	.006	.34918146
	Weighted median	.0005	-.0042	.005	.82952325
	Heterogeneity	Q-test = .7653533			0.6820
	Pleiotropy	.0013	-.0006	.003	.18238378
	Wald ratio	.0096977	-.0016872	.0210825	0.095
MMP-12	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.0033	-.0082	.0016	.18765355
	IVW	-.0021	-.0046	0	.11050337
	Weighted median	-.0022	-.0048	0	.10047767

	Heterogeneity	Q-test = 3.7309537			0.1548
	Pleiotropy	.0008	-.0014	.003	.48603189
	Wald ratio	-.0022196	-.0047799	.0003407	0.089
GAL	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	.0066	-.0096	.0228	.42540727
	IVW	-.002	-.0075	.003	.4578023
	Weighted median	-.0032	-.0094	.003	.30304541
	Heterogeneity	Q-test = 1.927584			0.3814
	Pleiotropy	-.0016	-.0045	.001	.26799435
NT-proBNP	Test	Beta	CIlow	CIhigh	*P*-value
	Wald ratio	-.0141376	-.0209243	-.0073509	4.4e-05
CD40	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	0.001	-0.002	0.004	0.396
	Wald	.0012891	-.0176632	.0202413	0.894
MCP-1	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	.006	-.0078	.0197	.395936
	IVW	.0041	-.0026	.011	.23557432
	Weighted median	.0043	-.0035	.012	.28374138
	Heterogeneity	Q-test = 2.2002025			0.6990
	Pleiotropy	-.0003	-.0018	.001	.75611867
	Wald ratio	-.0063391	-.0312806	.0186024	0.618
ECP	Test	Beta	CIlow	CIhigh	*P*-value

	IVW	0.003	-0.004	0.010	0.436
	Wald ratio	.0039936	-.0038691	.0118564	0.319
CASP-8	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	0.003	-0.003	0.009	0.406
	Wald ratio	-.0010336	-.0111644	.0090973	0.842
PAPPA	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.0016	-.0079	.0047	.6156199
	IVW	-.0008	-.0046	.003	.65494535
	Weighted median	-.0015	-.0058	.003	.47686673
	Heterogeneity	Q-test = 6.5847285			0.6803
	Pleiotropy	.0002	-.0009	.001	.76703536
	Wald ratio	.0001064	-.0186593	.018872	0.99
CD40L	Test	Beta	CIlow	CIhigh	*P*-value
	Wald ratio	-.0143979	-.0380188	.009223	0.232
HSP-27	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	0.003	-0.002	0.008	0.227
	Wald ratio	.0026247	-.0025226	.0077719	0.32
TM	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	.0011	-.0061	.0083	.76519525
	IVW	.0001	-.0036	.004	.98804686
	Weighted median	.0001	-.004	.004	.98091861
	Heterogeneity	Q-test = .94707711			0.8141

	Pleiotropy	-.0003	-.0019	.001	.73493893
	Wald ratio	.0009975	-.0034018	.0053969	0.657
GDF-15	Test	Beta	CIlow	CIhigh	*P*-value
	Wald ratio	.0024397	-.003407	.0082864	0.413
TIM-1 (KIM-1)	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.0014	-.0062	.0034	.56696709
	IVW	-.0003	-.003	.002	.80687169
	Weighted median	-.0006	-.0034	.002	.6449583
	Heterogeneity	Q-test = 10.397451			0.1089
	Pleiotropy	.0003	-.0007	.001	.52608466
	Wald ratio	-.0004154	-.0032648	.0024341	0.775
IL-6	Test	Beta	CIlow	CIhigh	*P*-value
	Wald ratio	.0034345	-.0044334	.0113023	0.392
U-PAR	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	.0032	-.0369	.0434	.87484286
	IVW	.0005	-.0059	.007	.87939535
	Weighted median	.0034	-.0058	.013	.47245486
	Heterogeneity	Q-test = 10.574956			0.0605
	Pleiotropy	-.0003	-.004	.003	.89095638
	Wald ratio	.0089965	-.0060103	.0240034	0.240
TRAIL-R2	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	0.005	0.001	0.010	0.039

	Wald ratio	.0048796	-.0002341	.0099934	0.061
LOX-1	Test	Beta	CIlow	CIhigh	*P*-value
	MR Egger	-.0251	-.0843	.0341	.40604307
	IVW	-.0016	-.0101	.007	.70710332
	Weighted median	-.0069	-.018	.004	.22632227
	Heterogeneity	Q-test = 7.1765584			0.0665
	Pleiotropy	.0022	-.0032	.008	.42549637
	Wald ratio	-.0140713	-.0328733	.0047307	0.142
MMP-10	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	-0.003	-0.008	0.002	0.253
	Wald ratio	-0.005	-0.011	0.001	0.134
LEP	Test	Beta	CIlow	CIhigh	*P*-value
	IVW	0.011	-0.004	0.027	0.157
	Wald ratio	-0.004	-0.025	0.017	0.708

Supplemental Table VII. Mendelian randomization analysis for proteins vs plaque. The Wald ratio is given for the cis-SNP.

ADM	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	-.3598	-.9226	.203	.21015146
	IVW	-.0272	-.1959	.142	.75241995
	Weighted median	-.0322	-.2117	.147	.72482511
	Heterogeneity	Q-test = .055			0.97
	Pleiotropy	.0423	-.026	.111	.22457913
	Wald ratio	-.0767247	-.3057126	.1522632	0.511
AGRP	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.066	-0.302	0.433	0.727
CA-125	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.013	-0.125	0.151	0.853
	Wald ratio	-.1312036	-.4033294	.1409221	0.345
MMP-12	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	-.0582	-.1728	.0565	.31995942
	IVW	-.0507	-.11	.009	.09427343
	Weighted median	-.055	-.115	.005	.07263621
	Heterogeneity	Q-test = 3.66			0.1597
	Pleiotropy	.0049	-.0483	.058	.85705835

	Wald ratio	-.054968	-.115138	.005202	0.073
GAL	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	.1703	-.1578	.4984	.30898891
	IVW	.1129	-.0064	.232	.06354459
	Weighted median	.1199	-.0243	.264	.10305043
	Heterogeneity	Q-test = 1.70			0.4274
	Pleiotropy	-.0111	-.07	.048	.71302568
NT-proBNP	Test	Beta	CIlow	CIhigh	P-value
	Wald ratio	-.0480679	-.2006298	.1044941	0.537
CD40	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.044	-0.027	0.114	0.229
	Wald ratio	.0364905	-.0362215	.1092026	0.325
MCP-1	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	.1121	-.2004	.4246	.48204383
	IVW	-.0407	-.193	.112	.60040622
	Weighted median	-.0161	-.1992	.167	.86362596
	Heterogeneity	Q-test = 3.60			0.4619
	Pleiotropy	-.0208	-.0578	.016	.27237402
	Wald ratio	-.5118859	-1.132933	.1091614	0.106

ECP	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.029	-0.127	0.186	0.715
	Wald ratio	.0303514	-.1411608	.2018636	0.729
CASP-8	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.087	-0.056	0.231	0.233
	Wald ratio	-.0144703	-.2535302	.2245896	0.906
PAPPA	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	.0035	-.1491	.156	.96418686
	IVW	.01	-.079	.099	.82596516
	Weighted median	-.0079	-.1074	.092	.87579888
	Heterogeneity	Q-test = 7.87			0.54
	Pleiotropy	.0013	-.0234	.026	.91831104
	Wald ratio	-.1095745	-.5360287	.3168798	0.615
CD40-L	Test	Beta	CIlow	CIhigh	P-value
	Wald ratio	-.0366492	-.5755323	.5022339	0.894
HSP-27	Test	Beta	CIlow	CIhigh	P-value
	IVW	-0.089	-0.196	0.018	0.104
	Wald ratio	-.1003208	-.2108405	.0101989	0.075
TM	Test	Beta	CIlow	CIhigh	P-value

	MR Egger	-.09	-.3036	.1235	.40868774
	IVW	-.0126	-.0974	.072	.77066475
	Weighted median	-.0215	-.1097	.067	.63220423
	Heterogeneity	Q-test = 5.17			0.1594
	Pleiotropy	.021	-.0285	.071	.40506449
	Wald ratio	-.0289277	-.1291412	.0712858	0.572
GDF-15	Test	Beta	CIlow	CIhigh	P-value
	Wald ratio	-.1447547	-.2774255	-.0120838	0.032
TIM-1 (KIM-1)	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	-.037	-.1236	.0497	.40320932
	IVW	.0066	-.0561	.069	.83553837
	Weighted median	-.0028	-.0698	.064	.93496294
	Heterogeneity	Q-test = 2.2			0.8999
	Pleiotropy	.0127	-.0047	.03	.15300234
	Wald ratio	-.0101765	-.0777486	.0573955	0.768
IL-6	Test	Beta	CIlow	CIhigh	P-value
	Wald ratio	-.1614196	-.3445498	.0217107	0.084
U-PAR	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	-.3264	-.935	.2822	.29320363

	IVW	-.094	-.2392	.051	.20424098
	Weighted median	-.0269	-.2112	.157	.77437583
	Heterogeneity	Q-test = 4.3			0.4996
	Pleiotropy	.0222	-.0343	.079	.44098203
	Wald ratio	-.2858131	-.6247237	.0530974	0.098
TRAIL-R2	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.026	-0.084	0.137	0.642
	Wald ratio	.0312297	-.082286	.1447453	0.590
LOX-1	Test	Beta	CIlow	CIhigh	P-value
	MR Egger	.3064	-.686	1.2988	.54505471
	IVW	-.0818	-.2827	.119	.4246994
	Weighted median	-.1532	-.4059	.1	.23482173
	Heterogeneity	Q-test = 1.9			0.5755
	Pleiotropy	-.0361	-.1263	.054	.43362355
	Wald ratio	-.1857411	-.6227482	.2512661	0.405
MMP-10	Test	Beta	CIlow	CIhigh	P-value
	IVW	0.049	-0.068	0.166	0.408
	Wald ratio	0.032	-0.124	0.188	0.691
LEP	Test	Beta	CIlow	CIhigh	P-value
	IVW	-0.082	-0.420	0.257	0.637
	Wald ratio	-0.187	-0.631	0.258	0.411

Supplemental Table VIII. Basic information on incident cases and follow-up details in the different cohorts.

	MDC	PIVUS	CARDIPP	SAVA-control	IMPROVE
Number of incident myocardial infarction	447	84	25	39	116
Number of incident ischemic stroke	392	89	29	39	59
Number of incident myocardial infarction or ischemic strokes (combined end-point)	754	147	45	66	175
Median follow-up (and range) for combined endpoint (years)	23.2 (0.1-25.2)	15.0 (0.2-15.9)	7.4 (0.1-9.6)	5.0 (0.1-7.6)	3.02 (2.98-3.11)
Person years at risk for combined end-point (PYAR)	95992	11928	4596	5322	9846

Supplemental Table IX. Relationships between cardiovascular proteins and incident atherosclerotic cardiovascular disease (either myocardial infarction or ischemic stroke) in the discovery phase in the MDC study. This table only show the proteins with pFDR<0.05 following adjustment for age. HR= hazard ratio.

	Age and sex-adjusted				Adjusted for CV risk factors			
Protein	HR	95%CI low	95%CI high	p-value	HR	95%CI low	95%CI high	p-value
Caspase-8 (CASP-8)	1.29693	3.36356	4.002823	2.82e-14	1.248571	3.212341	3.803798	1.45e-10
Matrix metalloproteinase-12 (MMP-12)	1.303431	3.353485	4.075527	3.22e-12	1.192438	3.001163	3.64006	.000021
T-cell immunoglobulin and mucin domain 1 (TIM-1)	1.287883	3.306863	3.998823	1.97e-11	1.178214	2.971301	3.571551	.000042
Growth/differentiation factor 15 (GDF-15)	1.28146	3.273959	3.990833	3.12e-10	1.168826	2.929993	3.557294	.000236
Urokinase plasminogen activator surface receptor (U-PAR)	1.259859	3.218772	3.88064	1.17e-09	1.152577	2.89794	3.486854	.001
Hepatocyte growth factor (HGF)	1.221403	3.108064	3.732208	1.51e-07	1.074655	2.693927	3.205923	.082
Interleukin-1 receptor antagonist protein (IL-1RA)	1.214096	3.086383	3.695072	2.87e-07	1.100759	2.75385	3.306863	.024
Cathepsin D (CTSD)	1.203218	3.055673	3.654649	1.00e-06	1.065027	2.677812	3.167682	.116
Interleukin-6 (IL-6)	1.165325	2.980229	3.465996	3.00e-06	1.076807	2.721002	3.186745	.047
Lectin-like oxidized LDL receptor 1 (LOX-1)	1.17586	2.995167	3.521898	4.00e-06	1.107383	2.798266	3.287081	.006
Cathepsin L1 (CTSL1)	1.187678	3.016207	3.589454	4.00e-06	1.122996	2.837717	3.350133	.002
N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	1.181754	2.992173	3.578701	.000015	1.196021	3.028296	3.632787	4.00e-06
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)	1.116278	2.89215	3.234906	.000017	1.062899	2.712851	3.101854	.058

Adrenomedullin (AM)	1.182937	2.986195	3.589454	.000022	1.09856	2.75385	3.287081	.022
Cystatin-B (CSTB)	1.158354	2.935859	3.47641	.000077	1.060775	2.672462	3.142441	.13
Placenta growth factor (PlGF)	1.166491	2.941736	3.528949	.000101	1.085456	2.729177	3.234906	.039
Tumor necrosis factor receptor 1 (TNF-R1)	1.162997	2.935859	3.511348	.00012	1.071436	2.691235	3.186745	.085
Macrophage colony-stimulating factor 1 (CSF-1)	1.154884	2.924139	3.469463	.000141	1.091988	2.751098	3.244626	.023
Fibroblast growth factor 23 (FGF-23)	1.143393	2.89794	3.414394	.000236	1.073581	2.710139	3.177199	.061
Follistatin (FS)	1.145682	2.89794	3.431509	.000302	1.059715	2.672462	3.136163	.131
Tumor necrosis factor receptor 2 (TNF-R2)	1.145682	2.89794	3.431509	.000315	1.072508	2.702021	3.180378	.07
Stem cell factor (SCF)	.8772178	2.263699	2.565106	.00034	.9559975	2.425409	2.803868	.244
Vascular endothelial growth factor A (VEGF-A)	1.125244	2.851941	3.350133	.001	1.040811	2.630043	3.067921	.288
Galanin peptides (GAL)	.8842636	2.272771	2.593478	.001	.9436499	2.396478	2.770423	.139
C-C motif chemokine 20 (CCL20)	1.118513	2.849091	3.300256	.001	1.046028	2.651167	3.074063	.213
C-C motif chemokine 3 (CCL3)	1.116278	2.846243	3.29037	.001	1.074655	2.718282	3.170851	.05
Interleukin-8 (IL-8)	1.112934	2.826389	3.293662	.002	1.056541	2.675135	3.111174	.128
Resistin (RETN)	1.115162	2.826389	3.313483	.003	1.065027	2.693927	3.142441	.088
Fatty acid-binding protein 4 (FABP4)	1.12637	2.829217	3.383802	.003	1.015113	2.529445	3.037394	.737
Leptin (LEP)	1.134282	2.820742	3.455614	.006	1.013085	2.462064	3.120521	.833
Osteoprotegerin (OPG)	1.108491	2.795469	3.306863	.007	1.03977	2.622164	3.07099	.311
Interleukin-18 (IL-18)	1.097462	2.773195	3.25763	.012	1.011061	2.552313	2.974274	.784
Tissue-type plasminogen activator (t-PA)	1.099659	2.77597	3.267418	.012	1.025315	2.583125	3.022245	.53
Matrix metalloproteinase-7 (MMP-7)	1.10186	2.773195	3.283796	.013	1.015113	2.562543	2.989183	.704
Eosinophil cationic protein (ECP)	1.093081	2.764888	3.234906	.015	1.055485	2.664456	3.114286	.152

Myeloperoxidase (MPO)	1.093081	2.764888	3.234906	.015	1.043938	2.640584	3.074063	.245
Tumor necrosis factor ligand superfamily member 14 (TNFSF14)	1.086542	2.756606	3.209131	.019	1.019182	2.580544	2.989183	.605

Supplemental Table X. Relationships between cardiovascular proteins and incident atherosclerotic cardiovascular disease (either myocardial **infarction or ischemic stroke) in the secondary meta-analysis performed using all samples.** This table only show the proteins with p<0.00058 in the meta-analysis following adjustment for age and sex and p<0.05 for the p-value also adjusted for CV risk factors. HR= hazard ratio.

	Age and sex-adjusted				Adjusted for CV risk factors			
Protein	HR	95%CI low	95%CI high	p-value	HR	95%CI low	95%CI high	p-value
Matrix metalloproteinase-12 (MMP-12)	1.324515	1.248755	1.404871	8.57e-21	1.202559	1.128907	1.281016	1.06e-08
Growth/differentiation factor 15 (GDF-15)	1.307067	1.229887	1.38909	6.49e-18	1.181907	1.105645	1.263428	9.05e-07
T-cell immunoglobulin and mucin domain 1 (TIM-1)	1.26365	1.191341	1.340348	7.05e-15	1.159051	1.088634	1.234023	3.92e-06
Urokinase plasminogen activator surface receptor (U-PAR)	1.252502	1.179787	1.329698	1.61e-13	1.147482	1.076778	1.222829	.0000224
Interleukin-1 receptor antagonist protein (IL-1RA)	1.232943	1.163066	1.307019	2.00e-12	1.106741	1.035832	1.182504	.0026813
Interleukin-6 (IL-6)	1.197999	1.137395	1.261833	9.06e-12	1.102903	1.040307	1.169266	.0010178
Caspase-8 (CASP-8)	1.200119	1.137295	1.266414	2.94e-11	1.164389	1.102227	1.230058	5.41e-08
Hepatocyte growth factor (HGF)	1.222652	1.151791	1.297872	4.13e-11	1.075624	1.007826	1.147983	.0281872

N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	1.205935	1.138968	1.27684	1.33e-10	1.207319	1.139463	1.279215	1.73e-10
Cystatin-B (CSTB)	1.195346	1.129323	1.265229	7.49e-10	1.093263	1.028638	1.161947	.004127
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)	1.148929	1.098896	1.201239	9.87e-10	1.094285	1.036845	1.154907	.0010556
Lectin-like oxidized LDL receptor 1 (LOX-1)	1.185866	1.121422	1.254014	2.23e-09	1.196907	1.128169	1.269833	2.58e-09
Adrenomedullin (AM)	1.200169	1.126934	1.278164	1.35e-08	1.10572	1.036381	1.179698	.002354
Vascular endothelial growth factor A (VEGF-A)	1.167355	1.103222	1.235217	7.99e-08	1.085515	1.022872	1.151995	.0068164
Fibroblast growth factor 23 (FGF-23)	1.165049	1.101071	1.232743	1.15e-07	1.092145	1.029192	1.158949	.0036151
Tumor necrosis factor receptor 1 (TNF-R1)	1.177516	1.108369	1.250977	1.21e-07	1.088463	1.022796	1.158345	.0075856
Tumor necrosis factor receptor 2 (TNF-R2)	1.165905	1.098907	1.236987	3.70e-07	1.094236	1.029319	1.163247	.0039006
Follistatin (FS)	1.160758	1.093658	1.231975	9.25e-07	1.077557	1.013595	1.145556	.0167332
Placenta growth factor (PlGF)	1.162622	1.094306	1.235204	1.08e-06	1.087623	1.023109	1.156206	.0070967
Cathepsin L1 (CTSL1)	1.15399	1.088197	1.223761	1.73e-06	1.10677	1.042277	1.175254	.000927

Interleukin-8 (IL-8)	1.139499	1.0796	1.202722	2.14e-06	1.078184	1.019048	1.140752	.0089067
C-C motif chemokine 3 (CCL3)	1.131917	1.074657	1.192227	2.89e-06	1.086286	1.025154	1.151063	.0050998
Macrophage colony-stimulating factor 1 (CSF-1)	1.147142	1.080569	1.217817	6.79e-06	1.08522	1.021904	1.152459	.0076662
Resistin (RETN)	1.124967	1.062331	1.191297	.0000561	1.075952	1.014216	1.141446	.0151725
Protein S100-A12 (EN-RAGE)	1.179089	1.080398	1.286796	.0002208	1.144343	1.047005	1.250729	.0029513

Supplemental Table XI. Mendelian randomization of proteins vs coronary heart disease for the proteins being related to incident atherosclerotic disease in the observational part of the study. The SNPs used are given in Supplemental Table I.

	Only cis-SNP				Cis and trans-SNPs			
Protein	**beta**	**95%CI-lower**	**95%CI-higher**	***P*-value**	**beta**	**95%CI-lower**	**95%CI-higher**	***P*-value**
ADM	-0.144	-0.29	0	0.04765	-0.009	-0.1	0.09	0.85506
CCL3	-0.013	-0.07	0.04	0.63217	0.012	-0.04	0.06	0.64243
CSTB	0.022	-0.01	0.06	0.24206	0.019	-0.02	0.05	0.30183
FGF-23	0.005	-0.27	0.28	0.97345	0.06	-0.04	0.16	0.23263
FS	0.178	0.03	0.32	0.01682	0.046	-0.04	0.14	0.30817
GDF-15	-0.005	-0.08	0.07	0.89053	-0.023	-0.1	0.05	0.54571
IL-6	na	na	na	na	na	na	na	na
IL-8	0.16	-0.01	0.33	0.07295	0.16	-0.01	0.33	0.07295
LOX-1	-0.202	-0.42	0.01	0.06702	0.028	-0.06	0.12	0.53854
MMP-12	-0.058	-0.1	-0.02	0.0022	-0.054	-0.09	-0.02	0.00404
NT-proBNP	0.015	-0.07	0.1	0.74186	0.015	-0.07	0.1	0.74186
SCF	-0.036	-0.31	0.24	0.79547	-0.128	-0.18	-0.08	8.23E-04
TNF-R1	na	na	na	na	na	na	na	na
TNF-R2	-0.04	-0.19	0.11	0.61076	0.146	0.04	0.26	0.00906
TRAIL-R2	-0.013	-0.08	0.05	0.68636	-0.018	-0.08	0.05	0.58213
U-PAR	-0.042	-0.22	0.14	0.64995	0.047	-0.04	0.14	0.28947
VEGF-A	-0.044	-0.09	0	0.03881	-0.013	-0.05	0.02	0.49281

Supplemental Table XII. Mendelian randomization of proteins vs ischemic stroke for the proteins being related to incident atherosclerotic disease in the observational part of the study. The SNPs used are given in Supplemental Table I.

	Only cis-SNP				Cis and trans-SNPs			
Protein	**beta**	**95%CI-lower**	**95%CI-higher**	***P*-value**	**beta**	**95%CI-lower**	**95%CI-higher**	***P*-value**
ADM	-0.113	-0.27	0.04	0.14247	-0.167	-0.28	-0.06	0.00301
CCL3	-0.002	-0.06	0.05	0.93189	0.027	-0.03	0.08	0.32998
CSTB	-0.012	-0.05	0.03	0.56229	-0.016	-0.05	0.02	0.42934
FGF-23	-0.316	-0.61	-0.02	0.03801	0.011	-0.1	0.12	0.83304
FS	0.089	-0.07	0.24	0.25955	0.072	-0.02	0.17	0.1414
GDF-15	0.046	-0.03	0.12	0.2535	0.046	-0.03	0.12	0.2535
IL-6	na	na	na	na	na	na	na	na
IL-8	-0.034	-0.3	0.23	0.79795	-0.034	-0.3	0.23	0.79795
LOX-1	-0.011	-0.26	0.24	0.92917	-0.103	-0.2	-0.01	0.03283
MMP-12	-0.099	-0.14	-0.06	5.54E-07	-0.092	-0.13	-0.05	2.77E-03
NT-proBNP	-0.044	-0.14	0.05	0.36657	-0.044	-0.14	0.05	0.36657
SCF	0.278	-0.03	0.58	0.07245	-0.053	-0.11	0	0.05494
TNF-R1	-0.019	-0.28	0.24	0.88472	0.001	-0.16	0.17	0.98906
TNF-R2	-0.113	-0.27	0.04	0.14649	0.184	0.07	0.29	0.00103
TRAIL-R2	0.019	-0.05	0.09	0.60433	0.017	-0.05	0.09	0.63827
U-PAR	-0.075	-0.26	0.11	0.43294	0.023	-0.07	0.11	0.6138
VEGF-A	0.007	-0.04	0.05	0.76119	0.02	-0.02	0.06	0.3309

Major Resources Table

Data & Code Availability

Description	Source / Repository	Persistent ID / URL
Statistical code	GitHub	https://github.com/UppsalaClinicalResearchCenter/code_using_STATA16