

Protein Full Name	Abbreviation	Literature Inflammatory Categorization*	n available	% missing	Median (pg/ml)	25 %ile (pg/ml)	75th %ile (pg/ml)	Inter-CV, % QC1/QC2	Intra-CV, % QC1/QC2
Alpha-1-microglobulin	A1M		7277	1	11100000	8800000	14200000	7.9/7.3	3.9/3.9
Disintegrin and metalloproteinase domain-containing protein 15	ADAM15		7290	1	333	181	654	3.3/3.0	8.3/3.9
Adipsin	Adipsin		7285	1	863000	724000	1050000	16.3/19.0	5.1/4.3
Adrenomedullin	ADM	Yes	7312	1	297	252	352	10.9/6.3	5.0/6.3
Alpha-1 acid glycoprotein	AGP1	Yes	7334	0	670000000	555000000	805000000	4.6/5.7	8.1/8.3
Angiotensin-like 3	ANGPTL3		7318	0	23000	16800	30300	4.0/4.8	17.6/12.0
Apolipoprotein A-1	APOA1	Yes	7328	0	596000000	488000000	724000000	7.1/7.3	28.9/11.8
Apolipoprotein B	APOB		7265	1	684000000	569000000	823000000	13.4/13.4	3.0/6.6
Beta-2-microglobulin	B2M		7282	1	1450000	1240000	1710000	17.7/14.0	3.7/4.2
Butyrylcholinesterase	BCHE		7316	1	5990000	4990000	7140000	14.9/8.9	8.6/8.4
AMBIP-bikunin (BIKUNIN)	BIKUNIN		7308	1	178000000	156000000	207000000	6.3/9.8	2.9/7.1
N-terminal prohormone of brain natriuretic peptide	NTproBNP		7265	1	128	67.5	260	4.4/7.2	13.3/10.3
Complement C2	C2		7269	1	443000000	400000000	491000000	16.1/11.9	3.2/3.9
Monocyte differentiation antigen CD14	CD14	Yes	7267	1	15400000	13500000	17800000	15.4/14.5	3.5/3.6
Cluster of differentiation 163	CD163	Yes	7330	0	103000	72400	142000	3.4/4.3	8.5/4.8
Soluble CD40 ligand	CD40L	Yes	6348	14	36.8	25.4	55.7	3.1/4.9	14.8/14.1
CD5 antigen-like	CD5L	Yes	7339	0	208000	162000	266000	12.3/5.7	3.0/2.4
Cadherin 13	CDH13		7271	1	52100	25400	127000	2.7/4.7	9.3/5.2
Ceruloplasmin	Ceruloplasmin		7340	0	1270000000	1080000000	1535000000	5.0/3.5	9.4/5.4
Tetranectin	CLEC3B		7334	0	4540000	4040000	5040000	5.4/2.8	8.5/5.8
Clusterin**	Clusterin	Yes	7327	0	51100000	43800000	63600000	16.5/12.6	11.2/9.1
Contactin 1	CNTN1		7328	0	46300	39700	54300	6.1/5.3	7.8/7.6
Collagen, type XVIII, alpha 1	COL18A1		7297	1	134000	112000	158000	3.0/5.9	17.1/12.9
C-Reactive Protein	CRP	Yes	7284	1	848000	353000	2170000	14.5/9.9	5.1/8.2
Chemokine (C-X-C motif) ligand 16	CXCL16		7321	0	1090	933	1280	2.8/3.5	13.5/11.1
Cystatin-C	Cystatin C		7317	1	537000	478000	612000	9.8/5.1	3.2/3.1
Dipeptidyl dipeptidase	DPP4		7328	0	54000	41400	69300	2.5/2.3	7.8/3.4
EGF containing fibulin-like extracellular matrix protein 1	EFEMP1		7328	0	48500000	40100000	59800000	9.7/9.1	4.8/3.8
Fibrinogen	FBN		7311	1	449000000	377000000	537000000	9.7/7.0	3.8/2.9
Fibroblast growth factor 23	FGF23		6976	5	46.2	34.15	67.3	5.5/5.7	13.4/14.0
Glyceraldehyde 3-phosphate dehydrogenase	GAPDH		7283	0	71300	50500	96900	19.0/14.2	3.7/3.8
Growth differentiation factor 15	GDF15		7348	0	466	353	661	11.9/6.8	5.4/5.0
Granule membrane protein 140	GMP140	Yes	7332	0	15800	12900	19200	14.8/12.1	4.9/4.4
Glycoprotein V (platelet)	GP5		7324	0	875	737	1050	15.1/7.6	3.9/3.5
Granulin	GRN	Yes	7333	0	20000	17200	23300	6.4/4.4	4.2/1.2
Hemopexin	Hemopexin		7327	0	775000000	681000000	883000000	4.7/3.4	7.7/5.6
Insulin-like growth factor 1	IGF1	Yes	7276	1	6350	4540	8550	6.8/3.7	9.1/5.5
Insulin-like growth factor-binding protein 1	IGFBP1		7002	5	7140	3440	14300	6.9/5.4	2.5/2.5
Insulin-like growth factor binding protein 2	IGFBP2		7306	1	9730000	6180000	14700000	8.7/10.2	2.8/6.0
Insulin-like growth factor-binding protein 3	IGFBP3		7333	0	224000	190000	271000	15.2/18.0	3.9/4.4
Plasma kallikrein**	KLKB1	Yes	7343	0	6460000	5470000	7630000	16.2/24.5	10.2/3.2
LDL receptor	LDLR	Yes	7295	1	137000	68400	295000	3.4/3.9	8.9/4.7
Leptin	Leptin	Yes	6824	7	3610	1580	8880	9.6/3.2	15.8/7.0
Leptin receptor	Leptin-R		5673	23	2010	1040	3100	5.5/6.0	10.7/9.1
Lipoprotein(a)	LPA		7081	4	57200000	19900000	187000000	15.5/14.0	9.8/8.2
Melanoma cell adhesion molecule	MCAM		7291	1	145000	125000	171000	11.1/5.1	4.5/3.8
Monocyte chemoattractant molecule 1	MCP1	Yes	7316	1	166	135	202	3.3/6.1	11.1/13.7
Matrix metalloproteinase 8	MMP8	Yes	6343	14	309	155	517	8.3/5.6	16.9/13.9
Matrix metalloproteinase 9	MMP9	Yes	7339	0	46000	36100	63300	8.1/10.0	4.7/3.9
Myeloperoxidase	MPO		7348	0	9550	7430	12100	13.2/9.6	3.8/4.4
Myoglobin	Myoglobin		7333	0	12800	9970	16900	6.6/6.2	6.6/8.0
Neural cell adhesion molecule	NCAM		7326	0	279000	233000	333000	7.2/4.3	2.4/1.6
Notch 1	Notch1	Yes	7323	0	149	118	186	6.2/5.5	2.3/2.3
Neuronal cell adhesion molecule	NRCAM		6991	5	6410	2900	13800	3.4/2.5	9.0/4.4
Osteocalcin	Osteocalcin		7165	3	2750	1770	4090	5.1/6.3	8.8/10.7
Plasminogen activator inhibitor 1	PAI1	Yes	7331	0	16500	11400	23900	3.6/4.2	10.8/12.3
Peripheral myelin protein 2	PMP2		7299	1	521	322	864	3.1/4.7	5.8/6.6
Serum paraoxonase/arylesterase 1	PON1		7336	0	30100	21200	42500	7.4/7.6	4.2/3.9
Pro-platelet basic protein	PPBP	Yes	7306	1	1180000	616000	2340000	6.0/6.4	3.0/3.8
Lithostathine-1-alpha	REG1A		7326	0	85400	67000	113000	7.7/8.8	6.9/11.3
Resistin	Resistin		7299	1	6480	5270	7970	5.0/4.6	11.2/11.0
Serum amyloid A1	SAA1	Yes	7169	2	237000	128000	449500	21.9/23.4	13.6/8.5
Stromal cell-derived factor 1	SDF1		7310	1	344	268	453	15.6/8.4	4.8/7.0
Protein Z-dependent protease inhibitor	SERPINA10		7327	0	111000	95600	127000	7.0/6.0	3.4/4.7
Interleukin-6 receptor beta	sGP130	Yes	7345	0	58700	52100	66100	9.1/3.9	3.0/3.0
Intercellular adhesion molecule 1	siCAM1	Yes	7321	1	18700	16000	22300	11.2/9.3	4.5/4.5
Receptor for advanced glycation endproducts	sRAGE	Yes	7297	1	3440	2750	4240	5.6/4.0	14.5/15.0
Tissue inhibitor of metalloproteinases 1	TIMP1	Yes	7335	0	31400	27700	35900	13.2/8.5	4.3/5.4
TSC22D3 domain family member 3	TSC22D3		7088	4	1589	1266	1920	9.3/15.9	9.0/12.2
Uncarboxylated MGP	UCMGP		7310	0	45500	33300	61700	17.8/17.8	11.5/10.1
Vascular endothelial growth factor	VEGF		6028	18	21.9	12.7	37	4.3/6.0	14.7/14.0

Supplementary Table 1: Protein Biomarker Assay Characteristics and Inflammatory Dataset

*Proteins were categorized as inflammatory using the Gene Ontology AmiGo2 and QIAGEN Ingenuity Pathway Analysis tools and their inflammatory related terms.

**These proteins could not be clearly categorized as pro-inflammatory or anti-inflammatory and were excluded when generating the AIS.

Protein Full Name	Abbreviation	Common Gene ID	Uniprot KB ID	Gene Ontology Term ¹	Ingenuity Pathway Analysis Term ²
Adrenomedullin	ADM	ADM	P35318	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Alpha-1 acid glycoprotein	AGP1	ORM1	P02763	Inflammatory response	Inflammatory response
Apolipoprotein A-1	APOA1	APOA1	P02647	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Monocyte differentiation antigen CD14	CD14	CD14	P08571	Inflammatory response	Inflammation, Inflammatory response
Cluster of differentiation 163	CD163	CD163	Q86VB7	Inflammatory response	Inflammatory response
Soluble CD40 ligand	CD40L	CD40LG	P29965	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
CD5 antigen-like	CD5L	CD5L	O43866	Inflammatory response	Inflammation
Clusterin	Clusterin	CLU	P10909	Inflammatory response	Inflammation, Chronic inflammatory disorder
C-Reactive Protein	CRP	CRP	P02741	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Granule membrane protein 140	GMP140	SELP	P16109	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Granulin	GRN	GRN	P28799	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Insulin-like growth factor 1	IGF1	IGF1	P05019	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Plasma kallikrein**	KLKB1	KLKB1	P03952	Inflammatory response	Inflammation, Inflammatory response
LDL receptor	LDLR	LDLR	P01130	Inflammatory response	Inflammation, Inflammatory response
Leptin	Leptin	LEP	P41159	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Monocyte chemoattractant molecule 1	MCP1	CCL2	P13500	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Matrix metalloproteinase 8	MMP8	MMP8	P22894	Inflammatory response	Inflammation, Inflammatory response
Matrix metalloproteinase 9	MMP9	MMP9	P14780	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Notch 1	Notch1	NOTCH1	P46531	Inflammatory response	Inflammation, Inflammatory response
Plasminogen activator inhibitor 1	PAI1	SERPINE1	P05121	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Pro-platelet basic protein	PPBP	PPBP	P02775	Inflammatory response	Inflammatory response
Serum amyloid A1	SAA1	SAA1	P0DJJ8	Inflammatory response	Inflammatory response, Chronic inflammatory disorder
Interleukin-6 receptor beta	sGP130	IL6ST	P40189	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Intercellular adhesion molecule 1	sICAM1	ICAM1	P05362	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Receptor for advanced glycation endproducts	sRAGE	AGER	Q15109	Inflammatory response	Inflammation, Inflammatory response, Chronic inflammatory disorder
Tissue inhibitor of metalloproteinases 1	TIMP1	TIMP1	P01033	Inflammatory response	Inflammation, Chronic inflammatory disorder

Supplementary Table 2: Inflammatory Protein Identification

¹Using the Gene Ontology AmiGO2 tool, inflammatory terms in the "GO class (direct)" category were used to identify proteins with inflammatory annotations.

²Following an Ingenuity Pathway Analysis network overlay disease and functions analysis, inflammatory terms in the "Functions" category were used to identify proteins with inflammatory annotations.

AIS Score Breakdown

Protein	AIS = -20.28	AIS = + 20.28
SAA1	0.4468	0.9987
AGP1	-0.5481	-0.7737
Leptin	-1.8849	2.8137
ADM	-1.4840	1.0643
PAI1	-2.1465	1.6066
sICAM1	-0.9879	-0.4547
CD14	0.1729	0.2308
TIMP1	-0.1786	1.7700
GRN	-0.5705	1.0409
CD5L	1.0163	2.3500
GMP140	-1.6678	1.5486
MCP1	-1.8349	0.7506
MMP8	0.3314	1.8124
CD163	-1.6248	0.6313
CD40L	-0.0831	-1.0924
MMP9	-0.3717	2.0538
PPBP	-1.5059	-0.7029
LDLR	-1.2219	0.4540
Notch1	-0.4169	0.3042
sGP130	-0.8122	-0.1549
APOA1	-1.6908	0.2775
IGF1	-0.8255	1.7749
sRAGE	-0.9892	1.3561
CRP	-1.4047	0.6272

Supplementary Table 4: Aggregate Inflammatory Score Breakdown

The rank normalized values of the 24 inflammatory proteins used to generate Aggregate Inflammatory Scores are presented for two participants: AIS = -20.28 and +20.28. In accordance with the previously detailed modification of anti-inflammatory protein values, the values of sRAGE, IGF1, and APOA1 counter those of pro-inflammatory proteins. As such, high raw values for an anti-inflammatory protein are reflected as a negative value to demonstrate its anti-inflammatory effect. Reflecting the summation of pro-inflammatory and anti-inflammatory protein values, the scores illustrate differences in the degree of systemic inflammation between the two participants. The participant in a more pro-inflammatory state (AIS = +20.28) possesses higher levels of the flagship pro-inflammatory markers CRP and MCP1 and lower values of the flagship anti-inflammatory markers sRAGE, IGF1, and APOA1.

PCA Score Breakdown- PC1

Proteins	Loadings
TIMP1	224.71689
ADM	214.23554
GMP140	85.48873
CD14	80.80614
APOA1	26.80809
AGP1	4.06615
KLKB1	1.11161
MMP9	-1.98561
sGP130	-4.08385
Clusterin	-7.49015
SAA1	-15.39233
sRAGE	-24.88182
LDLR	-34.75381
CD5L	-35.59362
CRP	-36.61915
GRN	-37.34057
sICAM1	-37.56678
PPBP	-38.02289
PAI1	-38.25375
MCP1	-39.86615
Notch1	-41.27009
CD163	-45.00174
Leptin	-48.13498
IGF1	-49.30999
CD40L	-50.60084
MMP8	-51.06503

Supplementary Table 5: Principal Component Analysis PC1 Loadings

PCA was used to capture factors within the scaled, imputed dataset of 26 inflammatory proteins. The first principal component (PC1) captured the largest degree of variance within the protein dataset (89.7%) and was selected to construct the PCA inflammatory score. The PC1 loadings for the individual proteins are listed above.

Risk Factor	AIS			PCA Score		
	Beta (95% CI)	Standard Error	P Value	Beta (95% CI)	Standard Error	P Value
Triglycerides (mg/dL)	0.006 (0.006 - 0.006)	> 0.000	4.12E-69	> 0.000 (> 0.000 - > 0.000)	> 0.000	4.34E-14
Total Cholesterol (mg/dL)	0.184 (0.076 - 0.292)	0.055	8.93E-04	-0.01 (-0.014 - -0.006)	0.002	1.52E-06
HDL-Cholesterol (mg/dL)	-0.371 (-0.414 - -0.328)	0.022	3.66E-61	-0.004 (-0.006 - -0.002)	0.001	1.06E-05
Glucose (mg/dL)	0.118 (0.073 - 0.163)	0.023	1.92E-07	0.002 (0.000 - 0.004)	0.001	9.50E-03
SBP (mmHg)	0.019 (-0.010 - 0.048)	0.015	1.86E-01	-0.002 (-0.004 - 0.000)	0.001	1.81E-05
DBP (mmHg)	0.197 (0.158 - 0.236)	0.020	4.51E-22	0.004 (0.002 - 0.006)	0.001	3.48E-07

Model: Risk Factor = Inflammatory Score + Age + Sex + Cohort + BMI

Supplementary Table 6: Medication exclusion cross-sectional analysis

Two regression models were used utilizing either the AIS or the PCA score as the independent variable and the continuous risk factors as the dependent variable with adjustments for age, sex, cohort, and BMI. In the analysis of each risk factor, participants using medications that affect the respective risk factor were excluded: lipid-lowering, blood pressure, or diabetic medication. Only participants with fasting measurements were included in triglycerides, total cholesterol, HDL, and glucose analyses. Triglyceride levels were log transformed (\log_{10}) in order to obtain normality. Bonferroni corrected p value = 3.33E-03 (0.05/15).

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

A

Risk Factor	Discovery ¹			Validation ²		
	Beta ³ (95% CI)	Standard Error	P Value	Beta ³ (95% CI)	Standard Error	P Value
Age (years)	0.26 (0.22 - 0.30)	0.02	9.77E-54	0.26 (0.22 - 0.30)	0.02	4.29E-55
Sex (Male)	2.55 (1.96 - 3.14)	0.30	2.15E-17	1.97 (1.38 - 2.56)	0.30	3.23E-11
Never vs. Current Smokers	3.35 (2.51 - 4.19)	0.43	1.74E-14	3.17 (2.33 - 4.01)	0.43	2.78E-13
Never vs. Former Smokers	0.33 (-0.34 - 1.00)	0.34	3.42E-01	0.15 (-0.54 - 0.84)	0.35	6.72E-01
Former vs. Current Smokers	3.21 (2.31 - 4.11)	0.46	4.24E-12	3.19 (2.27 - 4.11)	0.47	2.12E-11

B

Risk Factor	Discovery ¹			Validation ²		
	Beta ⁴ (95% CI)	Standard Error	P Value	Beta ⁴ (95%CI)	Standard Error	P Value
Triglycerides (mg/dL)	0.009 (0.009 - 0.009)	> 0.000	4.52E-93	0.009 (0.009 - 0.009)	> 0.000	8.47E-101
Total Cholesterol (mg/dL)	0.364 (0.219 - 0.509)	0.074	8.39E-07	0.545 (0.400 - 0.690)	0.074	1.61E-13
HDL-Cholesterol (mg/dL)	-0.550 (-0.601 - -0.499)	0.026	1.40E-95	-0.530 (-0.583 - -0.477)	0.027	5.24E-79
Glucose (mg/dL)	0.529 (0.447 - 0.611)	0.042	3.75E-35	0.689 (0.601 - 0.777)	0.045	1.81E-50
SBP (mmHg)	0.402 (0.341 - 0.463)	0.031	1.60E-38	0.453 (0.392 - 0.514)	0.031	9.85E-46
DBP (mmHg)	0.206 (0.169 - 0.243)	0.019	3.88E-27	0.217 (0.180 - 0.254)	0.019	6.65E-30
BMI (kg/m ²)	0.261 (0.243 - 0.279)	0.009	4.26E-173	0.272 (0.254 - 0.290)	0.009	4.88E-179

C

Outcome	Discovery ¹			Validation ²		
	OR ⁵	95% CI	P Value	OR ⁵	95% CI	P Value
Hypertension	1.59	(1.47 - 1.72)	4.72E-29	1.76	(1.62 - 1.91)	3.69E-40
Diabetes	2.19	(1.88 - 2.56)	3.37E-23	2.60	(2.22 - 3.05)	4.33E-32
Obesity	2.63	(2.39 - 2.90)	1.76E-85	2.79	(2.53 - 3.08)	2.65E-92

Note: Replication threshold: $p < 3.33 \times 10^{-3} = 0.05/15$ traits

¹Total study population of 7,287 participants split by pedigree (n=3,645)

²Total study population of 7,287 participants split by pedigree (n=3,642)

³Model: AIS = Age/Sex/Smoking Status + Age + Sex + Cohort

⁴Model: Risk Factor = AIS + Age + Sex + Cohort

⁵Model: Outcome = AIS + Age + Sex + Cohort

Supplementary Table 7: AIS: Internal Validation of Cross-sectional Associations with Cardiometabolic Risk Factors

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

A

Risk Factor	Discovery ¹			Validation ²		
	Beta ³	Standard Error	P Value	Beta ³	Standard Error	P Value
Age (years)	6.74 (6.13 - 7.35)	0.31	1.14E-100	6.30 (5.71 - 6.89)	0.30	1.74E-90
Sex (Male)	3.00 (-7.88 - 13.88)	5.55	5.89E-01	-4.69 (-15.69 - 6.31)	5.61	4.03E-01
Never vs. Current Smokers	26.40 (11.05 - 41.75)	7.83	7.53E-04	32.75 (17.83 - 47.67)	7.61	1.76E-05
Never vs. Former Smokers	-4.87 (-17.51 - 7.77)	6.45	4.50E-01	5.56 (-7.30 - 18.42)	6.56	3.97E-01
Former vs. Current Smokers	35.30 (17.84 - 52.76)	8.91	7.67E-05	33.96 (14.83 - 53.09)	9.76	5.11E-04

B

Risk Factor	Discovery ¹			Validation ²		
	Beta ⁴	Standard Error	P Value	Beta ⁴	Standard Error	P Value
Triglycerides (mg/dL)	> 0.000 (> 0.000 - > 0.000)	> 0.000	5.98E-19	> 0.000 (> 0.000 - > 0.000)	> 0.000	1.20E-32
Total Cholesterol (mg/dL)	-0.011 (-0.019 - -0.003)	0.004	4.48E-03	0.002 (-0.006 - 0.010)	0.004	5.30E-01
HDL-Cholesterol (mg/dL)	-0.013 (-0.015 - -0.011)	0.001	1.10E-19	-0.012 (-0.016 - -0.008)	0.002	2.42E-14
Glucose (mg/dL)	0.020 (0.016 - 0.024)	0.002	3.46E-17	0.021 (0.017 - 0.025)	0.002	1.00E-17
SBP (mmHg)	0.015 (0.011 - 0.019)	0.002	2.73E-19	0.019 (0.015 - 0.023)	0.002	3.95E-30
DBP (mmHg)	0.002 (0.000 - 0.004)	0.001	7.60E-02	0.006 (0.004 - 0.008)	0.001	4.07E-08
BMI (kg/m ²)	0.008 (0.006 - 0.010)	0.001	6.80E-48	0.008 (0.006 - 0.010)	0.001	5.95E-57

C

Outcome	Discovery ¹			Validation ²		
	OR ⁵	95% CI	P Value	OR ⁵	95% CI	P Value
Hypertension	1.36	(1.24 - 1.49)	4.26E-11	1.46	(1.33 - 1.60)	3.90E-16
Diabetes	1.61	(1.40 - 1.84)	8.15E-12	1.63	(1.43 - 1.86)	1.21E-13
Obesity	1.63	(1.49 - 1.79)	5.73E-26	1.77	(1.62 - 1.95)	6.98E-34

Note: Replication threshold: $p < 3.33 \times 10^{-3} = 0.05/15$ traits

¹Total study population of 7,287 participants split by pedigree (n=3,645)

²Total study population of 7,287 participants split by pedigree (n=3,642)

³ Model: PCA Score = Age/Sex/Smoking Status + Age + Sex + Cohort

⁴ Model: Risk Factor = PCA Score + Age + Sex + Cohort

⁵ Model: Outcome = PCA Score + Age + Sex + Cohort

Supplementary Table 8: Principal Component Analysis Score: Internal Validation of Cross-sectional Associations with Cardiometabolic Risk Factors

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

Outcome	AIS			PCA Score		
	OR	95% CI	P Value	OR	95% CI	P Value
New Onset Hypertension	1.20	(1.08 - 1.33)	9.90E-04	1.17	(1.03 - 1.32)	1.33E-02
New Onset Diabetes	1.09	(0.93 - 1.28)	2.96E-01	0.94	(0.81 - 1.10)	4.51E-01

Note: Outcome = Inflammatory Score + Baseline Age + Sex + Cohort + Years to Follow-up Exam
+ Relevant Risk Factor (baseline SBP and DBP for hypertension, baseline glucose for diabetes, and
baseline BMI for obesity) + Baseline BMI

Supplementary Table 9: Logistic Regression: Prospective Associations of PCA and AIS Scores with New-onset Hypertension, Diabetes, and Obesity with BMI Adjustments

Logistic regression models were used to explore the prospective associations of the AIS and PCA score with new-onset hypertension and diabetes with an additional adjustment for baseline BMI. There were 948 new-onset cases of hypertension of the 3,220 participants at risk with follow-up events data and 306 new-onset cases of diabetes of the 5,709 participants at risk with follow-up events data. Odds ratios (OR) are presented per 1-SD increase in the respective inflammatory score.

Outcome	OR	95% CI	P Value
New Onset Hypertension	1.22	(1.09 - 1.36)	6.23E-04
New Onset Diabetes	1.04	(0.88 - 1.23)	6.64E-01

Model: Outcome = Inflammatory Score + Baseline Age + Sex + Cohort + Years to Follow-up Exam + Relevant Risk Factor (baseline SBP and DBP for hypertension and baseline glucose for diabetes) + Baseline BMI + Baseline hsCRP

Supplementary Table 10: AIS and CRP Sensitivity Analyses

To investigate the independence of the AIS from the predictive capabilities of CRP, the prospective analysis of the AIS and new-onset hypertension, diabetes, and obesity at the follow-up exam was repeated but with the additional adjustment of baseline BMI and baseline hsCRP levels. Odds ratios (OR) are presented per 1-SD increase in the AIS.

Outcome	OR	95% CI	P Value
New Onset Hypertension	1.18	(1.04 - 1.33)	9.50E-03
New Onset Diabetes	0.94	(0.80 - 1.09)	4.23E-01

Model: Outcome = Inflammatory Score + Baseline Age + Sex + Cohort + Years to Follow-up Exam + Relevant Risk Factor (baseline SBP and DBP for hypertension and baseline glucose for diabetes) + Baseline BMI + Baseline hsCRP

Supplementary Table 11: PCA Score and CRP Sensitivity Analyses

To investigate the independence of the PCA score from the predictive capabilities of CRP, the prospective analysis of the PCA score and new-onset hypertension and diabetes at the follow-up exam was repeated but with the additional adjustment of baseline BMI and baseline hsCRP levels. Odds ratios (OR) are presented per 1-SD increase in the PCA score.

Primary Outcomes ²	AIS			PCA Score			hsCRP ¹		
	HR ⁴	95% CI	P Value	HR ⁴	95% CI	P Value	HR ⁴	95% CI	P Value
New-onset CVD	1.25	1.14 - 1.37	1.21E-06	1.22	1.13 - 1.33	8.81E-07	1.12	1.06 - 1.19	1.21E-04
All-cause Mortality	1.32	1.23 - 1.42	1.20E-14	1.40	1.31 - 1.49	< 1.00E-20	1.06	1.02 - 1.09	6.82E-04
Secondary Outcomes³									
Coronary Heart Disease	1.09	0.95 - 1.25	2.20E-01	< 1.00	0.87 - 1.14	9.67E-01	1.11	1.02 - 1.22	1.61E-02
Heart Failure	1.54	1.36 - 1.74	1.83E-11	1.52	1.37 - 1.69	2.30E-15	1.09	1.04 - 1.14	7.63E-05
Atherothrombotic Stroke	1.22	0.98 - 1.52	7.74E-02	1.26	1.04 - 1.52	1.81E-02	0.93	0.72 - 1.19	5.87E-01
Revascularization Procedure	1.23	1.09 - 1.40	1.11E-03	1.14	1.02 - 1.28	2.60E-02	1.08	1.03 - 1.13	6.83E-04
CVD Death	1.42	1.22 - 1.64	3.43E-06	1.61	1.42 - 1.81	8.48E-15	1.09	1.03 - 1.15	1.84E-03

¹high sensitivity CRP (mg/L)

²All-cause Mortality: 1070 events / 3488 at risk; New-onset CVD: 627 events / 3101 at risk

³Coronary Heart Disease: 288 events / 3188 at risk; Heart Failure: 319 events / 3465 at risk; Atherothrombotic Stroke: 109 events / 3453 at risk; Revascularization Procedure: 332 events / 3494 at risk; CVD Death: 249 events / 3453 at risk

⁴Hazard ratios are presented per 1-SD increase in the respective inflammatory score

Supplementary Table 12: Proportional Hazards Regression: Associations of AIS, PCA Score, and high sensitivity CRP with New-onset All-cause Mortality and Cardiovascular Disease

Risk Factor*	Beta	Standard Error	P Value
Age (years)	0.03 (0.03 - 0.03)	< 0.01	2.22E-27
Sex	0.41 (0.29 - 0.53)	0.06	2.50E-13
Never vs Current Smokers	1.22 (1.06 - 1.38)	0.08	8.64E-53
Never vs Former Smokers	0.05 (-0.07 - 0.17)	0.06	4.15E-01
Former vs Current Smokers	1.27 (1.09 - 1.45)	0.09	9.22E-48

Risk Factor**	Beta	Standard Error	P Value
Triglycerides (mg/dL)	0.02 (0.02 - 0.02)	< 0.01	9.46E-82
Total Cholesterol (mg/dL)	-0.22 (-0.61 - 0.17)	0.20	2.62E-01
HDL (mg/dL)	-1.92 (-2.06 - -1.78)	0.07	1.22E-163
Glucose (mg/dL)	0.91 (0.67 - 1.15)	0.12	1.16E-14
SBP (mmHg)	0.57 (0.41 - 0.73)	0.08	4.19E-12
DBP (mmHg)	0.09 (-0.01 - 0.19)	0.05	6.41E-02

Outcome***	OR	95% CI	P Value
New Onset Hypertension	1.32	(1.20 - 1.45)	4.74E-09
New Onset Diabetes	1.35	(1.17 - 1.55)	3.01E-05
New Onset Obesity	< 1.00	(0.87 - 1.14)	9.40E-01

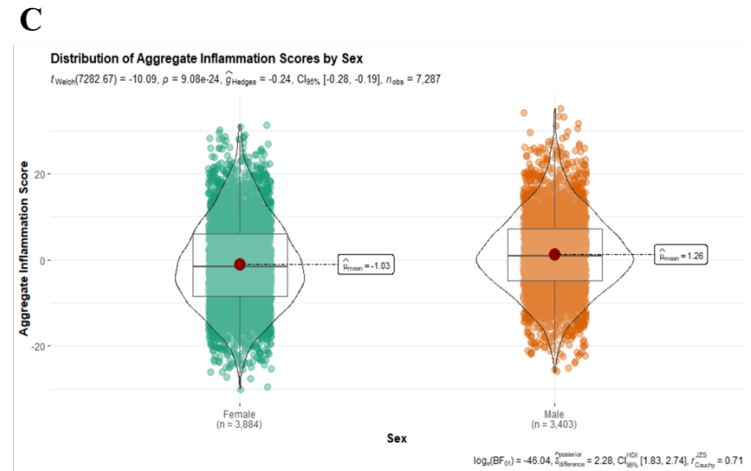
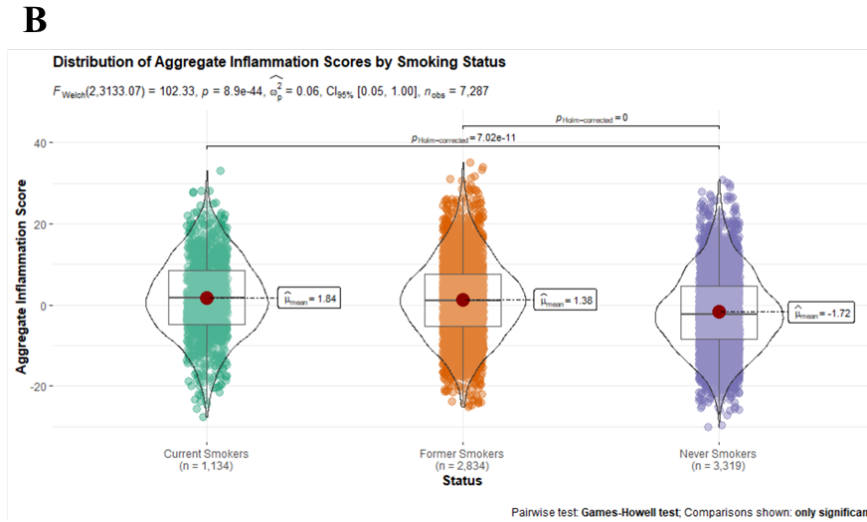
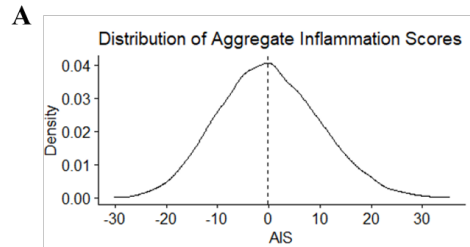
*Cross sectional analyses: Model 2 (Pathway AIS = Risk Factor + Age + Sex + Cohort + BMI)

**Cross sectional analyses: Model 2 (Risk Factor = Pathway AIS + Age + Sex + Cohort + BMI)

***Prospective analyses: Model 2 (Outcome = Pathway AIS + Baseline Age + Sex + Cohort + Years to Follow-up Exam + Relevant Risk Factor (baseline blood pressure, glucose, or BMI))

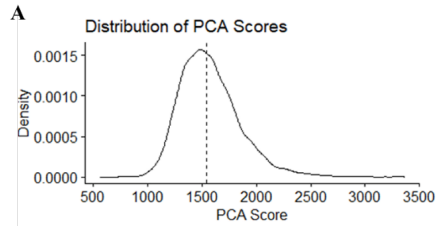
Supplementary Table 13: Complement System Pathway AIS Associations with Cardiometabolic Risk Factors and New Onset of Disease

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

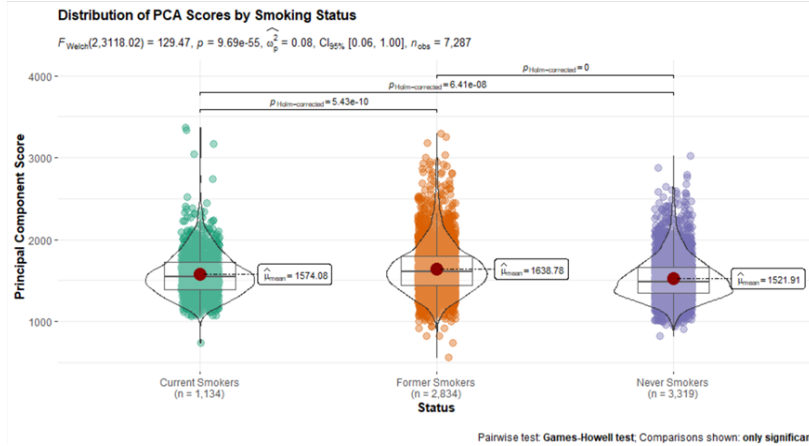


Supplementary Figure 1: Distribution of Aggregate Inflammation Scores (AIS) in the study population.

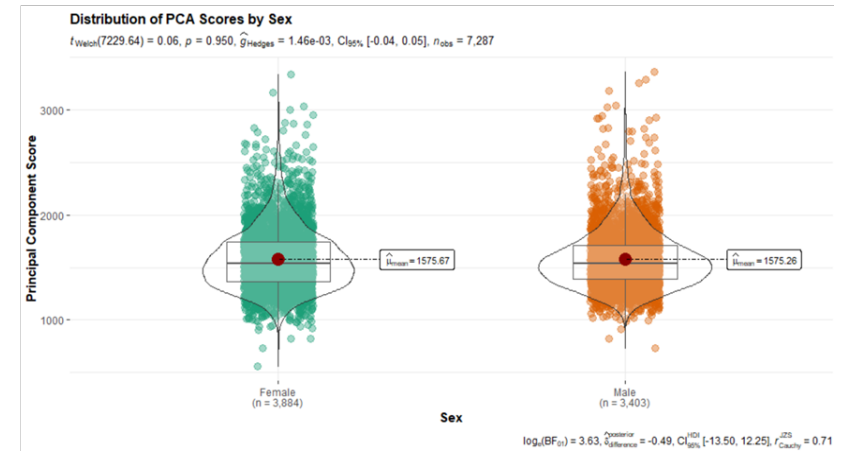
(A) Density plot of AIS for the 7,287 participants. The dashed vertical line denotes the median AIS (-0.270) in the total population. (B) Boxplots comparing the distributions of the AIS by smoking status (current smokers, former smokers, and never smokers). Statistically significant differences in AIS were observed between current and never smokers and between former and never smokers. Current smokers had the highest mean AIS. (C) Boxplots comparing the distributions of the AIS by sex. A statistically significant difference in mean AIS was observed between males and females, with males having greater scores.



B

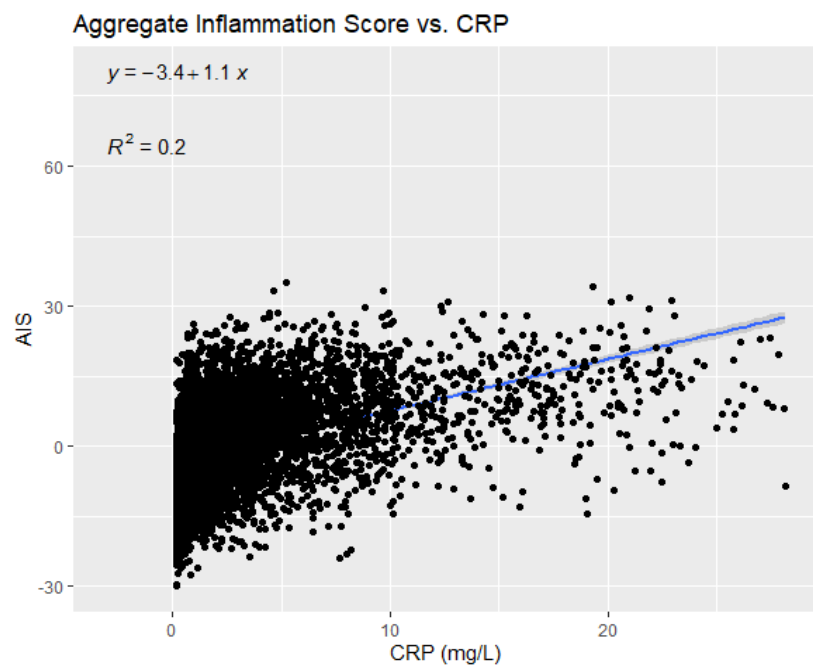


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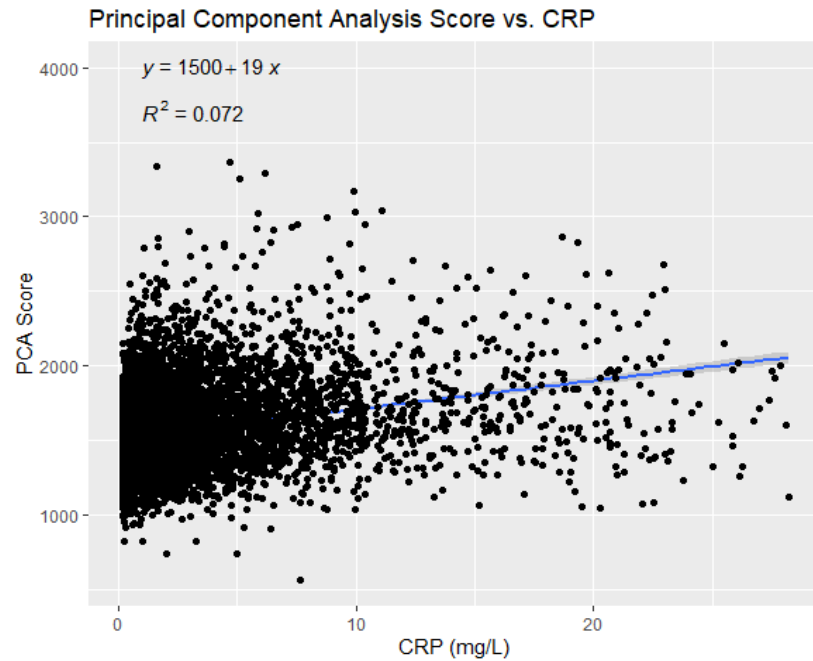
Supplementary Figure 2: Distribution of Principal Component Analysis (PCA) scores in the study population.

(A) Density plot of PCA scores for the 7,287 participants. The dashed vertical line denotes the median PCA score (1538.931) in the total population. (B) Boxplots comparing the distributions of the PCA scores by smoking status (current smokers, former smokers, and never smokers). Statistically significant differences in PCA scores were observed between all smoking groups, with current smokers having the highest mean PCA scores. (C) Boxplots comparing the distributions of the PCA score by sex. No statistically significant difference in PCA scores were observed between males and females.



Supplementary Figure 3: Correlations between AIS and CRP

The relationship between participant AIS and their CRP levels was explored. The high sensitivity CRP (hsCRP) levels were measured at baseline using a different protein measurement assay than the CRP data that was used to contrast the inflammatory scores. The Pearson coefficient of correlation between the PCA scores and hsCRP levels demonstrated a moderate correlation (0.45). Linear regression analyses demonstrated a moderate correlation between the AIS and hsCRP levels.



Supplementary Figure 4: Correlations between PCA Score and CRP

The relationship between participant PCA scores and their CRP levels was explored. The high sensitivity CRP (hsCRP) levels were measured at baseline using a different protein measurement assay than the CRP data that was used to contrast the inflammatory scores. The Pearson coefficient of correlation between the PCA scores and hsCRP levels demonstrated a moderately weak correlation (0.27). Linear regression analyses demonstrated a moderate correlation between the PCA score and hsCRP levels.