GlycA and CRP are genetically correlated: insight into the genetic architecture of inflammageing.

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Supplementary Material.

Table S1. List of 70 inflammatory mediators presented from the Olink 96 panel

Inflammatory Factors
TNF-related_apoptosis-inducing_ligand
Adenosine_deaminase
Axin-1
Caspase_8
Chemokine_C-C_motif_ligand_11
Chemokine_C-C_motif_ligand_19
Chemokine_C-C_motif_ligand_20
Chemokine_C-C_motif_ligand_23
Chemokine_C-C_motif_ligand_25
Chemokine_C-C_motif_ligand_28
Chemokine_C-C_motif_ligand_3
Chemokine_C-C_motif_ligand_4
chemokine_C-X3-C_motif_ligand_1
cluster_of_differentiation_244
cluster_of_differentiation_5
cluster_of_differentiation_6
cluster_of_differentiation_6
cluster_of_differentiation_8_alpha
Colony_Stimulating_Factor_1
CUB_domain_containing_protein_1
C-X-C_motif_chemokine_11
C-X-C_motif_chemokine_ligand_1
C-X-C_motif_chemokine_ligand_10
C-X-C_motif_chemokine_ligand_5
C-X-C_motif_chemokine_ligand_6
C-X-C_motif_chemokine_ligand_9
Cystatin_D
Delta_and_Notch-like_epidermal_growth-factor-related_receptor
EN-RAGE
Fibroblast_Growth_Factor-21
Fibroblast_Growth-Factor-19
Flt-3_Ligand
Hepatocyte_Growth_Factor

Inteleukin_6
Interferon_gamma
Interleukin_10
Interleukin_10RB
Interleukin_12B
Interleukin_15RA
Interleukin_17C
Interleukin_18
Interleukin_18R1
Interleukin_7
Interleukin_8
latency-associated_peptide_TGF_beta1
Leukemia_inhibitory_factor_receptor
matrix_metalloproteinases-1
matrix_metalloproteinases-10
Monocyte_Chemoattractant_Protein-1
Monocyte_Chemoattractant_Protein-2
Monocyte_Chemoattractant_Protein-4
Neurotrophin-3
Oncostatin_M
Osteoprotegerin
Programmed_death-ligand_1
Signaling_Lymphocytic_Activation_Molecule_Family_Member_1
Sirtuin_2
STAM_Binding_Protein
Stem_cell_factor
Sulfotransferase_1A1
TNF_Receptor_Superfamily_Member_9
TNF_Superfamily_Member_14
TNF-related_activation-induced_cytokine
TNF-related_weak_inducer_of_apoptosis
Transforming_growth_factor_alpha
Tumor_necrosis_factor
Tumor_Necrosis_Factor_B
Urokinase-type_plasminogen-activator
Vascular_Endothelial_Growth_Factor_A
X4E_BP1

Table S2. Correlations between **GlycA** and Inflammatory Mediators

Variable	GlycA Correlations	GlycA SE	GlycA p-values
ADA	0.0355	0.0259	1.70E-01
AXIN1	0.0368	0.0257	1.52E-01
CASP.8	0.0884	0.0256	5.52E-04
CCL11	-0.0062	0.0270	8.19E-01
CCL19	0.1425	0.0284	1.14E-08
CCL20	0.0844	0.0258	1.10E-03
CCL23	0.1844	0.0254	6.14E-13
CCL25	-0.0748	0.0272	6.11E-03
CCL28	-0.0709	0.0266	7.68E-04
CCL3	0.1844	0.0254	6.14E-13
CCL4	0.0908	0.0255	3.83E-04
CD244	0.0272	0.0257	2.91E-01
CD40	0.1153	0.0256	7.08E-06
CD5	0.1101	0.0256	1.85E-05
CD6	0.0210	0.0263	4.25E-01
CD8A	0.0191	0.0249	4.45E-01
CDCP1	0.0931	0.0299	1.91E-03
CSF.1	0.1348	0.0256	1.56E-07
CST5	-0.0239	0.0265	3.68E-01
CX3CL1	-0.0458	0.0255	7.23E-02
CXCL1	0.0563	0.0257	2.85E-02
CXCL10	0.0283	0.0259	2.76E-01
CXCL11	0.0938	0.0251	1.89E-04
CXCL5	0.0813	0.0255	1.46E-03
CXCL6	0.0453	0.0258	7.95E-02
CXCL9	0.0020	0.0282	9.42E-01
DNER	-0.1279	0.0256	6.81E-07
EN.RAGE	0.1056	0.0260	5.07E-05
FGF.19	0.0109	0.0259	6.74E-01
FGF.21	0.1774	0.0255	4.78E-12
Flt3L	-0.0235	0.0267	3.79E-01
HGF	0.2368	0.0260	<2.00E-16
IFN.gamma	0.0306	0.0254	2.35E-01
IL.10RB	0.1117	0.0255	1.28E-05
IL.12B	0.0843	0.0257	1.07E-03

IL.15RA	0.1108	0.0281	8.54E-05
IL.17C	-0.0201	0.0276	4.68E-01
IL.18R1	0.2325	0.0244	<2.00E-16
IL10	0.0693	0.0261	7.96E-03
IL18	0.0850	0.0256	9.18E-04
IL6	0.1670	0.0316	1.48E-07
IL7	0.0994	0.0262	1.52E-04
IL8	0.0880	0.0266	9.62E-04
LAP.TGF.beta.1	0.0968	0.0256	1.59E-04
LIF.R	-0.0571	0.0262	2.91E-02
MCP.1	0.0681	0.0260	8.95E-03
MCP.2	0.0770	0.0260	3.14E-03
MCP.4	0.0438	0.0257	8.89E-02
MMP.1	0.0772	0.0252	2.22E-03
MMP.10	0.0814	0.0256	1.50E-03
NT.3	-0.0534	0.0252	3.40E-02
OPG	0.0271	0.0271	3.18E-01
OSM	0.2153	0.0255	<2.00E-16
PD.L1	0.0894	0.0254	4.46E-04
SCF	-0.0109	0.0260	6.76E-01
SIRT2	0.0315	0.0280	2.61E-01
SLAMF1	0.0670	0.0266	1.18E-02
ST1A1	0.0743	0.0257	3.93E-03
STAMBP	0.0495	0.0258	5.51E-02
TGF.alpha	0.1283	0.0259	8.21E-07
TNF	0.1054	0.0255	3.75E-06
TNFB	-0.0168	0.0252	5.06E-01
TNFRSF9	0.0455	0.0263	8.36E-02
TNFSF14	0.2049	0.0251	7.07E-16
TRAIL	0.0230	0.0258	3.72E-01
TRANCE	0.0671	0.0255	8.68E-03
TWEAK	-0.1278	0.0258	7.81E-07
uPA	-0.0931	0.0262	3.94E-04
VEGFA	0.1965	0.0259	5.32E-14
X4E.BP1	0.0511	0.0253	4.39E-02

Correlations were adjusted for age and standardized.

Of the 70 correlations, 44 are significantly correlated with GlycA

Table S3. Correlations between hsCRP and inflammatory mediators

Variable	hsCRP correlations	hsCRP SE	hsCRP p-values
ADA	-0.0204	0.0286	4.77E-01
AXIN1	0.0520	0.0282	6.52E-02
CASP.8	0.0073	0.0282	7.95E-01
CCL11	-0.0022	0.0996	9.42E-01
CCL19	0.1462	0.0274	1.10E-07
CCL20	0.0856	0.0274	1.84E-03
CCL23	0.0516	0.0285	7.06E-02
CCL25	-0.0015	0.0300	9.61E-01
CCL28	-0.0280	0.0296	3.44E-01
CCL3	0.1343	0.0285	2.59E-06
CCL4	0.0997	0.0283	4.46E-04
CD244	0.0492	0.2821	8.16E-02
CD40	0.0828	0.0283	3.45E-03
CD5	0.0755	0.0281	7.29E-03
CD6	0.0147	0.0287	6.09E-01
CD8A	0.0563	0.0273	3.97E-02
CDCP1	0.1168	0.0330	4.20E-04
CSF.1	0.1470	0.0283	2.39E-07
CST5	0.0316	0.0293	2.82E-01
CX3CL1	-0.0419	0.0281	1.36E-01
CXCL1	0.0472	0.0282	9.38E-02
CXCL10	0.0502	0.0288	8.15E-02
CXCL11	0.0956	0.0276	5.54E-04
CXCL5	0.0405	0.0280	1.49E-01
CXCL6	0.0346	0.0282	2.21E-01
CXCL9	0.0579	0.0319	6.98E-02
DNER	-0.1426	0.0282	4.75E-07
EN.RAGE	0.0918	0.0285	1.29E-04
FGF.19	0.0286	0.0285	3.17E-01
FGF.21	0.0614	0.0283	3.02E-02
Flt3L	0.0069	0.0293	8.13E-01
HGF	0.1477	0.0297	7.31E-07
IFN.gamma	0.0551	0.0283	5.19E-02
IL.10RB	0.1036	0.0281	2.37E-04
IL.12B	0.0704	0.0283	1.29E-02

IL.15RA	0.0953	0.0322	3.08E-03
IL.17C	0.0682	0.0311	2.85E-02
IL.18R1	0.1618	0.0274	4.29E-09
IL10	0.1048	0.0287	2.68E-04
IL18	0.0594	0.0282	3.54E-02
IL6	0.2553	0.0382	3.81E-11
IL7	0.0563	0.0290	5.24E-02
IL8	0.0491	0.2960	9.72E-02
LAP.TGF.beta.1	0.0906	0.0282	1.33E-03
LIF.R	0.0022	0.0286	9.39E-01
MCP.1	0.0625	0.0291	3.17E-02
MCP.2	0.0319	0.0288	1.74E-01
MCP.4	0.0081	0.0285	7.78E-01
MMP.1	0.0660	0.0279	1.79E-02
MMP.10	0.0551	0.0282	5.05E-02
NT.3	-0.0219	0.0277	4.30E-01
OPG	0.0698	0.0301	2.38E-02
OSM	0.1539	0.0283	6.22E-08
PD.L1	0.0760	0.0279	6.60E-03
SCF	-0.0328	0.0282	2.45E-01
SIRT2	0.0163	0.0313	6.02E-01
SLAMF1	0.1030	0.0297	5.50E-04
ST1A1	0.0089	0.0287	7.57E-01
STAMBP	0.0295	0.0283	2.96E-01
TGF.alpha	0.0784	0.0285	6.00E-03
TNF	0.1137	0.0282	5.93E-05
TNFB	-0.0114	0.0278	6.82E-01
TNFRSF9	0.1023	0.0290	4.42E-04
TNFSF14	0.1305	0.0280	3.51E-06
TRAIL	0.0742	0.0285	9.22E-03
TRANCE	0.0097	0.0281	7.29E-01
TWEAK	-0.1172	0.0285	3.97E-05
uPA	-0.0063	0.0290	8.29E-01
VEGFA	0.1587	0.0289	4.65E-08
X4E.BP1	0.0236	0.0280	4.00E-01

Correlations were adjusted for age and standardized.

Of the 70 correlations, 36 are significantly correlated with hsCRP

Table S4. PRS results for GlycA and CRP

Base. GWAS	Threshold	PRS.R2	Full.R2	Null.R2	Coefficient	Stand Error	P	Num_SNP
GlycA – target phenotype								
B_NGF	0.3904	0.0047	0.0167	0.0120	-197.16	69.70	4.73E-03	86767
CRP	0.0525	0.0084	0.0205	0.0120	479.34	125.94	1.46E-04	24677
CTACK	0.0004	0.0015	0.0136	0.0120	-3.80	2.35	1.06E-01	321
EOTAXIN	0.0076	0.0015	0.0136	0.0120	-25.62	15.75	1.04E-01	4562
FGF_BASIC	0.0005	0.0018	0.0138	0.0120	6.86	3.95	8.25E-02	390
GCSF	0.2646	0.0029	0.0150	0.0120	-191.20	85.64	2.57E-02	69225
GROA	0.0026	0.0045	0.0166	0.0120	16.04	5.76	5.43E-03	1632
HGF	0.0047	0.0032	0.0152	0.0120	29.60	12.68	1.97E-02	3025
IFN_gamma	0.0301	0.0008	0.0128	0.0120	34.43	29.48	2.43E-01	13752
IL10	0.3433	0.0030	0.0151	0.0120	-212.77	93.28	2.27E-02	81302
IL12	0.1460	0.0049	0.0170	0.0120	-184.79	63.64	3.74E-03	46700
IL13	0.0009	0.0012	0.0133	0.0120	-5.42	3.73	1.46E-01	721
IL16	0.0003	0.0032	0.0153	0.0120	3.93	1.67	1.86E-02	186
IL17	0.0003	0.0032	0.0152	0.0120	-7.56	3.23	1.95E-02	277
IL18	0.0000	0.0023	0.0144	0.0120	0.23	0.11	4.64E-02	6
IL1B	0.0069	0.0025	0.0145	0.0120	-19.80	9.65	4.03E-02	3979
IL1RA	0.0001	0.0014	0.0134	0.0120	1.22	0.80	1.25E-01	41
IL2	0.0001	0.0019	0.0140	0.0120	2.20	1.21	7.00E-02	93
IL2RA	0.0021	0.0019	0.0139	0.0120	9.66	5.41	7.43E-02	1384
IL4	0.0174	0.0027	0.0147	0.0120	-49.91	23.22	3.17E-02	8899
IL5	0.0002	0.0050	0.0171	0.0120	4.56	1.55	3.38E-03	144
IL6	1.0000	0.0017	0.0138	0.0120	-256.67	149.02	8.52E-02	133811
IL7	0.0679	0.0029	0.0150	0.0120	-65.97	29.43	2.51E-02	25883
IL8	0.0017	0.0020	0.0140	0.0120	-9.39	5.12	6.67E-02	1209
IL9	0.0504	0.0023	0.0143	0.0120	-53.39	27.05	4.85E-02	20691
IP10	0.0005	0.0013	0.0134	0.0120	-3.87	2.55	1.30E-01	386
MCP1	0.0833	0.0010	0.0131	0.0120	-64.51	48.49	1.84E-01	30681
MCP3	0.0035	0.0052	0.0173	0.0120	-11.94	3.98	2.74E-03	2199
MCSF	0.0001	0.0038	0.0158	0.0120	-1.93	0.76	1.08E-02	59
MIF	0.0001	0.0008	0.0129	0.0120	1.11	0.94	2.35E-01	60
MIG	0.0487	0.0048	0.0168	0.0120	-72.30	25.28	4.29E-03	20112
MIP1A	0.0003	0.0043	0.0164	0.0120	5.47	2.00	6.44E-03	248

MIP1B	0.2459	0.0012	0.0133	0.0120	-115.26	79.88	1.49E-01	65930
PDGF	0.0449	0.0029	0.0150	0.0120	86.18	38.51	2.53E-02	19340
RANTES	0.0013	0.0021	0.0141	0.0120	-8.34	4.42	5.96E-02	959
SCF	0.0001	0.0013	0.0134	0.0120	-2.00	1.32	1.31E-01	50
SCGF	0.0004	0.0042	0.0162	0.0120	6.80	2.54	7.43E-03	350
SDF1A	0.0953	0.0016	0.0137	0.0120	-83.10	50.02	9.68E-02	33579
TNF_A	0.0032	0.0042	0.0162	0.0120	-17.93	6.68	7.36E-03	2036
TNF_B	0.0051	0.0023	0.0143	0.0120	-11.39	5.78	4.88E-02	2834
TRAIL	0.0700	0.0019	0.0140	0.0120	85.59	47.24	7.02E-02	27026
VEGF	0.0049	0.0025	0.0146	0.0120	-23.60	11.32	3.71E-02	3167
CRP – target phenotype							
B_NGF	0.0001	0.0005	0.0013	0.0008	38.01	25.75	1.40E-01	84
CRP	0.0001	0.0071	0.0079	0.0008	864.20	155.34	2.81E-08	507
CTACK	0.0122	0.0013	0.0021	0.0008	737.42	315.68	1.95E-02	6432
EOTAXIN	0.0025	0.0007	0.0015	0.0008	361.04	208.77	8.38E-02	1784
FGF_BASIC	0.0044	0.0004	0.0012	0.0008	-358.94	277.27	1.96E-01	2841
GCSF	0.0002	0.0013	0.0022	0.0008	151.87	63.17	1.62E-02	182
GROA	0.0001	0.0017	0.0026	0.0008	32.43	11.76	5.83E-03	42
HGF	0.0388	0.0022	0.0030	0.0008	2526.22	819.79	2.07E-03	16920
IFN_gamma	0.0001	0.0004	0.0012	0.0008	-34.84	27.18	2.00E-01	43
IL10	0.0063	0.0014	0.0022	0.0008	816.14	331.20	1.38E-02	3851
IL12	0.0000	0.0008	0.0016	0.0008	11.29	6.21	6.89E-02	13
IL13	0.0098	0.0018	0.0026	0.0008	793.16	286.06	5.58E-03	5469
IL16	0.1295	0.0003	0.0011	0.0008	1075.56	944.12	2.55E-01	41281
IL17	0.0002	0.0004	0.0012	0.0008	79.30	63.41	2.11E-01	192
IL18	0.1069	0.0004	0.0013	0.0008	-1213.68	900.54	1.78E-01	36606
IL1B	0.0009	0.0006	0.0014	0.0008	121.57	74.53	1.03E-01	608
IL1RA	0.0020	0.0021	0.0029	0.0008	390.15	128.89	2.48E-03	1435
IL2	0.0015	0.0007	0.0015	0.0008	-187.34	106.85	7.96E-02	1027
IL2RA	0.3143	0.0006	0.0014	0.0008	-2375.38	1487.98	1.10E-01	76236
IL4	0.0126	0.0008	0.0016	0.0008	-864.17	473.95	6.83E-02	6744
IL5	0.0000	0.0011	0.0019	0.0008	4.33	2.01	3.12E-02	1
IL6	0.0003	0.0012	0.0020	0.0008	-151.93	67.34	2.41E-02	209
IL7	0.0023	0.0013	0.0021	0.0008	311.91	132.34	1.85E-02	1592
IL8	0.0281	0.0002	0.0011	0.0008	-480.02	466.23	3.03E-01	12903
IL9	0.0192	0.0009	0.0017	0.0008	773.62	392.08	4.85E-02	9498
IP10	0.0157	0.0007	0.0015	0.0008	-627.41	357.22	7.91E-02	8275
MCP1	0.0954	0.0011	0.0019	0.0008	-2693.09	1229.10	2.85E-02	33867
MCP3	0.0001	0.0006	0.0014	0.0008	-24.82	15.29	1.05E-01	96
MCSF	0.0784	0.0008	0.0016	0.0008	-1195.01	652.87	6.73E-02	28887

MIF	0.0044	0.0002	0.0011	0.0008	196.45	191.37	3.05E-01	2798
MIG	0.0000	0.0011	0.0020	0.0008	6.92	3.13	2.71E-02	2
MIP1A	0.0154	0.0010	0.0019	0.0008	727.29	345.39	3.53E-02	7966
MIP1B	0.0005	0.0006	0.0014	0.0008	-107.63	68.69	1.17E-01	585
PDGF	0.0148	0.0006	0.0015	0.0008	-868.73	531.28	1.02E-01	8100
RANTES	0.3018	0.0005	0.0014	0.0008	2172.89	1422.49	1.27E-01	74301
SCF	0.0007	0.0008	0.0017	0.0008	-219.66	116.39	5.92E-02	540
SCGF	0.0001	0.0008	0.0017	0.0008	-42.38	22.26	5.71E-02	65
SDF1A	0.0358	0.0008	0.0017	0.0008	-1469.06	764.70	5.48E-02	15848
TNF_A	0.0045	0.0013	0.0022	0.0008	-449.89	186.96	1.62E-02	2691
TNF_B	0.0019	0.0010	0.0018	0.0008	-162.52	79.27	4.04E-02	1146
TRAIL	0.0011	0.0018	0.0026	0.0008	-391.97	141.91	5.77E-03	857
VEGF	0.0082	0.0006	0.0014	0.0008	-547.90	348.68	1.16E-01	4841

Table S5. MR GlycA as exposure using the IVW method

Outcome	Instrumental Variables	Estimate	SE	95% Confidence Interval	P-value	Heterogeneity
hsCRP	21	0.085	0.024	0.039, 0.132	<0.001	0.1698
FGF	38	0.276	0.063	0.153, 0.399	<0.001	0.6936
HGF	41	0.375	0.064	0.250, 0.500	<0.001	0.6368
IL6	41	0.266	0.060	0.147, 0.384	<0.001	0.7227
IL7	36	0.380	0.095	0.195, 0.566	<0.001	0.6706
TNFA	37	0.301	0.088	0.129, 0.474	0.001	0.9659
VEGF	45	0.377	0.074	0.232, 0.523	<0.001	0.9801

Table S6. MR hsCRP as the exposure, using the IVW method

Outcome	Instrumental Variables	Estimate	SE	95% Confidence Interval	P-value	Heterogeneity
HGF	34	1.222	0.102	1.022, 1.422	<0.001	1.0000
IL6	46	0.276	0.052	0.174, 0.379	<0.001	0.8245
IL10	38	0.360	0.072	0.218, 0.502	<0.001	0.9966
TNFA	35	0.554	0.119	0.321, 0.787	<0.001	0.9999
VEGF	35	0.274	0.067	0.143, 0.405	<0.001	0.9442

Table S7. Gene Ontology results: enrichment analysis r for GlycA and CRP variables for gene ontology (GO) terms

GO ID (Term)	Class	Variable	Rank (Node)	Annotated	Significant	Expected	p-value (Fisher test)
GO:0007156 (Homophilic cell adhesion via plasma membrane)	BP	GlycA	1	163	147	123.6	3.60E-06
		CRP	1	160	133	110.7	1.40E-05
GO:0005515 (protein binding)	MF	GlycA	1	13852	10967	10836.8	4.00E-08
		CRP	2	13581	9564	9406.4	5.90E-07
GO:0005829 (cytosol)	CC	GlycA	1	5137	4156	3898.3	1.00E-25
		CRP	1	4984	3673	3443.7	2.50E-19

GO terms are found in three classes: biological process (BP), molecular function (MF), and cellular component (CC).