

Table S1: Pairwise correlation between DNAm age estimates, DNAm Age acceleration estimates and chronological age.

Pairwise Correlation	HorvathAge	HannumAge	PhenoAge	GrimAge	IEAA	EEAA	PhenoAA	GrimAA
Chronological Age	0.863***	0.898***	0.824***	0.855***	0.020	0.002	-0.005	-0.026
HorvathAge		0.899***	0.843***	0.781***	0.499***	0.27***	0.229***	0.06*
HannumAge			0.853***	0.812***	0.228***	0.424***	0.196***	0.062*
PhenoAge				0.797***	0.264***	0.283***	0.563***	0.158***
GrimAge					0.109***	0.134***	0.16***	0.497***
IEAA						0.417***	0.436***	0.175***
EEAA							0.496***	0.255***
PhenoAA								0.316***

IEAA: intrinsic epigenetic age acceleration; EEAA: extrinsic epigenetic age acceleration; GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration.

P-values were calculated from Pearson's correlation tests.

*** p-value ≤ 0.001 , ** p-value ≤ 0.01 , * p-value ≤ 0.05 .

Table S2: Associations of DNAm Age acceleration with education and lifestyle factors (Model 1)

	GrimAA		PhenoAA		IEAA		EEAA	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	4.044	1.69×10^{-35}	-0.211	0.647	1.331	2.16×10^{-5}	2.449	1.26×10^{-10}
Education								
HS/GED	-0.696	0.060	-1.049	0.065	-0.754	0.049	-1.080	0.019
At least some college	-1.780	7.56×10^{-7}	-1.600	0.004	-0.879	0.018	-1.912	2.19×10^{-5}
Smoking								
Former smoker	2.474	5.30×10^{-17}	1.541	0.004	1.090	0.003	0.243	0.578
Current smoker	7.793	1.16×10^{-88}	2.325	1.42×10^{-4}	0.213	0.603	0.886	0.074
Continuous ln(drinks/week)	1.535	2.76×10^{-9}	0.810	0.038	0.368	0.164	0.084	0.792
Physical activity	-0.119	0.185	-0.132	0.337	-0.027	0.765	-0.207	0.064
BMI	-0.013	0.552	0.070	0.044	0.044	0.060	0.039	0.169

IEAA: intrinsic epigenetic age acceleration; EEAA: extrinsic epigenetic age acceleration; GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration~ age + gender + lifestyle risk factor (one at a time)

Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (<0.05) are bolded.

Table S3: Associations of DNAm Age acceleration with education and lifestyle factors (including physical activity) using multivariable models (Model 2)

	GrimAA		PhenoAA		IEAA		EEAA	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	2.497	3.47×10^{-8}	-0.826	0.113	1.054	0.003	2.504	6.66×10^{-9}
Education								
HS/GED	-0.056	0.854	-0.787	0.169	-0.683	0.077	-1.033	0.027
At least some college	-0.589	0.049	-1.028	0.073	-0.791	0.039	-1.723	2.20×10^{-4}
Smoking								
Former smoker	2.324	4.56×10^{-15}	1.355	0.012	0.981	0.007	0.060	0.892
Current smoker	7.513	2.71×10^{-78}	2.039	0.001	0.106	0.805	0.709	0.174
Continuous								
ln(drinks/week)	0.491	0.022	0.594	0.139	0.402	0.138	-0.007	0.983
BMI	0.043	0.021	0.088	0.014	0.039	0.103	0.035	0.222
Physical activity (hrs/day)	-0.047	0.522	-0.073	0.594	0.006	0.951	-0.141	0.208

IEAA: intrinsic epigenetic age acceleration; EEAA: extrinsic epigenetic age acceleration; GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration~ gender + education + age + smoking + alcohol consumption + BMI + physical activity

Beta is the regression coefficient of the respective variable from the regression model as stated above

Significant p values (<0.05) are bold

Table S4: Associations of DNAm Age acceleration with education and lifestyle factors using multivariable models in hypertensive participants (Model 2, N=771)

	GrimAA		PhenoAA		IEAA		EEAA	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	2.338	1.60 × 10⁻¹¹	-0.512	0.440	1.519	0.001	2.708	7.87 × 10⁻⁷
Education								
HS/GED	0.026	0.941	-1.059	0.125	-0.942	0.041	-1.177	0.036
At least some college	-0.222	0.519	-1.650	0.017	-1.357	0.003	-2.227	6.64 × 10⁻⁵
Smoking								
Former smoker	2.512	5.62 × 10⁻¹³	1.425	0.032	1.177	0.008	0.428	0.426
Current smoker	7.998	3.27 × 10⁻⁵⁴	2.384	0.004	-0.077	0.888	0.675	0.311
Continuous								
ln(drinks/week)	0.390	0.146	0.691	0.193	0.084	0.813	-0.445	0.303
BMI	0.041	0.064	0.091	0.039	0.008	0.786	0.032	0.374

IEAA: intrinsic epigenetic age acceleration; EEAA: extrinsic epigenetic age acceleration; GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration~ gender + education + age + smoking + alcohol consumption + BMI

Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (< 0.05) are bold.

Table S5: Association of DNAm Age acceleration with education and lifestyle factors adjusting for blood cell proportions

	GrimAA		PhenoAA	
	beta	p-value	beta	p-value
Gender (male)	2.018	1.27×10^{-13}	-1.879	1.64×10^{-4}
Education				
HS/GED	-0.265	0.351	-0.964	0.069
At least some college	-0.821	0.003	-1.321	0.013
Smoking				
Former smoker	2.445	2.24×10^{-18}	1.609	0.001
Current smoker	7.762	3.36×10^{-88}	2.748	5.88×10^{-6}
Continuous ln(drinks/week)	0.409	0.043	0.574	0.124
BMI	0.040	0.023	0.082	0.013

GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration~ age + gender + education + smoking + alcohol consumption + BMI + CD8T + CD4T + NK + Bcell + Mono

Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (<0.05) are bolded.

Table S6: Interaction between lifestyle risk factors and gender on GrimAA, adjusting for blood cell proportions

	GrimAA		GrimAA		GrimAA	
	Interaction Model ¹		Interaction Model ²		Interaction Model ³	
	beta	p-value	beta	p-value	beta	p-value
Gender (male)	2.897	8.97 × 10⁻¹³	1.359	3.19 × 10⁻⁴	2.202	1.25 × 10⁻⁵
Education						
HS/GED	0.187	0.566	-0.268	0.344	0.170	0.601
At least some college	-0.401	0.215	-0.803	0.004	-0.454	0.161
Smoking						
Former smoker	2.469	9.43 × 10⁻¹⁹	2.419	2.48 × 10⁻¹²	2.481	7.53 × 10⁻¹³
Current smoker	7.769	2.02 × 10⁻⁸⁸	6.962	8.60 × 10⁻⁵⁷	7.010	1.89 × 10⁻⁵⁷
Continuous ln(drinks/week)	0.413	0.040	0.319	0.116	0.322	0.111
BMI	0.043	0.013	0.040	0.021	0.043	0.013
Gender (male)*Education						
HS/GED	-1.605	0.009			-1.579	0.009
At least some college	-1.290	0.012			-1.060	0.041
Gender (male)*Smoking						
Former smoker			0.548	0.329	0.424	0.453
Current smoker			2.254	3.26 × 10⁻⁴	2.135	0.001

GrimAA: DNAm GrimAge acceleration; HS/GED: High School/General Education Development.

¹Model: GrimAA~ age + alcohol consumption + BMI + smoking + gender*education + CD8T + CD4T + NK + Bcell + Mono

²Model: GrimAA~ age + alcohol consumption + BMI + education + gender*smoking + CD8T + CD4T + NK + Bcell + Mono

³Model: GrimAA~ age + alcohol consumption + BMI + gender*education + gender*smoking + CD8T + CD4T + NK + Bcell + Mono

Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (<0.05) are bolded.

No other interactions between sex and lifestyle factors on GrimAA or other age acceleration measures were significant.

Table S7: Associations of GrimAge components with education and lifestyle risk factors (Model 2)

	DNAmADM		DNAmB2M		DNAmCystatinC		DNAmGDF15	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	-24.430	5.03×10^{-68}	-10371.390	0.309	5642.568	0.001	15.123	0.075
Education								
HS/GED	0.280	0.834	-13470.036	0.234	143.005	0.938	5.113	0.584
At least some college	-0.216	0.869	-17908.017	0.125	-3026.581	0.093	-6.152	0.501
Smoking								
Former smoker	0.145	0.909	8278.261	0.434	-1508.296	0.386	22.241	0.013
Current smoker	3.299	0.027	26030.929	0.038	4489.474	0.028	73.695	4.41×10^{-12}
Continuous ln(drinks/week)	1.015	0.284	9866.188	0.205	241.873	0.851	7.462	0.259
BMI	0.384	3.86×10^{-6}	168.349	0.812	269.670	0.017	0.449	0.435

	DNAmLeptin		DNAmPACKYRS		DNAmPAI1		DNAmTIMP1	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	-7239.797	1.47×10^{-228}	4.532	1.71×10^{-12}	993.852	5.78×10^{-8}	151.862	0.041
Education								
HS/GED	-101.940	0.481	0.437	0.526	-71.098	0.720	-72.823	0.373
At least some college	-106.616	0.453	-0.890	0.183	-56.631	0.769	-134.668	0.093
Smoking								
Former smoker	70.520	0.609	9.007	6.12×10^{-37}	488.310	0.010	-68.760	0.377
Current smoker	98.138	0.543	26.131	3.52×10^{-138}	727.241	0.001	208.182	0.023
Continuous ln(drinks/week)	28.087	0.784	0.975	0.047	780.226	4.78×10^{-8}	-23.520	0.684
BMI	42.474	2.34×10^{-6}	-0.119	0.005	116.191	3.53×10^{-20}	9.956	0.048

DNAmADM: DNAm surrogate of adrenomedullin (ADM); DNAmB2M: DNAm surrogate of beta-2 microglobulin (B2M), DNAmGDF15: DNAm surrogate of growth differentiation factor 15 (GDF15); DNAmCystatinC: DNAm surrogate of Cystatin C (CystatinC); DNAmLeptin: DNAm surrogate of leptin (Leptin); DNAmPAI1: DNAm surrogate of plasminogen activation inhibitor 1 (PAI1); DNAmTIMP1: DNAm surrogate of Issue inhibitor metalloproteinase 1 (TIMP1); DNAmPACKYRS: DNAm surrogate of the amount of cigarettes smoked (PACKYRS); HS/GED: High School/General Education Development.

Model: DNAm GrimAge components ~ age + gender + education + smoking + alcohol consumption + BMI + CD8T + CD4T + NK + Bcell + Mono
Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (<0.05) are bolded.

Table S8: Associations of DNAm GrimAge components with demographic and lifestyle factors, adjusting for blood cell proportions

	DNAmADM		DNAmB2M		DNAmCystatinC		DNAmGDF15	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	-24.903	1.97×10^{-69}	-19758.128	0.060	2155.375	0.175	9.652	0.267
Education								
HS/GED	-0.339	0.795	-14150.526	0.208	-310.759	0.854	4.524	0.626
At least some college	-1.033	0.420	-18218.918	0.117	-3764.063	0.025	-7.352	0.419
Smoking								
Former smoker	0.445	0.721	8330.040	0.430	-575.282	0.721	24.216	0.006
Current smoker	3.207	0.031	30438.674	0.017	6426.126	0.001	76.924	1.09×10^{-12}
Continuous ln(drinks/week)	0.849	0.360	10392.573	0.183	81.129	0.946	8.213	0.214
BMI	0.386	1.85×10^{-6}	215.658	0.759	287.189	0.006	0.506	0.375

	DNAmLeptin		DNAmPACKYRS		DNAmPAI1		DNAmTIMP1	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Gender (male)	-7211.810	1.84×10^{-220}	4.267	8.07×10^{-11}	908.208	9.96×10^{-7}	48.579	0.502
Education								
HS/GED	-75.093	0.604	0.208	0.763	-133.675	0.495	-114.991	0.137
At least some college	-80.669	0.570	-1.158	0.082	-137.007	0.473	-190.078	0.013
Smoking								
Former smoker	62.129	0.652	9.057	1.97×10^{-37}	560.518	0.003	-44.452	0.546
Current smoker	93.209	0.572	26.167	2.29×10^{-135}	794.468	3.98×10^{-4}	241.527	0.006
Continuous ln(drinks/week)	10.989	0.915	0.900	0.067	738.914	1.75×10^{-7}	-34.049	0.535
BMI	42.915	1.78×10^{-6}	-0.123	0.004	115.526	1.87×10^{-20}	10.085	0.034

DNAmADM: DNAm surrogate of adrenomedullin (ADM); DNAmB2M: DNAm surrogate of beta-2 microglobulin (B2M), DNAmGDF15: DNAm surrogate of growth differentiation factor 15 (GDF15); DNAmCystatinC: DNAm surrogate of Cystatin C (CystatinC); DNAmLeptin: DNAm surrogate of leptin (Leptin); DNAmPAI1: DNAm surrogate of plasminogen activation inhibitor 1 (PAI1); DNAmTIMP1: DNAm surrogate of Issue inhibitor metalloproteinase 1 (TIMP1); DNAmPACKYRS: DNAm surrogate of the amount of cigarettes smoked (PACKYRS); HS/GED: High School/General Education Development.

Model: DNAm GrimAge components ~ age + gender + education + smoking + alcohol consumption + BMI + CD8T + CD4T + NK + Bcell + Mono
Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (<0.05) are bolded.

Table S9: Associations between education and lifestyle factors on longitudinal change in DNAm Age acceleration (Model 4)

	GrimAA		PhenoAA		IEAA		EEAA	
	beta	p-value	beta	p-value	beta	p-value	beta	p-value
Age	0.050	0.010	0.081	0.034	-0.006	0.820	0.050	0.050
Gender (male)	0.692	0.057	1.448	0.052	0.381	0.500	1.184	0.692
Education								
HS/GED	-0.078	0.819	0.121	0.866	-0.382	0.545	-0.512	-0.078
At least some college	-0.106	0.745	-0.530	0.446	0.320	0.590	-0.696	-0.106
Smoking								
Former smoker	0.295	0.397	0.154	0.825	-0.409	0.510	-0.095	0.295
Current smoker	0.636	0.188	2.029	0.031	-0.530	0.440	0.404	0.636
Continuous								
ln(drinks/week)	-0.090	0.737	-0.469	0.426	0.243	0.626	-0.877	-0.090
BMI	0.050	0.028	0.079	0.082	0.047	0.207	0.026	0.050

IEAA: intrinsic epigenetic age acceleration; EEAA: extrinsic epigenetic age acceleration; GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration₂ ~ DNAm Age acceleration₁ + gender + education₁ + Age₁ + smoking₁ + alcohol consumption₁ + BMI₁ + Δtime + ΔBMI + Δalcohol consumption. People whose smoking status changed between phases were excluded.

Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (p<0.05) are bolded.

Table S10: Associations between education and lifestyle factors and longitudinal change of DNAm Age acceleration, adjusting for blood cell proportions

	GrimAA		PhenoAA	
	beta	p-value	beta	p-value
Age	0.014	0.359	0.019	0.568
Gender (male)	0.214	0.480	0.764	0.304
Education				
HS/GED	-0.220	0.487	0.034	0.961
At least some college	-0.100	0.726	-0.386	0.583
Smoking				
Former smoker	-0.014	0.963	-0.025	0.971
Current smoker	0.192	0.637	1.890	0.109
Continuous ln(drinks/week)	0.047	0.842	-0.323	0.581
BMI	0.027	0.211	0.042	0.353

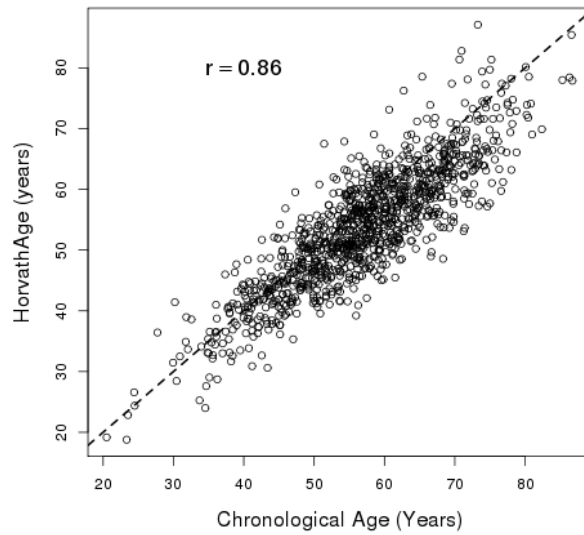
GrimAA: DNAm GrimAge acceleration; PhenoAA: DNAm PhenoAge acceleration; HS/GED: High School/General Education Development.

Model: DNAm Age acceleration₂ ~ DNAm Age acceleration₁ + gender + education₁ + Age₁ + smoking₁ + alcohol consumption₁ + BMI₁ + Δtime + ΔBMI + Δalcohol consumption + ΔCD8T + ΔCD4T + ΔNK + ΔBcell + ΔMono. People whose smoking status changed were excluded.

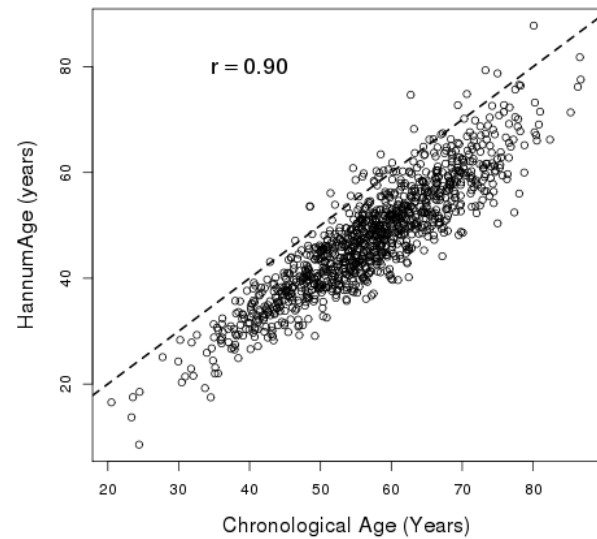
Beta is the regression coefficient of the respective variable from the regression model as stated above.

Significant p values (p<0.05) are bolded.

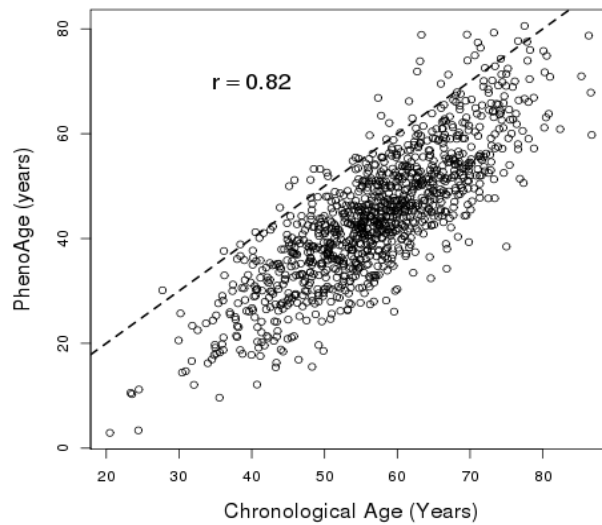
Figure S1: Scatterplots of DNAm Age estimators vs. chronological age for participants in the Genetic Epidemiology Network of Arteriopathy (GENOA, Phase 1). Chronological age is on the X axis, and the Y axis is (A) HorvathAge; (B) HannumAge; (C) PhenoAge; (D) GrimAge.



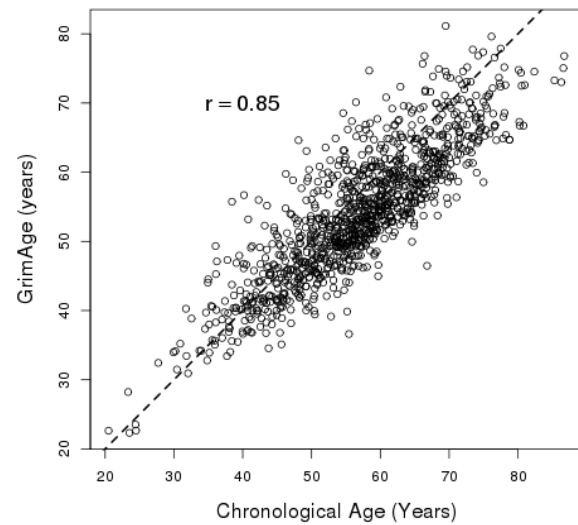
(a)



(b)



(c)



(d)