**Table S1.** Regression results for the association between epigenetic age acceleration and blood pressure in GENOA African Americans (n=1390)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Blood pressure** | **Epigenetic age acceleration**  | **Model 1** | **Model 2** | **Model 3** |
| β | *P* | β | *P* | β | *P* |
| SBP | IEAA | 0.119 | 0.321 | 0.116 | 0.176 | 0.073 | 0.401 |
| EEAA | 0.149 | 0.127 | 0.188 | **0.015** | 0.147 | 0.051 |
| DBP | IEAA | -6.0E-3 | 0.924 | -0.040 | 0.374 | -0.011 | 0.797 |
| EEAA | -0.021 | 0.678 | -0.072 | 0.073 | -0.049 | 0.203 |

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; EAA, epigenetic age acceleration; IEAA, intrinsic epigenetic age acceleration; EEAA, extrinsic epigenetic age acceleration

Model 1: Blood pressure = epigenetic age acceleration + chronological age + sex + time between methylation and blood pressure

Model 2: Blood pressure = Model 1 covariates + (SBP or DBP) + antihypertensive medication

Model 3: Blood pressure = Model 2 covariates + smoking + diabetes + BMI

P-values <0.05 are in bold.

**Table S2.** Beta coefficient for IEAA association with target organ damage measures in Model 2 and with Model 3 covariates added separately

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Target organ damage**  | **Model 2** | **Model 2** **+ smoking** | **Model 2** **+ diabetes** | **Model 2** **+ BMI** | **Model 2** **+ albuminuria** |
| **β** | ***P*** | **β** | ***P*** | **Δβ (%)** | **β** | ***P*** | **Δβ (%)** | **β** | ***P*** | **Δβ (%)** | **β** | ***P*** | **Δβ (%)** |
| UACR | 0.017 | **0.036** | 0.016 | **0.041** | 2.4 | 9.1E-3 | 0.233 | 45.5 | 0.016 | **0.044** | 4.3 | . | . |  |
| RWT | 5.4E-4 | **0.041** | 5.3E-4 | **0.045** | 1.4 | 4.7E-4 | **0.074** | 12.4 | 5.3E-4 | **0.044** | 2.2 | 5.2E-4 | **0.050** | 4.1 |
| ABI | -1.9E-3 | **0.028** | -1.6E-3 | 0.057 | 15.9 | -1.8E-3 | **0.035** | 4.5 | -2.0E-3 | **0.019** | -6.2 | . | . |  |

Abbreviations: IEAA, intrinsic epigenetic age acceleration; UACR, urinary albumin to creatinine ratio; RWT, relative wall thickness; ABI, ankle-brachial index

Only associations in which the beta coefficient for epigenetic age acceleration was significant (p<0.05) in Model 2 and non-significant (p>0.05) in Model 3 are shown. β and *P* represent the beta coefficient for IEAA from the specified regression model, *P* represents the correspondingp-value for the beta coefficient, and Δβ represents the percentage change in β from Model 2 to the specified model.

Model 2: Target organ damage = epigenetic age acceleration + chronological age + sex + time between methylation and target organ damage + SBP + DBP + antihypertensive medication

P-values <0.05 are in bold.

**Table S3.** Regression results for the association between epigenetic age acceleration and target organ damage measures among GENOA African Americans, adjusting for array type or limiting analyses to those with EPIC data

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target organ damage** | **Epigenetic age acceleration** | **Original Model 1 (N=1,416)** | **Model 1, Adjusting for Array Type (N=1,416)** | **Original Model 1 in EPIC only (N=1,074)** |
| β | *P* | β | *P* | β | *P* |
| eGFR (n=1389) | IEAA | -0.082 | 0.444 | -0.083 | 0.440 | 1.1E-3 | 0.993 |
| EEAA | 0.119 | 0.180 | 0.119 | 0.180 | 0.080 | 0.430 |
| UACR\* (n=1390) | IEAA | 0.023 | **0.004** | 0.023 | **0.004** | 0.017 | 0.059 |
| EEAA | 0.010 | 0.187 | 0.010 | 0.187 | 0.013 | 0.095 |
| RWT (n=1352) | IEAA | 6.2E-4 | **0.022** | 6.2E-4 | **0.022** | 7.1E-4 | **0.016** |
| EEAA | -3.4E-5 | 0.886 | -3.4E-5 | 0.885 | 1.9E-4 | 0.448 |
| LVMI (n=1346) | IEAA | 0.163 | **0.007** | 0.163 | **0.007** | 0.118 | 0.062 |
| EEAA | 0.131 | **0.005** | 0.131 | **0.005** | 0.171 | **0.001** |
| ABI (n=1359) | IEAA | -2.1E-3 | **0.014** | -2.1E-3 | **0.014** | -1.6E-3 | 0.107 |
| EEAA | -1.2E-3 | 0.075 | -1.2E-3 | 0.077 | -1.4E-3 | 0.080 |
| WMH\*(n=758) | IEAA | -4.2e-3 | 0.333 | -4.1E-3 | 0.340 | -3.3E-4 | 0.942 |
| EEAA | 6.8e-3 | 0.068 | 6.9E-3 | 0.068 | 8.0E-3 | **0.040** |

Abbreviations: IEAA, intrinsic epigenetic age acceleration; EEAA, extrinsic epigenetic age acceleration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; RWT, relative wall thickness; LVMI, left ventricular mass index; ABI, ankle-brachial index; WMH, white matter hyperintensity

Original Model 1: Target organ damage = epigenetic age acceleration + chronological age + sex + time between methylation and target organ damage measure

\*Variables were natural log transformed prior to analysis.

P-values <0.05 are in bold.

|  |
| --- |
| **Table S4.** Regression results for the association between epigenetic age acceleration and target organ damage measures among GENOA African Americans, adjusting for educational attainment |
| **Target Organ Damage** | **Epigenetic Age Acceleration** | **Model 1a** | **Model 2a** | **Model 3a** |
| β | *P* | β | *P* | β | *P* |
| eGFR (n=1389) | IEAA | -0.073 | 0.501 | -0.032 | 0.767 | -0.026 | 0.805 |
| EEAA | 0.139 | 0.122 | 0.114 | 0.204 | 0.106 | 0.241 |
| UACR\* (n=1390) | IEAA | 0.022 | **0.006** | 0.016 | **0.048** | 8.1E-3 | 0.288 |
| EEAA | 7.8E-3 | 0.299 | 5.4E-3 | 0.427 | 6.0E-5 | 0.993 |
| RWT (n=1352) | IEAA | 6.4E-4 | **0.020** | 5.6E-4 | **0.036** | 4.7E-4 | 0.078 |
| EEAA | -1.7E-5 | 0.943 | -2.8E-5 | 0.904 | -9.4E-5 | 0.693 |
| LVMI (n=1346) | IEAA | 0.155 | **0.010** | 0.103 | 0.070 | 0.062 | 0.261 |
| EEAA | 0.119 | **0.011** | 0.110 | **0.017** | 0.092 | **0.032** |
| ABI (n=1359) | IEAA | -1.9E-3 | **0.030** | -1.6E-3 | 0.056 | -1.4E-3 | 0.087 |
| EEAA | -7.6E-4 | 0.271 | -6.1E-4 | 0.365 | -4.9E-4 | 0.460 |
| WMH\* (n=758) | IEAA | -4.6E-3 | 0.298 | -5.8E-3 | 0.186 | -8.0E-3 | 0.071 |
| EEAA | 6.4E-3 | 0.094 | 6.6E-3 | 0.077 | 5.6E-3 | 0.128 |

Abbreviations: IEAA, intrinsic epigenetic age acceleration; EEAA, extrinsic epigenetic age acceleration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; RWT, relative wall thickness; LVMI, left ventricular mass index; ABI, ankle-brachial index; WMH, white matter hyperintensity

Model 1a: Target organ damage = epigenetic age acceleration + chronological age + sex + time between methylation and target organ damage measure + educational attainment

Model 2a: Target organ damage = Model 1 covariates + SBP + DBP + antihypertensive medication + educational attainment

Model 3a: Target organ damage = Model 2 covariates + smoking + diabetes + BMI + educational attainment

Model 3 for RWT and LVM also includes microalbuminuria and macroalbuminuria.

All models for WMH also include total intracranial volume (TIV).

\*Variables were natural log transformed prior to analysis.

P-values <0.05 are in bold.

**Table S5.** Regression results for the association between epigenetic age acceleration and target organ damage measures among GENOA African Americans with hypertension

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target organ damage** | **Epigenetic age acceleration** | **Model 1** | **Model 2** | **Model 3** |
| β | *P* | β | *P* | β | *P* |
| eGFR (n=1126) | IEAA | -0.054 | 0.647 | -0.053 | 0.647 | -0.032 | 0.785 |
| EEAA | 0.118 | 0.232 | 0.093 | 0.342 | 0.097 | 0.323 |
| UACR\* (n=1127) | IEAA | 0.021 | **0.026** | 0.019 | **0.035** | 9.3E-3 | 0.290 |
| EEAA | 0.012 | 0.152 | 7.9E-3 | 0.304 | 7.4E-4 | 0.924 |
| RWT (n=1092) | IEAA | 3.7E-4 | 0.220 | 3.9E-4 | 0.176 | 3.0E-4 | 0.306 |
| EEAA | -1.7E-4 | 0.505 | -2.2E-4 | 0.379 | -2.9E-4 | 0.250 |
| LVMI (n=1086) | IEAA | 0.124 | 0.062 | 0.115 | 0.073 | 0.070 | 0.254 |
| EEAA | 0.127 | **0.017** | 0.111 | **0.035** | 0.085 | 0.083 |
| ABI (n=1097) | IEAA | -2.3E-3 | **0.020** | -2.1E-3 | **0.028** | -1.7E-3 | 0.061 |
| EEAA | -1.3E-3 | 0.112 | -1.0E-3 | 0.177 | -8.8E-4 | 0.246 |
| WMH\* (n=592) | IEAA | -5.8E-3 | 0.226 | -5.7E-3 | 0.223 | -8.5E-3 | 0.075 |
| EEAA | 8.5E-3 | **0.040** | 8.2E-3 | **0.041** | 7.1E-3 | 0.071 |

Abbreviations: IEAA, intrinsic epigenetic age acceleration; EEAA, extrinsic epigenetic age acceleration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; RWT, relative wall thickness; LVMI, left ventricular mass index; ABI, ankle-brachial index; WMH, white matter hyperintensity

Model 1: Target organ damage = epigenetic age acceleration + chronological age + sex + time between methylation and target organ damage measure

Model 2: Target organ damage = Model 1 covariates + SBP + DBP + antihypertensive medication

Model 3: Target organ damage = Model 2 covariates + smoking + diabetes + BMI

Model 3 for RWT and LVM also includes microalbuminuria and macroalbuminuria.

All models for WMH also include total intracranial volume (TIV).

\*Variables were natural log transformed prior to analysis.

P-values <0.05 are in bold.

**Table S6.** Heritability estimates of epigenetic age acceleration and target organ damage measures among GENOA African Americans

|  |  |  |  |
| --- | --- | --- | --- |
| **Measure** | **h2 in Model 1** | **h2 in Model 2** | **h2 in Model 3** |
| IEAA | 0.480\*\*\* | 0.508\*\*\* | 0.503\*\*\* |
| EEAA | 0.607\*\*\* | 0.601\*\*\* | 0.603\*\*\* |
| eGFR | 0.418\*\*\* | 0.398\*\*\* | 0.439\*\*\* |
| UACRa | 0.381\*\*\* | 0.377\*\*\* | 0.331\*\*\* |
| RWT | 0.276\*\*\* | 0.259\*\*\* | 0.249\*\*\* |
| LVMI | 0.577\*\*\* | 0.520\*\*\* | 0.451\*\*\* |
| ABI | 0.354\*\*\* | 0.355\*\*\* | 0.317\*\*\* |
| WMHa | 0.346\*\*\* | 0.323\*\* | 0.325\*\* |

Abbreviations: IEAA, intrinsic epigenetic age acceleration; EEAA, extrinsic epigenetic age acceleration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; RWT, relative wall thickness; LVMI, left ventricular mass index; ABI, ankle-brachial index; WMH, white matter hyperintensity; h2, heritability estimate

Model 1: Epigenetic age acceleration or target organ damage measure = chronological age + sex

Model 2: Epigenetic age acceleration or target organ damage measure = Model 1 covariates + SBP + DBP + antihypertensive medication

Model 3: Epigenetic age acceleration or target organ damage measure = Model 2 covariates + smoking + diabetes + BMI + albuminuria

aVariables were natural log transformed prior to analysis.

†p<0.1, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

**Figure S1**. Scatterplots of DNAm age and epigenetic age acceleration from 102 duplicated samples using 450K and EPIC array data



A) Horvath DNAm age (r=0.88), B) Hannum DNAm age (r=0.95), C) Intrinsic DNAm age acceleration (IEAA, r=0.70), D) Extrinsic DNAm age acceleration (EEAA, r=0.84). Linear regression lines are shown.

**Figure S2**. Distributions of epigenetic age acceleration measures

1.  B)

A) Intrinsic epigenetic age acceleration (IEAA); B) extrinsic epigenetic age acceleration (EEAA). Negative values indicate that the epigenetic age of the individual is younger than expected, while positive values indicate that epigenetic age is older than expected.