SUPPLEMENTAL MATERIAL

Methods

DNA Methylation Analyses

Supplemental Figure 1: **Meta-Analyses Evaluating Associations Between Chronological Age and Incident Atrial Fibrillation Following Adjustment with Epigenetic Age Measures.** Analyses involving epigenetic measures also adjusted for sex, race, and technical factors. (A) Unadjusted (B) Horvath clock, (C) Hannum clock, (D) DNAm PhenoAge clock, (E) DNAm PAI-1, (F) DNAm GrimAge clock.

HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Technical factors include cell types, sample batch, laboratory site, and follow-up visit. CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 2: Meta-Analyses of Multivariable Models Evaluating Associations Between Chronological Age and Incident Atrial Fibrillation Following Adjustment with Epigenetic Age Measures. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 3: Meta-Analyses of Competing Risk Regression Models Evaluating Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Subdistribution Hazard Ratios (competing risk of death) are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for chronological age, sex, race, smoking variables, and technical factors (including cell types, sample batch, laboratory site, and follow-up visit).

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 4: Meta-Analyses of Multivariable Competing Risk Regression Models Evaluating Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Subdistribution Hazard Ratios (competing risk of death) are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 5: Evaluation of the Risk Predictive Capacity of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation Through Time-Dependent C-statistics. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Models additionally include technical factors (cell types, sample batch, laboratory site, and follow-up visit).

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 6: Evaluation of the Impact of the Addition of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation on the Time-Dependent C-statistic for the Intermediate Model. (**A**) Intermediate Model (**B**) Horvath clock, (**C**) Hannum clock, (**D**) DNAm PhenoAge clock, (**E**) DNAm PAI-1, (**F**) DNAm GrimAge clock.

Intermediate model include technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, race, smoking variables.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 7: Change in the Time-Dependent C-statistics for the Intermediate Model for Incident Atrial Fibrillation Prediction Following the Addition of 5 Epigenetic Age Acceleration Measures. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Intermediate model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, race, smoking variables.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 8: Evaluation of the Impact of the Addition of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation on the Time-Dependent C-statistic for the Multivariable Model. (**A**) Multivariable Model (**B**) Horvath clock, (**C**) Hannum clock, (**D**) DNAm PhenoAge clock, (**E**) DNAm PAI-1, (**F**) DNAm GrimAge clock.

Multivariable model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 9: Change in the Time-Dependent C-statistics for the Multivariable Model for Incident Atrial Fibrillation Prediction Following the Addition of 5 Epigenetic Age Acceleration Measures. (**A**) Multivariable Model (**B**) Horvath clock, (**C**) Hannum clock, (**D**) DNAm PhenoAge clock, (**E**) DNAm PAI-1, (**F**) DNAm GrimAge clock.

Multivariable model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status,

smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 10: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation Stratified by Positive and Negative Epigenetic Age Acceleration Status for the Intermediate Model. (**A**) Horvath clock; Positive EAA, (**B**) Horvath clock; Negative EAA, (**C**) Hannum clock; Positive EAA, (**D**) Hannum clock; Negative EAA, (**E**) DNAm PhenoAge clock; Positive EAA, (**F**) DNAm PhenoAge clock; Negative EAA (**G**) DNAm PAI-1; Positive EAA, (**H**) DNAm PAI-1; Negative EAA, (**I**) DNAm GrimAge clock; Positive EAA, (**J**) DNAm GrimAge clock; Negative EAA.

HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for chronological age, sex, race, smoking variables, and technical factors.

Technical factors include cell types, sample batch, laboratory site, and follow-up visit.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 11: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation Stratified by Positive and Negative Epigenetic Age Acceleration Status for the Multivariable Model. (**A**) Horvath clock; Positive EAA, (**B**) Horvath clock; Negative EAA, (**C**) Hannum clock; Positive EAA, (**D**) Hannum clock; Negative EAA, (**E**) DNAm PhenoAge clock; Positive EAA, (**F**) DNAm PhenoAge clock; Negative EAA (**G**) DNAm PAI-1; Positive EAA, (**H**) DNAm PAI-1; Negative EAA, (**I**) DNAm GrimAge clock; Positive EAA, (**J**) DNAm GrimAge clock; Negative EAA.

HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 12: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Body Mass Index. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 unit increase in Body Mass Index.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 13: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Systolic Blood Pressure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 unit increase in Systolic Blood Pressure.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 14: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Diastolic Blood Pressure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 unit increase in Diastolic Blood Pressure.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 15: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Prevalent Use of Anti-Hypertensive Medication. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Odds ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 16: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Prevalent Diabetes. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Odds ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 17: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Myocardial Infarction. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Hazard ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 18: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Congestive Heart Failure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

Hazard ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 19: **Proportion of Treatment Effect (PTE) for Body Mass Index on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 20: **Proportion of Treatment Effect (PTE) for Systolic Blood Pressure on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 21: **Proportion of Treatment Effect (PTE) for Diastolic Blood Pressure on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 22: **Proportion of Treatment Effect (PTE) for Anti-Hypertensive Medication on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 23: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 24: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 25: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.

PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 26: Two-Sample Mendelian Randomization Analysis of Horvath Epigenetic Age Acceleration (EAA) Measures and Atrial Fibrillation (AF). (A) Forest plot demonstrating collective inverse variance weighted effect estimate and individual effect of each genetic variant associated with the Horvath EAA measure on atrial fibrillation. (**B**) Scatter plot of associations for each Horvath EAA genetic variant with atrial fibrillation (y-axis) and Horvath EAA (x-axis) with line representing inverse variance weighted estimate.

ORs are per 5-year increment in Intrinsic (Horvath) EAA; EAA = epigenetic age acceleration, AF = atrial fibrillation, CI = confidence intervals

Supplemental Table 1: Clinical Variables Included in Model 1 Evaluating for Associations Between Measures of Epigenetic Age Acceleration and Incident Atrial Fibrillation

Supplemental Table 2: Clinical Variables Included in Model 2 Evaluating for Associations Between Measures of Epigenetic Age Acceleration and Incident Atrial Fibrillation

BMI = body mass index, kg/m^2 = kilograms/meters^2, BP = blood pressure, mm Hg = millimeters of mercury

Supplemental Table 3: Sensitivity Analyses Evaluating Associations of the DNAm GrimAge Clock with Incident Atrial Fibrillation in the Framingham Heart Study Adjusting for the "Training" Subgroup of Study Participants used for its Derivation

*Model 1: Adjusted for technical covariates; Model 2: Adjusted for technical covariates and chronological age; Model 3: Adjusted for technical covariates and chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

**No Train and Train: Cox models unadjusted and adjusted for the subgroup of study participants used to derive the DNAm GrimAge clock, respectively.

HR = hazard ratio, CI = confidential interval

Supplemental Table 4: Associations of Chronological Age and Epigenetic Age Measures with Incident Atrial Fibrillation Adjusted for Technical Factors

Supplemental Table 5: Results of sensitivity analyses for Mendelian randomization analyses of Epigenetic Age Acceleration Measures on Atrial Fibrillation.

Methods

DNA Methylation Analysis

Following DNA extraction from whole blood using the Gentra Puregene Blood Kit (Qiagen, Venlo, Netherlands), samples for each cohort underwent bisulphite conversion using the deep-well EZ-96 DNA Methylation Kit (Zymo Research, Irvine, CA). Bisulphite conversion efficiency was determined by polymerase chain reaction amplification using the Universal Methylated Human DNA Standard (Zymo Research). Samples were then amplified and hybridized to the Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA). The methylation score for each CpG dinucleotide was represented as a continuous variable between 0 and 1, reflecting the proportion methylated, and was calculated by dividing the fluorescence intensity of the methylated bead type by the sum of the intensities of the methylated and unmethylated bead types.

Additional details regarding patient selection and the methylation analyses specific to each cohort are provided below.

Framingham Heart Study (FHS)

All FHS Offspring study participants attending their 8th examination underwent methylation analysis provided sufficient DNA was available. The methylation assay was performed at 3 centers (Johns Hopkins University, University of Minnesota, and Illumina), normalized separately, and pooled together after adjusting for batch effects. Raw data were normalized and corrected for background noise using the "DASEN" R package. Exclusion criteria for samples consisted of: 1) multi-dimensional scale plot outliers, 2) high missing rate (>1%), 3) poor matching to SNP genotype when compared to previous genotyping and/or 1000 Genome imputation, defined as a correlation

coefficient < 0.85, 4) gender prediction by DNA methylation data mismatch, 5) history of leukemia during or before methylation analysis.

Atherosclerosis Risk in Communities Study (ARIC)

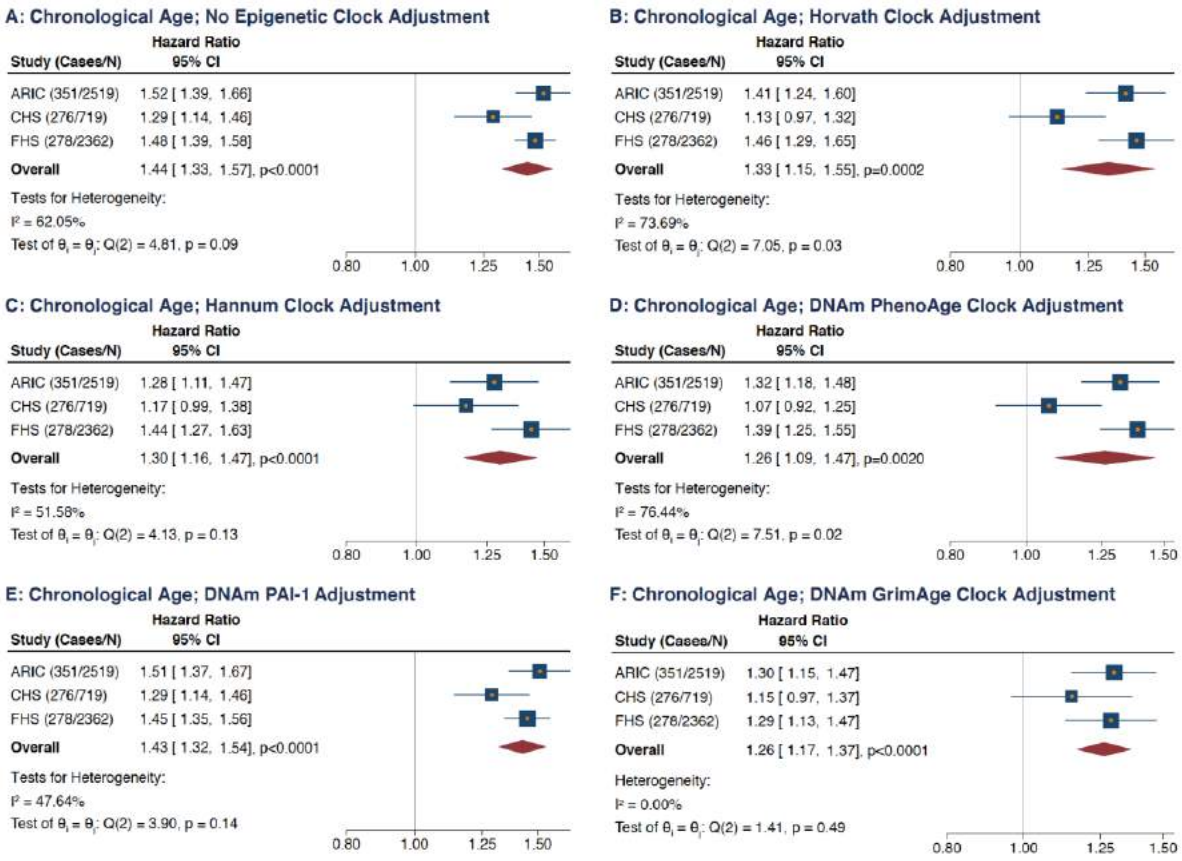
Methylation data were obtained from a subset of Black participants from Jackson, Mississippi, and Forsyth County, North Carolina. DNA methylation was measured in blood collected at ARIC visits 2 (1990-1992) or 3 (1993-1995), and limited to participants who had not restricted use of their DNA, had at least 1 μg of DNA available for the array, and had genome-wide genotyping data available. Samples that did not meet quality control specifications, including failed bisulfite conversion, pass rate <95%, or possible sex mismatches, based on evaluation of X or Y chromosome CpG sites, were excluded. An average normalization was applied to minimize scanner-to-scanner variation followed by additional normalization using the Horvath online calculator: https://dnamage.genetics.ucla.edu/new.

Cardiovascular Health Study (CHS)

DNA methylation in CHS was measured on a randomly selected subset of 336 White and 329 Black participants who participated in the 3rd annual follow-up visit and had DNA available from that visit. The White study participants had no baseline history of coronary vascular disease (defined as coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack). An additional 105 participants were selected based on medication use and availability of DNA at both the 3rd and 7th annual follow-up visits. These participants were all White, except for one Black individual.

Methylation measurements were performed at the Institute for Translational Genomics and Population Sciences at the Harbor-UCLA Medical Center Institute for Translational Genomics and Population Sciences (Los Angeles, CA). Quality control was performed in the minfi R package (version 1.12.0). Samples with low median intensities below 10.5 (log2) across the methylated and unmethylated channels, samples with a proportion of probes failing detection of > 0.5%, samples with quality control probes falling greater than 3 standard deviation from the mean, sex-check mismatches, failed concordance with prior genotyping, or > 0.5% of probes with a detection p-value > 0.01 were removed. Probes with >1% of values below detection were also removed. Methylation values were normalized using the SWAN quantile normalization method.[23] Since white blood cell proportions were not directly measured in CHS, they were estimated from the methylation data using the Houseman method.[24]

Supplemental Figure 1: **Meta-Analyses Evaluating Associations Between Chronological Age and Incident Atrial Fibrillation Following Adjustment with Epigenetic Age Measures.** Analyses involving epigenetic measures also adjusted for sex, race, and technical factors. (A) Unadjusted (B) Horvath clock, (C) Hannum clock, (D) DNAm PhenoAge clock, (E) DNAm PAI-1, (F) DNAm GrimAge clock.



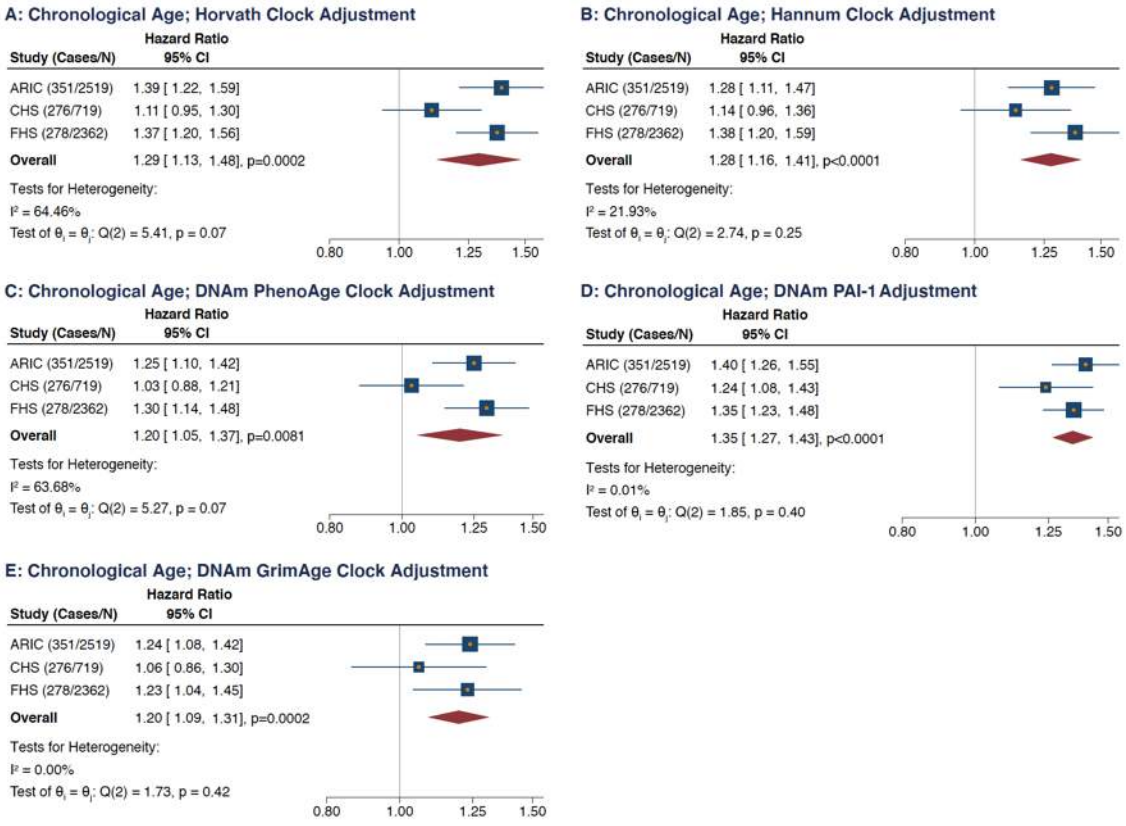
HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Technical factors include cell types, sample batch, laboratory site, and follow-up visit.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 2: Meta-Analyses of Multivariable Models Evaluating Associations Between Chronological Age and Incident Atrial Fibrillation Following Adjustment with Epigenetic Age Measures. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



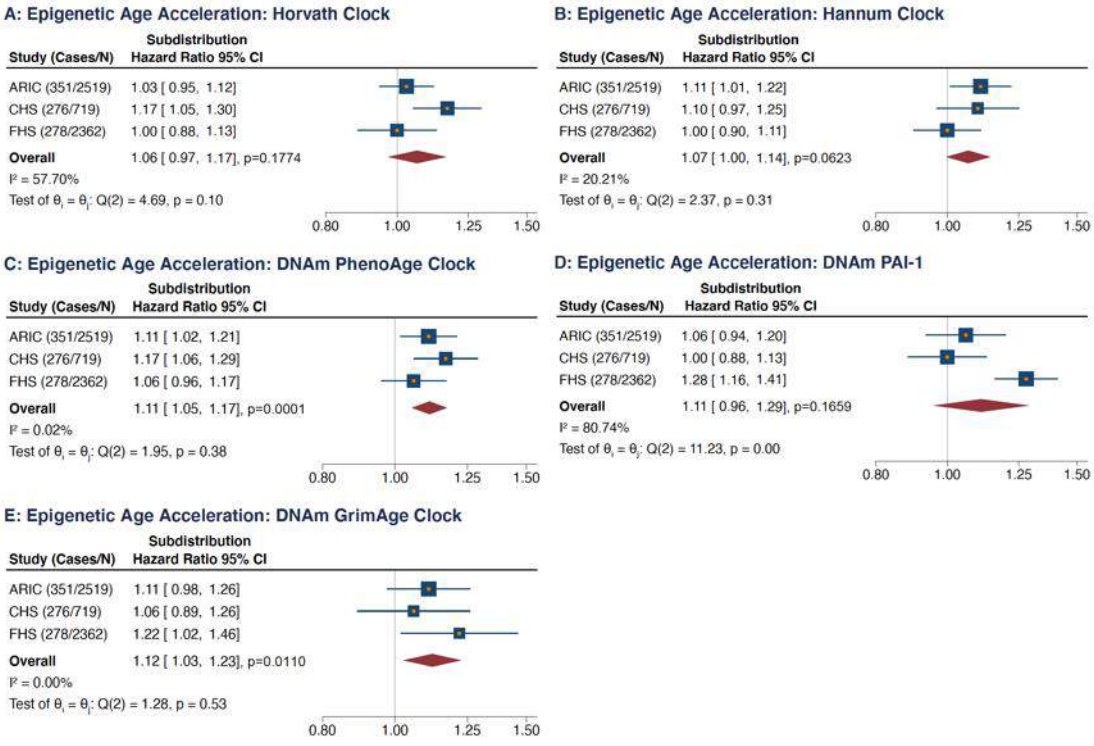
HRs are per 5-year increment in each age measure**,** per standard deviation increment for DNAm PAI-1.

Analyses also adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 3: Meta-Analyses of Competing Risk Regression Models Evaluating Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



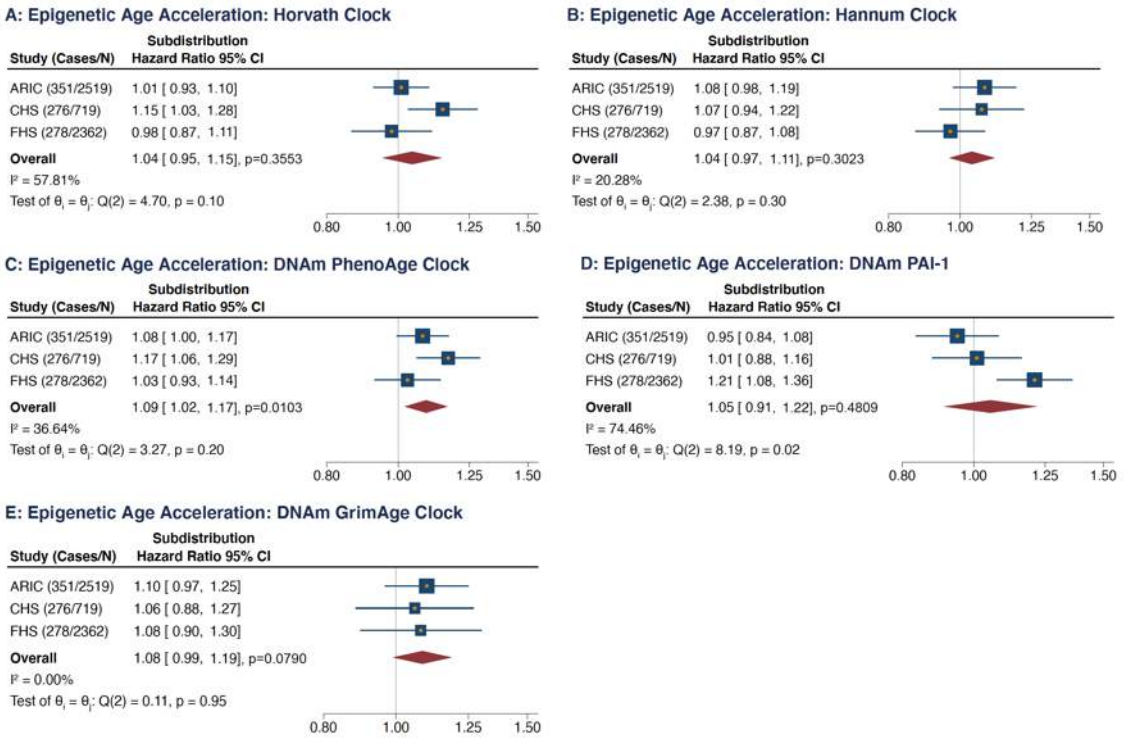
Subdistribution Hazard Ratios (competing risk of death) are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for chronological age, sex, race, smoking variables, and technical factors (cell types, sample batch, laboratory site, and follow-up visit).

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 4: Meta-Analyses of Multivariable Competing Risk Regression Models Evaluating Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



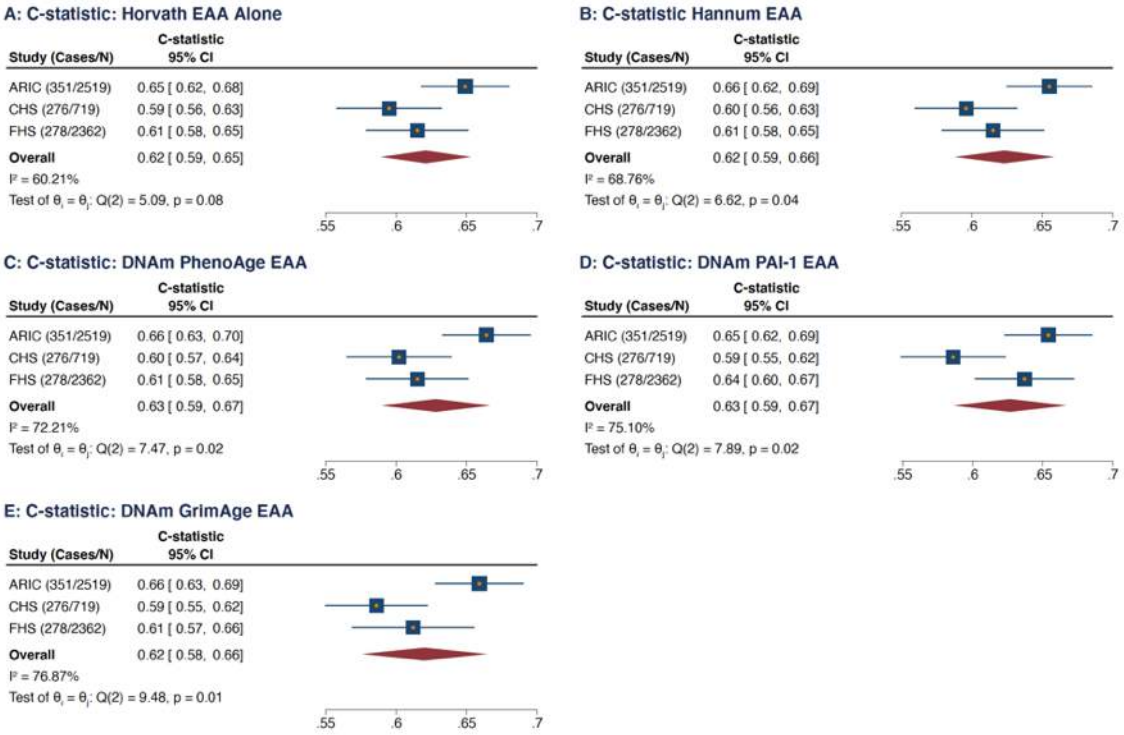
Subdistribution Hazard Ratios (competing risk of death) are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 5: Evaluation of the Risk Predictive Capacity of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation Through Time-Dependent C-statistics. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

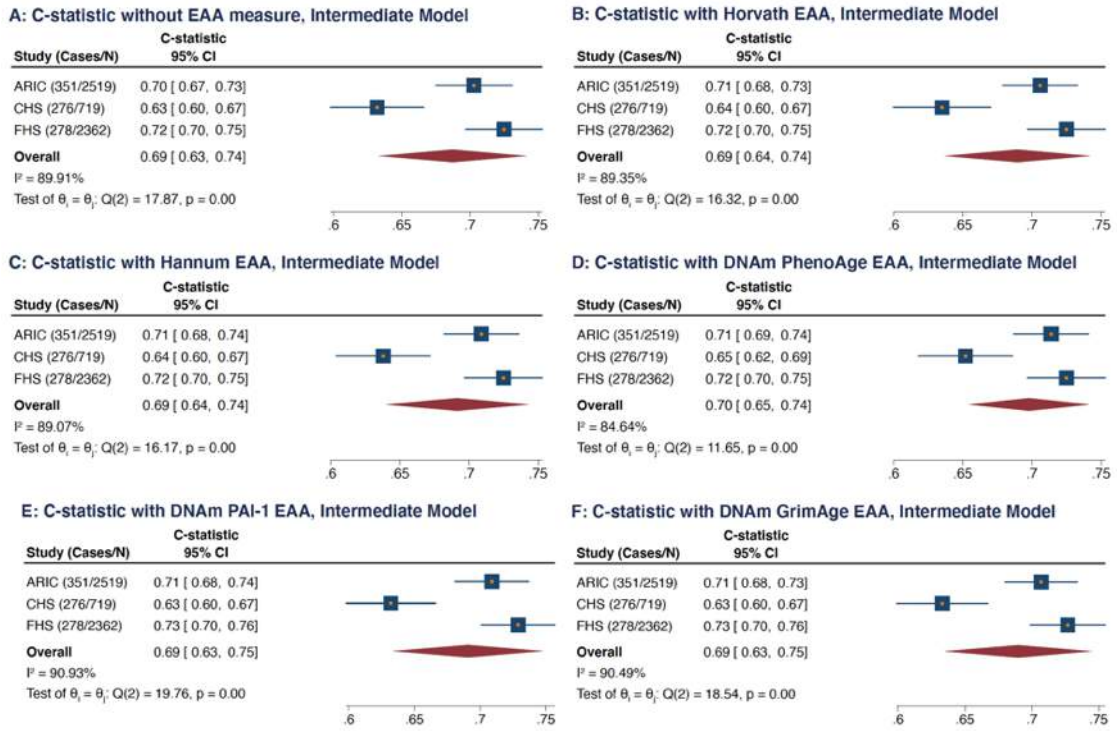


Models additionally include technical factors (cell types, sample batch, laboratory site, and follow-up visit).

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 6: Evaluation of the Impact of the Addition of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation on the Time-Dependent C-statistic for the Intermediate Model. (**A**) Intermediate Model (**B**) Horvath clock, (**C**) Hannum clock, (**D**) DNAm PhenoAge clock, (**E**) DNAm PAI-1, (**F**) DNAm GrimAge clock.

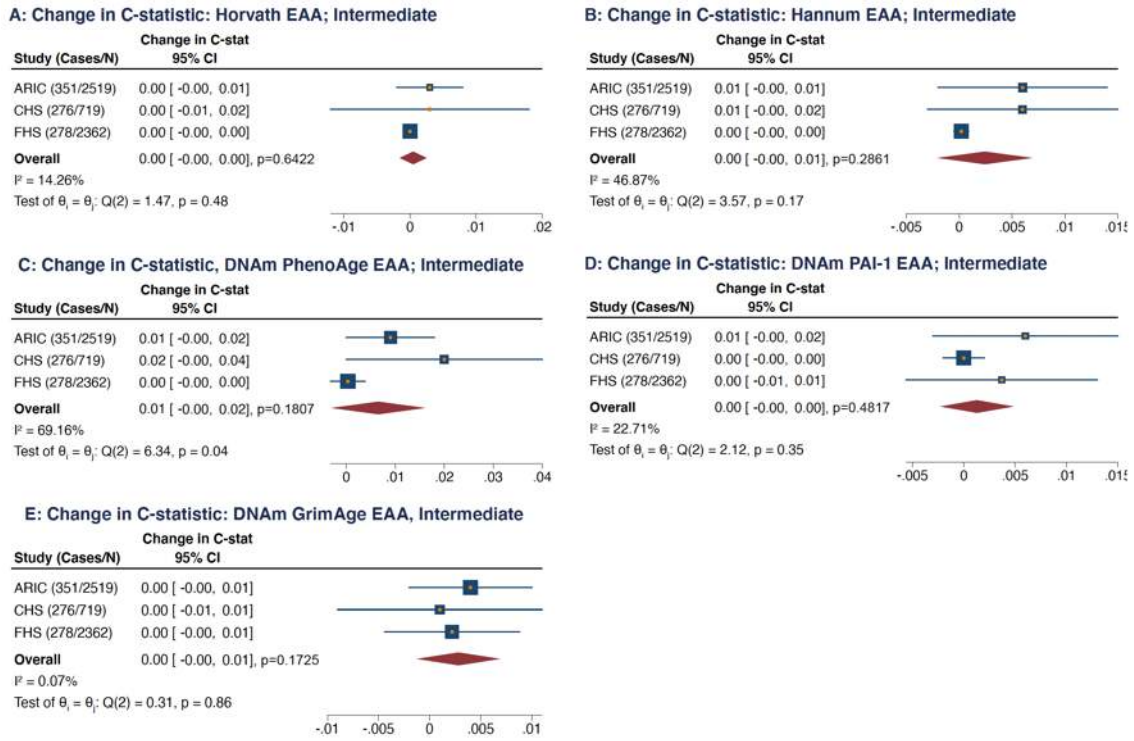


Intermediate model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, race, smoking variables.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 7: Change in the Time-Dependent C-statistics for the Intermediate Model for Incident Atrial Fibrillation Prediction Following the Addition of 5 Epigenetic Age Acceleration Measures. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.

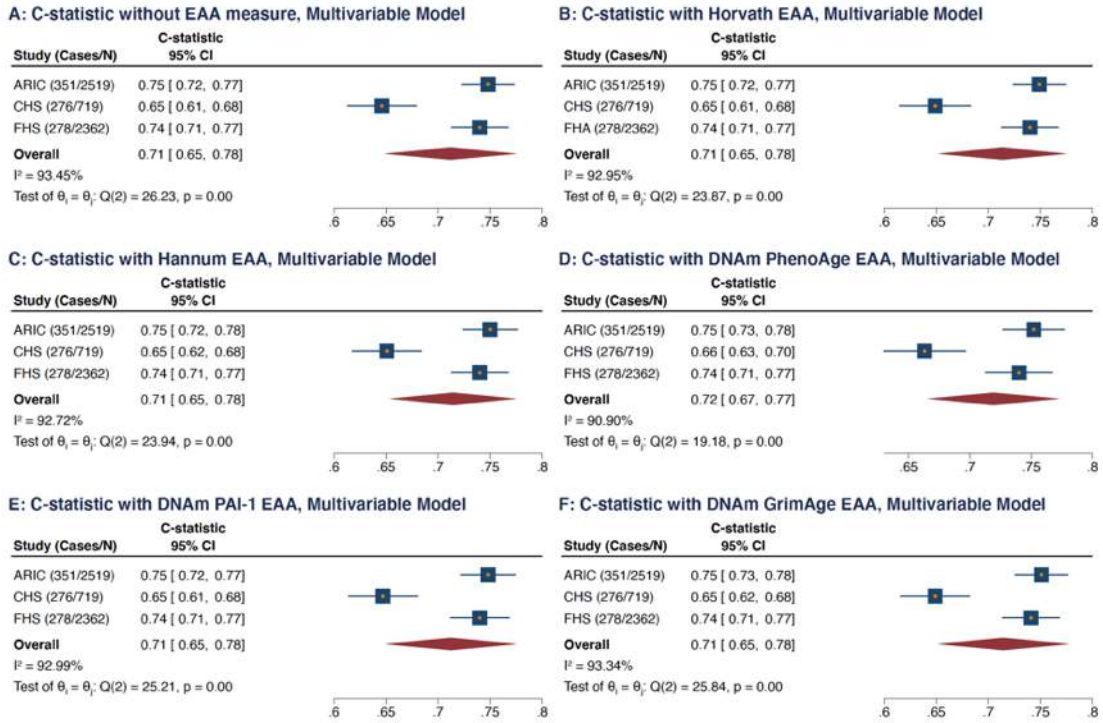


Intermediate model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, race, smoking variables.

EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 8: Evaluation of the Impact of the Addition of 5 Epigenetic Age Acceleration Measures for Incident Atrial Fibrillation on the Time-Dependent C-statistic for the Multivariable Model. (**A**) Multivariable Model (**B**) Horvath clock, (**C**) Hannum clock, (**D**) DNAm PhenoAge clock, (**E**) DNAm PAI-1, (**F**) DNAm GrimAge clock.

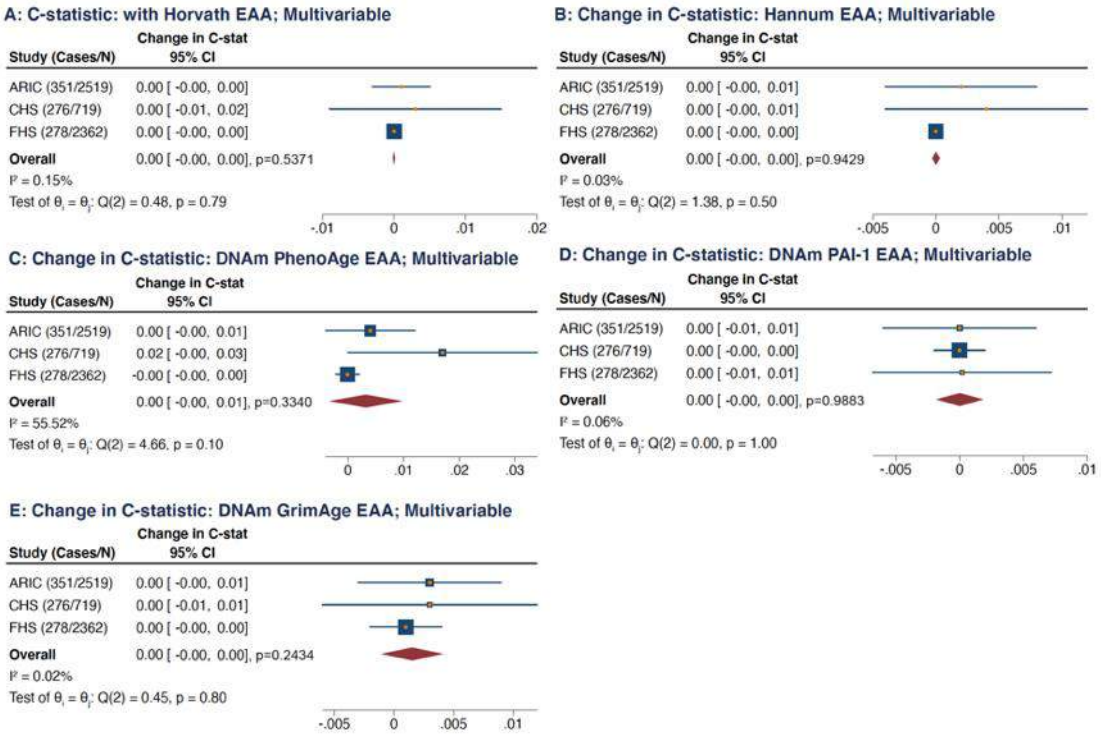


Multivariable model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 9: Change in the Time-Dependent C-statistics for the Multivariable Model for Incident Atrial Fibrillation Prediction Following the Addition of 5 Epigenetic Age Acceleration Measures. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock

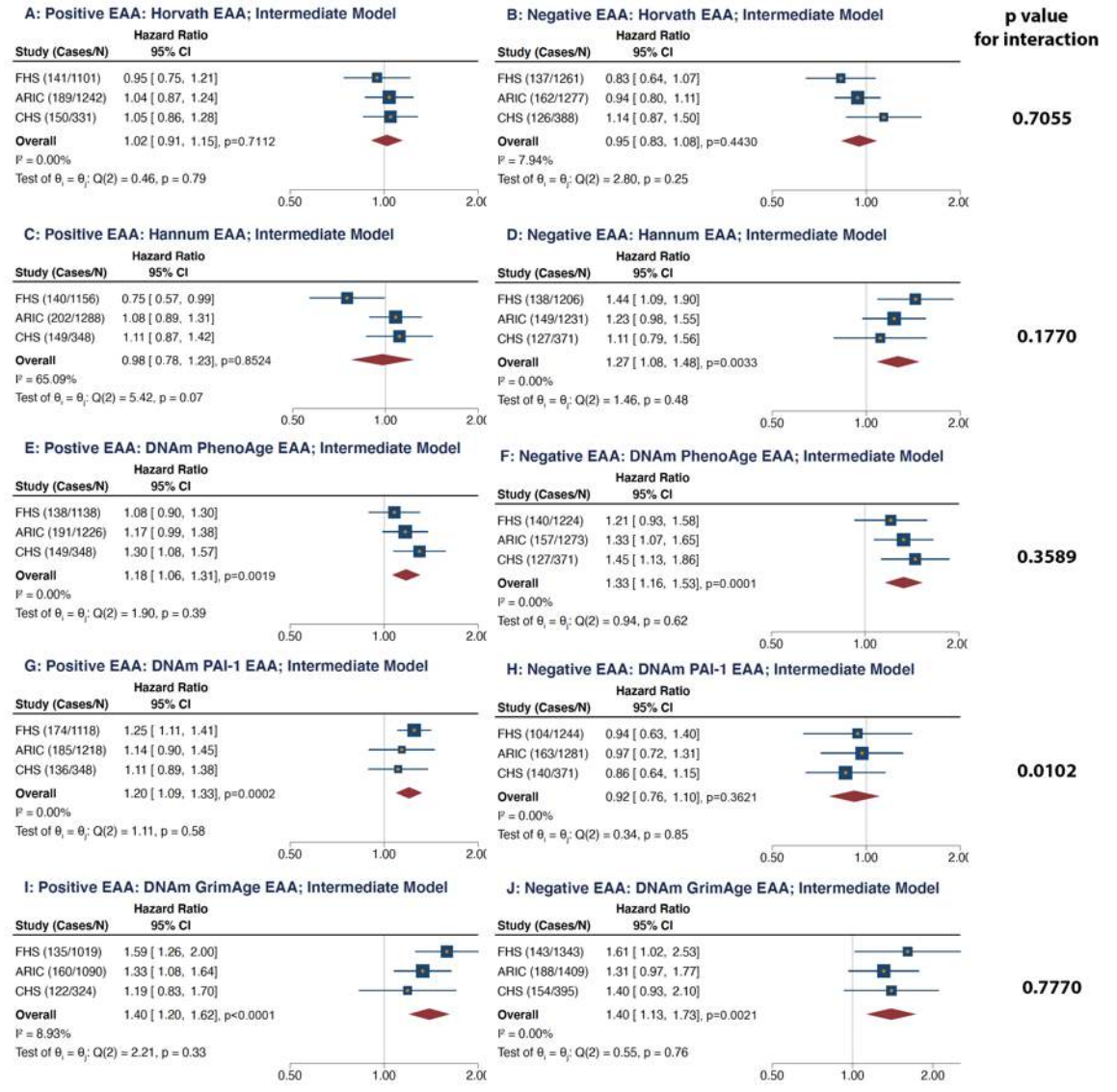


Multivariable model includes technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 10: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation Stratified by Positive and Negative Epigenetic Age Acceleration Status for the Intermediate Model. (**A**) Horvath clock; Positive EAA, (**B**) Horvath clock; Negative EAA, (**C**) Hannum clock; Positive EAA, (**D**) Hannum clock; Negative EAA, (**E**) DNAm PhenoAge clock; Positive EAA, (**F**) DNAm PhenoAge clock; Negative EAA (**G**) DNAm PAI-1; Positive EAA, (**H**) DNAm PAI-1; Negative EAA, (**I**) DNAm GrimAge clock; Positive EAA, (**J**) DNAm GrimAge clock; Negative EAA.



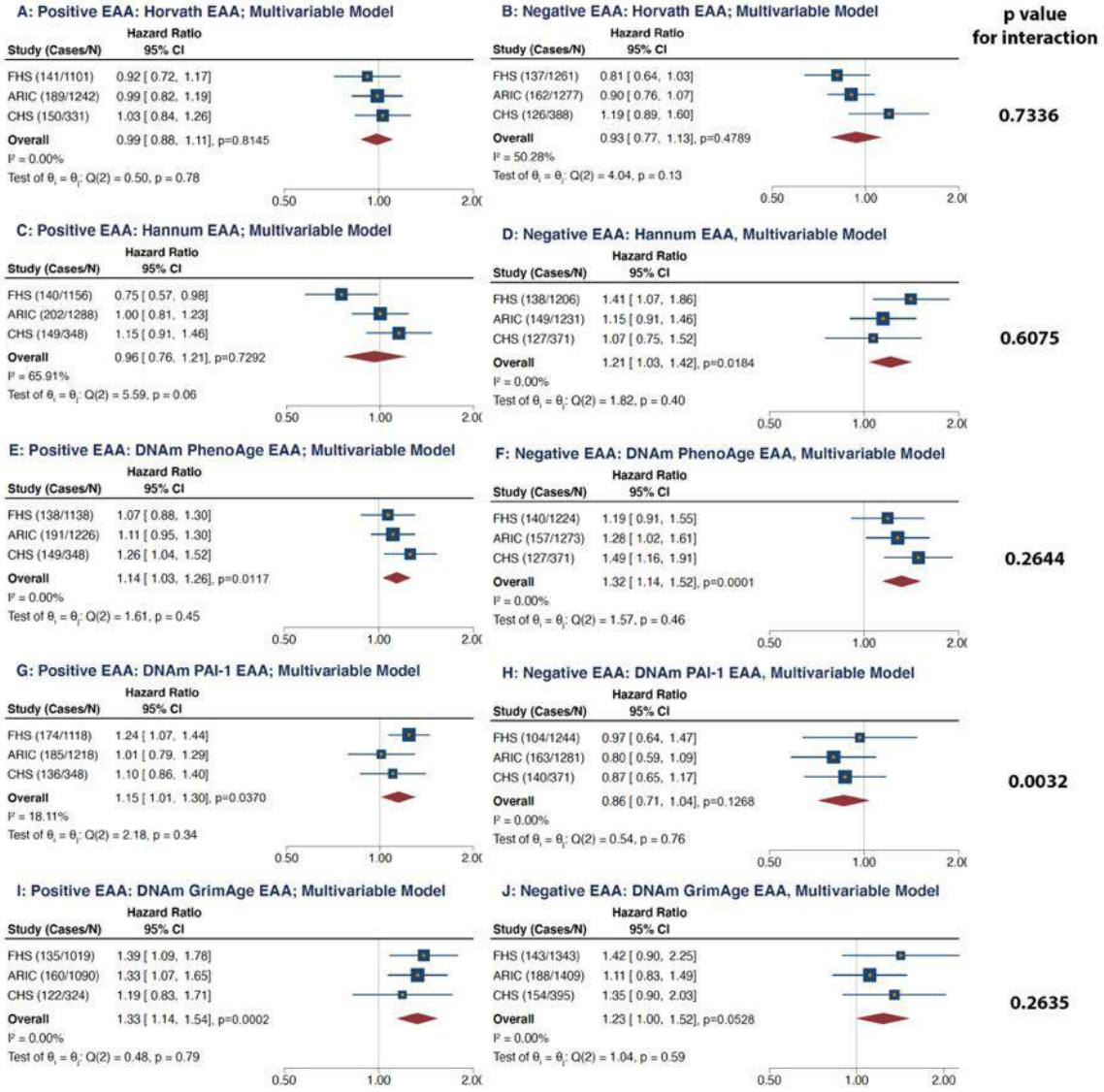
HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for chronological age, sex, race, smoking variables, and technical factors. Technical factors include cell types, sample batch, laboratory site, and follow-up visit.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 11: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation Stratified by Positive and Negative Epigenetic Age Acceleration Status for the Multivariable Model. (**A**) Horvath clock; Positive EAA, (**B**) Horvath clock; Negative EAA, (**C**) Hannum clock; Positive EAA, (**D**) Hannum clock; Negative EAA, (**E**) DNAm PhenoAge clock; Positive EAA, (**F**) DNAm PhenoAge clock; Negative EAA (**G**) DNAm PAI-1; Positive EAA, (**H**) DNAm PAI-1; Negative EAA, (**I**) DNAm GrimAge clock; Positive EAA, (**J**) DNAm GrimAge clock; Negative EAA.



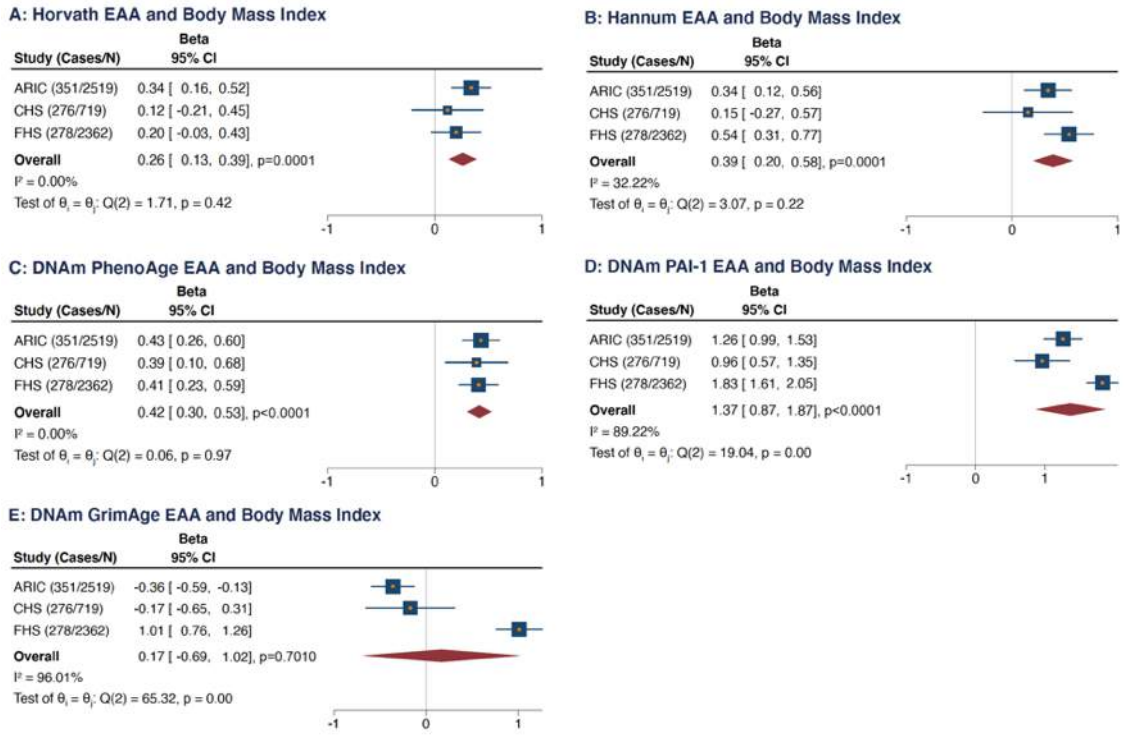
HRs are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, female sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 12: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Body Mass Index. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



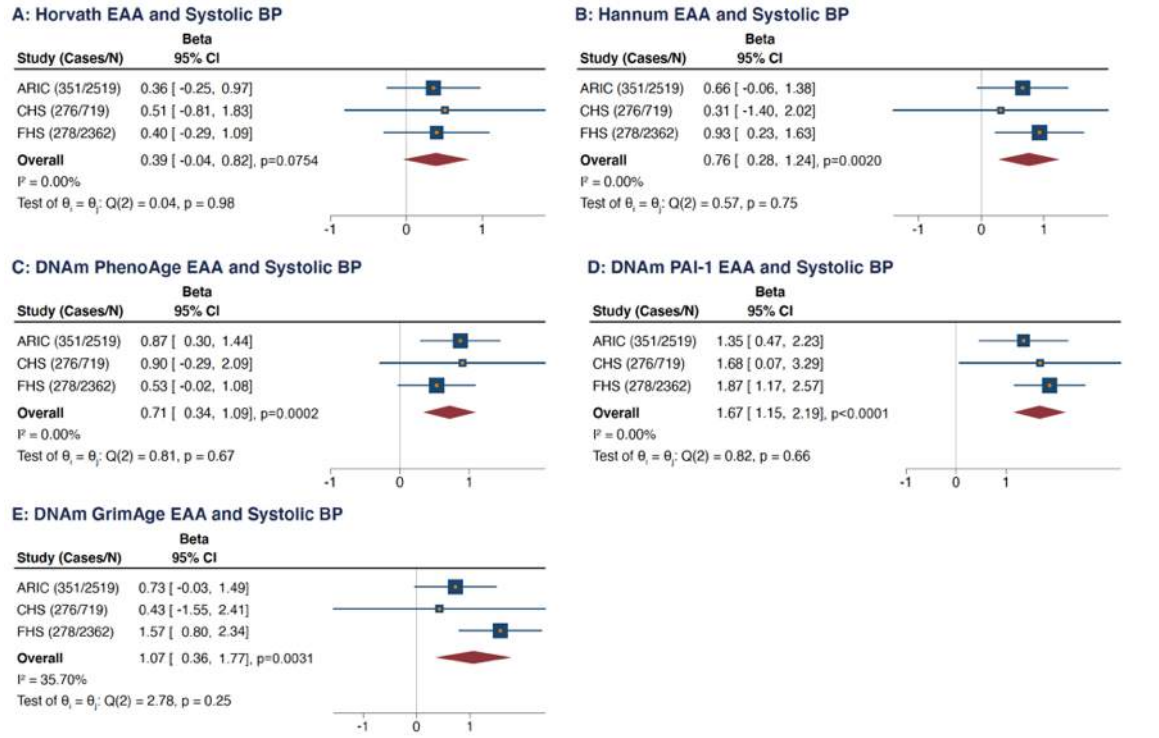
Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 unit increase in Body Mass Index.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 13: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Systolic Blood Pressure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



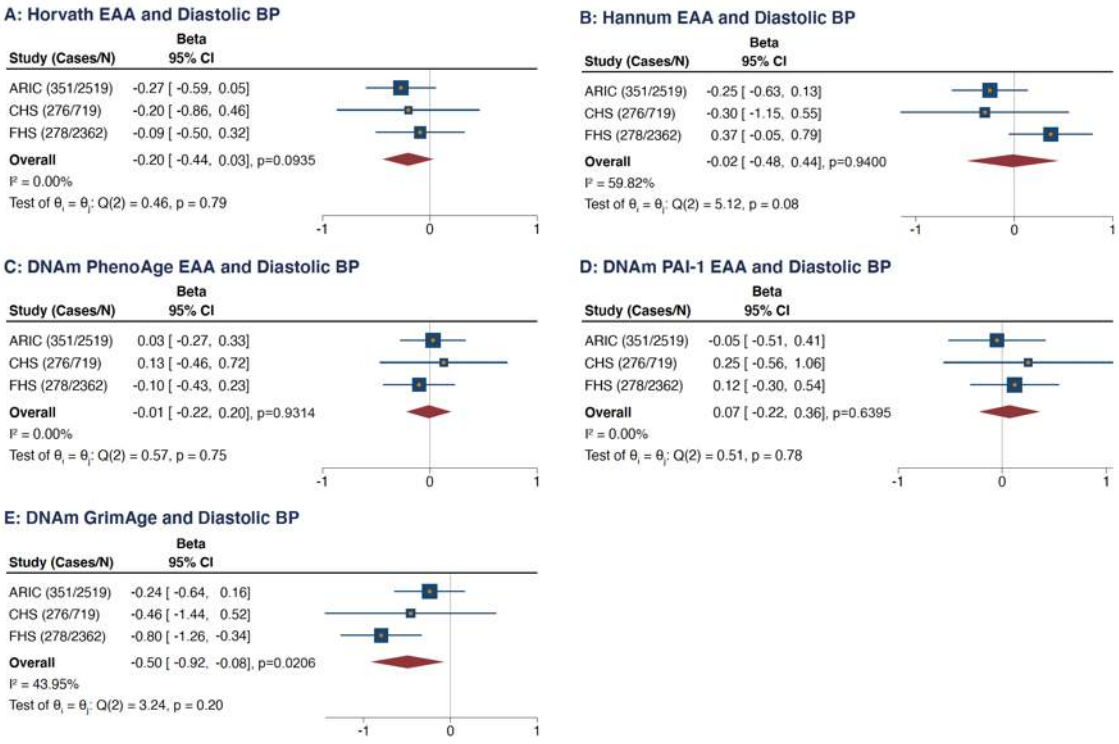
Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 mm Hg increase in Systolic Blood Pressure.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 14: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Baseline Diastolic Blood Pressure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



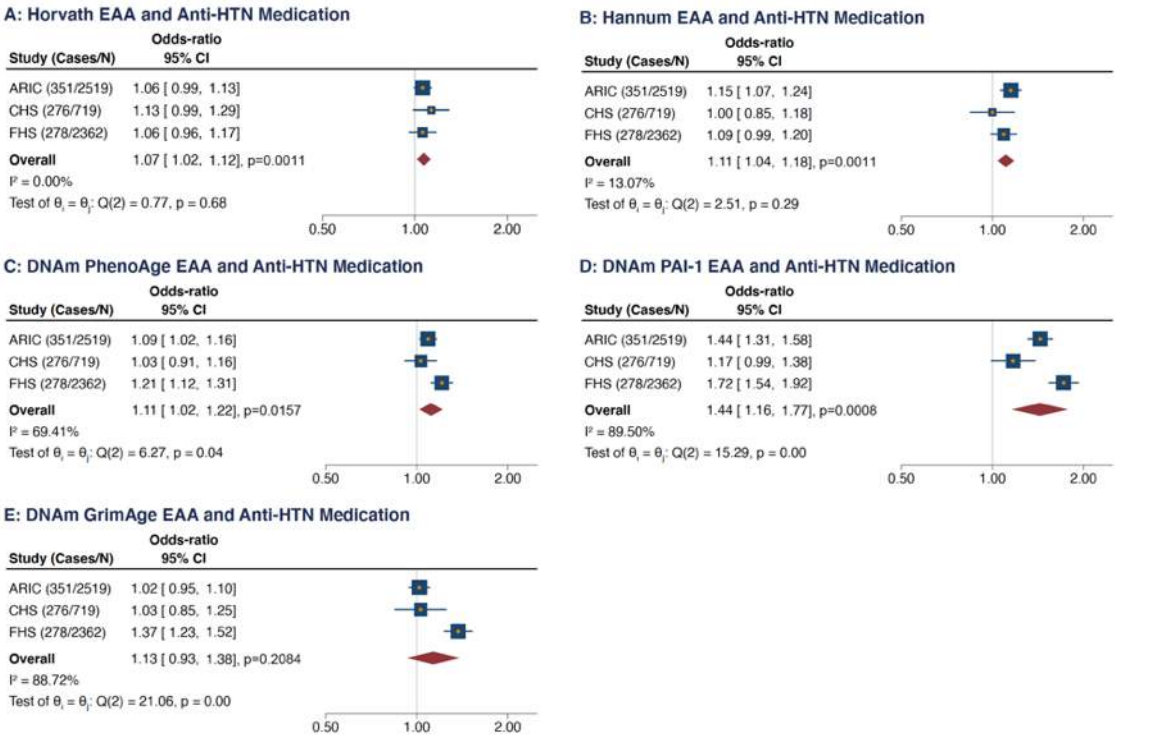
Beta coefficients are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1 and per 1 unit increase in Body Mass Index.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 15: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Prevalent Use of Anti-Hypertensive Medication. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



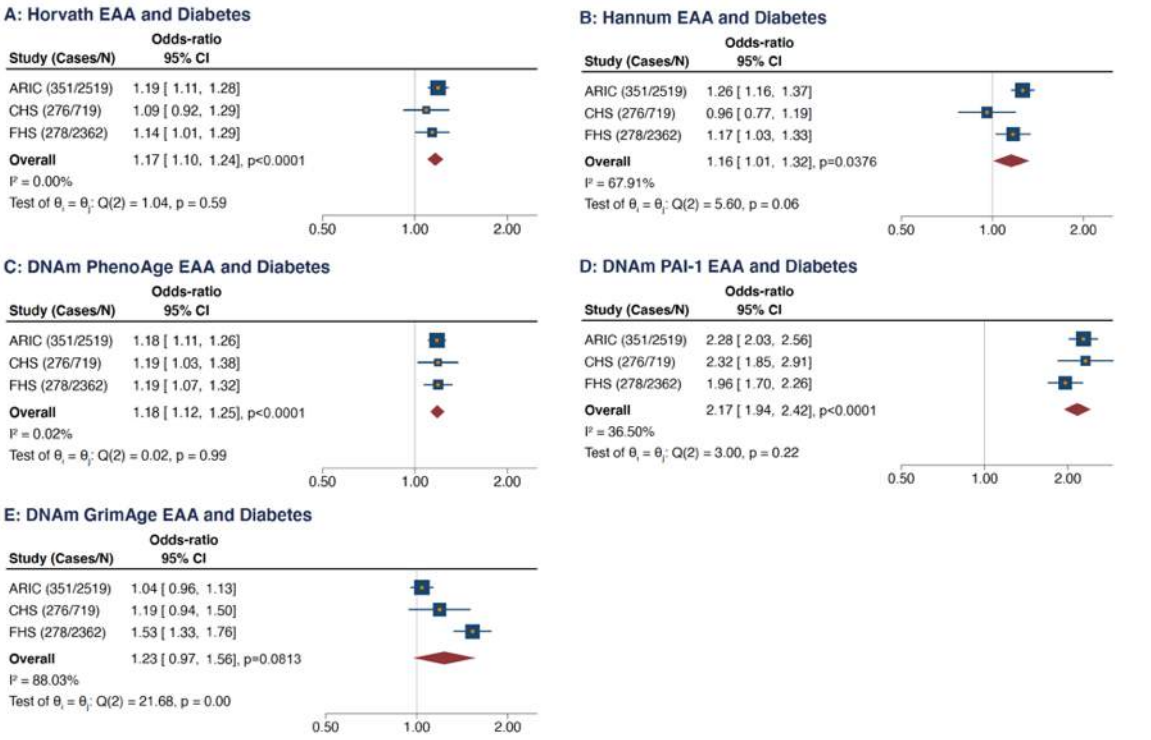
Odds ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 16: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Prevalent Diabetes. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



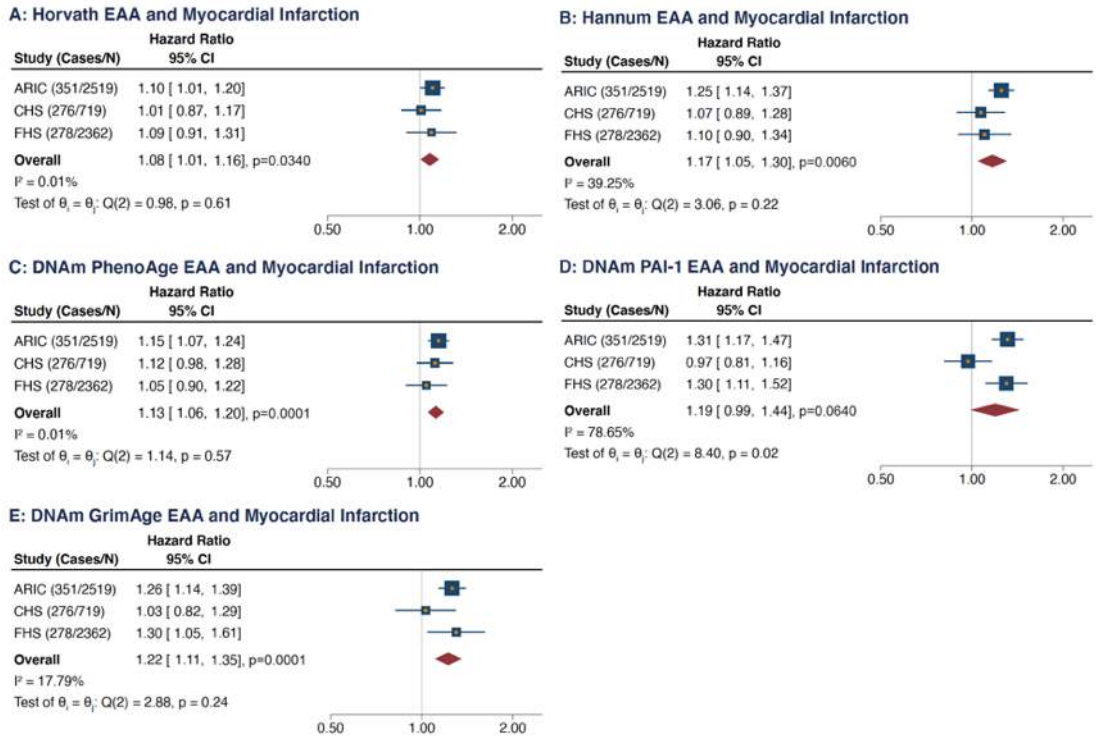
Odds ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 17: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Congestive Heart Failure. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



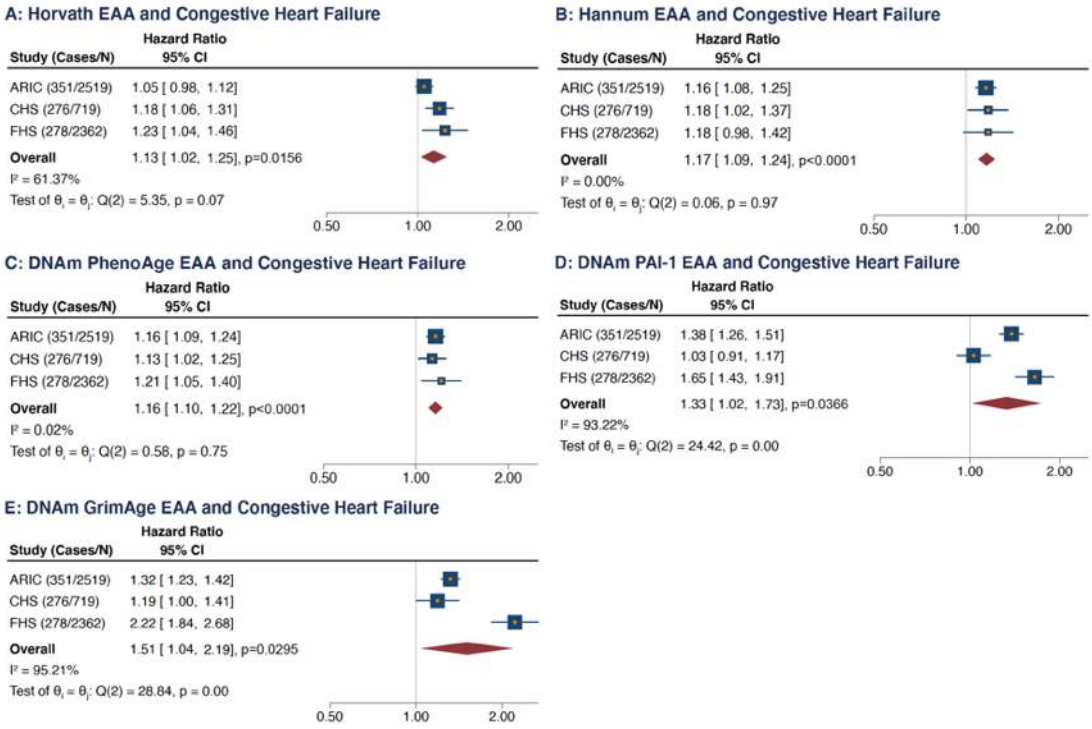
Hazard ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 18: Meta-Analyses of the Associations Between 5 Epigenetic Age Acceleration Measures and Incident Myocardial Infarction. (**A**) Horvath clock, (**B**) Hannum clock, (**C**) DNAm PhenoAge clock, (**D**) DNAm PAI-1, (**E**) DNAm GrimAge clock.



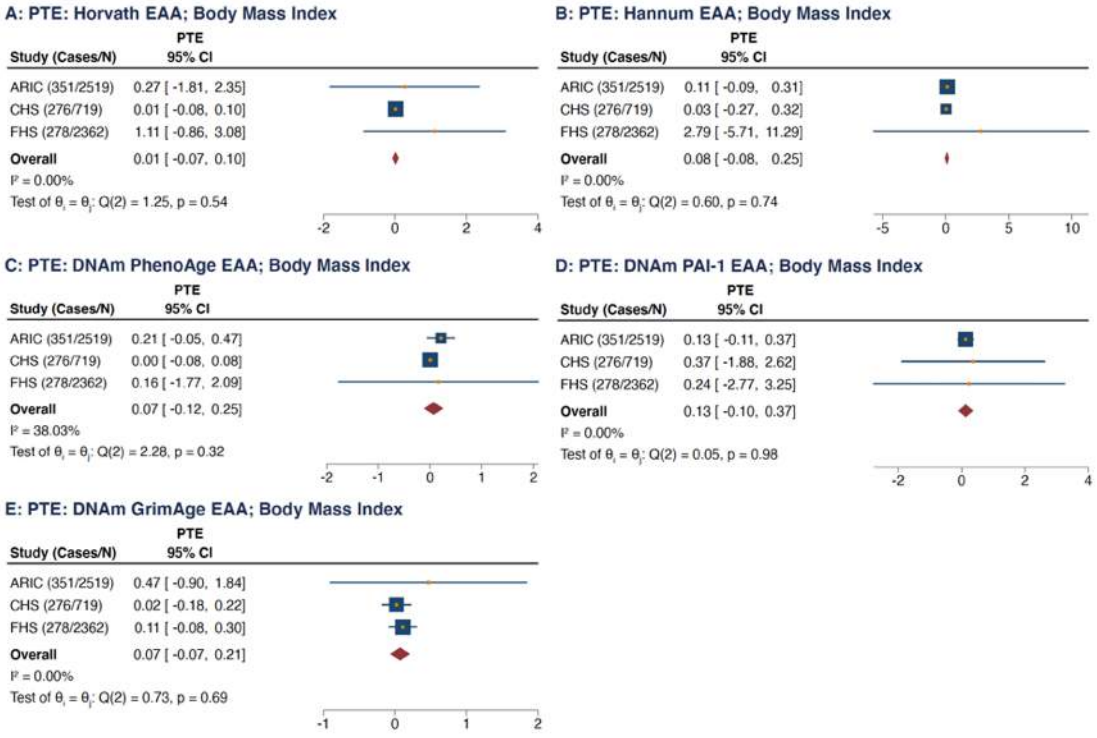
Hazard ratios are per 5-year increment in each age measure, per standard deviation increment for DNAm PAI-1.

Analyses adjusted for technical factors (cell types, sample batch, laboratory site, and follow-up visit), chronological age, sex, and race.

CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

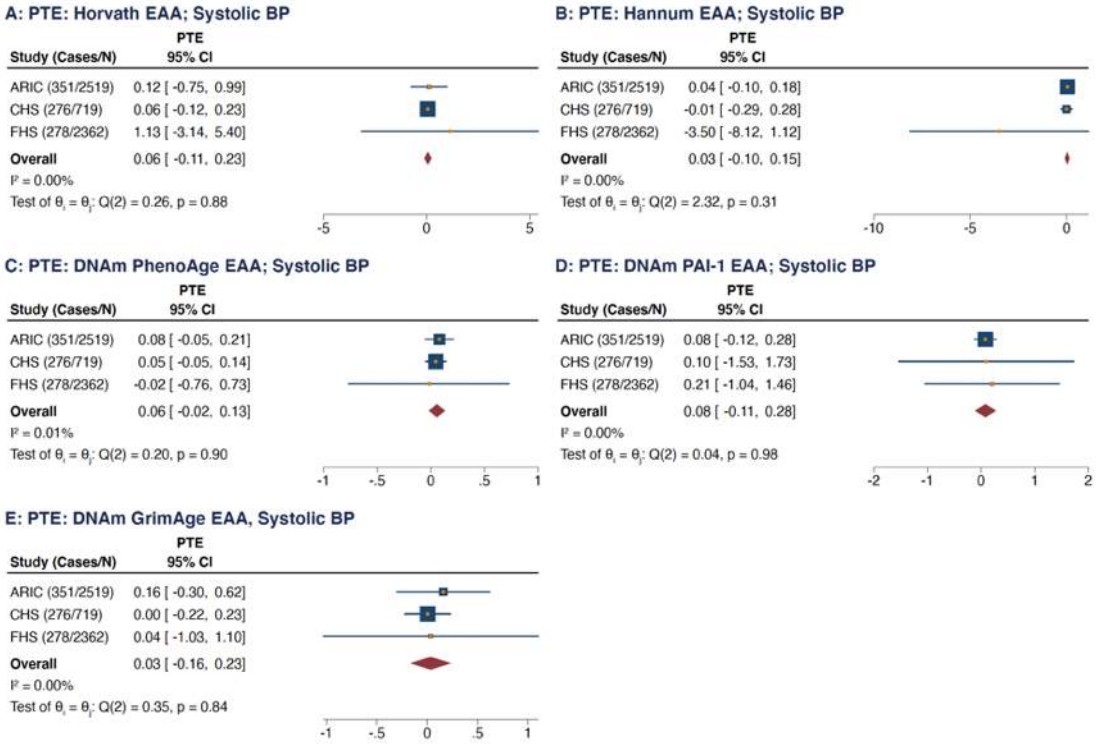
Supplemental Figure 19: **Proportion of Treatment Effect (PTE) for Body Mass Index on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

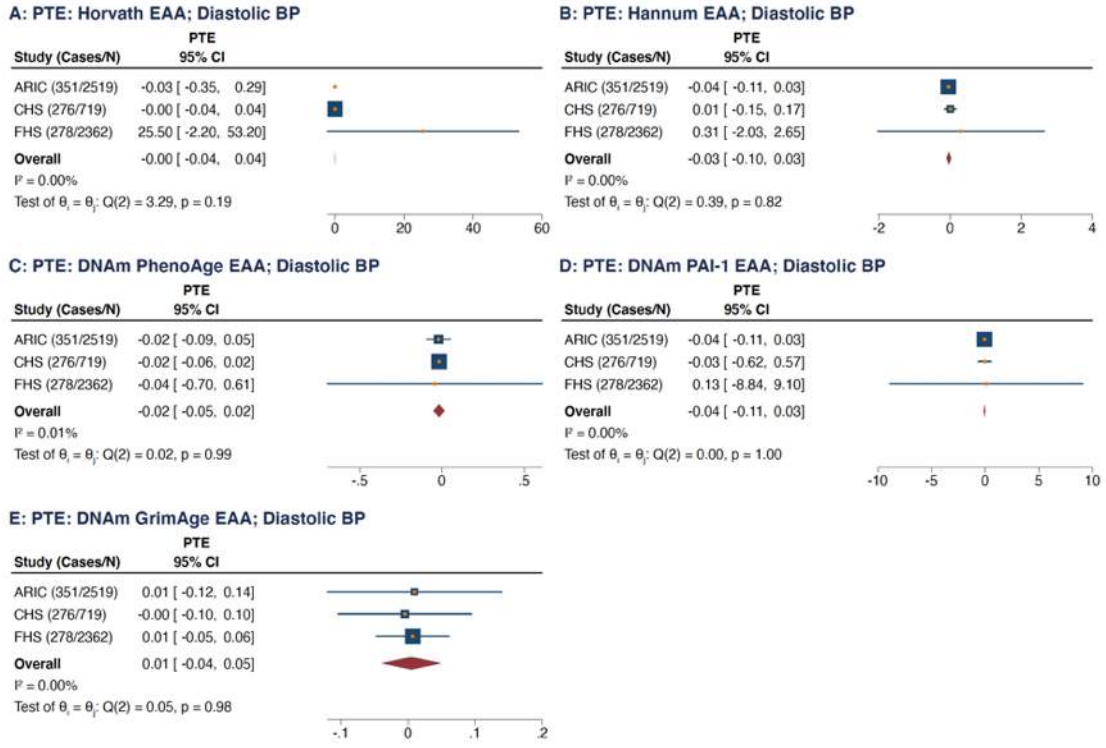
Supplemental Figure 20: **Proportion of Treatment Effect (PTE) for Systolic Blood Pressure on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

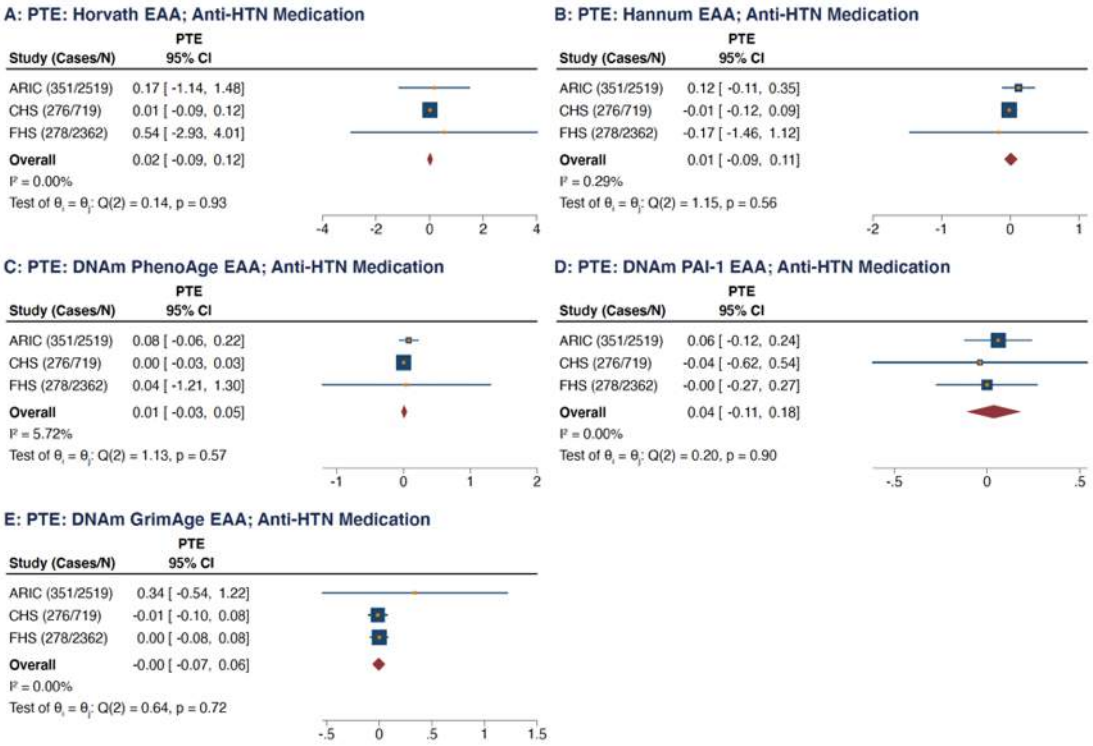
Supplemental Figure 21: **Proportion of Treatment Effect (PTE) for Diastolic Blood Pressure on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

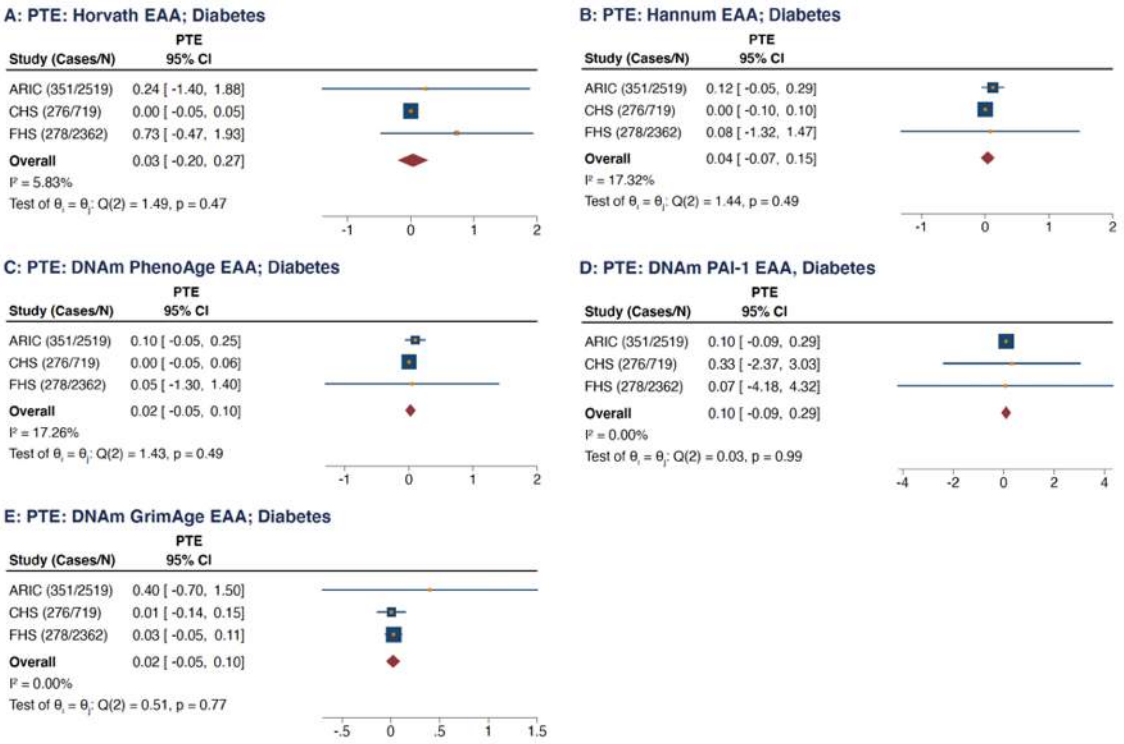
Supplemental Figure 22: **Proportion of Treatment Effect (PTE) for Anti-Hypertensive Medication on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

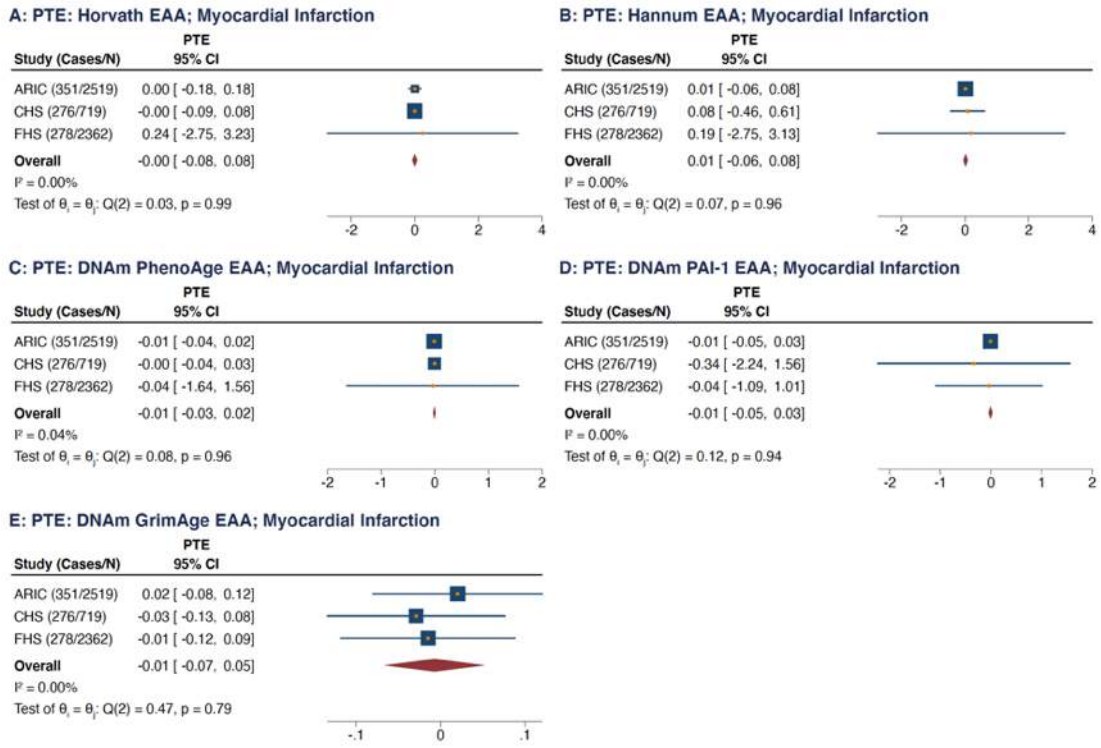
Supplemental Figure 23: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

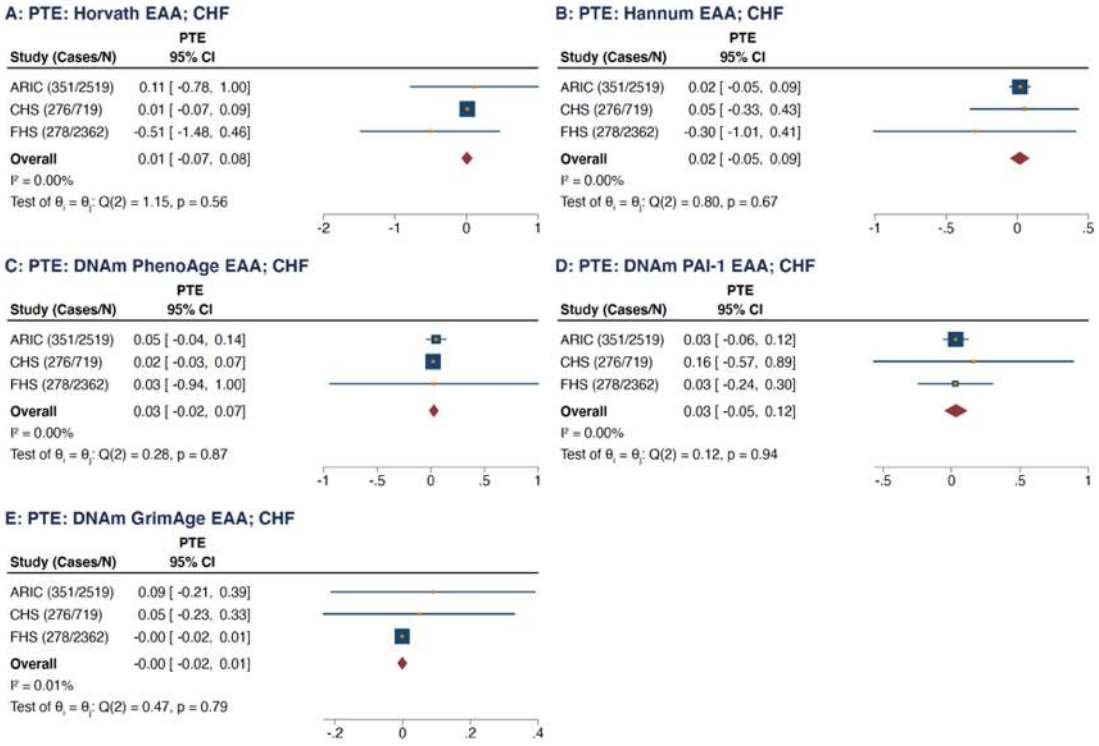
Supplemental Figure 24: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

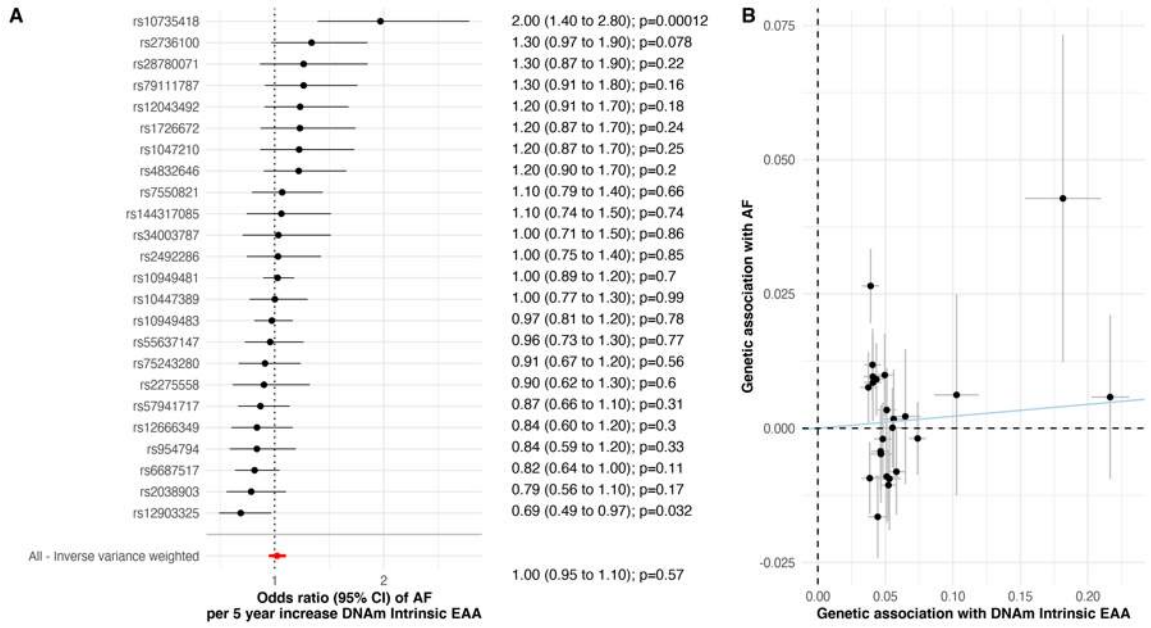
Supplemental Figure 25: **Proportion of Treatment Effect (PTE) for Diabetes on the Association Between 5 Epigenetic Age Acceleration Measures and Incident Atrial Fibrillation.** (A) Horvath clock, (B) Hannum clock, (C) DNAm PhenoAge clock, (D) DNAm PAI-1 epigenetic predictor**,** (E) DNAm GrimAge clock.



PTE = Proportion of Treatment Effect, EAA = epigenetic age acceleration, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study.

Tests for overall effect heterogeneity performed with the Q- and I-squared statistics.

Supplemental Figure 26: Two-Sample Mendelian Randomization Analysis of Horvath Epigenetic Age Acceleration (EAA) Measures and Atrial Fibrillation (AF). **(A)** Forest plot demonstrating collective inverse variance weighted effect estimate and individual effect of each genetic variant associated with the Horvath EAA measure on atrial fibrillation. (**B**) Scatter plot of associations for each Horvath EAA genetic variant with atrial fibrillation (y-axis) and Horvath EAA (x-axis) with line representing inverse variance weighted estimate.



Odds ratios are per 5-year increment in Intrinsic (Horvath) EAA; EAA = epigenetic age acceleration, AF = atrial fibrillation, CI = confidence intervals

Supplemental Table 1: Clinical Variables Included in the Intermediate Mode Evaluating for Associations Between Measures of Epigenetic Age Acceleration and Incident Atrial Fibrillation

Clinical Variables
Chronological Age (years)
Sex (Male/Female)
Race (White/Black)
Cigarette Smoking (Current, Past, Never [reference])
Cigarette Smoking - Pack Years

Supplemental Table 2: Clinical Variables Included in the Multivariable Model Evaluating for Associations Between Measures of Epigenetic Age Acceleration and Incident Atrial Fibrillation

Clinical Variables
Chronological Age (years)
Sex (Male/Female)
Race (White/Black)
BMI (kg/m^2)
Cigarette Smoking (Current, Past, Never [reference])
Cigarette Smoking - Pack Years
Systolic BP (mm Hg)
Diastolic BP (mm Hg)
Hypertensive Medication (Yes/No)
Diabetes Mellitus (Yes/No)
Prior Heart Failure
Prior Myocardial Infarction

BMI = body mass index, kg/m^2 = kilograms/meters^2, BP = blood pressure, mm Hg = millimeters of mercury

Supplemental Table 3: Sensitivity Analyses Evaluating Associations of DNAm GrimAge Epigenetic Age Acceleration with Incident Atrial Fibrillation in the Framingham Heart Study Adjusting for the "Training" Subgroup of Study Participants used for Derivation of the DNAm GrimAge clock.

Model*	DNAm GrimAge EAA HR (95% CI)	
	No Train**	Train**
1	1.18 (1.03-1.35)	1.18 (1.03-1.35)
2	1.15 (0.96-1.38)	1.15 (0.95-1.38)

*Model 1: Adjusted for technical covariates, chronological age and sex; Model 2: Adjusted for technical covariates, chronological age, sex, body mass index, smoking status, smoking pack year, systolic blood pressure, diastolic blood pressure, hypertensive medication, diabetes, history of congestive heart failure, history of myocardial infarction.

**No Train and Train: Cox models unadjusted and adjusted for the subgroup of study participants used to derive the DNAm GrimAge clock, respectively.

EAA = epigenetic age acceleration, HR = hazard ratio, CI = confidential interval

Supplemental Table 4: Associations of Chronological Age and Epigenetic Clocks with Incident Atrial Fibrillation Adjusted for Technical Factors

Cohort	Chronological Age	Epigenetic Clocks; HR (95% CI)				
	HR (95% CI)	Horvath	Hannum	DNAm PhenoAge	DNAm PAI-1	DNAm GrimAge
FHS	1.46 (1.37-1.57)	1.35 (1.26-1.45)	1.36 (1.26-1.46)	1.30 (1.22-1.39)	1.33 (1.22-1.46)	1.46 (1.35-1.58)
ARIC	1.51 (1.38-1.66)	1.27 (1.19-1.35)	1.39 (1.29-1.49)	1.33 (1.25-1.42)	1.28 (1.14-1.43)	1.45 (1.34-1.57)
CHS	1.30 (1.15-1.47)	1.26 (1.16-1.37)	1.28 (1.16-1.41)	1.27 (1.18-1.38)	1.05 (0.93-1.19)	1.26 (1.11-1.41)
Meta-Analysis						
Combined Estimate	1.44 (1.34-1.54)	1.29 (1.24-1.35)	1.35 (1.30-1.42)	1.30 (1.25-1.36)	1.22 (1.06-1.40)	1.40 (1.29-1.52)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.0056	<0.0001
Tests for Overall Effect						
Heterogeneity						
Q-statistic (p-value)	0.153	0.350	0.395	0.689	0.010	0.080
I-squared (%)	44.02	5.49	0.00	0.00	79.81	63.14

HRs are per 5-year increment in each age measure and per standard deviation increment for DNAm PAI-1**.** Cox models for chronological age are unadjusted and those for epigenetic measures are only adjusted for technical factors, including cell types, sample batch, laboratory site, and follow-up visit. HR = hazard ratio, CI = confidence intervals, FHS = Framingham Heart Study, ARIC = Atherosclerosis Risk in Communities, CHS = Cardiovascular Health Study

Supplemental Table 5: Results of sensitivity analyses for Mendelian randomization analyses of Epigenetic Age Acceleration Measures on Atrial Fibrillation.

Exposure	Intercept of MR-Egger (95% CI) for directional pleiotropy	Cochran's Q for heterogeneity	Effect Estimate from MR-RAPS (95% CI)
Horvath EAA	0.0022 (-0.009 to 0.013); p=0.70	40; p=0.014	1.02 (0.95 to 1.09); p=0.62
Hannum EAA	-0.0053 (-0.022 to 0.011); p=0.55	3.3; p=0.85	1.04 (0.923 to 1.16); p=0.54
DNAm PhenoAge EAA	-0.0015 (-0.016 to 0.013); p=0.84	12.4; p=0.34	1.03 (0.96 to 1.11); p=0.36
DNAm PAI-1 EAA	-0.044 (-0.150 to 0.058); p=0.46	3.1; p=0.38	1.12 (0.92 to 1.36); p=0.25
DNAm GrimAge EAA	0.11 (-0.017 to 0.240); p=0.23	3.1; p=0.38	1.12 (0.92 to 1.36); p=0.25

CI = confidence interval, EAA = Epigenetic Age Acceleration