

SUPPLEMENTARY DATA

Supplementary Table 1. Average pairwise correlations between chronological age, epigenetic age based on the Horvath method, and epigenetic age based on Hannum.

	Age	Epigenetic age (Horvath)	Epigenetic age (Hannum)
Age	-	0.74	0.81
Epigenetic age (Horvath)	0.74	-	0.76
Epigenetic age (Hannum)	0.81	0.76	-

Supplementary Table 2. Correlations between estimated blood cell abundances and chronological age.

Cohort	Plasmablasts	CD8+CD28- CD45RA-	CD8+ naive	CD4+ naive	CD8+ total	CD4+ total	NK cells	B cells	Monocytes	Granulocytes
ARIC	0.03	0.16	-0.22	-0.13	-0.06	-0.08	0.13	-0.08	0.09	0.04
FHS	0.23	0.36	-0.38	-0.22	-0.19	-0.23	0.20	-0.27	0.17	0.16
InCHIANTI	0.06	0.32	-0.43	-0.34	-0.19	-0.20	0.23	-0.20	0.08	0.11
KORA	0.20	0.48	-0.53	-0.37	-0.07	-0.37	0.12	-0.22	0.20	0.16
LBC1921	0.03	0.03	-0.14	-0.09	0.10	0.01	0.05	-0.07	0.10	-0.07
LBC1936	0.11	0.04	-0.05	-0.09	-0.03	0.00	-0.05	-0.13	-0.09	0.05
NAS	0.04	0.28	-0.21	-0.07	0.01	-0.16	0.12	-0.10	-0.01	0.08
RSIII	0.11	0.20	-0.26	-0.16	-0.10	-0.14	0.06	-0.16	0.14	0.11
TwinsUK	-0.02	0.21	-0.35	-0.08	-0.14	0.07	0.27	-0.02	0.10	-0.14
WHI White	0.09	0.21	-0.17	-0.13	-0.13	-0.10	0.17	-0.12	0.10	0.04
WHI Black	0.12	0.24	-0.21	-0.13	-0.07	-0.17	0.16	-0.18	0.11	0.07
WHI Hispanic	0.08	0.26	-0.21	-0.15	-0.11	-0.13	0.17	-0.10	0.03	0.08
MEAN	0.09	0.23	-0.26	-0.16	-0.08	-0.12	0.14	-0.14	0.09	0.06

The values shown are robust correlation coefficients (biweight midcorrelation, which is based on medians). Colors reflect the direction and magnitude of the correlation coefficients (blue=negative correlation, red=positive correlation).

Supplementary Table 3. Descriptive statistics of measures of epigenetic age acceleration by cohort.

Epigenetic age acceleration measure	Cohort	SD	Min	25th percentile	Median (50th percentile)	75th percentile	Max
<i>AgeAccel</i>	ARIC	5.081	-34.380	-3.191	-0.100	3.220	25.620
<i>AgeAccel</i>	FHS	4.621	-16.490	-3.110	-0.367	2.460	35.160
<i>AgeAccel</i>	InCHIANTI	4.999	-33.600	-3.084	-0.338	2.223	29.770
<i>AgeAccel</i>	KORA	4.937	-24.810	-3.423	-0.117	2.905	20.660
<i>AgeAccel</i>	LBC1921	6.971	-24.240	-3.884	-0.170	3.943	39.730
<i>AgeAccel</i>	LBC1936	6.485	-30.160	-3.879	0.116	3.801	42.100
<i>AgeAccel</i>	NAS	5.365	-16.930	-3.706	-0.498	2.909	32.830
<i>AgeAccel</i>	RSIII	6.003	-18.570	-4.325	-0.046	4.276	20.050
<i>AgeAccel</i>	TwinsUK	4.108	-13.760	-2.514	0.274	2.899	13.560
<i>AgeAccel</i>	WHI (white)	5.153	-22.560	-2.843	-0.103	3.443	22.790
<i>AgeAccel</i>	WHI (Black)	6.091	-21.900	-5.424	-1.977	1.824	39.930
<i>AgeAccel</i>	WHI (Hispanic)	4.494	-14.080	-3.831	-0.535	2.458	14.790
<i>AgeAccel</i>	BLSA	4.828	-11.620	-2.966	0.290	3.197	25.180
<i>AgeAccel</i>	ARIC	5.914	-38.770	-3.766	0.105	3.648	39.350
<i>AgeAccelHannum</i>	FHS	5.279	-23.480	-3.303	-0.174	3.001	36.680
<i>AgeAccelHannum</i>	InCHIANTI	6.028	-43.640	-3.152	0.431	3.573	31.490
<i>AgeAccelHannum</i>	KORA	4.996	-30.280	-3.266	-0.314	2.711	37.410
<i>AgeAccelHannum</i>	LBC1921	7.203	-25.140	-4.574	-0.821	3.722	51.840
<i>AgeAccelHannum</i>	LBC1936	6.670	-27.520	-4.172	0.131	4.183	31.650
<i>AgeAccelHannum</i>	NAS	5.161	-12.250	-3.310	-0.787	2.511	22.750
<i>AgeAccelHannum</i>	RSIII	6.090	-18.600	-3.825	0.115	4.152	17.970
<i>AgeAccelHannum</i>	TwinsUK	5.246	-17.040	-2.949	0.320	3.821	20.260
<i>AgeAccelHannum</i>	WHI (white)	5.557	-23.460	-3.644	-0.086	3.441	21.760
<i>AgeAccelHannum</i>	WHI (Black)	6.317	-23.490	-4.773	-0.891	3.045	31.480
<i>AgeAccelHannum</i>	WHI (Hispanic)	5.357	-12.740	-2.139	1.133	4.469	20.880
<i>AgeAccelHannum</i>	BLSA	5.709	-15.720	-2.942	0.429	3.801	31.730
<i>AgeAccelHannum</i>	ARIC	4.928	-34.020	-3.010	-0.057	3.068	23.810
<i>IEAA</i>	FHS	4.491	-16.010	-2.901	-0.199	2.547	32.160
<i>IEAA</i>	InCHIANTI	4.783	-30.930	-2.898	-0.374	2.364	29.470
<i>IEAA</i>	KORA	4.647	-29.350	-3.276	-0.114	2.761	18.740
<i>IEAA</i>	LBC1921	6.228	-22.890	-3.664	0.135	3.554	24.600
<i>IEAA</i>	LBC1936	6.162	-26.310	-3.596	0.035	3.718	34.090
<i>IEAA</i>	NAS	4.929	-24.190	-3.019	-0.458	2.694	22.500
<i>IEAA</i>	RSIII	5.130	-16.610	-3.330	-0.026	3.387	15.190
<i>IEAA</i>	TwinsUK	4.016	-14.590	-2.257	0.234	2.718	13.100
<i>IEAA</i>	WHI (white)	4.797	-21.460	-2.608	0.183	3.287	21.440

<i>IEAA</i>	WHI (Black)	5.588	-20.320	-3.202	0.067	3.197	42.660
<i>IEAA</i>	WHI (Hispanic)	4.333	-13.520	-3.971	-1.397	1.864	12.480
<i>IEAA</i>	BLSA	4.488	-10.370	-2.658	0.017	3.330	23.120
<i>EEAA</i>	ARIC	6.673	-32.940	-4.096	0.135	4.149	38.560
<i>EEAA</i>	FHS	5.800	-26.100	-3.607	0.113	3.315	38.250
<i>EEAA</i>	InCHIANTI	6.710	-44.360	-3.327	0.576	4.236	33.630
<i>EEAA</i>	KORA	5.405	-26.610	-3.526	-0.339	3.189	37.600
<i>EEAA</i>	LBC1921	7.745	-21.180	-5.262	-0.973	4.306	52.120
<i>EEAA</i>	LBC1936	7.116	-30.590	-4.439	0.168	4.589	31.530
<i>EEAA</i>	NAS	5.596	-13.730	-3.443	-0.579	2.987	23.540
<i>EEAA</i>	RSIII	6.861	-22.380	-4.392	0.267	4.794	21.080
<i>EEAA</i>	TwinsUK	5.840	-22.790	-3.409	0.401	4.023	23.020
<i>EEAA</i>	WHI (white)	6.089	-22.710	-3.888	0.015	4.008	22.320
<i>EEAA</i>	WHI (Black)	6.906	-27.600	-5.735	-1.382	2.827	27.900
<i>EEAA</i>	WHI (Hispanic)	5.779	-14.310	-1.679	2.371	5.651	23.450
<i>EEAA</i>	BLSA	6.256	-18.040	-3.435	0.921	4.724	29.230

Supplementary Table 4. Pairwise correlations (mean and standard error (SE) across cohorts) between blood cell counts estimated from DNA methylation profiles (rows) and several measures of epigenetic age acceleration (columns).

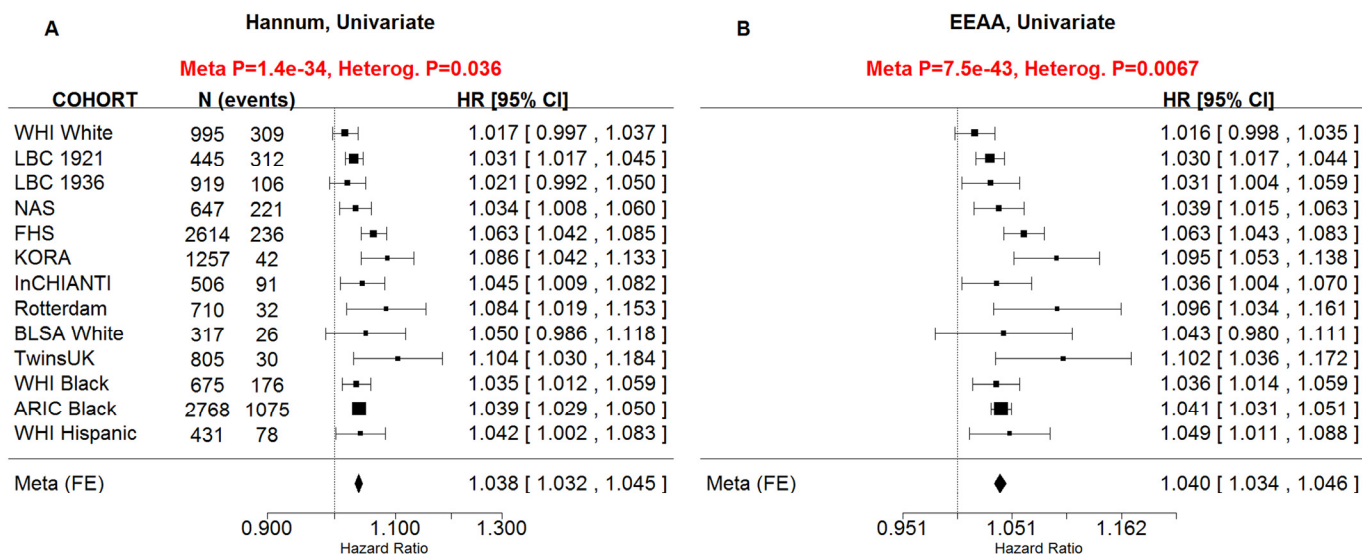
BloodCell	<i>AgeAccel</i> average <i>r</i> (SE)	<i>IEAA</i> average <i>r</i> (SE)	<i>EEAA</i> average <i>r</i> (SE)	<i>AgeAccel_{Hannum}</i> average <i>r</i> (SE)	<i>IEAA.Hannum</i> average <i>r</i> (SE)
Plasma Blast	0.02 (0.031)	0 (0.002)	0.28 (0.034)	0.20 (0.033)	0 (0.018)
Exhausted CD8+	0.18 (0.039)	0 (0.009)	0.50 (0.033)	0.29 (0.044)	0 (0.046)
CD8.naive	-0.18 (0.043)	0 (0.011)	-0.52 (0.04)	-0.35 (0.048)	0 (0.05)
CD4.naive	-0.09 (0.033)	0.07 (0.017)	-0.36 (0.038)	-0.28 (0.041)	0.06 (0.046)
CD8T	0.19 (0.026)	0 (0.023)	0 (0.046)	0 (0.041)	-0.01 (0.024)
CD4T	-0.20 (0.032)	0 (0.004)	-0.46 (0.034)	-0.34 (0.036)	0 (0.026)
NK	0.13 (0.026)	0 (0.002)	0.17 (0.042)	0.10 (0.042)	0 (0.03)
Bcell	-0.08 (0.051)	-0.11 (0.028)	-0.05 (0.068)	-0.01 (0.061)	-0.02 (0.035)
Monocyte	0.05 (0.026)	0 (0.006)	0.12 (0.042)	0.07 (0.04)	0 (0.019)
Granulocyte	-0.03 (0.033)	0 (0.005)	0.16 (0.049)	0.14 (0.042)	0 (0.018)

AgeAccel=universal measure of age acceleration based on Horvath estimate. *IEAA*=intrinsic epigenetic age acceleration based on the Horvath estimate. *EEAA* = extrinsic epigenetic age acceleration which is an enhanced version of the Hannum estimate. *AgeAccel_{Hannum}*=universal measure of age acceleration based on the Hannum estimate. *IEAA.Hannum*=intrinsic epigenetic age acceleration based on Hannum estimate. By design, the intrinsic measures have only weak correlations with blood cell counts. By contrast, *AgeAccel_{Hannum}* and *EEAA* have moderately strong correlations with blood cell counts.

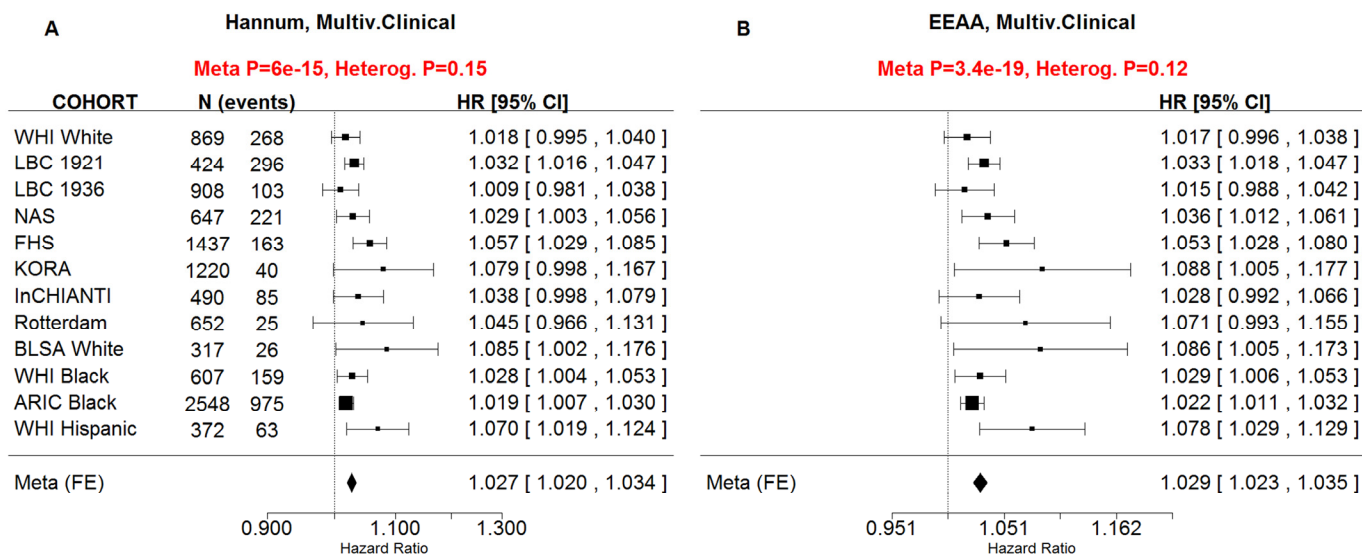
Supplementary Table 5. Leave-one-out analysis by cohort for relating *EEAA* to time to death.

Cohort removed	Age-adjusted model	Fully adjusted model
(None)	1.04 (p=1.81x10 ⁻⁴²)	1.02 (p=1.94x10 ⁻⁷)
ARIC	1.04 (p=1.00x10 ⁻²⁶)	1.03 (p=1.09x10 ⁻⁶)
FHS	1.04 (p=1.23x10 ⁻³⁴)	1.02 (p=5.09x10 ⁻⁶)
LBC 1921	1.04 (p=1.17x10 ⁻³⁸)	1.02 (p=3.21x10 ⁻⁶)
LBC 1936	1.04 (p=1.94x10 ⁻⁴¹)	1.02 (p=1.39x10 ⁻⁷)
WHI (Whites)	1.04 (p=2.61x10 ⁻⁴³)	1.02 (p=2.77x10 ⁻⁷)
WHI (Blacks)	1.04 (p=3.46x10 ⁻⁴⁰)	1.02 (p=7.42x10 ⁻⁷)
WHI (Hispanics)	1.04 (p=4.29x10 ⁻⁴¹)	1.02 (p=6.17x10 ⁻⁷)
NAS	1.04 (p=3.91x10 ⁻⁴⁰)	1.02 (p=2.42x10 ⁻⁷)
InCHIANTI	1.04 (p=1.98x10 ⁻⁴¹)	1.02 (p=7.38x10 ⁻⁷)
Rotterdam	1.04 (p=4.35x10 ⁻⁴¹)	1.02 (p=2.16x10 ⁻⁷)
KORA	1.04 (p=1.93x10 ⁻³⁹)	1.02 (p=3.76x10 ⁻⁷)
TwinsUK	1.04 (p=3.76x10 ⁻⁴¹)	1.02 (p=4.66x10 ⁻⁷)

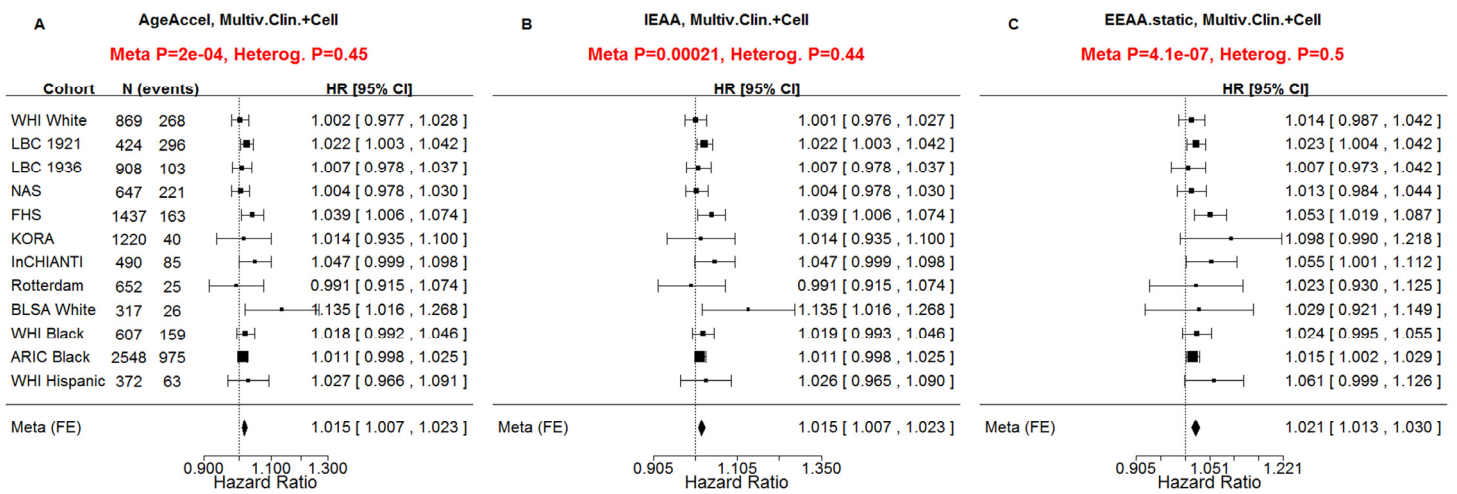
The table reports hazards ratios and corresponding p-values based on a Cox regression. The fully adjusted model includes the following covariates: body mass index, educational level, alcohol intake, smoking pack-years, prior history of diabetes, prior history of cancer, hypertension status, self-reported recreational physical activity.



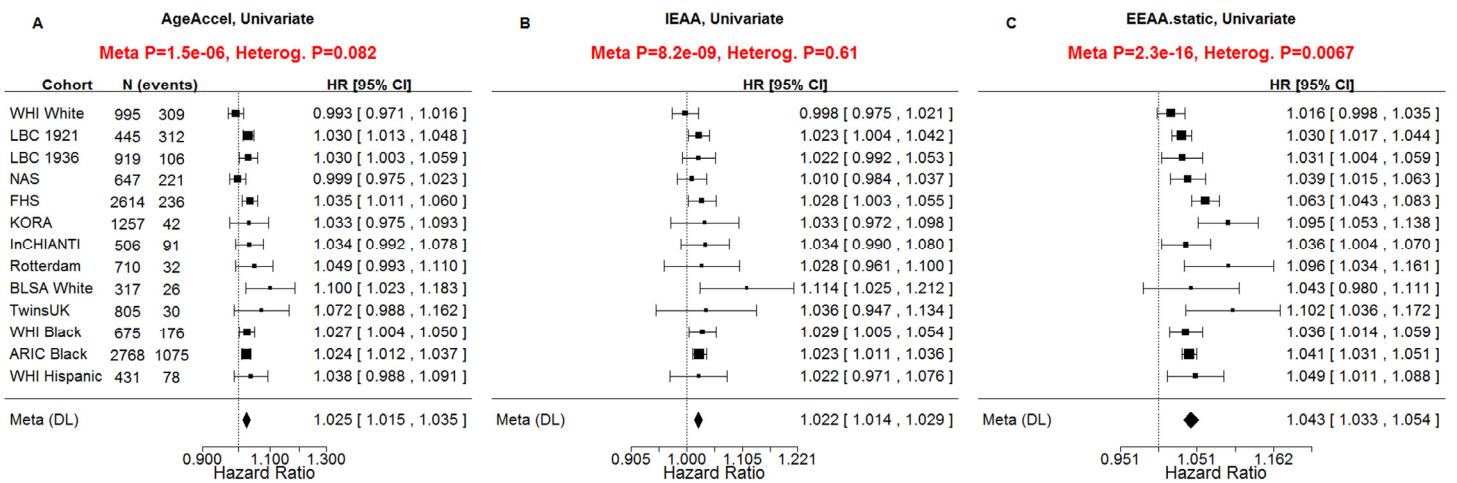
Supplementary Figure 1. Univariate Cox regression model analysis of all-cause mortality, contrasting existing and novel measures of age acceleration. The rows correspond to the different cohorts. Each row depicts the hazard ratio and a 95% confidence interval. To combine the coefficient estimates from the respective studies into a single estimate, we applied a fixed-effect model weighted by inverse variance (implemented in the metafor R package [30]). **(A)** This measure of age acceleration is based on Hannum et al [1]. Specifically, we estimated the age using the 71 CpGs and coefficient values from Hannum. Next, the measure of age acceleration was defined as residuals resulting from regressing the epigenetic age estimate on chronological age. **(B)** Extrinsic epigenetic age acceleration (EEAA). The sub-title of each plot reports the meta-analysis p-value and a heterogeneity test p-value (Cochran's Q-test). It is not appropriate to compare the hazard ratios and confidence intervals of the different measures directly because the measures have different scales/distributions. However, it is appropriate to compare the meta-analysis p-values (colored in red).



Supplementary Figure 2. Multivariate Cox regression model analysis of all-cause mortality, contrasting existing and novel measures of age acceleration. The multivariate Cox regression model included the following additional covariates: chronological age, body mass index (category), educational level (category), alcohol intake, smoking pack years, prior history of diabetes, prior history of cancer, hypertension status, recreational physical activity (category). The rows correspond to separate cohorts. Each row depicts the hazard ratio (HR) and a 95% confidence interval. **(A)** Age acceleration based on Hannum et al [6], **(B)** Extrinsic epigenetic age acceleration (EEAA). The sub-title of each plot reports the meta-analysis p-value and a heterogeneity test p-value (Cochran's Q-test).



Supplementary Figure 3. Multivariate Cox regression analysis of all-cause mortality adjusted for blood cell counts and clinical covariates. A multivariate Cox regression model was used to relate the censored survival time (time to all-cause mortality) to (A) the universal measure of age acceleration (AgeAccel), (B) intrinsic epigenetic age acceleration (IEAA), (C) extrinsic epigenetic age acceleration (EEAA). The multivariate Cox regression model included blood cell counts (exhausted CD8+ T cells, naïve CD8+, CD4+ T cells, natural killer, monocytes, granulocytes, and plasmablasts) and clinical covariates (chronological age, body mass index, educational level, alcohol intake, smoking pack years, prior history of diabetes, prior history of cancer, hypertension status, recreational physical activity). The rows correspond to the different cohorts. Each row depicts the hazard ratio (HR) and a 95% confidence interval. Estimates were meta-analyzed using a fixed-effect model weighted by inverse variance. The sub-title of each plot reports the meta-analysis p-value and a heterogeneity test p-value (Cochran's Q-test).



Supplementary Figure 4. Random effects meta-analysis for univariate Cox models. The figure is analogous to Figure 2 in our article except that it uses a random-effects meta-analysis (DerSimonian-Laird) instead of a fixed-effects model. A univariate Cox regression model was used to relate the censored survival time (time to all-cause mortality) to (A) the universal measure of age acceleration (AgeAccel), (B) intrinsic epigenetic age acceleration (IEAA), (C) extrinsic epigenetic age acceleration (EEAA). To combine the coefficient estimates from the respective studies into a single estimate, we applied the DerSimonian-Laird random effects model. The sub-title of each plot reports the meta-analysis p-value and a heterogeneity test p-value (Cochran's Q-test).