Web Material for

Eleven Telomere, Epigenetic Clock, and Biomarker-Composite Quantifications of Biological Aging: Do They Measure the Same Thing?

Web Appendix 1. Detailed Description of Biological Aging Measures

Telomere length. Telomere length was measured from leukocyte DNA collected at ages 26 and 38 years. Leukocyte DNA was extracted from blood using standard procedures (1,2). DNA was stored at -80°C. All DNA samples were assayed for leukocyte telomere length at the same time. Leukocyte telomere length was measured using a validated quantitative PCR method (3), as previously described (4), which determines mean telomere length across all chromosomes for all cells sampled. The method involves two quantitative PCR reactions for each subject; one for a single-copy gene (S) and the other in the telomeric repeat region (T). All DNA samples were run in triplicate for telomere and single-copy reactions.

Measurement artifacts (e.g., differences in plate conditions) may lead to spurious results when comparing leukocyte telomere length measured on the same individual at different ages. To eliminate such artifacts, we assayed DNA triplicates from the same individual from all time points, on the same plate. CV for triplicate Ct values was 0.81% for the telomere (T) and 0.48% for the single-copy gene (S). We computed change in telomere length as the Age-38 T/S ratio – Age-26 T/S ratio. Telomere data were available for N=829 Study members at age 38, for N=812 Study members at age 26, and for N=758 Study members at both ages of measurement.

Epigenetic Clocks. Epigenetic clocks were calculated using leukocyte DNA collected at ages 26 and 38 years. 500ng of DNA from each sample was treated with sodium bisulfite, using the EZ-96 DNA Methylation kit (Zymo Research, CA, USA). DNA methylation was quantified using the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc, CA, USA) run on an Illumina iScan System (Illumina, CA, USA) using the manufacturers' standard protocol. Briefly, these arrays simultaneously interrogate >485,000 methylation sites distributed across the genome. Samples were arranged into 96-well plates so that within-individual age-26 and -38 DNA samples were hybridized in the same row of the arrays (i.e. age 26 and 38 DNA samples from the same individual occupy array columns 1 and 2 of the same row). Array analysis was performed by the Duke University Molecular Physiology Institute Genomics Core Facility using the iScan platform (Illumina). Data quality control and normalization was carried out using the *Methylumi* Bioconductor package in the R statistical programming environment.

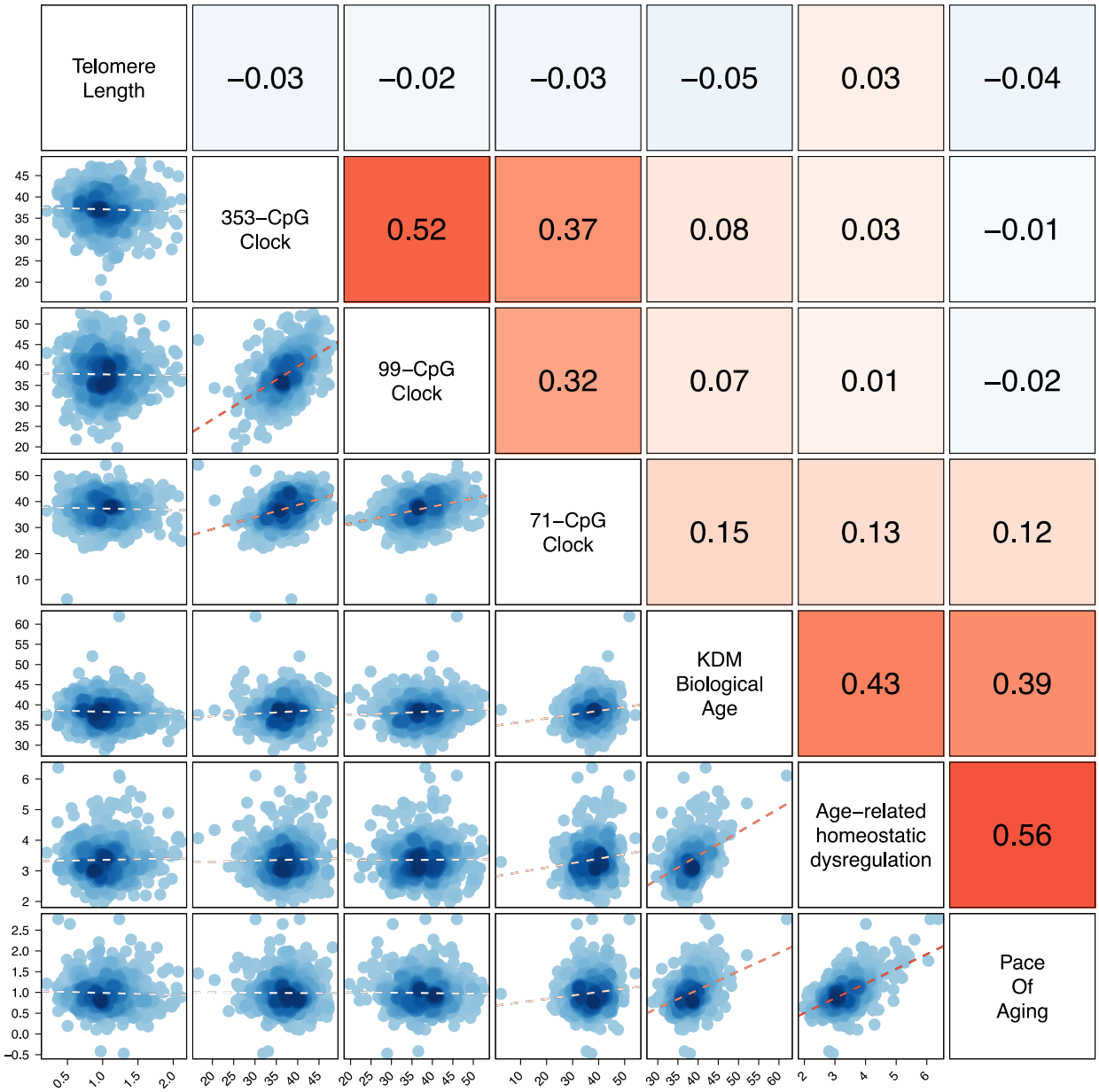
We analyzed three epigenetic clocks. The first clock, proposed by Horvath, included 353 CpG sites (5). The second clock, proposed by Hannum and colleagues, included 71 CpG sites (6). The third clock, proposed by Weidner and colleagues, included 99 CpG sites (7,8). Study members' epigenetic clock values for the 353-CpG and 71-CpG clocks were calculated using Horvath's website (https://labs.genetics.ucla.edu/horvath/dnamage/). Epigenetic clock values for the 99-CpG clock were calculated using the algorithm published by the Wagner lab (9,10). Epigenetic clock values were available for N=818 Study members at age 38, for N=821 Study members at age 26, and for N=743 Study members at both ages of measurement.

Biological Age. As described previously (11), we calculated each Study member's Biological Age at age 38 years using the Klemera-Doubal equation (12) and parameters Levine estimated from the NHANES-III dataset (13) for ten biomarkers: Glycated hemoglobin, Forced expiratory volume in one second (FEV_1), Blood pressure (systolic), Total cholesterol, C-reactive protein, Creatinine, Urea nitrogen, Albumin, Alkaline phosphatase, and Cytomegalovirus IgG. Data to calculate Biological Age data were available for N=904 Study members.

Age-Related Homeostatic Dysregulation. We measured age-related homeostatic dysregulation by applying the biomarker Mahalanobis distance method described by Cohen and colleagues (14–16) to Study members' age-38 biomarker values. The biomarker Mahalanobis distance method measures how aberrant an individual's physiology is relative to a reference norm (14). Cohen and colleagues used chronologically young individuals to form this reference norm for their calculations (15). They interpreted biomarker Mahalanobis distance from the reference as an indicator of age-related homeostatic dysregulation, a sign of biological aging. We formed our reference from the Dunedin Study members' biomarker values at age 26 years, the youngest age at which the biomarkers were measured. Thus, a Study member's biomarker Mahalanobis distance quantifies homeostatic dysregulation relative to the cohort's age-26 norm. We calculated Mahalanobis distance based on 18 biomarkers with repeated measures at ages 26 and 38 years (the same 18 biomarkers we previously used to compute Study members' Pace of Aging (11), see below). Distances were log transformed for analysis. Age-related Homeostatic Dysregulation was measured for N=954 Study members.

Pace of Aging. As described previously (11), we measured Pace of Aging with repeated assessments of a panel of 18 biomarkers taken at ages 26, 32, and 38 years. The biomarkers were: Apolipoprotein B100/A1 ratio, Blood pressure (mean arterial pressure), Body mass index (BMI) and Waist-hip ratio, C-reactive protein and white blood cell count, Cardiorespiratory fitness (VO_2Max), Creatinine clearance, Forced expiratory volume in one second (FEV_1) and Forced vital capacity ratio (FEV_1/FVC), Glycated hemoglobin, High density lipoprotein (HDL), Lipoprotein(a), Leukocyte telomere length (LTL), Periodontal disease, Total cholesterol, Triglycerides, Urea nitrogen. For each biomarker, we calculated the Study member's personal rate of change using mixed-effects growth models. We combined these rates of change into a single index scaled in years of physiological change occurring per one chronological year. The average Study member had Pace of Aging equal to one year of physiological change per one chronological year. The fastest-aging Study members experienced more than twice that rate of physiological change. The slowest-aging Study members experienced almost no change at all. Pace of Aging was measured for N=954 Study members.

Web Figure 1. Correlations among seven measures of biological aging in a birth cohort at chronological age 38 years. The figure shows a matrix of scatterplots and correlations illustrating relationships among seven measures of biological aging: Leukocyte telomere length, 353-, 99-, and 71-CpG epigenetic clocks, KDM Biological Age, Age-related Homeostatic Dysregulation, and Pace of Aging. Data are for n=800 Study members with complete data on all biological aging measures. Correlations are shown above the diagonal. (Correlations ≥0.07 are statistically significant at p<0.05.) Scatter plots are shown below the diagonal. Y-axis scales correspond to the biological aging metric listed to the right of the plot. X-axis scales correspond to the biological aging metric listed above the plot. Correlations between aging measures computed with adjustment for sex differences are reported in **Web Table 6**.



Web Table 1. Relationships among telomere length, epigenetic clocks, KDM Biological Age, Age-related Homeostatic Dysregulation, and Pace of Aging in a birth cohort at chronological age 38 years – Spearman correlations

		Spearman correlations						p-values for Spearman correlations					
		(1)	(2)	(3)	(4)	(5)	(6)	(1)	(2)	(3)	(4)	(5)	(6)
Spearman Correlations													
(1)	Telomere Length												
(2)	353-CpG Clock	-0.05						0.174					
(3)	99-CpG Clock	-0.04	0.53					0.282	5.66E-60				
(4)	71-CpG Clock	-0.04	0.41	0.34				0.276	3.06E-33	5.38E-23			
(5)	KDM Biological Age	-0.05	0.12	0.08	0.14			0.152	0.001	0.028	6.52E-05		
(6)	Age-related Homeostatic Dysregulation	0.02	0.04	0.03	0.09	0.40		0.652	0.272	0.390	0.013	8.35E-32	
(7)	Pace of Aging	-0.03	0.00	-0.01	0.12	0.36	0.48	0.351	0.905	0.711	0.001	1.48E-25	5.20E-47

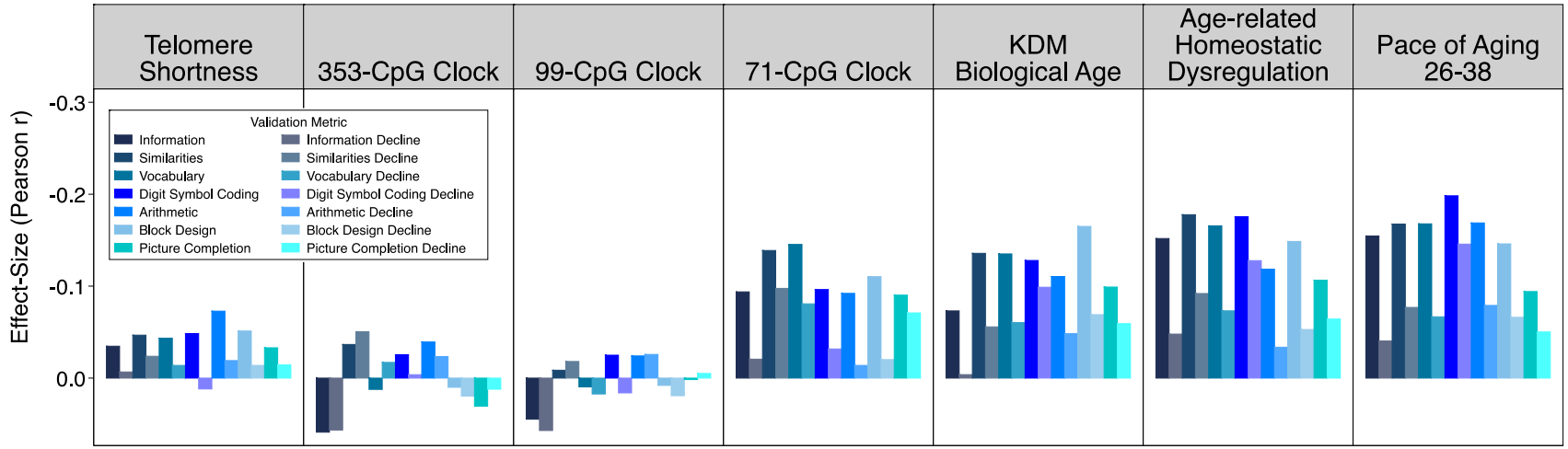
Web Table 2. Relationships among telomere length, epigenetic clocks, KDM Biological Age, Age-related Homeostatic Dysregulation, and Pace of Aging in a birth cohort at chronological age 38 years – Principal components analysis. Three principal components were estimated with eigenvalues of 1.00 or greater. Telomere length loaded most strongly on principal component three; 353- and 99-CpG epigenetic clocks loaded most strongly on principal component two and the 71-CpG clock loaded similarly on components one and two; clinical biomarker algorithm values loaded most strongly on principal component one.

	Principal Component		
	1	**2**	**3**
Eigen-value	2.05	1.71	1.00
Loadings			
Telomere Length	-0.05	-0.03	0.99
353-CpG Clock	0.32	0.53	0.03
99-CpG Clock	0.30	0.53	0.06
71-CpG Clock	0.37	0.35	0.01
KDM Biological Age	0.47	-0.23	-0.06
Age-related Homeostatic Dysregulation	0.48	-0.36	0.11
Pace of Aging	0.47	-0.37	-0.01

Web Table 3. Sex-adjusted Pearson correlations among telomere length, epigenetic clocks, KDM Biological Age, Age-related Homeostatic Dysregulation, and Pace of Aging

Sex-Adjusted Pearson Correlations		(1)	(2)	(3)	(4)	(5)	(6)
(1)	Telomere Length						
(2)	353-CpG Clock	-0.03					
(3)	99-CpG Clock	-0.02	0.52				
(4)	71-CpG Clock	-0.03	0.37	0.32			
(5)	KDM Biological Age	-0.05	0.08	0.07	0.15		
(6)	Age-related Homeostatic Dysregulation	0.03	0.02	0.00	0.10	0.43	
(7)	Pace of Aging	-0.04	-0.01	-0.02	0.12	0.39	0.57

Web Figure 2. Associations of cross-sectional biological aging measures and Pace of Aging with subtests of cognitive functioning and cognitive decline. The figure shows bar charts of effect-sizes (Pearson r) for each of the seven measures of biological aging. Effect-sizes were estimated for seven tests of cognitive function administered in parallel during childhood and age-38 assessments. The tests were subscales of the Wechsler Intelligence Tests. There were three tests of so-called "crystalized" cognitive functions (Information, Similarities, and Vocabulary), and four tests of so-called "fluid" cognitive functions (Digit Symbol Coding, Arithmetic, Block Design, and Picture Completion). All tests were scored so that higher values corresponded to indication of better cognitive functioning. Telomere length was reversed for this analysis so that higher values corresponded to shorter telomeres. Thus, the expected direction of association for all correlations was negative—because faster biological aging is expected to hasten cognitive decline. Standardized regression coefficients (interpretable as Pearson r) and their p-values are reported in the table below the figure. For each test, the graph plots the effect-size for association between biological aging and age-38 test performance first (darker shaded bars), followed by the effect-size for association between biological aging and actual decline in test performance between childhood and age 38 (lighter shaded bars).



	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	r / p-value													
Information														
Age 38	-0.03	0.314	0.06	0.090	0.04	0.196	-0.09	0.008	-0.07	0.027	-0.15	2.89E-06	-0.15	1.56E-06
Change from Childhood	-0.01	0.793	0.06	0.027	0.06	0.025	-0.02	0.435	0.00	0.879	-0.05	0.047	-0.04	0.093
Similarities														
Age 38	-0.05	0.181	-0.04	0.298	-0.01	0.808	-0.14	1.09E-04	-0.14	4.49E-05	-0.18	6.16E-08	-0.17	2.69E-07
Change from Childhood	-0.02	0.417	-0.05	0.087	-0.02	0.541	-0.10	0.001	-0.06	0.048	-0.09	0.001	-0.08	0.006
Vocabulary														
Age 38	-0.04	0.215	0.01	0.726	0.01	0.784	-0.15	5.25E-05	-0.14	5.07E-05	-0.17	4.92E-07	-0.17	2.71E-07
Change from Childhood	-0.01	0.589	-0.02	0.508	0.02	0.499	-0.08	0.002	-0.06	0.014	-0.07	0.003	-0.07	0.006
Digit Symbol Coding														
Age 38	-0.05	0.153	-0.03	0.456	-0.02	0.464	-0.10	0.006	-0.13	7.19E-05	-0.18	2.98E-08	-0.20	2.54E-10
Change from Childhood	0.01	0.665	0.00	0.894	0.02	0.557	-0.03	0.264	-0.10	1.40E-04	-0.13	7.23E-07	-0.15	1.15E-08
Arithmetic														
Age 38	-0.07	0.034	-0.04	0.256	-0.02	0.486	-0.09	0.009	-0.11	0.001	-0.12	2.67E-04	-0.17	1.47E-07
Change from Childhood	-0.02	0.467	-0.02	0.372	-0.03	0.327	-0.01	0.611	-0.05	0.055	-0.03	0.180	-0.08	0.001
Block Design														
Age 38	-0.05	0.137	0.01	0.772	0.01	0.817	-0.11	0.002	-0.16	5.08E-07	-0.15	5.07E-06	-0.15	6.30E-06
Change from Childhood	-0.01	0.599	0.02	0.456	0.02	0.466	-0.02	0.460	-0.07	0.006	-0.05	0.037	-0.07	0.008
Picture Completion														
Age 38	-0.03	0.345	0.03	0.383	0.00	0.962	-0.09	0.012	-0.10	0.003	-0.11	0.001	-0.09	0.004
Change from Childhood	-0.01	0.669	0.01	0.719	-0.01	0.881	-0.07	0.041	-0.06	0.068	-0.06	0.046	-0.05	0.116

Web Appendix 2. Does change between repeated cross-sectional measures of biological aging track the aging process?

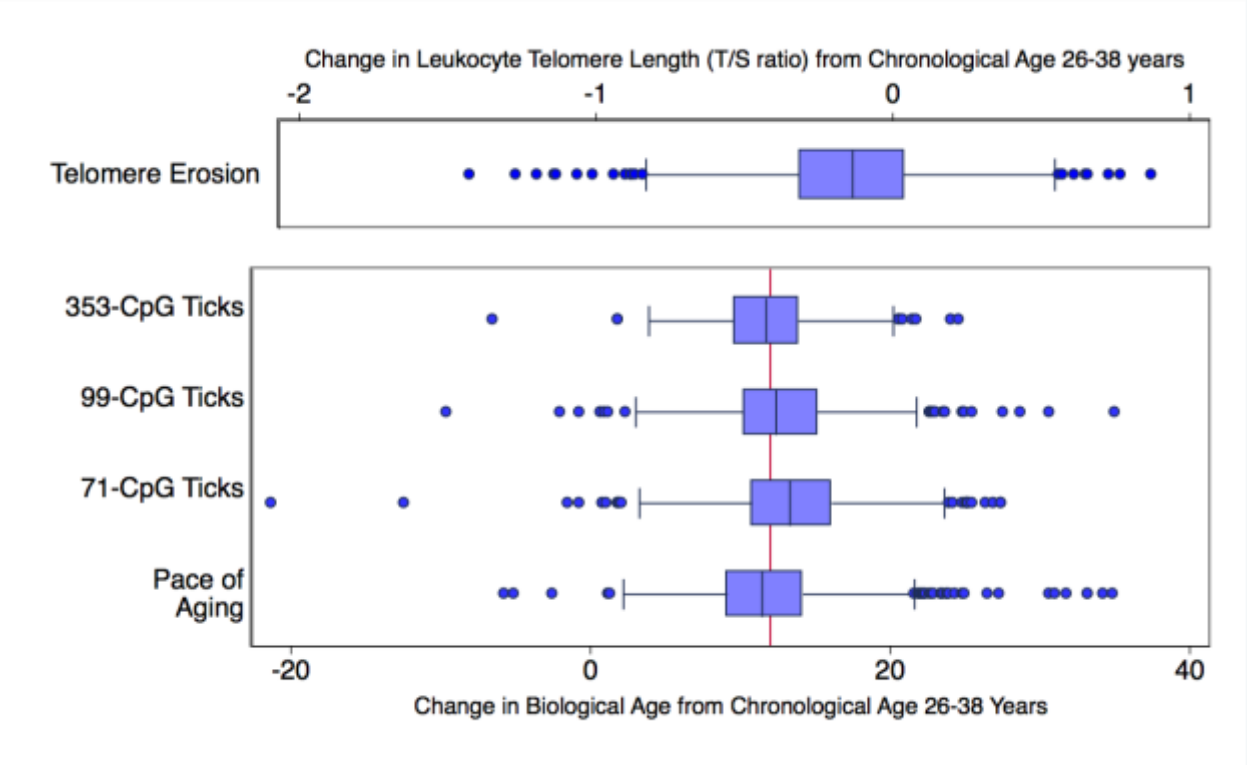
Most methods to quantify biological aging are designed for implementation using a cross-section of biomarker data. These cross-sectional methods could be used to measure changes in the rate of aging caused by geroprotective intervention if they were repeated, for example before and after administration of therapy. We were able to test if cross-sectional biological-age measures showed promise for such applications by testing within-person change in biological age estimates calculated from biological samples taken when Study members were aged 26 years and again when they were aged 38 years. We computed change scores (age-38 value – age-26 value) to test how much telomere erosion actually took place over these 12 years and how many "ticks" were registered by the epigenetic clocks. (We did not test change in the KDM Biological Age and Age-related Homeostatic Dysregulation measures because the necessary data were not available at the age-26 assessment.)

Study members experienced an average of 0.15 (SD=0.30) T/S ratio units of telomere erosion over the 12-year follow-up. This telomere erosion was equivalent to about one-half of one standard deviation of the variance in telomere length at age 38 years. Study members' epigenetic clocks ticked forward by 12-14 years (for the 353 CpG clock, M=12y, SD=3; for the 99 CpG clock, M=13y, SD=4; for the 71 CpG clock, M=14y, SD=5). This epigenetic "ticking" was equivalent to between 2 and 3 standard deviations of the variance in epigenetic clock values at age 38 years. For comparison purposes, we analyzed change in biological age as estimated by Pace of Aging. Because Pace of Aging estimates physiological-change-per-chronological-year, we multiplied each Study member's Pace of aging by 12 to estimate change in biological age between chronological ages 26 and 38 years (M=12y, SD=5). Telomere erosion, epigenetic ticking, and Pace of Aging were approximately normally distributed (**Web Figures 3 and 4**).

To test if a common aging process influenced changes in different measures of biological aging, we computed correlations among change scores. Correlations among change scores showed a pattern similar to correlations among cross-sectional measures (**Web Figure 5**). Telomere erosion was not correlated with epigenetic ticking. Epigenetic ticking was correlated across the three different clocks (r=0.17-0.42). Epigenetic ticking was weakly correlated with Pace of Aging (r=0.06-0.09). The correlation between telomere erosion and Pace of aging was relatively high (r=0.24) because telomere erosion is a component of the Pace of Aging. When telomere erosion was excluded from Pace of Aging the correlation was reduced to near zero. Results were similar when Spearman correlations were computed to reduce the influence of extreme values (**Web Table 4**).

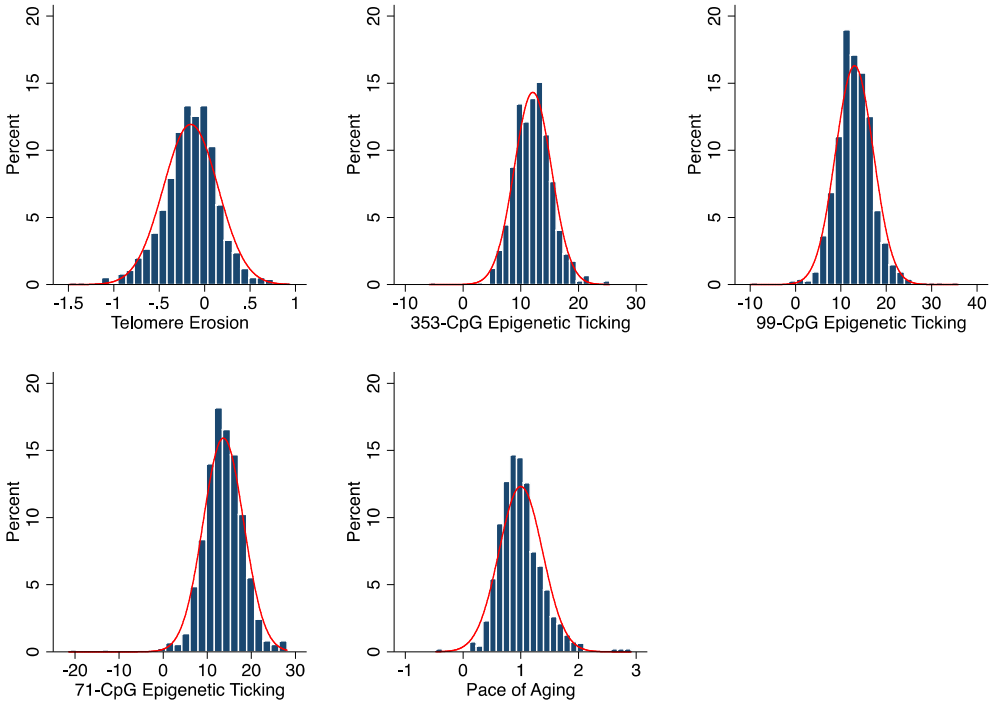
Change scores computed from repeated cross-sectional biological aging measures were not consistently associated with healthspan-related characteristics. Telomere erosion was not associated with healthspan-related characteristics (r=-0.04-0.03). Epigenetic ticking was also not associated with healthspan characteristics, with the exception of age-38 IQ score (r=0.11, p=0.003 for 353-CpG clock; r=0.09, p=0.017 for the 71-CpG clock) and self-rated health (r=-0.07, p=0.044 for the 71-CpG clock). Effect sizes are graphed in **Web Figures 6** and **7**.

Web Figure 3. Changes in cross-sectional measures of biological aging between chronological ages 26 and 38 years in the Dunedin cohort. Telomere and epigenetic clock measurements were made from DNA samples extracted from peripheral blood collected when Study members were aged 26 and 38 years. Repeated observations of each individual were assayed together on the same plate/ methylation array to reduce batch effects. Telomere erosion and epigenetic ticking were measured by subtracting age-26 values from age-38 values. For comparison purposes, Pace of Aging is plotted alongside the epigenetic clocks. Pace of Aging is estimated from three repeated measurements at ages 26, 32, and 38 years of 18 different biomarkers. Pace of Aging is scaled in years of physiological change per chronological year. For this graph, Pace of Aging was multiplied by 12 to reflect the years of biological aging estimated to have occurred between ages 26 and 38 years. The vertical red line in the bottom panel of the figure indicates a value of 12 years, the actual amount of chronological time elapsed during the measurement interval.

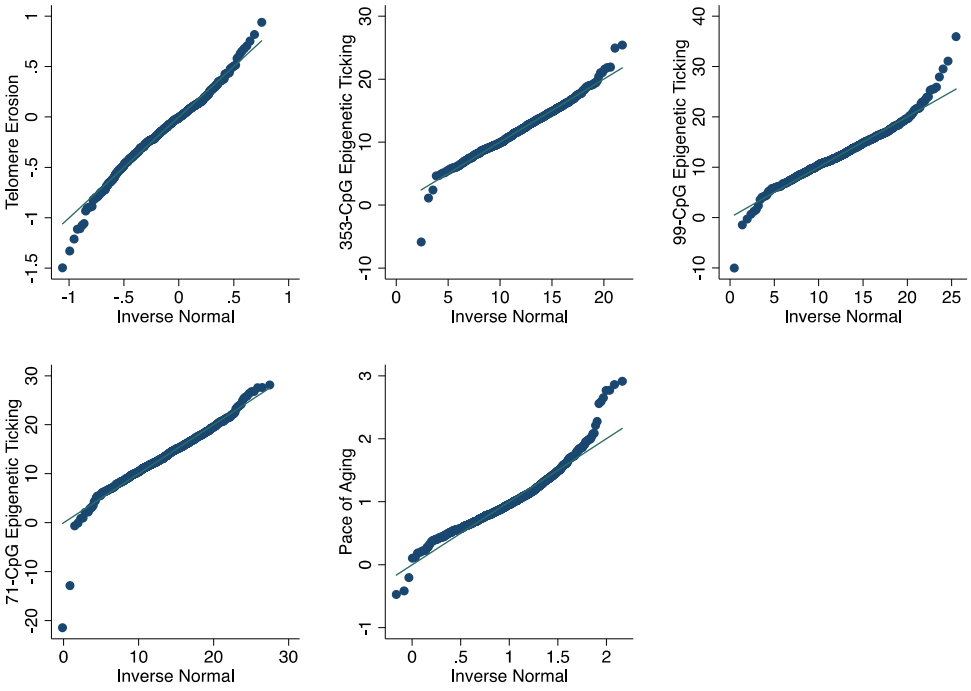


Web Figure 4. Distributions of telomere erosion, epigenetic ticking rates, and the Pace of Aging.

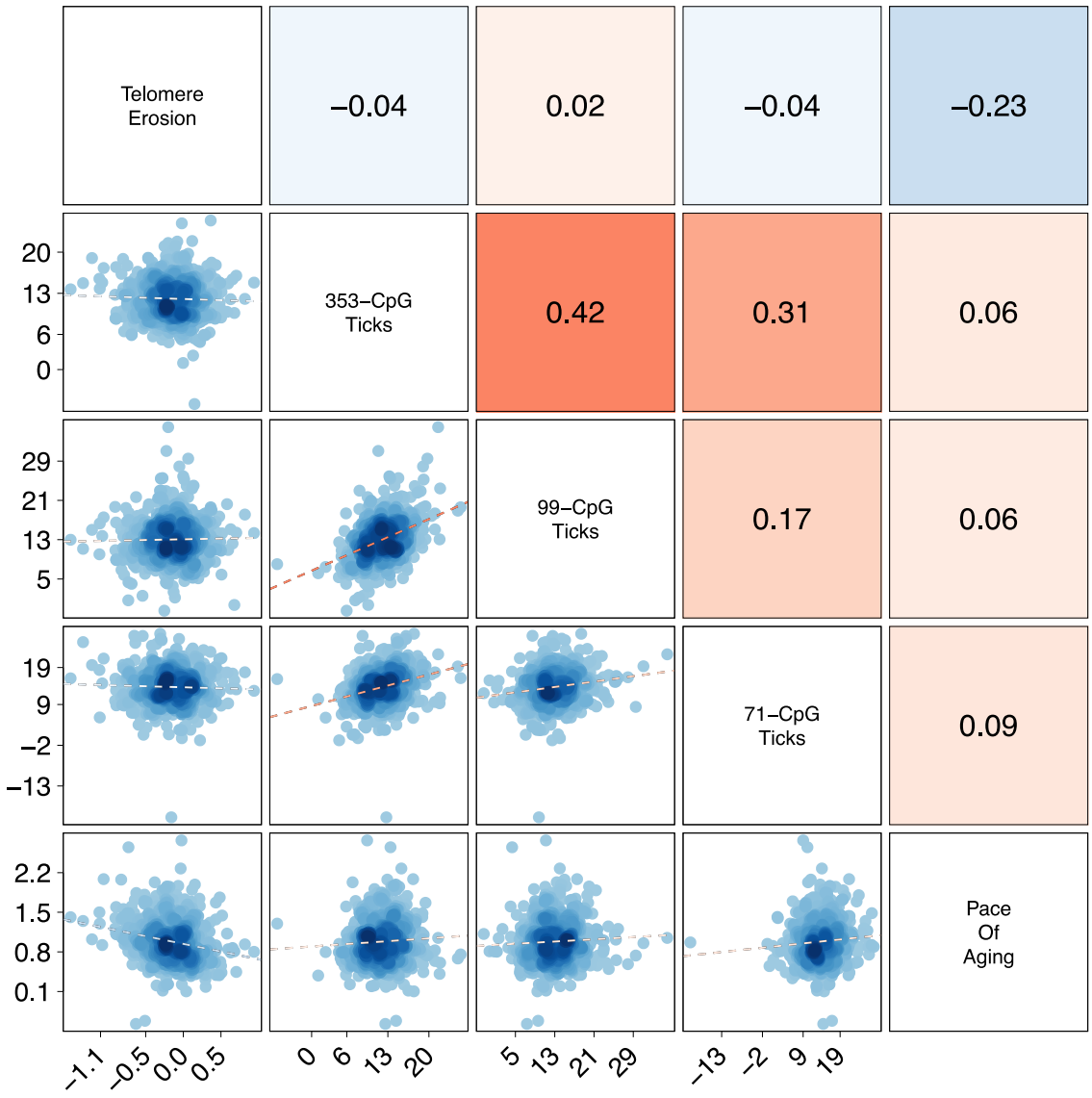
Panel A. Histograms



Panel B. Quantile plots



Web Figure 5. Correlations among longitudinal measures of biological aging. The figure shows a matrix of scatterplots and correlations illustrating relationships among 5 longitudinal measures of biological aging: telomere erosion, ticking of the 353-, 99-, and 71-CpG epigenetic clocks, and the Pace of Aging. Data are for n=733 Study members with complete data on all measures. Correlations are shown above the diagonal. (Correlations ≥0.07 are statistically significant at p<0.05.) Scatter plots are shown below the diagonal. Y-axis scales correspond to the biological aging metric listed to the left of the plot. X-axis scales correspond to the biological aging metric listed above the plot. Correlations between aging measures computed with adjustment for sex differences are reported in **Supplemental Table 5.**



Web Table 4. Relationships among telomere erosion, epigenetic ticking rates, and Pace of Aging – Spearman correlations.

		Spearman correlations				p-values for Spearman correlations			
		(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Spearman Correlations									
(1)	Telomere Erosion								
(2)	353-CpG Ticks	-0.04				0.336			
(3)	99-CpG Ticks	0.01	0.37			0.805	1.66E-25		
(4)	71-CpG Ticks	-0.02	0.33	0.16		0.527	8.71E-20	2.10E-05	
(5)	Pace of Aging	-0.24	0.10	0.07	0.10	8.31E-11	0.010	0.062	0.005

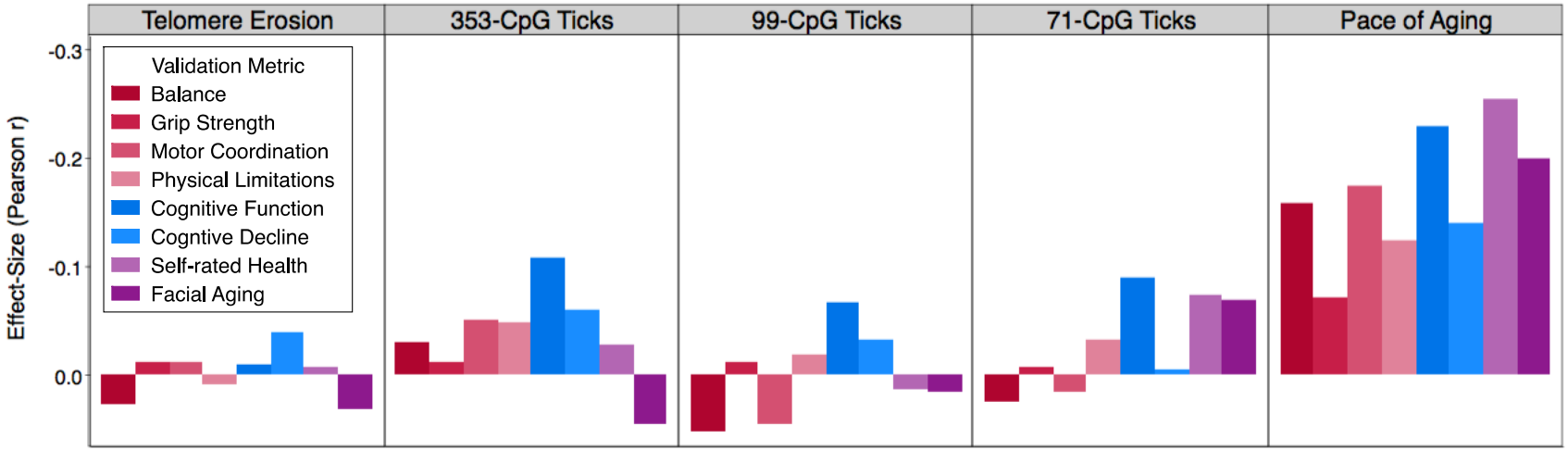
Web Table 5. Relationships among telomere erosion, epigenetic ticking rates, and Pace of Aging -- Principal components analysis. Two principal components were estimated with eigenvalues of 1.00 or greater. Telomere erosion and the Pace of Aging loaded most strongly on the second principal component. Loadings were in the opposite direction because negative values of telomere erosion indicate faster aging whereas positive values of the Pace of Aging indicate faster aging. Co-loadings of telomere erosion and Pace of Aging on a common factor reflect the inclusion of telomere erosion in the Pace of Aging algorithm. Epigenetic clocks loaded most strongly on the first principal component.

	Principal Component	
	1	**2**
Eigen-value	1.63	1.21
Loadings		
Telomere Erosion	-0.13	0.70
353-CpG Ticking	0.63	0.16
99-CpG Ticking	0.55	0.23
71-CpG Ticking	0.48	0.02
Pace of Aging	0.22	-0.65

Web Table 6. Sex-adjusted Pearson correlations among telomere erosion, epigenetic ticking rates, and Pace of Aging

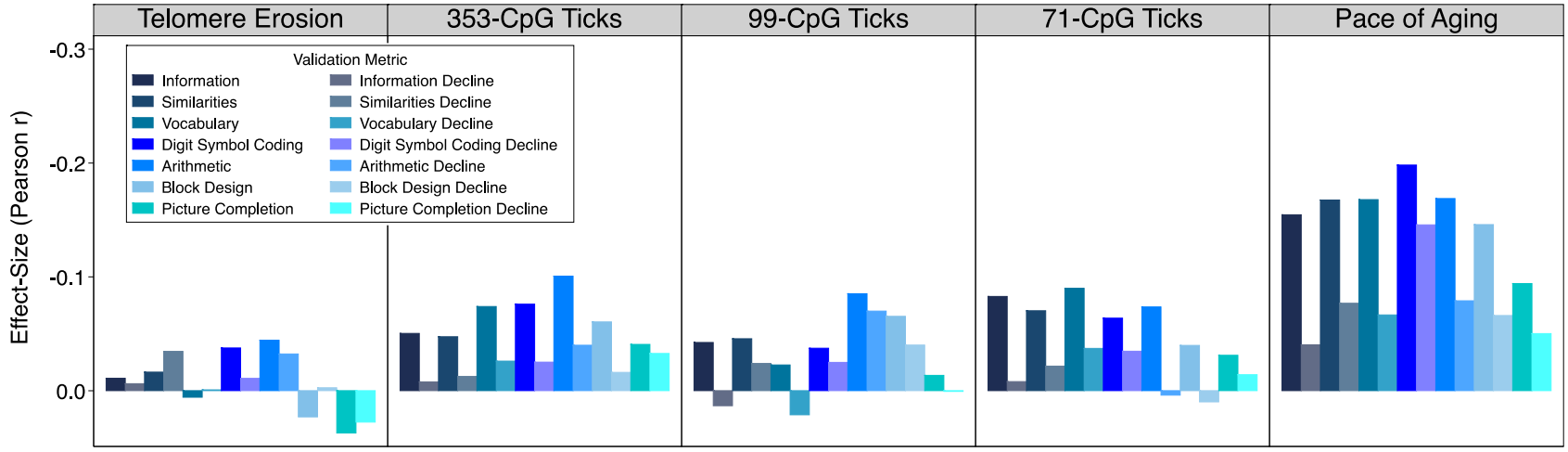
Sex-Adjusted Pearson Correlations		(1)	(2)	(3)	(4)
(1)	Telomere Erosion				
(2)	353-CpG Ticks	-0.04			
(3)	99-CpG Ticks	0.02	0.41		
(4)	71-CpG Ticks	-0.04	0.31	0.17	
(5)	Pace of Aging	-0.23	0.07	0.06	0.08

Web Figure 6. Associations of changes in cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics. The figure shows bar charts of effect-sizes for telomere erosion, ticking of 353-, 99-, and 71-CpG epigenetic clocks, and Pace of Aging. Effect-sizes were estimated for four measures of physical functioning (balance, grip strength, motor coordination, and self-reported physical limitations), cognitive functioning (IQ score at age 38 from the Wechsler Adult Intelligence Scale), cognitive decline (change in Wechsler-scale IQ score since childhood), and two measures of subjective aging (self-rated health and facial aging from assessments of facial photographs of the Study member by independent raters). Effect sizes for subtests of cognitive function and cognitive decline are graphed in **Supplemental Figure 6**. Healthspan-related characteristics were scored so that higher values indicated increased healthspan. Telomere erosion was scored for this analysis so that higher values corresponded to more telomere erosion. Thus, the expected direction of association for all correlations was negative—because faster biological aging is expected to shorten healthspan. Standardized regression coefficients (interpretable as Pearson r) and their p-values are reported in the table below the figure (next page).



Healthspan-related Characteristics	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	r / p-value									
Balance	0.03	0.442	-0.03	0.424	0.05	0.147	0.02	0.498	-0.16	1.27E-06
Grip Strength	-0.01	0.742	-0.01	0.745	-0.01	0.753	-0.01	0.876	-0.07	0.029
Motor Coordination	-0.01	0.779	-0.05	0.178	0.05	0.210	0.02	0.657	-0.17	1.25E-07
Physical Limitations	0.01	0.796	-0.05	0.189	-0.02	0.637	-0.03	0.371	-0.12	1.30E-04
IQ at 38	-0.01	0.797	-0.11	0.003	-0.07	0.071	-0.09	0.017	-0.23	1.83E-12
IQ change from childhood	-0.04	0.305	-0.06	0.109	-0.03	0.402	0.00	0.907	-0.14	2.80E-05
Self-rated Health	-0.01	0.878	-0.03	0.458	0.01	0.698	-0.07	0.044	-0.25	2.69E-15
Facial Aging	0.03	0.379	0.05	0.214	0.02	0.648	-0.07	0.066	-0.20	7.56E-10

Web Figure 7. Associations of changes in cross-sectional biological aging measures and Pace of Aging with subtests of cognitive functioning and cognitive decline. The figure shows bar charts of effect-sizes (Pearson r) for telomere erosion, ticking of 353-, 99-, and 71-CpG epigenetic clocks, and Pace of Aging. Effect-sizes were estimated for seven tests of cognitive function administered in parallel during childhood and age-38 assessments. The tests were subscales of the Wechsler Intelligence Tests. There were three tests of so-called "crystalized" cognitive functions (Information, Similarities, and Vocabulary), and four tests of so-called "fluid" cognitive functions (Digit Symbol Coding, Arithmetic, Block Design, and Picture Completion). All tests were scored so that higher values corresponded to indication of better cognitive functioning. Telomere erosion was scored for this analysis so that higher values corresponded to more telomere erosion. Thus, the expected direction of association for all correlations was negative—because faster aging is expected to hasten cognitive decline. Standardized regression coefficients (interpretable as Pearson r) and their p-values are reported in the table below the figure. For each test, the graph plots the effect-size for association between biological aging and age-38 test performance first (darker shaded bars), followed by the effect-size for association between biological aging and actual decline in test performance between childhood and age 38 (lighter shaded bars). Standardized regression coefficients (interpretable as Pearson r) and their p-values are reported in the table below the figure (next page).



	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	r / p-value									
Information										
Age 38	-0.01	0.762	-0.05	0.166	-0.04	0.244	-0.08	0.023	-0.15	1.56E-06
Change from	-0.01	0.819	-0.01	0.775	0.01	0.628	-0.01	0.771	-0.04	0.093
Similarities										
Age 38	-0.02	0.654	-0.05	0.197	-0.05	0.214	-0.07	0.056	-0.17	2.69E-07
Change from	-0.03	0.257	-0.01	0.686	-0.02	0.439	-0.02	0.487	-0.08	0.006
Vocabulary										
Age 38	0.01	0.875	-0.07	0.044	-0.02	0.539	-0.09	0.014	-0.17	2.71E-07
Change from	0.00	0.977	-0.03	0.334	0.02	0.431	-0.04	0.169	-0.07	0.006
Digit Symbol Coding										
Age 38	-0.04	0.287	-0.08	0.033	-0.04	0.294	-0.06	0.073	-0.20	2.54E-10
Change from	-0.01	0.710	-0.03	0.392	-0.02	0.394	-0.03	0.236	-0.15	1.15E-08
Arithmetic										
Age 38	-0.04	0.215	-0.10	0.005	-0.09	0.018	-0.07	0.042	-0.17	1.47E-07
Change from	-0.03	0.240	-0.04	0.151	-0.07	0.011	0.00	0.889	-0.08	0.001
Block Design										
Age 38	0.02	0.522	-0.06	0.096	-0.07	0.072	-0.04	0.273	-0.15	6.30E-06
Change from	0.00	0.925	-0.02	0.564	-0.04	0.150	0.01	0.723	-0.07	0.008
Picture Completion										
Age 38	0.04	0.308	-0.04	0.269	-0.01	0.714	-0.03	0.398	-0.09	0.004
Change from	0.03	0.434	-0.03	0.361	0.00	0.985	-0.01	0.695	-0.05	0.116

Web Table 7. Associations of cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics & cognitive subtests after adjustment for body-mass index. Adjustment was made by including body-mass index as a covariate in regressions.

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	BMI-Adjusted r / p-value													
Balance	0.00	0.972	-0.04	0.222	0.02	0.602	-0.06	0.121	-0.15	1.42E-05	-0.14	2.34E-05	-0.09	8.16E-03
Grip Strength	-0.06	0.076	0.00	0.960	-0.06	0.119	-0.05	0.186	-0.22	3.80E-10	-0.06	0.064	-0.09	0.011
Motor Coordination	0.00	0.891	0.00	0.990	0.05	0.184	-0.08	0.037	-0.10	5.48E-03	-0.17	7.29E-07	-0.14	4.87E-05
Physical Limitations	0.03	0.454	0.00	0.938	0.00	0.918	-0.05	0.182	-0.09	1.56E-02	-0.10	3.03E-03	-0.08	1.58E-02
IQ at 38	-0.06	0.102	-0.01	0.719	-0.01	0.815	-0.15	3.16E-05	-0.15	2.04E-05	-0.19	5.73E-09	-0.22	8.04E-11
IQ change from childhood	0.00	0.964	-0.04	0.244	-0.02	0.625	-0.09	0.012	-0.09	0.012	-0.12	0.001	-0.15	1.62E-05
Self-rated Health	-0.01	0.768	0.00	0.936	0.04	0.264	-0.04	0.207	-0.16	5.07E-06	-0.23	1.60E-12	-0.20	4.32E-09
Facial Aging	-0.07	0.046	0.00	0.969	0.01	0.723	-0.12	0.001	-0.23	4.83E-11	-0.22	2.80E-11	-0.21	8.93E-10

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	BMI-adjusted r / p-value													
Information														
Age 38	-0.03	0.399	0.06	0.086	0.05	0.181	-0.10	0.008	-0.07	0.044	-0.14	1.76E-05	-0.16	1.94E-06
Change from Childhood	0.00	0.875	0.05	0.035	0.05	0.039	-0.02	0.450	-0.01	0.777	-0.05	0.063	-0.05	0.071
Similarities														
Age 38	-0.04	0.214	-0.03	0.414	0.00	0.960	-0.14	1.63E-04	-0.12	7.63E-04	-0.17	8.85E-07	-0.16	3.36E-06
Change from Childhood	-0.02	0.420	-0.05	0.091	-0.02	0.613	-0.10	0.001	-0.05	0.085	-0.09	0.001	-0.08	0.007
Vocabulary														
Age 38	-0.04	0.272	0.02	0.570	0.02	0.648	-0.15	6.81E-05	-0.13	3.14E-04	-0.16	3.62E-06	-0.17	1.68E-06
Change from Childhood	-0.01	0.616	-0.01	0.590	0.02	0.476	-0.08	0.002	-0.06	0.025	-0.07	0.004	-0.07	0.011
Digit Symbol Coding														
Age 38	-0.04	0.234	-0.01	0.692	-0.02	0.631	-0.09	0.014	-0.10	2.63E-03	-0.15	2.15E-06	-0.19	1.61E-08
Change from Childhood	0.02	0.504	0.00	0.934	0.02	0.493	-0.03	0.245	-0.09	9.45E-04	-0.12	1.03E-05	-0.15	4.26E-08
Arithmetic														
Age 38	-0.07	0.052	-0.03	0.317	-0.02	0.517	-0.09	0.011	-0.09	0.007	-0.10	2.17E-03	-0.17	4.65E-07
Change from Childhood	-0.02	0.518	-0.03	0.339	-0.03	0.270	-0.02	0.565	-0.05	0.063	-0.03	0.186	-0.09	0.001
Block Design														
Age 38	-0.05	0.131	0.02	0.650	0.01	0.688	-0.10	0.004	-0.16	5.94E-06	-0.14	2.96E-05	-0.15	2.64E-05
Change from Childhood	-0.02	0.488	0.02	0.555	0.02	0.492	-0.02	0.499	-0.07	0.009	-0.05	0.050	-0.07	0.007
Picture Completion														
Age 38	-0.03	0.350	0.03	0.397	0.00	0.957	-0.09	0.018	-0.09	0.009	-0.10	0.003	-0.08	0.016
Change from Childhood	-0.01	0.661	0.01	0.765	-0.01	0.829	-0.07	0.049	-0.05	0.117	-0.06	0.081	-0.04	0.218

Web Table 8. Associations of changes in cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics and cognitive subtests after adjustment for change in body mass index. Adjustment was made by including change in body-mass index between age 26 and age 38 as a covariate in regressions.

Healthspan-related Characteristics	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	BMI-adjusted r / p-value									
Balance	0.02	0.524	-0.03	0.440	0.06	0.111	0.02	0.546	-0.10	5.69E-03
Grip Strength	0.00	0.973	0.00	0.977	0.00	0.954	0.01	0.764	-0.06	0.084
Motor Coordination	-0.02	0.628	-0.05	0.156	0.05	0.217	0.01	0.806	-0.15	4.97E-05
Physical Limitations	-0.01	0.847	-0.05	0.169	-0.02	0.590	-0.04	0.320	-0.10	6.25E-03
IQ at 38	-0.01	0.818	-0.10	0.008	-0.06	0.104	-0.08	0.025	-0.23	1.91E-10
IQ change from childhood	-0.04	0.282	-0.07	0.089	-0.03	0.409	0.01	0.854	-0.16	2.07E-05
Self-rated Health	0.00	0.982	-0.01	0.766	0.01	0.698	-0.08	0.036	-0.21	8.89E-10
Facial Aging	0.02	0.583	0.05	0.166	0.02	0.649	-0.08	0.030	-0.22	1.90E-09

Healthspan-related Characteristics	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	BMI-adjusted r / p-value									
Information										
Age 38	-0.01	0.766	-0.05	0.174	-0.05	0.211	-0.10	0.008	-0.16	6.13E-06
Change from Childhood	-0.01	0.705	-0.01	0.690	0.01	0.838	-0.02	0.548	-0.05	0.054
Similarities										
Age 38	-0.01	0.692	-0.05	0.225	-0.04	0.325	-0.07	0.053	-0.19	1.77E-07
Change from Childhood	-0.04	0.235	-0.01	0.648	-0.02	0.534	-0.02	0.468	-0.11	0.000
Vocabulary										
Age 38	0.01	0.741	-0.07	0.075	-0.02	0.673	-0.09	0.022	-0.18	1.11E-06
Change from Childhood	0.00	0.992	-0.02	0.413	0.03	0.319	-0.03	0.294	-0.08	0.005
Digit Symbol Coding										
Age 38	-0.05	0.198	-0.07	0.060	-0.04	0.328	-0.07	0.073	-0.18	1.39E-07
Change from Childhood	-0.02	0.562	-0.02	0.441	-0.02	0.476	-0.03	0.270	-0.15	1.06E-07
Arithmetic										
Age 38	-0.05	0.219	-0.10	0.009	-0.08	0.024	-0.06	0.091	-0.18	9.85E-07
Change from Childhood	-0.04	0.210	-0.04	0.164	-0.08	0.007	0.01	0.620	-0.09	0.002
Block Design										
Age 38	0.02	0.534	-0.05	0.168	-0.06	0.119	-0.03	0.430	-0.12	6.11E-04
Change from Childhood	0.00	0.971	-0.02	0.460	-0.04	0.166	0.02	0.565	-0.04	0.127
Picture Completion										
Age 38	0.05	0.169	-0.03	0.369	-0.02	0.640	-0.02	0.546	-0.08	0.024
Change from Childhood	0.04	0.241	-0.03	0.435	0.00	0.935	0.00	0.932	-0.04	0.240

Web Table 9. Associations of cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics & cognitive subtests after adjustment for age-in-months. Adjustment was made by including age-in-months as a covariate in regressions.

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	Age-in-months-Adjusted r / p-value													
Balance	0.00	0.897	-0.07	0.061	0.00	0.931	-0.08	0.022	-0.22	6.01E-11	-0.19	1.13E-08	-0.16	1.28E-06
Grip Strength	-0.06	0.071	0.00	0.963	-0.05	0.150	-0.05	0.164	-0.20	2.44E-09	-0.05	0.109	-0.07	0.029
Motor Coordination	-0.01	0.687	-0.02	0.541	0.03	0.457	-0.10	0.006	-0.15	5.82E-06	-0.19	2.73E-09	-0.17	1.22E-07
Physical Limitations	0.03	0.401	-0.02	0.656	-0.01	0.675	-0.07	0.043	-0.13	1.63E-04	-0.14	1.51E-05	-0.12	1.36E-04
IQ at 38	-0.06	0.081	-0.02	0.517	-0.02	0.627	-0.16	9.60E-06	-0.18	1.18E-07	-0.21	1.40E-10	-0.23	1.87E-12
IQ change from childhood	0.00	0.967	-0.04	0.287	-0.01	0.727	-0.09	0.014	-0.10	0.005	-0.11	0.001	-0.14	2.88E-05
Self-rated Health	-0.02	0.542	-0.02	0.641	0.03	0.414	-0.07	0.050	-0.22	9.60E-11	-0.28	4.75E-18	-0.25	3.44E-15
Facial Aging	-0.08	0.029	0.02	0.531	0.04	0.296	-0.10	0.004	-0.19	1.40E-08	-0.22	1.11E-11	-0.19	9.17E-10

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	Age-in-months-Adjusted r / p-value													
Information														
Age 38	-0.03	0.321	0.05	0.116	0.04	0.251	-0.10	0.005	-0.08	0.013	-0.15	3.50E-06	-0.15	1.57E-06
Change from Childhood	-0.01	0.798	0.05	0.046	0.05	0.046	-0.03	0.304	-0.01	0.561	-0.05	0.049	-0.04	0.095
Similarities														
Age 38	-0.05	0.188	-0.05	0.174	-0.02	0.550	-0.15	2.48E-05	-0.16	2.31E-06	-0.18	5.14E-08	-0.17	2.52E-07
Change from Childhood	-0.02	0.418	-0.06	0.042	-0.03	0.343	-0.11	0.000	-0.07	0.009	-0.09	0.001	-0.08	0.006
Vocabulary														
Age 38	-0.04	0.223	0.00	0.929	0.00	0.977	-0.16	1.35E-05	-0.15	5.63E-06	-0.16	5.00E-07	-0.17	2.64E-07
Change from Childhood	-0.01	0.590	-0.02	0.339	0.01	0.716	-0.09	0.001	-0.07	0.003	-0.07	0.003	-0.07	0.006
Digit Symbol Coding														
Age 38	-0.05	0.156	-0.03	0.416	-0.03	0.417	-0.10	0.004	-0.14	2.16E-05	-0.18	2.37E-08	-0.20	2.62E-10
Change from Childhood	0.01	0.665	0.00	0.861	0.02	0.583	-0.03	0.244	-0.11	4.12E-05	-0.13	4.82E-07	-0.15	1.24E-08
Arithmetic														
Age 38	-0.07	0.034	-0.04	0.253	-0.02	0.482	-0.09	0.009	-0.11	0.001	-0.12	2.97E-04	-0.17	1.48E-07
Change from Childhood	-0.02	0.467	-0.02	0.390	-0.03	0.344	-0.01	0.636	-0.05	0.067	-0.03	0.180	-0.08	0.001
Block Design														
Age 38	-0.05	0.136	0.01	0.727	0.01	0.764	-0.11	0.002	-0.17	5.70E-07	-0.15	6.30E-06	-0.15	6.36E-06
Change from Childhood	-0.01	0.598	0.02	0.365	0.02	0.365	-0.02	0.554	-0.07	0.009	-0.05	0.040	-0.07	0.008
Picture Completion														
Age 38	-0.03	0.332	0.04	0.258	0.01	0.740	-0.08	0.022	-0.09	0.007	-0.10	0.001	-0.09	0.004
Change from Childhood	-0.01	0.660	0.02	0.565	0.00	0.937	-0.06	0.063	-0.06	0.096	-0.06	0.044	-0.05	0.113

Web Table 10. Associations of changes in cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics and cognitive subtests after adjustment for change in age-in-months between assessments. Adjustment was made by including change in age-in-months index between the age-26 and -38 assessments as a covariate in regressions.

Healthspan-related Characteristics	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	Change in age-in-months-adjusted r / p-value									
Balance	0.03	0.397	-0.03	0.381	0.05	0.156	0.02	0.525	-0.15	4.98E-06
Grip Strength	-0.01	0.778	-0.01	0.723	-0.01	0.722	-0.01	0.859	-0.07	0.046
Motor Coordination	0.00	0.938	-0.07	0.084	0.03	0.401	0.01	0.890	-0.16	8.60E-07
Physical Limitations	0.01	0.732	-0.06	0.129	-0.03	0.474	-0.04	0.292	-0.13	9.62E-05
IQ at 38	-0.01	0.836	-0.12	0.002	-0.08	0.046	-0.09	0.012	-0.22	1.86E-11
IQ change from childhood	-0.04	0.309	-0.06	0.094	-0.03	0.365	-0.01	0.884	-0.14	2.29E-05
Self-rated Health	-0.01	0.715	-0.02	0.662	0.03	0.416	-0.07	0.076	-0.25	1.07E-14
Facial Aging	0.02	0.664	0.07	0.055	0.05	0.194	-0.05	0.179	-0.19	7.09E-09

Healthspan-related Characteristics	Telomere Erosion		353-CpG Ticks		99-CpG Ticks		71-CpG Ticks		Pace of Aging	
	Change in age-in-months-adjusted r / p-value									
Information										
Age 38	-0.01	0.879	-0.06	0.099	-0.06	0.133	-0.09	0.012	-0.15	5.33E-06
Change from Childhood	0.00	0.988	-0.02	0.482	0.00	0.998	-0.02	0.524	-0.04	0.066
Similarities										
Age 38	-0.01	0.778	-0.06	0.117	-0.06	0.108	-0.08	0.031	-0.16	4.77E-07
Change from Childhood	-0.03	0.342	-0.02	0.484	-0.04	0.248	-0.03	0.343	-0.08	0.002
Vocabulary										
Age 38	0.02	0.623	-0.10	0.010	-0.05	0.197	-0.11	0.004	-0.17	3.66E-07
Change from Childhood	0.01	0.727	-0.04	0.102	0.00	0.981	-0.05	0.051	-0.08	0.002
Digit Symbol Coding										
Age 38	-0.04	0.279	-0.08	0.032	-0.04	0.297	-0.06	0.074	-0.19	2.53E-09
Change from Childhood	-0.01	0.642	-0.02	0.485	-0.02	0.507	-0.03	0.291	-0.14	6.79E-08
Arithmetic										
Age 38	-0.05	0.209	-0.11	0.004	-0.09	0.014	-0.08	0.038	-0.17	2.84E-07
Change from Childhood	-0.03	0.226	-0.04	0.144	-0.07	0.009	0.00	0.881	-0.08	0.001
Block Design										
Age 38	0.02	0.530	-0.06	0.087	-0.07	0.060	-0.04	0.261	-0.13	5.45E-05
Change from Childhood	-0.01	0.792	-0.01	0.732	-0.03	0.234	0.02	0.570	-0.05	0.040
Picture Completion										
Age 38	0.03	0.432	-0.03	0.408	0.00	0.991	-0.02	0.545	-0.09	0.007
Change from Childhood	0.02	0.599	-0.02	0.578	0.02	0.622	0.00	0.936	-0.05	0.137

Web Table 11. Associations of cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics & cognitive subtests after adjustment for smoking. Adjustment was made by including the number of cigarettes smoked per day at age 38 years (17) as a covariate in regressions.

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	Smoking-Adjusted r / p-value													
Balance	0.00	0.988	-0.09	0.015	-0.04	0.295	-0.08	0.027	-0.19	3.26E-09	-0.15	1.50E-05	-0.12	6.41E-04
Grip Strength	-0.06	0.078	-0.01	0.748	-0.07	0.055	-0.05	0.171	-0.19	1.13E-08	-0.04	0.232	-0.06	0.068
Motor Coordination	-0.01	0.777	-0.03	0.374	0.00	0.892	-0.09	0.016	-0.12	2.33E-04	-0.16	2.40E-06	-0.14	4.96E-05
Physical Limitations	0.03	0.371	-0.03	0.463	-0.03	0.352	-0.07	0.050	-0.12	3.55E-04	-0.12	3.65E-04	-0.10	0.002
IQ at 38	-0.05	0.104	-0.05	0.147	-0.07	0.052	-0.15	2.09E-05	-0.14	1.86E-05	-0.15	4.17E-06	-0.17	1.86E-07
IQ change from childhood	0.01	0.864	-0.06	0.095	-0.05	0.157	-0.08	0.024	-0.06	0.053	-0.07	0.038	-0.09	0.006
Self-rated Health	-0.02	0.650	-0.05	0.140	-0.03	0.430	-0.07	0.042	-0.19	1.88E-09	-0.23	1.42E-12	-0.20	1.02E-09
Facial Aging	-0.07	0.043	-0.03	0.392	-0.04	0.239	-0.12	0.001	-0.19	6.29E-09	-0.16	8.05E-07	-0.14	3.28E-05

Healthspan-related Characteristics	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
	Smoking-adjusted r / p-value													
Information														
Age 38	-0.03	0.385	0.03	0.327	0.00	0.979	-0.09	0.012	-0.04	0.169	-0.10	3.58E-03	-0.10	2.47E-03
Change from Childhood	-0.01	0.840	0.04	0.084	0.04	0.163	-0.02	0.468	0.01	0.724	-0.02	0.364	-0.01	0.583
Similarities														
Age 38	-0.04	0.224	-0.06	0.077	-0.05	0.133	-0.13	1.61E-04	-0.11	8.26E-04	-0.13	1.43E-04	-0.12	4.98E-04
Change from Childhood	-0.02	0.464	-0.07	0.021	-0.05	0.103	-0.09	0.002	-0.04	0.149	-0.06	0.033	-0.04	0.134
Vocabulary														
Age 38	-0.04	0.283	-0.01	0.682	-0.04	0.311	-0.14	6.86E-05	-0.11	1.27E-03	-0.11	8.60E-04	-0.11	6.62E-04
Change from Childhood	-0.01	0.647	-0.03	0.249	0.00	0.890	-0.08	0.002	-0.05	0.056	-0.05	0.058	-0.04	0.119
Digit Symbol Coding														
Age 38	-0.04	0.187	-0.05	0.181	-0.06	0.073	-0.09	0.008	-0.11	7.84E-04	-0.13	3.88E-05	-0.16	9.30E-07
Change from Childhood	0.01	0.608	-0.02	0.481	-0.01	0.692	-0.03	0.319	-0.08	1.09E-03	-0.10	2.38E-04	-0.12	1.22E-05
Arithmetic														
Age 38	-0.07	0.042	-0.06	0.097	-0.06	0.109	-0.09	0.013	-0.09	0.005	-0.08	1.46E-02	-0.14	3.79E-05
Change from Childhood	-0.02	0.485	-0.03	0.224	-0.04	0.126	-0.01	0.651	-0.04	0.104	-0.02	0.453	-0.07	0.009
Block Design														
Age 38	-0.05	0.166	-0.01	0.829	-0.02	0.499	-0.11	0.003	-0.15	5.86E-06	-0.11	5.83E-04	-0.11	6.84E-04
Change from Childhood	-0.01	0.631	0.01	0.666	0.01	0.850	-0.02	0.491	-0.06	0.014	-0.04	0.162	-0.05	0.049
Picture Completion														
Age 38	-0.03	0.396	0.02	0.637	-0.02	0.492	-0.09	0.015	-0.09	0.009	-0.08	0.017	-0.07	0.048
Change from Childhood	-0.01	0.701	0.00	0.912	-0.02	0.537	-0.07	0.046	-0.05	0.108	-0.05	0.136	-0.03	0.330

Web Table 12. Associations of cross-sectional biological aging measures and Pace of Aging with healthspan-related characteristics & cognitive subtests after adjustment for socioeconomic status. Adjustment was made by including socioeconomic status at age 38 years as a covariate in regressions. Socioeconomic status was measured using the New Zealand Socioeconomic Index (18,19).

	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
Healthspan-related Characteristics	**Socioeconomic Status-Adjusted r / p-value**													
Balance	0.00	0.971	-0.07	0.030	-0.02	0.640	-0.06	0.073	-0.19	5.71E-09	-0.15	4.42E-06	-0.12	1.53E-04
Grip Strength	-0.06	0.079	0.00	0.904	-0.05	0.134	-0.05	0.147	-0.19	7.54E-09	-0.05	0.131	-0.07	0.037
Motor Coordination	0.00	0.888	-0.02	0.475	0.02	0.581	-0.06	0.080	-0.10	1.55E-03	-0.14	2.35E-05	-0.12	2.12E-04
Physical Limitations	0.03	0.377	-0.02	0.571	-0.02	0.593	-0.07	0.051	-0.12	3.32E-04	-0.13	6.53E-05	-0.12	5.11E-04
IQ at 38	-0.05	0.126	-0.04	0.146	-0.04	0.151	-0.11	5.20E-04	-0.10	7.31E-04	-0.10	6.54E-04	-0.14	2.77E-06
IQ change from childhood	0.01	0.861	-0.05	0.194	-0.02	0.479	-0.07	0.066	-0.06	0.081	-0.07	0.033	-0.10	0.003
Self-rated Health	-0.02	0.641	-0.03	0.310	0.01	0.823	-0.06	0.080	-0.19	2.91E-09	-0.24	8.59E-14	-0.22	1.19E-11
Facial Aging	-0.07	0.050	-0.01	0.827	0.00	0.964	-0.10	0.004	-0.19	5.07E-09	-0.19	1.45E-08	-0.16	5.22E-07

	Telomere Shortness		353-CpG Clock		99-CpG Clock		71-CpG Clock		KDM Biological Age		Age-related Homeostatic Dysregulation		Pace of Aging	
Healthspan-related Characteristics	**Socioeconomic Status-adjusted r / p-value**													
Information														
Age 38	-0.02	0.477	0.04	0.205	0.02	0.496	-0.05	0.092	-0.01	0.645	-0.06	5.16E-02	-0.08	0.009
Change from Childhood	-0.01	0.790	0.05	0.045	0.05	0.056	-0.01	0.595	0.01	0.705	-0.03	0.288	-0.03	0.296
Similarities														
Age 38	-0.04	0.254	-0.06	0.083	-0.03	0.300	-0.10	2.76E-03	-0.08	1.18E-02	-0.09	4.31E-03	-0.09	0.003
Change from Childhood	-0.02	0.407	-0.06	0.038	-0.03	0.270	-0.08	0.005	-0.04	0.172	-0.06	0.039	-0.05	0.082
Vocabulary														
Age 38	-0.03	0.340	-0.01	0.790	-0.01	0.670	-0.11	1.17E-03	-0.07	1.81E-02	-0.07	1.59E-02	-0.09	0.003
Change from Childhood	-0.01	0.573	-0.02	0.380	0.01	0.763	-0.07	0.005	-0.04	0.071	-0.05	0.051	-0.05	0.050
Digit Symbol Coding														
Age 38	-0.04	0.238	-0.04	0.214	-0.04	0.172	-0.07	0.050	-0.08	6.57E-03	-0.10	6.66E-04	-0.14	6.13E-06
Change from Childhood	0.01	0.668	-0.01	0.628	0.00	0.948	-0.02	0.487	-0.08	2.13E-03	-0.09	2.35E-04	-0.12	5.01E-06
Arithmetic														
Age 38	-0.06	0.051	-0.06	0.085	-0.05	0.161	-0.06	0.056	-0.06	0.042	-0.05	1.46E-01	-0.11	5.09E-04
Change from Childhood	-0.02	0.455	-0.03	0.264	-0.03	0.229	-0.01	0.607	-0.04	0.097	-0.03	0.299	-0.07	0.004
Block Design														
Age 38	-0.04	0.209	0.00	0.940	-0.01	0.822	-0.08	0.014	-0.13	8.41E-05	-0.09	6.86E-03	-0.09	0.003
Change from Childhood	-0.01	0.647	0.02	0.503	0.02	0.547	-0.02	0.562	-0.06	0.012	-0.04	0.121	-0.06	0.029
Picture Completion														
Age 38	-0.02	0.475	0.02	0.523	-0.01	0.806	-0.07	0.042	-0.07	0.030	-0.06	0.051	-0.06	0.068
Change from Childhood	-0.01	0.742	0.01	0.801	-0.01	0.743	-0.06	0.067	-0.05	0.145	-0.04	0.187	-0.03	0.298

REFERENCES

1. Bowtell DDL. Rapid isolation of eukaryotic DNA. *Anal. Biochem.* 1987;162(2):463–465.

2. Jeanpierre M. A rapid method for the purification of DNA from blood. *Nucleic Acids Res.* 1987;15(22):9611–9611.

3. Cawthon RM. Telomere measurement by quantitative PCR. *Nucleic Acids Res.* 2002;30(10):e47–e47.

4. Shalev I, Moffitt TE, Sugden K, et al. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. *Mol. Psychiatry*. 2013;18(5):576–581.

5. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol.* 2013;14(10):R115.

6. Hannum G, Guinney J, Zhao L, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol. Cell*. 2013;49(2):359–367.

7. Weidner CI, Lin Q, Koch CM, et al. Aging of blood can be tracked by DNA methylation changes at just three CpG sites. *Genome Biol.* 2014;15(2):R24.

8. Lin Q, Weidner CI, Costa IG, et al. DNA methylation levels at individual age-associated CpG sites can be indicative for life expectancy. *Aging*. 2016;8(2):394–401.

9. Weidner CI, Lin Q, Koch CM, et al. Aging of blood can be tracked by DNA methylation changes at just three CpG sites. *Genome Biol.* 2014;15(2):1–12.

10. Lin Q, Wagner W. Epigenetic Aging Signatures Are Coherently Modified in Cancer. *PLOS Genet*. 2015;11(6):e1005334.

11. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc. Natl. Acad. Sci. U. S. A.* 2015;112(30):E4104-4110.

12. Klemera P, Doubal S. A new approach to the concept and computation of biological age. *Mech. Ageing Dev.* 2006;127(3):240–248.

13. Levine ME. Modeling the rate of senescence: Can estimated biological age predict mortality more accurately than chronological age? *J. Gerontol. A. Biol. Sci. Med. Sci.* 2013;68(6):667–674.

14. Cohen AA, Milot E, Yong J, et al. A novel statistical approach shows evidence for multi-system physiological dysregulation during aging. *Mech. Ageing Dev.* 2013;134(3–4):110–117.

15. Li Q, Wang S, Milot E, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. *Aging Cell*. 2015;14(6):1103–1112.

16. Cohen AA, Milot E, Li Q, et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PloS One*. 2015;10(3):e0116489.

17. Belsky DW, Moffitt TE, Baker TB, et al. Polygenic risk and the developmental progression to heavy, persistent smoking and nicotine dependence: Evidence from a 4-decade longitudinal study. *JAMA Psychiatry*. 2013;70(5):534–542.

18. Milne BJ, Byun U, Lee A. New Zealand socio-economic index 2006. Wellington, NZ: Statistics New Zealand; 2013.

19. Belsky DW, Moffitt TE, Corcoran DL, et al. The Genetics of Success: How Single-Nucleotide Polymorphisms Associated With Educational Attainment Relate to Life-Course Development. *Psychol. Sci.* 2016;27(7):957–972.